ORPHAN DRUGS: NEED OF AN HOUR

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Summary

Orphan drugs have been defined as those drugs intended to treat either a rare disease or a more common disease where the sponsor cannot make any profit. As per the definition US FDA, orphan drugs are those drugs used in diseases or circumstances which occur so infrequently in USA, that there is no reasonable expectation that the cost of developing and making available, a drug for such disease or condition will be recovered from its sales in the USA. This review consolidates current trends and newer technologies and attempts to bring in to focus the changing needs and scope of orphan drugs to boost modern enthusiastic researchers to work more on orphan drugs development.

Keywords: Orphan drug, recent advances, orphan GPCRs, orphan drug act.

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Introduction

Orphan drugs are drugs with demonstrated or potential effectiveness in the diagnosis, prophylaxis, or treatment of an uncommon disease that remain unavailable because of lack of commercial interest on the part of pharmaceutical manufacturers.

These drugs have been termed "orphans" not only because they are not available to most physicians and their patients but also because the research required to permit marketing approval is not conducted, due to lack of financial incentives for manufacturers (1). Orphan drugs have been defined in USA as those drugs intended to treat either a rare disease or a more common disease where the sponsor cannot make any profit (2,3). Rare disease or condition is any disease or condition which affects less than two hundred thousand persons in the United States or affects more than two hundred thousands persons in the United States, but, for which there is no reasonable expectation that the cost of developing and making available, a drug for such disease or condition will be recovered from its sales in US. About two decades ago or so, Alzheimer's or Parkinson's disease were labeled as rare diseases. In geriatric patients, these diseases has become common now and the pharmaceutical industries, with their research and development, have come out with newer drugs and better dosage forms for drug delivery. Thus, the orphan drug shift from its 'orphan drug' status to frequently used drugs with good market potential (2). Table 1 represents classification of orphan drugs based on their commercial potential and availability for marketing (2). This article reviews historical background and discovery of orphan drugs, recent advances from the point of view of orphan drugs and orphan drug act.

Table no. 1: Classification of orphan drug based on commercial potential and availability for marketing.

Categorization of the drug	Description of the drug	Anticipated profit for the new drug
Type 1	Therapeutic orphan with no or little commercial potential	Poor to marginal
Type 2	Therapeutic orphan with commercial potential	Good to excellent
Type 3	Orphan drugs for rare disease that can be currently treated	Variable
Type 4	Unprofitable drug for common Disease	Poor to marginal
Type 5	Orphan drug used for both a rare and common disease	Variable

Historical background and discovery of Orphan Drugs:

The phrase "drugs that wouldn't die" is taken from an article by Weintraub and Northington (4). They described case histories of five unprofitable drugs that were taken off the market, but later were reintroduced as a result of pressure from physicians, patients and other health professionals. Each of these drugs is an orphan, either based on the small size of the disease population or because the drug is unprofitable and only benefits a small segment of patients with a common disease. Some of the potential drugs get killed by over publicity. An example of such a drug is thalidomide, which was initially used indiscriminately and injudiciously. The drug had teratogenic effect, which led to serious adverse effects in large population, particularly children and this was followed by large number of court cases for teratogenicity (2). Discovery to orphan drugs is similar to that of non-orphan drugs i.e. preclinical evaluations and clinical trials. Preclinical activities leading to discovery of orphan drugs include chemical synthesis targeted to find a drug for the treatment of rare diseases, biological testing of compound/molecules in an animal model of a rare disease with the aim of finding a new activity, serendipitously found biological activities in animal studies that suggest a potential clinical usefulness of molecule/compound in treating a rare disease and a new theory proposed to suggest that the lead molecule has activity for a rare disease (2,5). Most common mode of discovery of orphan drug is by serendipitously found clinical activity in patients with a specific rare disease. These patients often have a co-existent rare disease along with the disease for which he/she is being treated and during the course of treatment; it is found to have activity for the rare disease with which the patient is suffering in some other cases, the physicians managing their patients with a rare disease have a personal belief or theory that the drug might be helpful for the treatment of a rare disease and they test the drug and thus some of the drugs for rare diseases or novel indications for humans were found (2,4).

