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ORPHAN DRUGS-CREATING RARE DISEASES, A PUBLIC-HEALTH AND STUDY PRIORITY

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ABSTRACT
Research in rare diseases has promoted considerably toward the existing understanding in the pathophysiology of the common diseases. However, medical requirements of patients with rare diseases have always been mistreated or ignored by the society and pharmaceutical industries based on their small figures and unprofitableness. The Orphan Drug Act (1983) was the initial serious effort to address the unmet medical requirements for patients with rare diseases and to deliver incentive for the pharmaceutical industry to encourage orphan drug development. The procedure of drug expansion for rare diseases is not unlike from common diseases but includes momentous cost and infrastructure. The drug-approving authority must work-out their scientific decision and ensure due flexibility while evaluating data at various stages of orphan drug development. The emergence of patent cliff combined with the administration incentives led the pharmaceutical industry to understand the good commercial scenarios in developing an orphan drug despite the small market size. Really, many drugs that were given orphan designation completed up being blockbusters, the present review scientifically examined the tasks associated with living with a rare disorder in grown-ups. Results were categorized according to three areas: consequences of living with a rare disorder, social aspects of living with a rare disorder, and Indian scenario of orphan drugs.

KEYWORDS: Orphan, Orphan drug act, Clinical study, Repurposed drugs, Psychological & social impact.

INTRODUCTION
Rare diseases are frequently called “orphan” diseases; the word “Orphan” is resultant from the Greek word “Orphanos,” which denotes to a child who is deprived of paternal care. Rare diseases are a collection of disorder disturbing so few people that drug development for such ailments is well thought-out unprofitable and abandoned by the pharmaceutical firms.[1] Thus, rare diseases are very much like an orphan kid who has not any parents and essential efforts in the former time for their drug development, as no pharmaceutical firm was enthusiastic to adopt them.[2] An orphan drug can be well-defined as one that is used to treat an orphan disease. For example, haemarginate, used to cure variegate porphyria acute intermittent porphyria and hereditary coproporphyria[3], is an orphan drug.

Medical orphans
An orphan virus, such as hepatitis G[3], is not related to a recognized disease. The period was announced as long ago as 1954 by Melnick, who described “new viruses, tentatively called “orphan viruses” (as we recognize so little to what diseases they belong), from patients supposed of having nonparalytic poliomyelitis’.[4] The term is not fully appropriate – a virus that is primarily considered an orphan may ultimately find its missing disease. The similar could be said of orphan genes and enzymes. For example, numerous enzymes have catalytic sites capable of being occupied by millimolar concentrations of ethanol[5]; their physiological roles are not known, at least not yet.

Orphan receptors are receptors that have been recognized from gene arrangements but have no known endogenous ligand or physiological function. One such, a member of the family of opioid receptors, is called ORL1 or OP4, though it is slowly losing its orphan status. An endogenic ligand, diversely called nociceptin[6] and orphanin FQ[7], has been known, but even non-selective ligands with high affinities for OP1, OP2, and OP3 receptors have very low attraction for ORL1[8,9] and its physiological role is not identified. On the other pointer, there are high-affinity ligands that outline subtypes of the ORL1 receptor.[10]

There are roughly 7000 diverse types of rare diseases and disorders with additional being discovered today. It has been stated that there are about 250 new rare cases reported every single year, however, the satisfactory treatment is accessible only for 200-300 orphan diseases.

It is notorious that the 80% of these rare diseases are of genetic origin and the rest have environmental, bacterial, viral or unidentified origin.[11] In general orphan diseases are often chronic, progressive, disabling; more life-threatening and maximum of these have effective or curative treatment, having low occurrence and high complexity.[12]

ORPHAN DISEASES

It is a common concept that the word "orphan" with respect to diseases accepts its origins in the "orphan drug act (ODA)." Yet, contrary to general belief, the use of the "orphan" terminology in the situation of diseases can be first outlined back to a newspaper penned by Dr. Harry Shirkey, a well-known pediatrician in Alabama, the United States of America (USA). He had used the word "orphan" in context to the pediatric population, who were being deprived from clinical trials as the efficacy and safety assessment of drugs in children was not considered to financially and logically possible by the drug developers. Hereafter, the infants and children were being slowly demoted to the standing of "therapeutic or pharmaceutical orphans".[13] However, in the years afterward, the word "orphan" increased acceptance in the context of numerous diseases that were being likewise abandoned since they affected solitary a small size of the patient populace worldwide and drug development against these diseases were believed to be financially unsatisfactory. Despite the many efforts made over the ages to define and describe out orphan diseases, until date, there exists no general definition for orphan diseases.

