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Review Article

Empowering W.H.O. as a Global Authority and Centralized Pool of Resources for Speedy Development of Orphan drugs at Reduced Cost

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Abstract

Orphan drugs are the drugs that are used to treat a rare disease affecting a very small segment of population. Since new drug development and approval process requires an expenditure of about US$ 1 billion and a time of 10-12 years, therefore, no company is willing to come forward for development of an orphan drug because of low returns. As a consequence rare diseases are becoming global menace. Incentives offered by developed countries i.e. U.S.A., EU & Japan are inadequate. Even no single developed country can afford development of large number of orphan drugs owing to increased cost of drug development amalgamated with low financial return for thousands of rare diseases. There is a strong need for adopting unified approach by creating a centralized pool of resources under the auspices of World Health Organization (W.H.O.) for speedy development of orphan drugs. Developed countries like U.S.A, EU and developing countries with emerging economies such as China and India can play vital role in such a unified approach. This will naturally avoid unnecessary duplication of efforts, resources and facilitate speedy development of orphan drugs at a reduced cost for benefit of all concerned at a global level. People residing in both the developing counties as well as developed world will be equally benefited by this approach. Approval by W.H.O. alone should suffice the purpose for introduction of new orphan drugs all over the world as a special case in order to avoid unnecessary delays and to save precious lives.

Key words: *Orphan drugs, Rare disease, W.H.O.*

Introduction

Orphan drugs are the drugs that are used to treat diseases so rare that sponsor are reluctant to develop them under usual marketing conditions [1]. A rare disease is usually considered to be one that does not affect more than 650 to 1000 people per million persons. Examples of such diseases are Chronic lymphatic leukemia, Goucher's disease, AIDS, cystic fibrosis, snake bite, blepharospasm (uncontrolled rapid blinking). In Europe, a rare disease is defined as one that affects one person in 2,000, whereas in the USA and Japan, the definition of a rare disease is one that afflicts fewer than 200,000 and 50,000 patients, respectively [1,2,3]. Rare diseases affect a restricted number of people; hence the main criterion to identify a rare disease is the prevalence level (Table 1).

Around 6000 rare diseases have been described on a worldwide scale[4]. It's a global menace that has unfortunately received little attention. W.H.O. estimates that more than 12 million people, mostly in Asia & Africa, are attacked each year by dogs, snakes or scorpions. Shockingly only 1 percent of them receive treatment. The reason – production of serum to treat rabies and of anti-venom treatment against snakebites have plummeted because the demand has fallen in wealthier countries. With profit margins minimal, pharmaceutical companies have unfortunately discontinuous supplying the life saving sera. Treatment with the leftover stock have become unaffordable in developing countries which desperately need them Dr. Hans Hogerzeil, Director of W.H.O. Department of Medical Policy & Standards told the *TIMES of INDIA* correspondent that W.H.O. will soon define a global standard for the production, quality control and regulation of therapeutic sera to be used as guidance by regulatory authorities & manufacturers, besides facilitating transfer of technology to developing countries. So there is a need to harmonies the regulatory requirements of different countries [5]. Similar to snake bites & scorpion bites thousands of rare diseases exist for which patients do not get the treatment. Some of the rare diseases specified by NORD (National Organization for Rare Diseases) have been exemplified in table 2.

Table 1: Prevalence threshold for rare diseases in developed countries [1,3,6]

	USA	*Europe*	*Australia*	*Japan*
Upper Limit of incidence in terms of a rare disease per 10,000 of population	7.5	5.0	1.1	4.0
Upper Limit in terms of affected individuals for the country, i.e. maximum size of market in the country.	200,000	185,000	2,000	50,000

Table 2: Some examples of rare diseases [4,6]

