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Review Article

# Challenges in orphan drug development and regulatory requirements in India

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## Abstract

While regulatory policy is well-defined in the United States and Europe for the development of orphan drugs, Indian guidelines on rare diseases is still transforming. In India due to lack of a transparent definition and regulatory approval process for rare diseases therefore until now, has deterrent pharmaceutical industries to pursue drug development for rare diseases. The orphan medication program can help pharmaceutical organizations in gaining benefits and recouping their venture even with little patient population in the developed nation. In 2001 a conference was assemble by the Indian Drugs Manufacturers Association (IDMA) where a gathering of pharmacologists mentioned the Indian government to set up the Orphan Drug Act in India. Since, guidelines for the orphan drug have not been made by the Indian government. Indian rare disease patient relies upon developed nations approved orphan drugs. Developing countries are likewise feeling they ought to plan something for the elevation of orphan drug research and manufacturing. The lack of regulatory guidelines of orphan drug antagonistically affecting the monetary development of Indian medical businesses. One of the significant reasons is that the pharmaceutical company isn't quick to look into the improvement of orphan drugs as these medications don't catch a huge market. However, in this article, we have attempted to concentrate on drug regulation of United States and it has been noted that the two biggest populated nation India and China, both need national enactment for orphan drugs and rare diseases, which carries a significant negative effects on their patient population with rare diseases.

**Keywords:** Orphan Drug, rare diseases, orphan drug act, orphan drug regulations, and recent initiatives

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## 1. Introduction

A therapeutic item assigned as an orphan drug is one that has been grown explicitly to treat rare medical condition alluded to as "orphan diseases". It might be characterized as medication that are not created by the pharmaceutical companies for monetary reasons yet which react to general well-being needs. Around 80% of rare diseases have been recognized as hereditary origins. Other rare diseases are the consequences of contaminations (bacterial or viral) and sensitivities or are because of degenerative and proliferative causes. (1)

Orphan drugs are significant medical problem and an important challenge for the clinical community. (2) Modern society still has a shortage of effective treatment options for patients with rare diseases. As a result of this, the demand for public health protection has increased the economic burden of a terminally ill patient. (3) Presently also the country i.e. India and China lacks the effective treatment of patients with rare diseases. There are around 7000 distinct sorts of rare diseases and disorders with more being found today. It has been accounted that there are around 250 new rare disease cases announced each year, nonetheless, the adequate treatment is accessible just for 200-300 orphan diseases. It is realized that 80% of these rare diseases are of hereditary source and the rest have an ecological, bacterial, viral or unknown sources or origin. (4) Substantially, orphan diseases are usually chronic, disabling and life-threatening and a large portion of these have compelling and curative treatment, having low commonness and high complexity. (5)

Orphan drug development is also an exorbitant procedure as other drug development. Due to less profit on investment industries show immaterial enthusiasm for the advancement of treatment for rare diseases. (6) Generally, orphan drug research is reliant on government incentive. USFDA, EMEA, Japan and numerous different offer advantages for example, convention helps, quick track endorsement, waiver of expenses, and marketing exclusivity.

The United States was the first nation to present an orphan drug act in 1983, after that number of different nations has followed the program, for instance, Japan (1993), Singapore (1997), Australia (1998), and the European Union (2000). European Union acts were made a much later than the USA. Since it is a gathering of 28 nations and its abilities with respect to well-being are particularly scattered. (4)

The incentives given by government to the developers and manufacturers of orphan drugs have prompted the development of research in this area. Momentous development has found in orphan drug assignments, 12% to 291 in the USA.

The orphan drug deals were expanded by 7.7% to $97bn from 2013 to 2014 and are assessed to develop by 11.7% every year from 2015 to 2020 to $178bn. The orphan drugs deal will get 20.2% of overall world prescription sales of 2020.

**The Orphan Drug Act (ODA) of 1983** (7)

Before 1983 the Orphan Drug Act (ODA), the FDA had affirmed just 58 orphan designations, with less than 10 endorsed in the decade before the ODA was passed (Pharma, 2013). After the ODA, existing medications that certified must be reapproved to pick up market exclusivity and the advantages of the act. The ODA has a few sections, yet its primary aim is to diminish expenses and increases the profits to the orphan drug production. Furthermore, by reducing development time, the ODA permits the FDA to assist orphan drug designation endorsements over different medications. In 1997 congress made a half duty credits on R and D consumptions a lasting element of the act. This credits goes towards clinical preliminary costs of medications that have gotten official orphan drug status by the FDA. The most challenged arrangement of the ODA is the 7 years of market exclusivity rights that pharmaceutical organizations can get for orphan items, which awards them a monopoly over the marketing of the medication for a specific sign.