But there are two essential elements that have consistently believed in every possible definition of rare or orphan diseases:

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

Several administrations and countries across the globe have applied these two crucial elements in their efforts to define "orphan" or "rare" diseases (Table 1).

The World Health Organization explains a disease as orphan or rare if it affects 6.5-10 out of every 10,000 people. Likewise, the European Union (EU) allots the term orphan to a disease if it has a occurrence of 5 in 10,000 people. The USA defines it as disturbing fewer than 2,00,000 people, with a measure of an prevalence of not as much as 7.5/10,000 in the overall population.[14]

Table 1: Definitions of orphan disease in different countries.[14]

Sr.No	Country	Total population affected (maximum limit)	Prevalence per 1000 of population
1.	WHO	-----	6.5-10
2.	USA	2,00,000	7.5
3.	Japan	50,000	4
4.	South Korea	20,000	4
5.	Australia	2,000	1.1
6.	Europe	------	5
7.	Taiwan	10,000	1
8.	China	5,00,000	-----

Limitations for Orphan disease

1. The doctors or physician, when confronted with the dilemma of dealing an orphan disease, are frequently reminded of the limits of their knowledge about these diseases as well as the lack of available therapeutic options. The mark of "orphan disease" may be of speculative interest to the medical public. However, for the patients, who tolerate these rare afflictions, it characterizes a daily fight against a rival, about whom not much is recognized.[15]
2. Over the centuries, the rarity of the incidence of these diseases has frequently led to the medical public turning a "blind eye" to the sufferings of a few. Additionally, the lack of profit generating potential of the "niche markets" has frequently discouraged the pharmaceutical industries from investment heavily into the research and development (R&D) for the orphan diseases.[16]
3. But, in the recent years, faced with a seeming revolution emergency in the R&D sector, growing drug development costs, gradually strict regulatory plans leading to immense decline in the drug approvals and disappointment of the "blockbuster model" of drug development, the pharmaceutical companies are here and now exhibiting a shift in drug development plans and are being seen to follow the rare and orphan disease markets very violently.[17]

Also, Table 1 lists some of the rare diseases that have donated significantly to our understating of the human genetics and molecular therapeutics and covered the way for treating more common disorders like coronary artery disease, crucial hypertension, and cancers.[18–23]

Table 2: The contribution of rare diseases toward the current thoughtful and treatment of common disorders.[18–23]

Rare disease	Associated pathology	Contribution to science	Treatment implication (common conditions)
Familial hypercholesterolemia	LDL-receptor mutation	Development of drugs preventing cholesterol synthesis (statins)[18]	Coronary artery disease
Wilms tumor	Childhood kidney tumor; mutation in WT-1 gene	Kudson 2-hit proposition; somatic cell gene mapping; model for epigenetic alteration	Childhood cancers
Osteoporosis pseudoglioma syndrome	Mutation in low density lipoprotein receptor related protein-5 (LRP-5)	LRP-5 constrains serotonin production in the gut and maintains bone mineral density[19]	Osteoporosis
Marfan syndrome	Augmented transforming growth factor-B (TGF-B)	Inhibition of TGF-B with drugs like Losartan[20]	Aortic aneurysm
Tangier's disease	Complete absence of plasma high density lipoprotein (HDL)	Building therapies to decrease cardiovascular mortality[21]	Myocardial infarction
Liddle's syndrome	Increased activity of epithelial sodium channel (ENaC)	Knowledge about pathology of hypertension[22]	Essential hypertension
Fanconi's anemia	FANC-Q gene mutation	Disease mechanisms of bone marrow failure[23]	Cancers