Pharmaceutical Institutes and Orphan Drug Studies (2)**:**

Academic chemist working at a pharmaceutical institute may synthesize compounds targeted towards a rare disease, as a result of scientific and social environment existing at the work place. An academician, who gets grants or financial support for his/her research activities and encouragement from managers and superiors, may develop a drug targeted towards a rare disease. There are certain advantages to academicians for developing drugs for rare diseases. They get public recognition and can publish papers in national and international journals. They may grants for new developments which may further their careers to newer heights.

They may get a chance to participate in preclinical and clinical studies and might also, be able to treat patients more effectively. The only disadvantage is that the clinical practice may take a backseat as physicians devote most of their time to academic research.

Pharmaceutical Industries and Orphan Drug Studies:

Companies are encouraged for research and development work for discovery of drugs intended for the treatment of rare diseases by providing the incentive in term of intellectual property and marketing exclusivity. In USA, granting orphan drug status may enable the sponsor to obtain 50% tax credit on the cost of clinical trials undertaken in USA, seven years of marketing exclusivity following the Marketing Authorization, written recommendations provided by the Food and Drug Administration concerning clinical and preclinical studies to be completed in order to register the new drug, and fast track procedure for the Food and Drug Administration to evaluate registration files (2). The involvement of pharmaceutical companies in the orphan drug development is likely to increase as a result of new regulation schemes. The close collaboration between small biotechnology companies and multinational pharmaceutical companies is increasing. It is expected that a lot of orphan drugs will be discovered by biotechnology companies and be developed in partnership with multinational companies or contract organizations. It is also expected that the orphan drug status will encourage the birth of new small and medium-size companies requiring highly qualified personnel (2,6).

Prevalence of Haarlemi and Beijing types of *Mycobacteriun tuberculosis* strains:

Parissa Farnia *et al*. (2005) identified the spoligopatterns of *Mycobacterium tuberculosis* strains with an international designation responsible for transmission and prevalence of Multi-Drug Resistance (MDR-TB) among native and immigrant population of Tehran (2000-2005). The study highlighted the epidemic potential of Haarlem I and Beijing genotypes among MDR-TB cases in Tehran territory. Multi-drug-resistance was defined as resistance to at least Isoniazid and Rifampicin (7). Non-adherence to therapy and inappropriate prescribing of anti-tuberculosis drugs has been associated with the development of multi-drug-resistant tuberculosis (MDR-TB) (8). However, in several instances, MDR-TB outbreaks were reported to be the results of the spread and transmission of particular strain of *M. tuberculosis* (9).

Using spoligotyping, strains and their variants have been found to belong to particular families (10,11). Case data were collected by trained technicians using standard questionnaires. Information was obtained on sex, age, country of birth, close contact (>8 h contact), previous TB history, present address and associated medical data such as HIV infection, tuberculin skin test and chest radiography finding (7). Primary isolation and culturing of Mycobacterial isolates were performed in accordance to procedures manual (12). Spoligotyping was performed as described by Kamerbeek *et al.* (13) with a commercially available kit, according to the instructions supplied by the manufacturer (Isogen Bioscience B.V., Maarsen, The Netherlands). The results obtained were entered in a binary format as an Excel spreadsheet (Microsoft) and compared with the published data (14-17). Reviewing the patients' questionnaires revealed that the majority of patients had either a previous history of TB (107, 40.6%) or had a close contact (83, 31%). The crowded and poor living condition (196, 74.5%), low-salary (230, 87.4%) and poor access to health services (177, 67.3%) were common factors increasing the risk of TB among native and immigrant population. A total of 27 distinct patterns were observed. Ten unique patterns (orphan patterns) were seen, and the remaining 253 strains were contained within 17 clusters. The result of the study shows that the most frequently occurring super families or clades among MDR-TB cases are Haarlem I (85, 32.3%), Beijing (53, 20%), CAS (32, 12.1%) and EAI (21, 7.9%) (7). The Haarlem I family of M. tuberculosis strains was first isolated from a patient living in Haarlem, The Netherlands (14). Today, its widespread distribution in different geographical regions of the world such as Asia, Europe and Africa has been documented (11,14). In addition, its ability to cause outbreaks has been reported in Argentina (18), in Czech Republic (19) and in Tunisia (11). Another identified super family was Beijing type of M. tuberculosis strains. This family was originally described by Van Soolingen *et al.* (20) in China and is reported to be highly prevalent throughout Asia and in the countries of the former Soviet Union. The results also showed that the East-African Indian (EAI) and Central Asian I (CAS) were the other most frequent super families in both communities (7). Until now, these strain families have been reported in different countries of the Middle East (Iran, Pakistan, and India), Oceanic (Australia), the United States and Europe (16,17). In Europe and Australia, they were regularly found to be linked with immigrants from Central Asia and Middle East (7). The study showed that the orphan strains of *Mycobacterium tuberculosis* have epidemic potential and it caused serious outbreaks. So from epidemiological point it is necessary to conduct extensive surveillance of MDR strains.