Since, the demonstration has been sanctioned, it has been altered for various occasion by congress. At first, orphan status was conceded to manufacturers of drug that exhibited that the improvement of an orphan drug would be unprofitable and the expenses would not be recovered through sales of United States. As long as there were no "sensible desire" that United States sales would surpass the improvement costs orphan drugs could be profitable around the globe. Orphan drugs exclusivity status was limited to drugs that couldn't be licensed, as some biotech drugs experienced issues in acquiring patents.

However, in 1995 another change to the ODA dropped those limitations. Even most orphan item could acquire patents, however it was a result of the extensive endorsement process that considerable dot of the patents expired before the item had the option to arrive at the market, making them redundant. In 1990, congress passed a proposition to restrain market exclusivity, President George H.W. Bush rejected the change. Recently, the FDA received the ODA on June 12, 2013, to "explain, streamline, and improve the orphan drug designation process".

**“Orphan Drugs” - Denotation in India**

By the Indian pharmacists and the government to actualize laws, the requirement for such a demonstration is consequently obvious from the activity, which would fortify the well-being framework and provide help to the various rare diseases sufferers throughout the country. In 2001, the Indian Drug Manufacturers Association organizes a gathering of a pharmacologist at a conference where the Indian Government was mentioned to establish the orphan drug act in India. (7)

**Understanding US FDA and global regulations for orphan drug development** (8)

First, a comprehension of the United States Food and Drug Administration (USFDA) administrative procedure for rare diseases clinical trials is fundamental for creating regulatory policy in India and China. This area targets around the regulatory pathway in the United States since it was the first nation to actualize a policy for the improvement of drugs to treat rare diseases with the orphan drug act of 1983, and has since approved the most drugs by means of this pathway. According to the USFDA an orphan drugs is one treating a disease influencing under 200,000 individuals in the US, or one that won't be gainful within 7 years following FDA endorsements. Beginning after drug approval, orphan drug get 7 years of market exclusivity, which is autonomous of patient status. Even after this 7 years monopoly lapses, new contenders can't enter the market without demonstrating that their drug is better than the current one. Up to one-portion of innovative work expenses can be recovered through assessment credits, with up-to $30 million every year in Rand D awards accommodated stage I and III clinical preliminaries. Once the drug is profitable, these incentives forces additionally incorporate a 15 year carry forward arrangements and a 3 year carry back can be applied. Moreover, Federal Food, Drug and Cosmetic Act (FFDCA) Section 520 permits prescription Drug User Fee Act (PDUFA) user expenses to be deferred, which brings about a normal investments funds of $2 million for organizations with under $50 million in income. This gives incentives to new businesses to create novel drugs for rare diseases. Section 505A under the FDA modernizations act of 1997 likewise gives an extra a half year or 6 months of patent exclusivity for drugs that pediatric population, which include 50% of the rare diseases population.

**Status of Orphan Disease Research in India**

Coming to the Indian situation, so far, ~450 rare diseases have been recognized in India. According to the published data of the national population statistics of 2011, it was evaluated statistically, in India, there was 72,611,605 rare diseases and disorder population. Now, the consciousness of rare diseases is increasing. Scenarios for some, rare diseases are likewise evolving. In India Cystic fibrosis was believed to be rare, however hereditary investigation has now demonstrated that the diseases is common yet was undiscovered earlier.