RARE DISEASE	*RARE DISEASE*
AIDS Dysmorphic syndrome	Growth Hormone Deficiency
Acquired Aplastic Anemia	Headache, Cluster
Acromegaly	Heart Block, Congenital
Agranulocytosis- Acquired	Heavy Metal Poisoning
Albinism	Hemophilia
Alkaptonuria	Hepatitis B
Amenorrhea- primary	Hyperkalemia
Anaphylaxis	Hypothyroidism
Anemia, Megaloblastic	Irritable Bowel Syndrome
Anemia, Pernicious	Keratomalacia
Anthrax	Klinefelter syndrome
Apnea, Infantile	Lactose intolerance
Benign Essential Tremors	Leukemia, hairy cell
Blastomycosis	Macular degeneration
Botulism	Meningitis, Meningococcal
Brain Tumors, General	Motor Neuron Disease
Brown Syndrome	Multiple Sclerosis
Brucellosis	Myasthenia Gravis
Bulimia	Narcolepsy
Burning Mouth Syndrome	Neutropenia
Cancers, Skin, General	Opportunistic Infections
Candidiasis	Osteopetrosis
Carboxylase Deficiency	Parkinson Disease
Carcinoid Syndrome	Phenyl ketonuria
Carcinoma, Renal Cell	Pheochromocytoma
Carcinoma, Squamous Cell	Pneumonia, Interstitial
Cat Eye Syndrome	Polycystic Kidney Disease
Cat Scratch Disease	Pompe Disease
Cataracts	Porphyria
Celiac Disease	Post Polio Syndrome
Cerebellar Degeneration	Prostatitis
Cholecystitis	Psoriasis
Cholera	Q – Fever
Chromosome10, monosomy	Rabies
Cystic Fibrosis	Renal Glycosuria
Dengue Fever	Retinitis Pigmentosa
Depersonalization Disorder	Retinoblastoma
Dyslexia	Retinopathy, diabetic
Ectodermal Dysplasias	Reye Syndrome
Elephantiasis	Rh Disease
Encephalitis, Japanese	Rheumatic Fever
Endomyocardial Fibrosis	Sickle Cell Disease
Factor 1X Deficiency	Smallpox
Fetal Alcohol Syndrome	Stenosis, Spinal
Filariasis	Stiff Person syndrome
Fructosuria	Thyroid Cancer
Galactosemia	Trisomy 13 Syndrome
Gastritis, Chronic, Erosive	Urticaria pigmentosa
Gastroesophageal Reflux	Varicella Zoster
Goodman Syndrome	Yellow Fever

Difficulties in the Development of Orphan Drugs

Orphan products, which benefit a very small but intensely needy segment of the population, typically are not brought to market by major pharmaceutical manufacturers because the cost of development and introduction does not justify the financial return[3].

Due to their extremely low prevalence, rare diseases as a whole have traditionally been neglected by large parts of the scientific, medical and political communities. With the exception of a few conditions that occur more frequently on a global or regional scale, such as cystic fibrosis and thalassaemia, knowledge and awareness of the vast majority of rare diseases is still scant or negligible.

Another possible explanation for difficulties in development of orphan drugs may lie in the significant cost of bringing new chemical entities (NCEs) to the market. Costs in excess of £300m per product are now considered to be the norm[7,8]. The high cost of new product development means that large markets, such as that for common diseases found in developed countries, will naturally be targeted more closely by the pharmaceutical industry to ensure adequate financial returns.

Rare diseases are a serious problem for human and public health. But it was not until the early 1980s that various countries, the first being the USA, introduced legislation and incentives to make the development of drugs for rare diseases more attractive for pharmaceutical companies.