The patients with rare diseases have paid markedly in the progress in the arenas of human genetics and molecular biology by their active contribution in research and development, but there have been very distant efforts to address the unmet need of those suffering with rare diseases. With over 6000 established rare diseases and 250 new rare diseases recognized every year, the ultimate right to health of those suffering from orphan diseases cannot be unnoticed simply based on their non-profitability.[24]

Genesis of Orphan Drug Act (ODA)[25]

The guidelines ensuing from the FD and C Act and the 1962 Amendment had specifically undesirable significances for orphan drugs. Because orphan drugs target small populations and yield lower returns, Asbury (1992) finds only 4 drugs that were on the marketplace to treat rare diseases by 1965. Legislature knowingly enlarged the expenses linked with drug development and caused pharmaceutical companies to emphasis their consideration on drugs that would make the most of profits and the opportunity of recouping their R and D costs. Many people measured rare diseases to be "orphaned" or essentially unnoticed by drug manufacturers, due to the focus on money-making "blockbuster" treatments, defined as drugs that are probable to generate over $1 billion in sales per annum. Because of their negligence, these treatments received the label "orphan drug." Ultimately, the impact of non-governmental organizations, like the National Organization for Rare Disorders (NORD) and patient advocacy groups, made orphan drug development a effort of public policy in the late 1970s and early 1980s. In 1980 Congress applied the Bayh-Dole Act (PL No. 96-517, 1984), allowing the receivers of government sponsored R and D to patent and licensed their research, tracked by the Orphan Drug Act in 1983. The chief objective of this act was to encourage the pharmaceutical industry and to deliver the much-needed thrust in drug development for rare diseases.[26] Table 3 lists the numerous encouragements and support provided to drug manufacturers under the ODA.

Table 3: Incentives provided to the manufacturer of orphan drugs under the ODA.[27,28]

Sr. No.	Incentive	Description
1.	Tax Credit	A sponsor may privilege tax repayment for half of the clinical research cost
2.	Exclusivity	There is a providing for 7-year exclusive marketing rights post endorsement of orphan product
3.	Waiver of Prescription Drug User Fees	The sponsor's fee as given by the Prescription Drug User Fee Act at the time of give in to a marketing application to FDA are waived
4.	Annual Grants	There is a facility for annual grants to pay for qualified clinical testing expenses Phase I clinical investigations: up to $200,000 per year for up to 3 years Phase II/Phase III clinical investigations: up to $400,000 of total costs per year for up to 4 years
5.	Study Design	FDA offers assistance for clinical research study design

Orphan drug development

The orphan drugs developed can be categorized into two major classes:

(i) Tew molecular entities, which comprise drugs developed primarily for rare disease indication; and

(ii) Repurposed drugs, which states the drugs already accepted for a disease condition (common or rare) being repurposed to treat a rare disease.[29]

- **Target selection**

Maximum of the rare diseases are genetic in nature and includes a definite gene mutation. The understanding of the fundamental genetic defect is so critical for developing rational therapeutics for rare diseases. Several tools accessible for identify the underlying pathology range from traditional gene mapping or linkage analysis to supplementary sophisticated tools like epigenetic, proteomics, and system biology.[30]

- **Drug discovery process**

Once the biological target is identified, the search for the therapeutic agent starts. The possible therapeutic agent could also inhibit the deleterious/excessive function [e.g., inhibition of tyrosine kinases in chronic myelogenous leukemia (CML)] or restore the mislaid function (e.g., enzyme replacement therapy for Gaucher's disease).[30] Developed a small molecule drug typically involve 4 steps. First is to form a large compound library using modern organic chemical synthetic methods (e.g., combinational chemistry). Second is the development of a precise assay procedure to study the interface between the biological target & the test compound. Third is the high-throughput screening of these compound libraries by means of an automated screening procedure employing robotic systems to recognize potential "hits." The final step is the chemical optimization of the "hits" by using techniques of computational chemistry, so as to recover the affinity of the test compound for its target.[31] A typical example of a discovery of an orphan drug is the research commenced by Brian Druker and his colleagues in the expansion of Gleevec for the treatment of CML.[32]