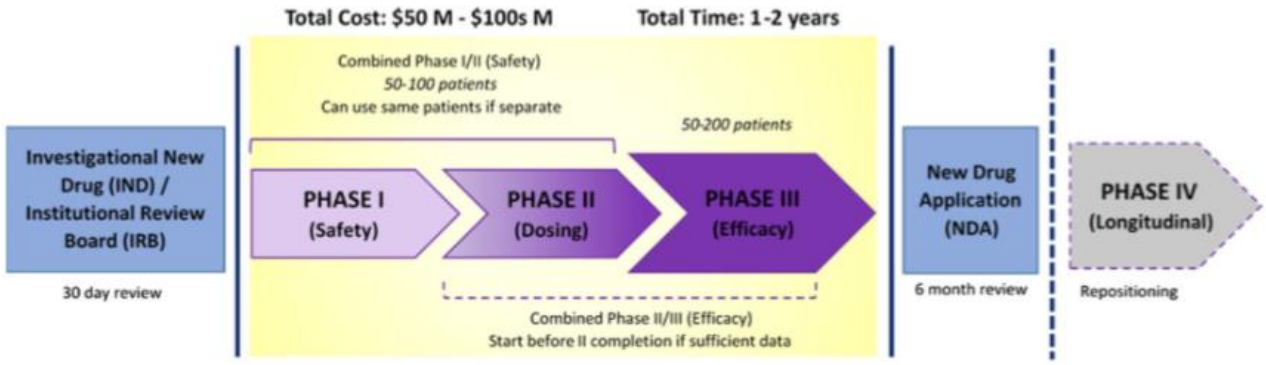


**Figure 1.** Regulatory representational of orphan drug development in the United States (8)

India has apparently higher rare diseases population than the world average, yet activities from the administration side are still less and in fact, India needs national enactment for orphan drugs and rare diseases. (9)

Towards rare disease scientific and patient communities communicated the requirements for government activities. The main endeavor to unite all specialists of rare diseases under a common platform was initiated by INSA, which directed the first of the sort rare diseases ailment workshop entitled "To develop a scientific program for research on rare diseases" in 2016, which pondered on issues, i.e. meaning of "rare disease, awareness of rare diseases, research avenues of rare diseases, strategies structure for boosting and boosting innovative work (R and D) endeavors, and confining reasonable enactment to guarantee association of the state in satisfying the unique needs of the rare diseases.

Dr. APJ Abdul Kalam tending to the issues of rare diseases stated," an organized exertion at the national level is the need of great important for more research and understanding rare diseases in the nation. There is an requirement for an entire ecosystem comprising of specialists, a library to record the predominance of rare diseases, biobanks, support groups, more research on discovery of drug, and an administrative structure. Every part is perplexing, and there is a ton of work ahead".

Recently, portability is found regarding rare diseases exploration in India. Various activities are in process which incorporates activity from the administrative side, activities from scholarly establishments, non-governmental associations, and other related divisions.

**Orphan Drug Regulation in India** (10)

In India until now the guidelines for orphan drug manufacturing or promoting have not been made. In India has around 6000-8000 rare ailments, being some of them Wilson Disease, Leishmaniosis, Norrie Disease, Cystic Fibrosis, Arthrogryposis and so on. A large portion of this ailments are hereditary in nature and don't have any treatment. Approximately, 72,611,64 individuals are affecting by these rare diseases in India. Due to lack of guidelines of orphan drugs unfavorably influences the monetary development of Indian restorative enterprises. The countries like U.S.A, Europe, Japan, and Australia have already made the guidelines for the orphan drugs. These guidelines have exceptional incentives forces for orphan drugs producer which improve the production of orphan medicinal products. These incentives forces are referenced guidelines for orphan drug in US and EU.

Indian government should immediately address the state of rare diseases. Appropriate enactment must be made for the guideline of orphan drugs. This would support the domestic pharmaceutical and biopharmaceutical industries of India to rapidly develop as a power to incorporate inside this huge universal space. By such enactment Indian rare diseases population could be profited. This enormous number of patients experiencing rare diseases should not be left to their own hopeless conditions with no thoughts and cure. Some rare diseases recorded in India are mentioned below:

- Haemophilia,
- Thalassemia,
- Sickle cell anaemia,
- Primary immunodeficiencies,
- Pompe disease,
- Hirschsprung's disease,
- Gaucher's disease,
- Haemangiomas, etc.

