ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 9, Issue 4, 2016

Online - 2455-3891
Print - 0974-2441

Review Article

ORPHAN DRUGS: THE CURRENT GLOBAL AND INDIAN SCENARIO

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Received: 04 May 2016, Revised and Accepted: 12 May 2016

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 toward orphan drugs. This has stemmed from an apparent innovation crisis in the domain of common diseases, progressively increasing stringency in the regulations, and the decline of the blockbuster business model. Further, the success stories of a few orphan drugs, for instance, eculizumab has gone a long way in breaking the myth of non-profitability associated with orphan drug development endeavor. This combined with the high degree of incentivization attached with orphan drug development makes it a very lucrative avenue for further investment by the pharmaceutical industry. Sadly, the Indian scenario with respect to orphan drugs is a throwback to the "dark ages." The progress seen across the developed nations, for instance, the United States of America has not permeated into the Indian market. India, with its huge population base, stands to provide a hugely lucrative market for orphan drug development. However, this point seems to have escaped the notice of the Indian authorities and the pharmaceutical sector in India. Thus, with the various patient advocacy groups and non-government organizations championing the cause of orphan diseased patients in India, the time is ripe for the concerned authorities and the pharma sector in India to take cognizance of this gaping lacuna in the health-care services and undertake measures to address this situation.

Keywords: Pharmaceutical touch-me-not, Orphan, Indian scenario.

INTRODUCTION

The term "orphan disease," broadly speaking, is attributed to diseases that affect only a small number of patients (so-called health orphans) [1]. The enigma surrounding the presentation of such diseases has often fascinated clinicians for centuries. This fascination is augmented by the fact that research into these diseases allows the scientists a unique opportunity to study human medical science from a different viewpoint and often, ends up providing new insights into more common diseases as well.

The physicians, when faced with the dilemma of treating an orphan disease, are often reminded of the limitations of their knowledge about these diseases as well as the scarcity of available therapeutic options. The moniker of "orphan disease" may be of academic interest to the medical community. However, for the patients, who bear these rare afflictions, it represents a daily struggle against an enemy, about whom not much is known [2]. Over the years, the rarity of the occurrence of these diseases has often led to the medical community turning a "blind eye" to the sufferings of a few. Further, the lack of profit generating potential of the "niche markets" has often discouraged the pharmaceutical industries from investing heavily into the research and development (R&D) for the orphan diseases.

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. 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. Further, we have suggested a few recommendations that could be adopted in a bid to improve the current situation in India by the concerned authorities.

ORPHAN DISEASES - THE DEFINITION

It is a popular notion that the term "orphan" with respect to diseases bears its origins in the "orphan drug act (ODA)." However, contrary to popular belief, the use of the "orphan" terminology in the context of diseases can be first traced back to an editorial penned by Dr. Harry Shirkey, an eminent pediatrician in Alabama, the United States of America (USA). He had used the term "orphan" in relation to the pediatric population, who were being sidelined from clinical trials as the efficacy and safety evaluation of drugs in children was not considered to financially and scientifically feasible by the drug developers. Hence, the infants and children were being slowly relegated to the status of "therapeutic or pharmaceutical orphans" [3]. However, in the years thereafter, the term "orphan" gained popularity in the context of various diseases that were being similarly abandoned because they affected only a small size of the patient population globally and drug development against these diseases were deemed to be financially unrewarding.

Despite the many attempts made over the years to define and delineate out orphan diseases, until date, there exists no universal definition for orphan diseases. However, there are two core elements that have consistently figured in every possible definition of rare or orphan diseases:

1. Total prevalence of the disease
2. Non-availability of the treatment for the disorder.

Various organizations and countries across the world have utilized these two key elements in their attempts to define "orphan" or "rare" diseases (Table 1). The World Health Organization defines a disease as orphan or rare if it affects 6.5-10 out of every 10,000 people. Similarly, the European Union (EU) assigns the term orphan to a disease if it has a prevalence of 5 in 10,000 people. The USA defines it as affecting fewer than 2,00,000 people, with a yardstick of an incidence of less than 7.5/10,000 in the general population [4]. However, a clear-cut definition,