- **Preclinical studies**

Once a group of candidate drugs is recognized and their capability to modify the wanted target is confirmed, then preclinical studies commence to study their pharmacokinetic properties and their toxicity. The drug estimation could be done by in vitro or in vivo method or both. The specific animal models are not accessible for many of the rare diseases; though, if an animal model of the rare disease occurs or could be made by genetic modification of animals, it could besides help to regulate the preclinical proof of efficacy of the particular drugs.[30]

- **Clinical studies**

Designing a clinical trial for an orphan drug is a major obstacle to get a regulatory approval for its marketing. Additional challenge is the identification and recruitment of an acceptable number of patients with rare diseases for clinical trial. It may take times to achieve the wanted sample size to make the study results statistically expressive. Though, studies have shown that once identified, the rare disease patients are easier to employee in a clinical trial. These patients are comparatively easier to retain; the normal dropout rates in rare disease trials are much lesser than that understood in typical clinical studies. Furthermore, the rare disease patients are much likely to receive the new medication or even experimental treatment. This decreases the recruitment cost and the need to over-recruit to counter dropouts during the clinical trials. The clinical trials are usually led in linear order: phase 1 tailed by phase 2 and then phase 3. The innovative trial designs with the aid of numerical analyses are being discovered so that the following phase of clinical trial could be started before the completion of the previous one. The innovative designs for rare disease trials are non-only cost-effective but also are fairly useful in reducing the transition time of drug from pilot batch to market and dropping the required sample size. The drug-approving expert must exercise their scientific judgment and confirm due flexibility while assessing the data at several phases of orphan drug development. Definitely, the US FDA has recently approved the Well stat Therapeutics' drug (uridine triacetate) for the treatment of hereditary orotic aciduria based on a 4 patient 6-week clinical trial.[33]

General, the nature of clinical studies to be directed for both rare diseases and common diseases is quite similar in terms of the cost and infrastructure. Built on the various studies, the variations in the clinical trial characteristics of orphan and non-orphan drugs are summarized in Table 4.[34,35]

Table 4: Comparison of clinical trial characteristics of orphan and non-orphan drugs.[34,35]

Sr.No.	Clinical trial characteristics	Non-orphan drugs	Orphan drugs
1.	Sample size	Large (n = 290)	Small (n = 96)
2.	Randomization	More common (80%)	Less likely (30%)
3.	Double blind	Common (33%)	Less common (4%)
4.	Primary endpoint	Measure disease progression	Measure disease response
5.	Comparator	Present in 80% trials	None in 70% trials
6.	Serious adverse events	Lesser (36%)	Higher (48%)
7.	Median duration clinical trial	Longer (6.9 years)	Shorter (5 years)
8.	Post marketing efficacy assessment	Done in 92% cases	Done in 60% cases

Repurposing drugs for orphan drug development

The uncertain financial incentive related with the development of an orphan drug requires cost-effective method for drug development. Repurposing of the approved drugs and recognizing new uses for the rejected drug candidates have been considered to be an

significant strategy to encounter this goal of cost-effective drug development for rare diseases. However, cost-effectiveness of repurposed drugs rests on upon how widely the drug candidate has been studied formerly. Recognized candidates like sildenafil, which have previously been approved for human use, offers substantial investments when repurposed as new therapies for rare diseases. Also, repurposing of the old drugs or discarded drug candidates, especially when combined with computational (in silico) methods, decreases the overall cost for drug development. This method looks to be the most rational strategy for the development of a new drug where the fundamental pathophysiology of the rare diseases is either not acknowledged or is not readily correctable. Indeed, the general use of repurposing has been a major victory for the development of new therapeutics for a diversity of rare diseases and accounts for just about 40% of all approved orphan drugs.[36]

Table 5: Approved and old drugs that are successfully repurposed for treating rare diseases.[36]

Sr.No.	Drug	Orphan indication(s)	Original indication
1.	Everolimus	Renal cell carcinoma	Transplant rejection
2.	Celecoxib	Familial adenomatous polyposis	Inflammation
3.	Ibuprofen	Patent ductus arteriosus	Inflammation
4.	Hydrocortisone	Adrenal insufficiency	Inflammation
5.	Histamine dihydrochloride	Acute myeloid leukemia	Gastrointestinal disorders
6.	Cladribine	Non-Hodgkin's lymphoma	Hairy cell leukemia
7.	Mitotane	Adrenal cortical carcinoma	Cushing disease
8.	Nitisinone	Tyrosinemia	Herbicide
9.	Canakinumab	Cryopirin-associated periodic syndromes	Rheumatoid arthritis
10.	Miglustat	Fabry disease	HIV