Miglustat and Cystic Fibrosis:

Caroline Norez *et al*. studied the rescue of functional delF508-CFTR by miglustat in human and mice epithelial cells. In the disease cystic fibrosis (CF), the most common mutation del508 results in endoplasmic reticulum retention of misfolded CF gene proteins (CFTR). Miglustat is an orally active orphan drug prescribed for the treatment of Gaucher disease (21). Loss of function and/or accumulation of mutant proteins in the endoplasmic reticulum leads to the development of protein misfolding diseases (22). Miglustat is an orally bioavailable orphan drug approved in Europe and USA for use in patients with type I Gaucher disease. According to human studies miglustat is well tolerated at 100 or 300 mg once or three times daily (23). Imino sugar therapy has also been proposed for other diseases (24) like Fabry disease (25). Miglustat rescues partially the abnormal processing of functional delF508-CFTR in human epithelial airway, tracheal gland serous and pancreatic duct cells as well as in the intestinal cells of delF508 mice. The mechanism of action involves, at least in part, the prevention of delF508/calnexin interaction in the endoplasmic reticulum. Because miglustat is a medicament prescribed in another orphan disease, it holds a great promise not only for CF therapy but also for an increasing number of protein-misfolding diseases (21).

Clomiphene Citrate and induction of ovulation:

Amin Rostami-Hodjegan *et al*. studied individual patient characteristics with respect to clomiphene citrate treatment. Clomiphene citrate is an orphan drug (26). Although the drug is the most commonly prescribed treatment for the induction of ovulation, many aspects of its clinical pharmacology remain to be elucidated (27). Normally, clomiphene is given in an oral dose of 50 mg daily for 5 days, starting on day 2-5 of the cycle. If ovulation occurs, this dosage regimen is maintained for 6-12 months or until the patient becomes pregnant. If ovulation has not been induced, the dose is increased by 50 mg each cycle to a maximum of 200-250 mg per day (26). Ineffective drug treatment and exposure of patients to unnecessarily high doses are responsible for a large health care burden. Considerable variability both in pharmacokinetics and pharmacodynamics makes the prediction of individual response difficult. However, pharmacogenetics might help to individualize drug treatment in accordance with the genetic make-up of the patient if the link between drug response and a complex interplay of parameters is well understood. A large number of genetic variants in the enzymes that metabolize drugs and their influence on variable response have been investigated (28).

However, to our knowledge, there have been no studies to investigate such factors in relation to infertility treatment with clomiphene. Although clomiphene is often prescribed to many infertile women all over the world, these patients constitute a small proportion of the overall population. Because the drug is off-patent and is used in a relatively small number of people, it has "orphan drug" status. Inevitably, there is scarcely any support from the pharmaceutical industry to carry out up-to-date studies on this old drug. However, such studies are needed, because it seems that new information on the capacity of individual patients to metabolize clomiphene might accelerate effective clomiphene treatment, reduce the cost involved with multiple clinic visits, and improve the rate of singleton pregnancies (26).

Chemical genetic and orphan genetic diseases:

Mitchell R. Lunn *et al*. studied the recent advances in the chemical genetics and how small-molecule tools can be used to study and treat orphan genetic diseases. Many orphan diseases have been identified that individually affect small numbers of patients but cumulatively affect ~6%–10% of the European and United States populations. Human genetics has become increasingly effective at identifying genetic defects underlying such orphan genetic diseases, but little progress has been made toward understanding the causal molecular pathologies and creating targeted therapies. Chemical genetics, positioned at the interface of chemistry and genetics can be used for elucidation of molecular mechanisms underlying diseases and for drug discovery (29). The pharmaceutical industry, faced with the large costs of drug discovery and development, generally neglects orphan diseases due to the paucity of patients. In 1983, the Orphan Drug Act (ODA) was enacted to promote the development of therapeutics for these orphan diseases by offering incentives to the pharmaceutical industry such as fee waivers, tax credits, and market exclusivity for 7 years (30). Congress reevaluated the rare disease research environment in 2002 and discovered that, in spite of the positive outcomes from the ODA, ''rare diseases and disorders [deserve] greater emphasis in the national biomedical research enterprise'' (31). In response to these conclusions, Congress passed the Rare Diseases Act (RDA) of 2002. The act increased government investment in the development of diagnostic tools and therapeutics for rare diseases by legislatively establishing the Office of Rare Diseases at the National Institutes of Health (NIH) and specifically designating appropriations for the study of rare diseases (31). Many countries have followed the United States model for promoting the discovery and development of therapeutics for orphan diseases. However, the definition of a rare disease varies (Table 2).