Table 1: Definitions of orphan disease in different countries [4]

Country	Total population affected (maximum limit)	Prevalence per 10000 of population
WHO	-	6.5-10
USA	2,00,000	7.5
Japan	50,000	4
South Korea	20,000	4
Australia	2,000	1.1
Europe	-	5
Taiwan	10,000	1
China	5,00,000	-

WHO: World Health Organization

in the Indian context seems to be lacking, which further highlights the glaringly abysmal attitude of the Indian medical community and the concerned authorities toward orphan diseases There have been attempts made by private organizations to rectify this situation. The initiatives being taken by non-profit organizations like Organization for Rare Diseases in India (ORDI) that defines a rare disease as one that affects 1 in 5000 people or less, is extremely commendable [5]. However, in light of the rarity of occurrence of orphan diseases and the lack of financial reward plaguing this sector, at least in the short term; it remains to be seen whether these privately undertaken initiatives can provide the necessary stimulus to set the government machinery in motion with regard to orphan diseases.

ORPHAN DRUGS - EXPANDING THE SCOPE OF THEIR DEFINITION

The designation of "orphan" status to any drug is bestowed on the basis of understanding that the concerned drug can be applied for the treatment of an orphan disease. However, if one cares to look beyond this cursory interpretation, the term orphan drugs encompasses a multitude of possibilities. Besides the rarity of a disease, the financial profits and feasibility also play a key role in the assignment of orphan status to a drug. For instance, the drugs and vaccines employed for the management of tropical diseases too fall under the category of orphan drugs [6]. One might argue that tropical diseases afflict millions of people and are not a rarity. The counter-argument to this is that in such cases, from a financial perspective, drug developers are always going to be in the red as the targeted population is financially incapable of affording the orphan medicaments unless provided at a subsidized price. Further, orphan status also applies to a few drugs that have received a fresh lease of life. These drugs may have been withdrawn from the market earlier but have got a newfound relevance after being recast in another role against rare affliction(s). The case of thalidomide embodies this best. After the landmark tragedy with thalidomide, it was withdrawn from the market in the mid-1960s. In the years to come, this tragedy acted as a stepping stone for revamping of the pharmaceutical industry. The stigma associated with thalidomide was immense and it propelled the development of a stronger global post-marketing surveillance program and an increase in public awareness about the side-effects of drugs. However, in recent years, thalidomide has found application against rare afflictions like lupus erythematosus. This has breathed a new life into its existence as a drug, albeit an orphan drug at that [7].

Why the shift to orphan drugs?

Over the years, orphan drugs had been relegated to the status of the "poor cousin" of the non-orphan drugs. The rarity of orphan diseases combined with the anticipated financial low yield has always discouraged the drug development enterprise in the domain of orphan diseases. However, in the recent years, there has been a shift in the approach among the drug companies. Orphan drugs are "pharmaceutical touch-me-not" entities, no more. There are many underlying reasons for this path-breaking shift in the perspective of the industry. Various top-notch pharmaceutical companies are pursuing the avenue of orphan drug development with renewed vigor. This has come about after the realization that orphan drug development is laced with a very high reward/risk ratio [8]. The monogenicity of most of the orphan disease pathology mitigates the correlation. The correlation is a critical measure of the risks of the portfolio of concerned candidate molecules. Despite the paucity of any information regarding correlations in various drug development projects, orphan drug development at a basic level, seems to be on solid grounds in terms of minimizing correlation, and hence, the risks associated with drug development [9]. Orphan diseases are commonly associated with genetic mutations that manifest generally as the absence or excess of certain key proteins. By deducing the underlying genetic mutation and determining its features, extremely targeted and compelling therapies can be developed that stand a better chance of seeing fruition after going through the rigors of pre-clinical and clinical trials as compared to that of non-orphan drugs. The recent figures too support this claim. Out of every 100 orphan drugs that have entered clinical trials between the period of 1993-2004, 22 have seen the light at the end of the tunnel [10]. These figures stack up very favorably against the 11% and 6-7% for non-orphan drugs and anti-cancer drugs respectively, during the same period [10].