The FDA has also recognized a database named as the Rare Disease Repurposing Database, which lists medicinal products that have established the orphan drug description and presently in use for common or rare diseases. It serves as a new reserve device for sponsors to identify capable candidates and develop them as drugs for rare diseases.[37]

Consequences of living with a rare disorder

Individuals living with rare disease or ailment have further impacted on psychological, social adjustment in addition to total well-being and health.

Restraints could be physical[38-41], dietary limitations[42,43], pain[44-46],) or problems with sleep, fatigue, tiredness, and exhaustion[47,48], worries about finding an accepting and understanding life partner or seeing the medical condition as a limit to additional relationships & the continuous need to manage and treat the consequences of the rare ailment with normal life.[49]

Psychological limits were more precisely described as dependence and lack of liberty related to the demands of treatment, doubt about the ailment evolution, attention problems as a moment of chronic and/or intense pain[50], or stress and emotional distress.[41]

Psychological and emotional influence of a rare condition on the individual

Psychological and emotional challenges were labelled as related to the physical limitations and limitations of the condition[41], attention problems[48], pain[44], dependence on others[38], dependency of treatment[43], or the social influence of other people's lack of understanding and information about the rare condition.[49]

Psychological challenges were also associated to the medical facets of the condition, more exactly patients' lack of information about the medical condition[50],

ambiguity about the future[38], ambiguity associated with the evolution, and progression of the condition[47], treatment related uncertainty.[51-53] Some research specifically cited the development or feeling of depression or psychological distress[38] for example, due to aloneness[40] lack of societal support[53] hopelessness and desperation[54] emotional distress and pain[44-45], disempowerment &, lack of confidence, guiltiness related to the risk of passing the condition on to children.[40] Other characteristics of emotional distress were feelings of fear, rage, blame, and loss.[45]

Social Stigma

One of the most salient characteristics of living with a rare disorder was somatic & physical constraints and limitations that were accompanying with the medical condition. More than a half of the included research papers conferred their effect on emotional and social modification, in addition to on overall well-being and health. Although some physical limitations are existing across quite a lot of medical conditions, other limitations are fundamentally linked to specific conditions. Whether challenges are specific to one ailment or more common, they need to be managed and treated to everyday life, in order to limit their psychological impact on emotional well-being, work, education, and social life.[55]

Further, adults with rare conditions designated psychological limits, such as a lack of independence and freedom due to the demands of treatment, ambiguity about the disease evolution, and emotional distress as a consequence of pain or other distressing characteristics of the conditions. The social impressions of other people's lack of understanding, or misconceptions about the rare condition, were also mentioned in most articles. Psychological distress also seemed to be directly interrelated to experiences of lack of information in health care providers, which caused patients' uncertainty about the doctors' ability to treat. The characteristic of rarity of a condition in itself was not, however, described as problematic in 2 of the included studies[56], as long as patients had initiate health professionals who were able to identify their needs. These findings point to the importance of particular evaluations of one's life situation, and the element that it is the patient's feelings and beliefs regarding their condition and its treatment that determine their capability to cope with the challenges they meet, more than having a rare condition in itself interventions should therefore aim at firming up individuals' coping strategies, and address the patients' subjective evaluation of stress, in accumulation to their insight of the medical follow-up of their condition, thereby enhancing feelings of control over the consequences and effect of the disease.[57]

Physical and psychological constrictions and limitations such as pain, physical limitations, sleep problems, or dietary limitations, are not precise to rare conditions only. Still, these challenges may become an additional burden because of the patients' experienced lack of information and understanding in society and in the health care system. Subsequently, findings from the present review support the hypothesis that the rarity of a condition poses some exclusive challenges. The inherent challenges associated with improving quality of care among individuals with rare disorders, therefore suggest the need to address the lack of information in health care settings and in the people in general.