Global Scenario

Rare diseases represent a global public health issue and patients living with a rare disease share the same fundamental issues wherever they live: access to diagnosis and information, access to care, social recognition, etc. Furthermore, research is global, drug development and market are global, and this is even truer in the "niche" of drugs or treating rare diseases. Rare diseases involves a relatively small number of individuals—from just ten to hundreds of thousands—together, rare diseases affect a major subsection of the population in developed countries, including 25 million US residents and about 6%−8% of the population of the European Union (EU), equivalent to 24−36 million people[2]. About 80% of identified rare diseases have a genetic origin, and the remainder are caused by infections, allergic and autoimmune disorders or poisonings, or have unknown causes [2,6]. The rare diseases are occurring through out the world. Rare diseases do unfortunately affect any human being, whether living in a rich or a poor country. Furthermore, being affected by a rare disease while living in a developing country does make one the poorest, liable to cumulating health and social vulnerabilities[9]. In case of developing countries a large segment of population lives below the poverty line without any access to essential medicines.

Even no single developed country can afford development of large number of orphan drugs owing to increased cost of drug development amalgamated with low financial return for such a large number of rare diseases.

The Orphan Drug Act was notified into law on January 4, 1983 in U.S.A.Australia, Canada, and Japan have evaluated how there governments can facilitate the development of medical products to treat rare disorders. These countries have established programs and/or policies to support the development of products to address unmet medical needs in small populations and to ensure their citizens access to such essential medicines.

Orphan drugs in U.S.A. [1,2,3,7]

Orphan drugs are covered by a specific legal system and are granted upon an application dossier submitted to office of Orphan Products and Development (OOPD}, including:

1) Standard Administrative data (name & address of sponsor, manufacturer, international non-proprietary name of the drug, trade name of the drug).
2) A Description of the disease & the intended condition of use.
3) The authorization given by sponsor to the FDA to publish information concerning product & the recognized indication.
4) The size & other characteristics of the population likely to be treated in USA.

5) A description of drug & its risk / benefit ratio.
6) The estimate of the cost of development & distribution of drug & an assessment of potential sales in U.S.A., confirming the commercial viability of marketing the drug in specific cases.

Incentives to orphan drugs providers are given in the following terms

1) A 50 percent tax credit on cost of clinical trials undertaken in the U.S.A.
2) A 7 year period of market exclusivity
3) Some written recommendations provided by FDA concerning clinical and preclinical studies.
4) A fast track procedure by FDA to evaluate registration files.

Orphan drugs in Japan [1,2,3,10,11,14]

Japan is the other country with an Orphan Drug Program. The program is similar to that in the U.S. with initiatives in place aimed at stimulating research and development in Orphan Drugs. To receive an Orphan Drug designation in Japan, the drug must be indicated for a disease, which has a prevalence of less than 0.05% in the population. The prevalence of disease cited in the U.S. definition equates to approximately 0.1% of the population. Orphan drug status is granted by Ministry of Health, Labor & Welfare (MHLW). Incentives for orphan drugs are provided in term of R&D, intellectual property and marketing. The Japanese government support for R&D on orphan drugs at two levels.

The Administrative Level

1) Orphan Drug benefit from a Fast- Track Market Authorization procedure.
2) Organization for Pharmaceutical Research & Safety provides consultation on developing protocols & some advice concerning the preparation of approval applications.
3) The Registration Validity Period is extended to 10 years for orphan drugs.

The Financial level

1) Some government funds such as the Drug Fund for side – effects relief & research Promotion, are available.
2) Reimburse the development cost up to 50 percent.
3) A 6 percent tax reduction for research & development expenses is granted.

Orphan drugs in Europe [1,2,3,8,9,12,13,16,18]

The EU "Regulation on orphan medicinal products" (No 141/2000) was passed by the European Parliament on March 9, 1999 and adopted at the parliament's plenary session held between December 13 and 17 of the same year. A Committee for Orphan Medicinal Products (COMP) will be set up to assist the European Medicines Evaluation Agency (EMEA) in administering the process. The following incentives will be provided for the pharmaceutical industry under the EU regulations:

1) **Market exclusivity** Products will be allowed 10 years' market exclusivity by the EMEA or member state.
2) **Regulatory assistance** Additional assistance in the form of free advice will be given by EMEA staff in overcoming any difficulties encountered while preparing clinical trial plans. Such difficulties are likely to be due to the natural limitation in numbers of patients entering clinical trials for safety, quality and efficacy.
3) **Fees** The EMEA's executive director, usually after consultation with the Committee for Proprietary Medicinal Products (CPMP), may grant a reduction in registration fees or waivers "in exceptional circumstances and for imperative reasons of public health".
4) **Cost and funding** The cost of introducing orphan drug legislation has not yet been fully determined. Apart from the implementation cost that should be shared by other European countries, there could be significant additional costs:
5) **Financial incentives** Financial incentives for the UK pharmaceutical industry, such as tax credits, licensing fee reductions or grants, could be considered by the government as a way of winning back industry confidence lost through years of implementing cost control systems.

Orphan drugs in Canada [3,11,18]

Legislative/Regulatory Instruments

The following legislative or regulatory instruments are relevant to the development and introduction of an Orphan Drug policy in Canada.

1) Cost Recovery, Financial Administration Act and Regulations

i. Cost recovery for drug approvals was introduced through regulation on September 1, 1995.

ii. There is a provision under the *Drug Evaluation Fees Regulations* for the reduction of fees for drugs with small market potential:

A person who files a submission, supplement or application referred to in any of sections 4 to 8 may apply to the Minister or Director, as the case may be, for a reduction in the fee payable under these Regulations. The Minister or Director shall grant an application made under subsection (2) where The Minister or Director has reasonable grounds to believe that, during the fee verification period, the applicant's revenue from sales in Canada of the drug in respect of which the submission, supplement or application relates will be less than 10 times the applicable fee calculated in accordance with sections 4 to 8 and 11.

iii. Most Orphan Drugs would qualify for this reduction on the basis of small market size.

2) Patent Protection, The Patent Act

Some Orphan Drugs may be unpatentable. These include those with previously expired patents and natural substances.

3) Research & Development Incentives, The Income Tax Act

i. Under the federal government's Scientific Research & Experimental Development (SR&ED) Tax Incentive Program certain research and development (R&D) by pharmaceutical companies is eligible for an R&D tax credit. Standard exclusion criteria are used to determine which expenditures qualify for SR&ED. The research must test a certain hypothesis and represent an advancement of science.

ii. Most R&D in Orphan Drugs would qualify for this tax credit.

Orphan drugs in Australia [1,3,11,15]

The concept of an orphan drug program in Australia was first considered in 1991, when a landmark review of the Australian drug evaluation process was undertaken. The 1996 review identified the problem of some medically-needed products not being available in Australia and recommended that an orphan drug program be considered to encourage companies to bring such important products to the Australian market. As a result of the government adopting that recommendation, an orphan drug program was established and began officially on January 1, 1998. Orphan designation is intended to drugs which aim to treat diseases with a prevalence of 2000 patients/ subjects or less in the Australian population.(18 million). Once orphan designation is granted, the TGA waives the evaluation fees., thus removing a major impediment to make these crucial drugs available.

The main characteristics of orphan drug policy in Australia are

1) A legal framework for orphan drug designation.
2) Waiver of application & evaluation & no annual registration fees.
3) 5 year exclusivity.
4) Regarding the funding TGA cover all the cost of the orphan drug designation process.
5) In Australia R& D is not supported by grants or tax incentives.

Orphan drugs in Singapore [1,18]

In Singapore 1991 Orphan Drugs Exemptions applies (defines legal imports in to the Singapore) as per following -:

1) An orphan designation is given for a life threatening and severely debilitating illness
2) An orphan drug is a medicinal product, which has been identified by any doctor or dentist as an appropriate and essential remedy with no effective substitute for the treatment of a rare disease.