Besides, orphan drugs seem to be bucking the earlier held belief that development of drugs for orphan diseases may not be financially rewarding. As per the recent report by Thomson-Reuters, the annual revenue potential of an orphan drug on an average is expected to in the range of 100-500 million US dollars [11]. The surprisingly high revenue expected by the sales of orphan drugs is due to their exorbitant pricing, which compensates for the minuscule patient size. This is best exemplified by Eculizumab, a humanized monoclonal antibody, developed by Alexion Pharmaceuticals under the trade name of Soliris and approved for the use against paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (HUS). Both the above conditions are extremely rare pathological states. PNH afflicts around 1-2 per million people [12], and atypical HUS incidence is expected to be around 3.3 per million pediatric patients [13]. However, the lack of any prior therapeutic alternatives coupled with the price of US$ 400,000 per patient annually, promises to boost the revenue generation with this drug. The high revenue generation potential of orphan drugs is further underlined by a recent statistic highlighted in the Thomson-Reuters report in 2012 stating that about 29% (25 out of 86 orphan drugs) of the top orphan drugs are anticipated to realize a financial windfall, amounting to more than 1 billion US dollars in their lifetime earnings [11], which was similar to the figures for non-orphan drugs (83 out of 291-29%). These figures point toward a possibility that the "blockbuster model" yardstick, against which the successes of non-orphan drugs are measured, may find pertinence, even in the case of orphan drugs.

Besides the other, more commonly cited reasons for this shift in industrial perspective, for instance, innovation crisis [14,15], consistently mounting drug costs [16], lower drug approval rates [17], and stringent drug regulations [18]; there are some very original reasons that have been in the making for quite a few years. In this day, one of the major factors that have compounded the need for seeking out niche markets is the saturation of the large disease markets, for instance, diabetes and hypertension [19]. This has led to renewed focus on certain quiescent, niche areas, [20] which are dominated predominantly by orphan diseases. Tapping into the niche disease/orphan disease market has some serious benefits in that there is very little competition from me-too or generic drugs [21]. In addition, demonstration of an incremental benefit by the follow-on drugs in markets which are already saturated with drugs is mighty difficult [17]. Contrastingly, in smaller niche patient populations as in the case of orphan diseases, it is much easier to demonstrate the incremental benefits by the follow-on drugs [21]. Further, incentivization of orphan disease research and drug development in various countries including tax benefits, accelerated approval, and increased the period of market exclusivity [22] have progressively driven the change in approach of pharmaceutical companies toward orphan diseases. Moreover, the public awareness and understanding of orphan diseases have increased manifold. The issues compounding the diagnosis and management

of orphan diseases can no more be ignored and swept under the carpet. Over the past few decades, the work of the patient advocacy groups including the academic researchers, politicians, and people in positions of authority has put the orphan disease and drugs firmly on the pharmaceutical drug development map [23]. Thus, the significant unmet needs of the patients suffering from rare diseases as pointed out in this segment along with the ever burgeoning public awareness about rare diseases have provided a new calling to the pharmaceutical industry.

THE INTERNATIONAL SCENARIO

Orphan diseases garnered a lot of attention for the first time in the 1980s, especially in the USA. The emergence of the case of a young boy with Tourette's syndrome was able to generate a lot of attention over the then existing pitiable situation of the orphan diseased patients. Amidst the huge outcry and the public pressure generated by this case, the first set of regulations and guidelines dedicated toward orphan diseases and orphan drugs, in the shape of orphan drugs act (ODA) was passed in the USA on January 28, 1983 [24]. Its primary objective was to promote the R&D into orphan diseases and ensure rapid development and approval of orphan drugs. Thereafter, many other countries across the world took a leaf out of USA's book and formulated their own regulations, customized as per the needs and demands in their own countries. In this segment, we aim to shed light on the existent regulations and guidelines and provide a comparison between the various countries' policies.

THE US ODA [25]

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. It was the first concrete step in the right direction toward overcoming the hurdles that had proved to be the major deterrents in the development of orphan drugs till then. 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.