Social consequences of living with a rare disorder

Patients raised up the matter of whether, when, how, and to whom they should expose the finding, and how they by doing this could risk negative social consequences, such as misapprehensions, social prohibiting, or stigma. Another chief theme was the challenging balance between sameness and modification, and the adults' search for an inner feeling of normalcy. Perceived difference gives the impression to be strongly allied with the disorder's constrictions and limitations, whether these alterations were visible or nonvisible to other people. Challenges seemed to be associated to whether the individual felt that the consequences of the ailment labeled them as socially different, in a way that inadequate their social participation or required adjustments in everyday life. On the other hand, examples from the literature on rare conditions have also confirmed that some individuals manage to find a positive balance between sameness and difference, following in the task of accepting their difference as improvement and a positive uniqueness.[58] The uncertainty of feeling both average and extraordinary has also been labelled in young people with more common medical conditions.[55] Such conclusions emphasize the need for further research exploring intrinsic and external factors, positive as well as negative, which may be related with the individual's emotional response to the challenges of living with a rare medical ailment.

The various social aspects designated by patients living with a rare condition, increases the issue of protective factors, such as social support, cited in several of the included articles of the present review. Significantly, social support meant the option to share experiences about the condition and its treatment, and receive crucial emotional support from peers and/or family. The loss of the family's social support when attainment adulthood further approves the importance of this factor in everyday life[43] as also confirmed in a recent literature review on evolution into adulthood when living with a medical condition.[55]

Positive aspects of living with a rare disorder

Several review papers described how adults with rare conditions had developed coping strategies that assisted them cope with the everyday challenges, strategies that could strengthen the development of positive results and resilience. Many coping strategies were specifically intended at normalizing everyday life, or included the development of self-management skills in order to deal with the social responses to the condition. In

standardizing everyday life, the patients recreate life and accept the situation as ordinary[59] Patients also described the requirement to build up a feeling of control in health care discussions by educating themselves about the medical aspects of their condition, as described above, and hence giving themselves as expert patients. Others described how inner processes, such as linking themselves with people with other more severe conditions, had aided them put their life result in perspective. Downward comparison is a well-known coping strategy in terms of firming up self-perceptions.[60]

Indian scenario of Orphan drugs

Approximately 450 rare diseases have been recognized in India. Now, the alertness for rare disease is growing. Time to time technical and patient communities stated the needs for government creativities toward rare disease. The first challenge to bring together all experts of rare disease under a common platform was initiated by INSA, which led the first of the kind rare disease workshop enabled "To Develop a Scientific Program for Research on Rare Diseases" in 2016, which reflected on issues such as definition of "Rare disease," rare disease alertness, rare disease research avenues, policy framework for boosting and incentivizing research and development (R and D) efforts, and enclosing suitable legislature to ensure involvement of the State in satisfying the special needs of rare diseases. In the INSA rare disease workshop (2016), the respected drug controller general of India (DCGI) stated that a policy for enhanced clearance of orphan drugs and fast-track endorsement is not in place because government needs clear-cut commendations regarding the definition of rare disease, mechanism for fast-track approval (e.g., waiver of a precise phase in orphan drug clinical trial). He again stated that genetic differences in Indian people permits Indian-centered studies, rather than using data from studies in other nations. He also requested for expert ideas on the need of changes in the drugs and cosmetic act to encounter the requirements of research in rare disease.

Table 6: Various initiatives are in process which comprises initiative from governing side, initiatives from academic institutes, non-governmental organization (NGO), and other linked sectors.[61]