3) The Orphan product should be approved in country of origin or any other country where it has been used.
4) Orphan drugs importee must maintain proper records including
   a) The quality imported or supplied.
   b) The date of reception or supply
   c) The name & address of the person for whom the orphan drug is provided.
5) So far there has been no other incentive, such as marketing exclusivity or subsidies in the orphan drug policy**.**

Need for harmonization as well as protecting interest of poor countries

Table 3 reveals wide variation in incentives offered to companies for development of orphan drugs by different countries. There is a strong need for international community to adopt a collaborative and unified approach for speedy development of orphan drugs on war footings. TGA modeled the system on the United States program and wishes to publicly acknowledge the enormous support obtained from the Food and Drug Administration (FDA) Office of Orphan Drug Products in constructing the Australian program. An official agreement also establishes a link between the FDA Office of Orphan Drug Products and the Australian TGA.

All other members of international community can also join hands on similar lines to adopt unified approach on war footing. Accordingly international community can easily create a centralized pool of resources both in terms of finance & scientific manpower under the auspices of W.H.O. Numerous teams comprising of leading scientists in the respective fields can be created at global level & each team can be given the responsibility of developing drug(s) for a particular disease(s). All the leading laboratories under public sector in various countries can be directed by respective governments to allow use of scientific manpower as well as infrastructure for development of orphan drugs in addition to their routine activities. Moreover, leading R&D laboratories in the private sector can be given grants out of centralized pool for development of orphan drugs. Since orphan drug will ultimately benefit people from every part of the world, therefore, every country should offer further incentives such as market exclusivity, regulatory assistance and complete exemption from all kinds of direct and indirect taxes.

In case of orphan drugs there is a need for harmonization. Due to the harmonization the process getting approval and process of developing the orphan drugs becomes

1. Simpler
2. Avoid unnecessary duplication of efforts.
3. Cost of developing the orphan drugs get reduced so it will provide the cost-effectiveness for rare disease therapies.
4. Time in the development of orphan drugs gets reduced.
5. The orphan drugs will be easily accessible to all the patients in all countries (especially in poor countries) so there is an equitable access to all needed segment of the population.
6. Pharmaceutical companies will also be benefited because the number of patients suffering from rare disease increases because the orphan drug will work at global level instead of using it in a specific country like Europe, Japan or U.S.A.
7. Prices should decrease as a result of a technological learning curve and an obvious link between volumes of sales and prices when reaching out more patients progressively worldwide**.**
8. There is a need at international level about a) awareness of rare diseases b) education of health professionals c) eliminate inequalities in diagnosis & access.
9. There is a need for shared responsibility between the clinician, the developer and the regulatory authorities.
10. There is a need for pool resources for development of orphan drugs.
11. There is a need for empowering W.H.O. as central pool of resources for speedy development of orphan drugs.
12. The W.H.O. will act as a central body and all the agencies involved in the development of orphan drugs such as U.S. FDA (office of orphan drug development), Japan MHW, Australia TGA; European union Committee of

TABLE 3: *Comparison of regulatory norms of orphan drugs in various countries* [1,2,3,7,8,10,11,12,13,14,15,18,19]

Date Established	*US*	*JAPAN*	*AUSTRALIA*	*EUROPE*	*CANADA*	*SINGAPORE*
	Jan.4, 1983	1993	Jan. 1., 1998	2000	1996	1991
Legislative Basis	US Orphan Drugs Act modified the Federal Food, Drug & Cosmetic Act.	Partial Amendments Law amended two previous laws. Orphan Drug Regulation 1993.	Additions made to the regulations to Therapeutic Goods Act, 1989	Regulation (EC) No. 141/ 2000.	In the early 1990s a Drug Directorate Renewal Project of Health Canada looked at Orphan Drug Policy.	Orphan Drugs Exemption. (Defines legal imports into Singapore)
Administration	FDA (Office of Orphan Product Development)	MHW (Ministry of Health & Welfare)	TGA (Therapeutic Goods Administration).	EMEA (Committee for Orphan Medicinal Products) COMP.	Health Canada. Emergency Drug Release Program (EDRP) / IND provide access to unapproved drugs.	None
Scope	Drugs (Devices & Food- R&D) only.	Drugs & Medical Devices.	Drugs	Drugs	DNA	DNA
No. Of orphan products approved / designated	238/1200	94/172	33/63	7/126	A large no. of drugs approved in US has approved in Canada.	DNA
Government. Grants	Yes	Yes	Not Available	Not Available	Yes. SRE&D tax incentive program supports R&D.	DNA
Market exclusivity	7 years.	Based on normal patent protection.	5 years (pending ratification by jurisdiction)	10 Years.	DNA	None
Prevalence	Less than 200,000. (75 per 100,000)	Less than 50,000. (40 per 100,000)	Less than 2000. (11 per 100,000)	Less than 50 per 100,000.	No official status	DNA