In addition, with an eye at streamlining and accelerating the process of gaining approval, the Office of Orphan Products Development (OOPD) was created within the Food and Drug Administration (FDA). It acts as an intermediary within the FDA that helps smooth out the process of granting the orphan drug status, which has to be sought before the application for marketing approval, new drug approval, or product license approval. Further, OOPD also carries out the evaluation, awarding and monitoring of the progress of orphan drugs grants.

The success of ODA is illustrated by a simple fact that the figure of only 38 orphan drugs that were in the market until 1983, almost increased by 10 times by the end of 2014 [26].

JAPANESE ORPHAN DRUG REGULATION [25]

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 the induction of few special provisions aimed at promoting R&D in the field of orphan drugs.

The new provisions in the Japanese guidelines suggested that the status of orphan drugs could be accorded to only those that would fulfill 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.

The according of orphan drug status is done by the ministry of health, labor and welfare on the basis of application outlining the estimated patient population size, development protocol, pre-clinical, and early clinical studies.

The Japanese government's incentivization of the R&D into orphan drugs occurs at two levels:

Administrative benefits

The Japanese regulations require priority evaluation of applications related to rare diseases, translating into fast-track marketing authorization and approval. An extended registration validity period of 10 years also provides added incentives to the sponsors.

Monetary benefits

These include reimbursements up to 50% of the development costs, in addition to a 6% tax waiver for R&D into rare diseases. Besides these measures, separate government funds provide the necessary fillip into orphan disease and drug research.

AUSTRALIAN ODA [25]

Australia is another country to have introduced orphan drugs regulations in 1997, close on the heels of USA and Japan's efforts. The Australian Therapeutic Goods Administration (TGA), being the leading agency, possesses the ability to grant the orphan status to the drugs. However, to qualify as an orphan drug in the eyes of the TGA, the concerned product must meet the safety requirements of not only TGA but also various other agencies around the world like US-FDA, the Medicines and Healthcare Products Regulatory Agency of the United Kingdom, the Therapeutic Products Directorate of Canada, the Medical Products Agency of Sweden, the Medicines Evaluation Board of the Netherlands, or the European Medicines Evaluation Agency (EMEA). In addition, the designation of orphan drugs is limited to those diseases which meet the prevalence criteria of 2000 patients in the total Australian population or a maximum of 12 persons per 10,000 people. The TGA promotes the R&D in orphan drugs by providing monetary benefits in the form of a waiver of application and evaluation fees as well as with provisions of a dedicated pathway for the evaluation of orphan drugs alone. The exclusive marketing period provided by TGA is 5 years. Further, by setting up of schemes like the Pharmaceutical Benefits Scheme, additional subsidies are provided to enhance the affordability of the drugs. However, the lack of added incentivization of the R&D and a dedicated law on the intellectual property rights of orphan drugs are the major drawbacks of these guidelines.

EUROPEAN ODA [25]

Owing to the complexities that arise from the differences in the competencies of the various countries constituting the EU, 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 drugs. The uniqueness of this committee lies in its inclusive nature, especially with the inclusion of patient representatives, which has provided a boost to the orphan drug development machinery in Europe. Under the aegis of the EU, the orphan drug sponsors are eligible for:

1. Scientific advice and consultation during the development phase of orphan drugs
2. Complete reduction for protocol assistance fee and follow-up fee
3. Complete waiver of fees for pre-authorization inspections, 50% decrease in the new applications for marketing approval to large sized enterprises, complete waiver for not only marketing

authorization but also for post-approval endeavors in the first year, only to small and medium-sized enterprises
4. The period of 10 years of exclusive marketing.

Besides these measures, there is a multitude of incentives provided by each country at a national level, as evidenced by an inventory detailed by the European Commission. Further, a detailed registry is maintained of the drugs designated as orphan drugs, termed as the Community register for Orphan Medicinal Products. However, the regulations are concerned with drugs that are intended for human use. Hence, it precludes veterinary medicines, medical devices, nutritional supplements, and dietary products.

