Essential drugs for rare diseases

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1. Introduction

Pharmaceutical companies or institutes introduce several drugs in the market after authorization by regulatory agencies of the respective country. The drug which comes first in the market is called as prototype drug and other related drugs with similar mechanism of action are called as congeners. Each pharmaceutical company obtains a patent on that congener and can market it exclusively till the end of patent life of that drug. Once the patent life is over, other pharmaceutical companies can market the drug with a generic name or their own trade name. Every new drug is given a new international non-proprietary name (INN) by an international body. The INN is also called as generic name of the drug, while every company can give a trade name for their own drug and is called as Brand name. As a result of market competition and a desire of promoting their own brand names, there are few thousand drugs with their own INNs and brand names in the global market.

In 1977, World Health Organization (WHO) suggested the concept of Essential Drugs. What WHO argues is "All such drugs, introduced in the global market are not necessary for majority of patients. Therapeutic needs of majority of patients can be met with selective few hundred drugs. These selective drugs, which can satisfy priority health needs of the majority of patients are termed as Essential Drugs by WHO"
The first list of Essential drugs was published by WHO in 1977. Every alternate year WHO revises the list. The latest 23rd edition of WHO essential drug list was published in 2023. From the year 2007, WHO has started publishing a separate list of essential drugs for children and 9th revised model list of essential drugs for children was published by WHO in 2023. All these lists are in public domain and any interested person can download them.

Every country can adopt a list of essential drugs based on WHO guidelines and can modify them as per their priorities. More than 170 countries all over the world have accepted the WHO concept and some of them have developed their own list of essential drugs. India has revised its list of essential drugs in the year 2022. The list was revised after 2015. The latest Indian list contains 384 essential drugs.

2. Economics of new drug development

Development of a new drug is a costly and adventurous decision, at least in an economic sense. It is usually advocated by international associations of pharmaceutical industries that development of a new drug costs them around 1 billion dollars ($). In terms of Rupees, it turns out to be 8500/crore Rupees. ($1 = Rs.85). A pharmaceutical company will invest this huge amount with the only expectation that they will plough back the invested amount after marketing permission to the drug. This is possible only if there are more patients, available for treatment of that indication. If the number of patients is small, then the price of a new drug can be prohibitively high making it unaffordable to the patient population. It is known that some drugs can cost as much as few million US $ per year in USA making it few crore Rupees annually if the drug is imported in India. This is unaffordable even for a prosperous family. Spinraza (Nusinersen), used for spinal muscular dystrophy costs $ 375,000 (Rs. 3.2 Cr.) per patient. Migalastat, used for Fabry's disease costs $ 310,000 (Rs. 2.63 Cr.) annually.

Unless the drug is accessible and affordable, an average family cannot use it especially if it is to be given repeatedly and more so if the entire expense turns out to be Out-of-Pocket (OOP). This is very much true in a country like India where it is mentioned that a fraction of population, every year goes below poverty-line only because the cost of treatment in unaffordable.

3. Rare diseases

The logic is very relevant in case of "Rare" diseases. There are various definitions of rare diseases in different countries and continents; but WHO defines rare diseases as "if 1 in 2000 persons are affected by the condition, then it can be termed as a rare disease". It is estimated that 300 million people are affected by rare diseases globally. It is also indicated that about 7-8 % of the population is affected by rare diseases. Nearly 5000 to 8000 rare diseases are known. These are identified in "Orphanet" a global online list of rare diseases. One latest estimate indicates the number of rare diseases to be 10,000 in number. In India, with a population of around 1.4 billion at least 100 million (10 crore) Indians are expected to be affected by rare diseases. It means one third of global population of rare diseases resides in India. Out of all rare diseases, around 400 rare diseases have been reported in India; but it is only tip of the iceberg.

Rare diseases are challenging to diagnose and treat for a number of reasons, particularly in India. First and foremost reason is that it is difficult to know, especially for parents of a child that their child is having a rare disease. A rare disease like Autism may not show expression till the age of 2 to 3. Further, parents may find symptoms of rare diseases as a delay in growth which may be found even in a normal child. The parents may take a child to a doctor later than recommended. The diagnosis of rare diseases is not simple because biomarkers for the diseases are not known in every case. Not all rare diseases are of pediatric nature. It is reported that about 80 % of rare diseases are of genetic origin and 50 % of the patients are children. It is further reported that 35% of the patients die before the age 1; 10% die between the age 1 to 5 and 12% die between the age 5 to 15. Treatment for all rare diseases remains elusive because pathophysiology of many rare diseases is not fully understood.

Thankfully, in 2021, a Policy for Rare Diseases has been launched by the Government of India. According to the policy, rare diseases seen in India are divided into three groups.

- Disorders that may be cured with just one therapy.
- that need long term treatment which is available at low cost, with documented evidence and require annual or frequent monitoring.
- Diseases requiring lifelong therapy where definitive treatment is available at high cost, but selection of right patient to benefit is challenging.