DNA – *Data not Available*

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TABLE 3 *(Contd)*: *Comparison of regulatory norms of orphan drugs in various countries* [1,2,3,7,8,10,11,12,13,14,15,18,19]

Date Established	*US*	*JAPAN*	*AUSTRALIA*	*EUROPE*	*CANADA*	*SINGAPORE*
	Jan.4, 1983	1993	Jan. 1., 1998	2000	1996	1991
Funding	Phase 1, II, III under dollar 100,000 per year by donations during 3 years. Phase II, III under $200 000 per year by donations during two years.	Under 50 percent of R&D cost 3% of the companies' incomes distributed to raise funds.	Fee waiver and possible market exclusivity for small companies	DNA	DNA	None
Financial return on products	If cost cannot be recovered	No, rather if drug is marketed, a portion of profits in excess of 100 million yen must be paid to the government	If cost cannot be recovered	If cost cannot be recovered	Cost recovery for drug approvals was introduced through regulation on September 1, 1995. Most Orphan Drugs would qualify for this reduction on the basis of small market size	None
Fee waiver	Yes	No	Yes	At least in parts	Yes	None
Protocol assistance	Provided under the act.	On request	On request	Provided under the regulation	DNA	DNA
Expedited assessment	Shorter in practice	High priority	Priority	Member state specific	Priority review on the basis of therapeutic advantage	DNA
Similar Products	Defined	Not known	As for US	Defined	DNA	DNA
Clinical Superiority	Defined	Not known	As for US	Defined	DNA	DNA
Removal of Orphan status	Yes	Not known	No	Period may be removed from 10 to 6 years, if product sufficient profitable	DNA	DNA
Faster Review	Yes	Yes	Priority given but effect uncertain	Member state specific	Yes	DNA

DNA – *Data not Available*

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orphan medicinal products (COMP) should work under the auspices of W.H.O.

13. W.H.O. can fund various agencies involved in the development of orphan drugs out of the centralized pool.
14. The orphan drugs should be developed at a region specific level and patients living with rare diseases do create patient groups in different parts of the world, regardless the level of economic development of their country or region, rare disease patient groups are managing together into international federations, such as by instance the one for Hemophilia, Cystic fibrosis.
15. Orphan drugs are good pilot project for healthcare innovations and are trendsetter for change in – regulatory framework, patient care & preventive medicines.
16. The tariffs and the excise duties for the orphan drugs in case of poor countries should be reduced to minimum.
17. In case of health care industry there is a need for unification of efforts on all part of the world with empowering W.H.O. as central pool of resources.

    Approval by W.H.O. alone should suffice the purpose for introduction of new orphan drugs all over the world as a special case for avoiding unnecessary delays and to save precious lives.

Conclusion

In case of orphan drugs there is a strong need for unified approach by developed countries such as U.S.A. and EU and developing countries particularly with emerging economies such as India, China, Russia and Brazil under the auspices of W.H.O. for avoiding unnecessary duplication of efforts and resources. Such an approach will also help in reducing the cost and time required for development of orphan drug(s). Immediate steps are needed to empower W.H.O. as an overall authority and centralized pool of resources for speedy development of orphan drugs. Approval by W.H.O. alone should suffice the purpose for introduction of new orphan drugs all over the world as a special case for avoiding unnecessary delays and to save precious lives.

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