Sr.No	Initiative	Description	Ref.
1.	CDSCO	By a circular 12-01/14-DC pt. 47 dated July 3, 2014, the CDSCO allotted a notice regarding waiver of clinical trial for support of new drug in the Indian population, for drugs which are previously approved outside India, and it was stated that this waiver can only be probable in case of orphan drugs for rare disease and drugs designated for diseases and condition where there is no therapy. In another conference at a later date between pharma shareholders and DCG(I), held on May 4, 2016, on discovering of possibilities to provide economical medicines for patients with rare diseases, IDMA and OPPI were given the accountability to frame the Indian definition of rare disease, JDC (ER) was given the duty to revise timelines for orphan drug approvals, and a distinct cell was suggested to address the issues of rare diseases, possibility of discrete pricing mechanism for orphan drugs, and possibility of custom duty exception.	[62,63]
2.	Pharmaceutical export promotion council initiative	Pharmaceutical export promotion council, Ministry of commerce and industry, India, implemented regular seminars, alertness campaigns regarding quality compliance and orphan drugs, excellence culture in good manufacturing practice (GMP) compliance overseas marketing strategies, opportunities for orphan drugs, IPR and contact with Food and Drug Administration (FDA) of other countries, etc., and takings care of orphan drug export and other related strategy such as GMP compliance, cognizance, and strategy maker in collaboration with FDA of other countries.	[64]
3.	Uttar Pradesh Government initiative	Occurrence of hemophilia incidence in India is predictable to be 1 in 5,000. However, for treatment purpose, clotting factors used are actual costly. In the time 2010, the Uttar Pradesh Government took an initiative to cover the price of clotting factor.	[61]
4.	ICMR initiative	Till now, 2 main initiatives initiated by ICMR are inviting schemes for orphan disease research and initiation of registry for rare disease & sponsoring /forming workshops/conferences/training programs on rare disease. The National Initiative for Rare Diseases (NIRD) was planned jointly by ICMR, AIIMS, JNU, and PRESIDE. It was obvious that first step is to recognize patients with rare disease. "Indian rare disease registry" was launched on April 27, 2017. This archive is intended to cover all rare and ultrarare diseases predominant in India. The archive is	[65,66]

		1St intended to be hospital based and later population based. The purpose of the registry is identification of the rare disease patients; use that information for policy framing and to guide future research. Other major profits are that monitoring prevalence, frequency, and natural history of disease will become easy with regard to the Indian framework.	
5.	Nongovernmental organization initiative	Organization for Rare Diseases India (ORDI; www.ordindia.org) is a nonprofit-based voluntarily organization which was well-known to deal with the rare disease ailment in the Indian people. The ORDI squad members belong to different disciplines that are science and nonscience background. ORDI deals with the matters interrelated to the rare disease such as unique challenges in dealing with rare disease.	[67]
6.	CSIR and IGIB initiative	IGIB, New Delhi, has directed project funded by CSIR, called as "Genomics for Understanding Rare Diseases India Alliance Network (GUaRDIAN)," for the drive to bring together and appreciate novel genetic variations to achieve translational applications by both clinicians and basic science researchers.	[61]
7.	JUDICIARY initiative	In November 2016, the Delhi high court had well-organized the government to confirm a policy on rare disease, draft of which was submitted by the Union Ministry of Health to the Delhi high court on May 25. The Delhi high court directed the Centre to device its National Policy for Treatment of Rare Diseases without delay.	[68,69,70]

CONCLUSION

Individuals with rare diseases must also have equivalent access to medicines as like patients for any other disease. Common principle of social justice and equality of vital commodities like medicines must be recognized for people exaggerated with rare diseases. The problem of rare disease needs distinct concern regardless of the business demands of the industry. Like US and Europe, India desires a strong Orphan drug reform or legislation to meet the need of this alarming condition. literature show more than 70 lakh people have been affected by rare diseases till 2011 in India, which is highest in this subcontinent. An indication at these cases shows sufferings of this abandoned populace of the culture due to lack of hard work by core research institutes, pharmaceutical manufacturing companies as well as government. Pharmaceutical businesses or research organizations in emerging countries like India should move focus towards core research and expansion rather than only developing copycat or mimicking generic versions of approved medicines. Yet, due to lack of government funding, it is understandable that pharma firms are not left with many options but to develop only money-making medicines for a larger patient populace. It is high time the Indian government takings initiative to encourage these trades by means of diverse special profitable provisions and policies. This may contain giving exclusivity provisions, exclusive/non-exclusive licensing opportunities and various developmental incentives. More, there is a prerequisite of a transparent evidence-based method towards orphan drug pricing and exception. However, counting these drugs in the DPCO may not make development of the same profitable for the manufactures. Attention should be taken such that benefits like profitability and affordability are balanced on the scale.

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