The policy document contains a list of rare diseases, however it is not comprehensive and might evolve in the future. Every group involves a list of specific diseases. For diseases specifically falling under group 3, the Government of India offers one-time financial assistance which was initially set at Rs. 20 Lakhs, but recently amended to Rs. 50 Lakhs.

Rare diseases exhibit various distinguishing traits. A few of them are listed below.

- Rare diseases are chronic, often degenerative, fall in the severe or very severe category, and are mostly life-threatening.
- About 50% of rare diseases develop in childhood.
- Disabling; the quality of life of individuals with uncommon diseases is frequently impacted by the lack or loss of autonomy.
- High psycho social burden: the suffering of patients with rare disease is exacerbated by psychological despair, the lack of therapeutic optimism and/or actual assistance for everyday living.
- Rare diseases can often be incurable due to the lack of appropriate therapeutic options. Symptomatic treatment may improve quality of life or life expectancy in some cases.
- Management of rare diseases is an ongoing challenge and families struggle to find appropriate care.

4. Some important observations

4.1 In 1981, National Organization of Rare Diseases (NORD) was formed in 1981 to take care of interests of persons with rare diseases in USA.

4.2 In 1983, USA became the first country to enact Orphan Drugs Act and offered incentives to pharmaceutical companies who manufacture “Orphan Drugs” acting on rare diseases. The Rare Diseases Act was passed in 2002 and by January 2020, USFDA approved 564 orphan drugs to treat 838 rare diseases.

4.3 In 1985, Japan and in 1997 Australia passed similar acts following USA.

4.4 In 2000, European Union passed The Orphan Medicinal Product Regulation (Regulation (EC) No 141/2000 and was followed by action plan on rare diseases in 2009. By March 2021, 260 medicinal products in Europe had market authorization for the treatment of rare diseases.

4.5 Various associations of stakeholders related to rare diseases have been formed. In Europe and 1000 rare-diseases related patient organizations together formed EURORDIS (the European Organization of Rare Diseases)

4.6 In December 2021, United Nations adopted a resolution, emphasizing importance of dealing with rare diseases, and requested member countries to take appropriate steps to provide affordable, accessible and good-quality care facilities for children and other dependents living with a rare disease and measures promoting the equal sharing of household responsibilities.

4.7 People living with rare diseases (PLWRDs) from all around the world, came together to form Rare Diseases International (RDI). More than 90 member organizations from 46 different nations make up RDI, which in turn represents patient groups with rare diseases in more than 150 countries worldwide.

4.8 In February 2017, International Rare Diseases Research Consortium (IRDiRC)defined its vision and identified three goals to be achieved by 2027 (1). The Rare Disease Treatment Access Working Group (RDTAWG) was established with three aims:

(1) To raise the standard of care for patients with rare diseases through facilitating the access to approved medications.

(2) To initiate research into the barriers to accessing medications for rare diseases, especially in low- and middle-income countries (LMICs).

(3) To identify opportunities to remove these barriers.

Based on various international databases, they have identified 204 essential drugs which can be used for treating different rare diseases (2).

4.9 Looking at the cost of developing a new drug (Rs. 8500 Cr.), limited market, and relatively less number of patients with rare disease, it is less likely that any pharmaceutical multinational company may launch an exclusive set of efforts for developing a new drug; as it may not be financially attractive. Still, in the USA, passing of Orphan Drugs Act has resulted in development of 564 orphan drugs due to incentives. As a result, next viable alternative is to explore if any of the existing approved drug can be repurposed for the treatment of rare disease(s). Since safety of existing approved drugs is established by regulatory authorities, cost of re purposing a drug for a rare diseases stays low. Pre-clinical and phase 1 clinical studies need not be repeated. What we need is only phase 2 and phase 3 clinical studies followed by marketing authorization from the regulatory authorities.

4.10 The Government of India has approved drugs related to four genetic diseases for marketing in India. The diseases are: Tyrosinemia, Gaucher disease, Wilson’s disease and Dravet-Lennox Gestaut Syndrome. Now drugs for these diseases will be available at a fractional price in India as compared to their international counterparts. Approvals for four more diseases are in pipeline. Some of the Indian pharmaceutical companies also have shown interest in providing drugs related to rare diseases in India.

Names of some of the rare diseases observed in India are mentioned as an illustration: Autism spectrum of disorders (ASD), Cockayne syndrome, Hemophilia, Thalasaemia, Sickle cell anemia, Fabry's disease, Gaucher disease, Pompe disease, Systemic Lupus Erythematosus (SLE), Autoimmune disease, Spinal Muscular Atrophy (SMA), Tyrosinemia, Phenylketonuria.

5. Conclusion

After declaration of policy for rare diseases by Government of India, few Indian pharmaceutical companies have started developing medicines for rare diseases at affordable prices. In future, we can expect that affordable treatment for few rare diseases will be a reality in India.

References

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