CURRENT SITUATION IN INDIA AND NEED FOR ORPHAN DRUG REGULATION IN INDIA

The increasing awareness about orphan diseases and drugs has sadly not percolated into the psyche of the populace within developing countries. The widespread ignorance, existent among the Indian medical community is a testimony to this lackadaisical attitude toward orphan diseases. Further, this ignorance cannot be attributed to a lack of afflicted victims. If one is to go by a few estimates, it is believed that by virtue of being the second most populous nation in the world, India has approximately 70 million cases of orphan diseases [27]. The fact that we are not able to comprehend the epidemiological impact of the orphan diseases in India can be attributed to the lack of proper registry of orphan disease cases. In light of this, the initiatives undertaken by non-profit non-government organizations (NGOs), for instance, ORDI is extremely commendable. It is by virtue of their efforts that orphan diseases can be "unofficially" defined as a disease that affects 1 in 5000 people or less in the Indian population [5]. Besides ORDI, there exist several other NGOs that are working in specific disease domains, for instance, the Foundation for Research on Rare Diseases and Disorders, Alzheimer's and Related Disorders Society of India, Down Syndrome Federation of India, Hemophilia Federation India, etc. However, the absence of any government patronization or support from the concerned authorities has placed a big question mark on the sustainability and the impact of the efforts of these NGOs.

Every day millions of Indians keep suffering from debilitating orphan diseases, for lack of any regulatory guidelines on orphan diseases. The absence of any viable framework or regulatory guidelines produces a manifold impact; the most significant of which is the non-accessibility and non-affordability of most of the 400 odd orphan drugs approved by the US-FDA. The huge population suffering from orphan diseases in India presents the pharmaceutical companies with a very lucrative opportunity to expand their operations. However, the attitude of the concerned authorities combined with the lack of any provisions aimed at promoting R&D in orphan drugs; often deters the industry from exhibiting any interest. In light of the reasons that have forced a paradigm shift in the pharmaceutical industry toward orphan drugs as well as the potential lucrativeness of this unexploited domain, it is high time that the Indian authorities wake up and address the situation in our country urgently.

In our opinion,

1. There needs to be a lucid and a clear definition of orphan drugs, with no room for ambiguity. A separate orphan drugs act or a small addendum to the Drugs and Cosmetics Act could suffice. We should also be clear on whether the definition of orphan drugs would include those applicable for human use or it would encompass drugs intended for veterinary use and medical devices and nutritional supplements as well.
2. Special incentives should be provided for R&D of orphan drugs. It may not be limited to monetary assistance alone. It could also include technical and personnel assistance in the form of collaborations with government laboratories and organizations as well for conducting basic research.
3. Efforts should be made to include NGOs in the process of procurement of drugs at reasonable rates from other countries.
4. Efforts should be made to raise public awareness regarding orphan diseases via organizing television and other media campaigns, conducting health camps, etc.
5. Besides, other incentives such as tax benefits and fee waivers, we could take a leaf out of EMEA's book and should also include patient advocacy group representatives in the whole process of granting orphan drug status and their approval for concerned diseases.

The whole process of introduction of orphan drugs regulations would be an evolving one. However, we believe that incorporation of these rudimentary suggestions would go a long way in providing India with a strong regulatory framework with respect to orphan drugs.

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.

However, the lack of interest in the Indian medical community regarding orphan drugs has led to poor awareness among the general public. Further, the blind eye shown by the concerned authorities to the plight of a substantial Indian population suffering from orphan diseases has led to a sense of disillusionment and disinterest within the Indian pharmaceutical network. Thus, the focus of the Indian pharmaceutical companies lies more on the common diseases that have proven to be a very lucrative option over the years.

However, the plight of the patients suffering from orphan diseases in India, cannot be ignored anymore, especially in light of the persistent efforts of various NGOs. Their efforts, though extremely commendable, are not sustainable and requires support from the authorities. Therefore, it is high time that the Indian Government woke up from its slumber and undertook measures to not only establish a comprehensive legislation but also actively went the extra mile of attracting the pharmaceutical companies with incentives with the aim of promoting the production of indigenous orphan drugs for the long-neglected Indian orphan diseased patients.

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