**Table 1** Incentive of Orphan Drugs Regulation in US and India (10)

| Items | US | | India |
|---|---|---|---|
| | Orphan | Other drugs | Other drugs |
| Market exclusivity | 7 years | 5year / 3years | 7-8 years |
| Protocol assistance and follow-up | Yes | No | No |
| Reduced/waived regulatory fees | Yes | No | No |
| Tax credit on clinical trials | Yes | No | No |
| Specific subsidies for clinical trials | Yes | No | No |

**Table 2** Recent initiatives taken by Indian Government Regarding Orphan Drugs (9)

| CDSCO Initiative | Non-governmental organization Initiative | CSIR & IGBI Initiative | Judiciary Initiative | Academic Initiative |
|---|---|---|---|---|
| By a around 12-01/14-DC pt. 47 dated July 3, 2014, the CDSCO gave a notification with respect to waiver of clinical preliminary of endorsement of new medication in the Indian population, only in the case of orphan drugs for rare diseases. In another gathering between Pharma stakeholders & DCGI, on May 4 2016, on exploring of possibilities to provide cheaper medicines for patients with rare diseases, IDMA and OPPI were given the responsibility to formulate the Indian definition of rare disease, JDC ( ER) was given the responsibility to revise timelines for orphan drug approvals, and a separate cell was suggested to address the issues of rare diseases, possibility of separate pricing mechanism for orphan drugs, and possibility of custom duty exemption | Association for Rare Diseases India (ORDI; www. ordindia.org) is a philanthropic based voluntarily association which was set up to manage the rare diseases condition in the Indian population. The ORDI colleagues have a place with various controls that are science and non-science foundation. ORDI manages the issues identified with the rare diseases, for example, remarkable difficulties in managing rare diseases. | IGIB, New Delhi, has directed undertaking subsidized by CSIR, named as "Genomics for Understanding Rare Diseases India Alliance Network (Guardian)," for the reason to unite and comprehend novel hereditary varieties to accomplish translational applications by the two clinicians and fundamental science specialists. | In November 2016, the Delhi high court had requested the legislature to settle a strategy on rare disease, draft of which was put together by the Union Ministry of Health to the Delhi high court on May 25. The Delhi high court guided the Center to actualize its National Policy for Treatment of Rare Diseases as soon as possible. | Various projects are running with regard to rare disease in different foundations, for example, AIIMS, PGIMER Chandigarh, CMC Vellore, and SGPGI Lucknow. |

**Policy Direction**

The policy aims at lowering the incidence and prevalence of rare diseases based on an integrated and comprehensive preventive strategy encompassing awareness generation and screening programs to prevent births of children with rare diseases, and, within the constraints on resources and competing health care priorities, enable access to affordable health care to patients of rare diseases which are amenable to one-time treatment.

Considering the limited data available on rare diseases, and in the light of competing health priorities, the focus shall be on prevention of rare diseases as a priority for all the three groups of rare diseases identified by Experts. Public Health and hospitals being a State subject, the Central Government shall encourage & support the States in their endeavor towards screening and prevention of rare diseases.

In addition, the following initiatives shall be taken for patients of Rare Diseases:

- Financial support up to Rs. 15 lakh under the Umbrella Scheme of Rashtriya Arogaya Nidhi shall be provided by the Central Government for treatment, of those rare diseases that require a one-time treatment (diseases listed under Group I). Beneficiaries for such financial assistance would not be limited to BPL families, but extended to 40% of the population who are eligible as per norms of Pradhan Mantri Jan Arogya Yojana, for their treatment in Government tertiary hospitals only.
- State Governments can consider supporting patients of such rare diseases that can be managed with special diets or hormonal supplements or other relatively low cost interventions (Diseases listed under Group II).
- Keeping in view the resource constraints, and a compelling need to prioritize the available resources to get maximum health gains for the community/population, the Government will endeavor to create alternate funding mechanism through setting up a digital platform for voluntary individual and corporate donors to contribute to the treatment cost of patients of rare diseases.

**Conclusion**

In the last few years, the orphan drug designations have expanded sharply. Nonetheless, India regardless of having an exceptionally huge number of patients with rare diseases that can turn into a gigantic market for residential pharmaceutical is lagging behind. This paper widely looked at orphan drug advancement and administrative policy in India and the US. In contrast to the most private human services framework in the United States, where advocacy can be divided across patient understanding groups and hospitals, a health care system framework that is generally open in India should exploit accessible information to make collected databases for diseases and genomic data. As India is still in the developing stage, there is a mishap in aspects of guidelines and improvement in orphan disease research. In the present situation, there is a solid need in the evaluation of the range and weight of rare diseases and

awareness program in mass with respect to the rare diseases. Strong arrangements and activities are required from the administrative and private institution for orphan diseases improvement and give a few incentives to the pharmaceutical organizations which could profit the both patients and pharmaceutical industries.

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**Conflict of Interest**

The authors declare that there is no conflict of interest regarding the publication of this article.

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