Table no. 2: Rare diseases definitions.

Country/Organization	Definition of Rare Disease
Australia	<2,000 Australians
European Community (EC)	<5:10,000 inhabitants
Japan	<4:10,000 Japanese
United States	<200,000 Americans
World Health Organization	0.65-1:1,000 people

With both the ODA and the RDA enacted, academia and industry were financially primed to identify, analyze, optimize, formulate, and market targeted therapeutics for rare diseases. Unfortunately, the scientific community possessed little knowledge about nearly all of these diseases. Recent scientific advances in many fields have, however, improved our knowledge of these diseases and our approach to understanding them. The advent of modern human genetics has revealed that many of the ~6,000 rare diseases are genetic in origin (32). These diseases include Huntington's disease, spinal muscular atrophy (SMA), amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease), Tourette syndrome, Crohn disease, cystic fibrosis, cystinosis, Duchenne muscular dystrophy, thallasemias, hemophilia, and rare cancers, such as sarcomas (29). The fatal pediatric disease spinal muscular atrophy is an example in which successful phenotype-based screens using high-throughput screening technologies have been applied to study of a rare disease. With any rare genetic diseases in human populations, both the political and scientific communities need to embrace the challenge to identify and define therapeutic candidates for disease treatment (29).

Orphan anticancer drug rejected (33)**:**

Trabectedin (ET743 or Yondelis) is an anticancer drug awarded orphan status which is used for third-line treatment of soft tissue sarcomas. The soft tissue sarcoma is a rare and difficult-to-treat cancer. This orphan drug has been denied authorization to be marketed in the EU. Despite showing early promise, several criticisms have been levelled against the drug, which the Committee for Propriety Medicinal Products (CPMP) has now decided are cause to reject the approval application. Jose María Fernández Sousa, Director of PharmaMar, the company developing trabectedin, issued a strong statement of disagreement with the committee's decision. "Trabectedin has demonstrated benefits in terms of response rate, tumour growth control, and overall survival. In addition, its safety profile is

better than that of the two standard drugs, particularly given its lack of cumulative toxicities."

G – Protein Coupled Receptors and Orphan Drugs:

G-protein coupled receptors in human platelets:

Stefan Amisten *et al*. detected several GPCRs not previously known to be expressed in platelets, including a functional adenosine A2B receptor. The findings could improve our understanding of platelet aggregation and provide new targets for drug development (34). The GPCR family comprises the most extensive class of pharmaceutically relevant target molecules, and more than 30% of the total drugs including orphan drugs on the market target GPCRs (35). An improved method for platelet mRNA purification, requiring smaller blood volumes and shorter processing times was used to generate a gene expression profile for human platelet G-protein coupled receptors (GPCRs). Using microarray screening verified with Real-Time Polymerase Chain Reaction (RT-PCR) mRNA expression of 28 GPCRs was found. Fourteen of these GPCRs are not previously known to be expressed in platelets. Among them the adenosine A_{2B}-receptor was further examined and confirmed to be expressed at the protein level and to be of functional importance. The HG-U133 microarray contains 331 non-olfactory GPCRs. 46 GPCRs were detected in the microarray hybridizations and RT-PCR with sequencing of the product confirmed the presence of 28 GPCRs in circulating platelets. The fact that only 28 (60.9%) of the 46 GPCRs could be verified by RT-PCR, stresses the need for validation of data obtained through microarray hybridizations. An improved method for platelet purification was used in combination with microarray hybridization and Quantitative RT-PCR (Q-RT-PCR) to identify several previously unknown G-protein coupled receptors expressed in circulating platelets: among them five orphan GPCRs and a functional adenosine A_{2B} receptor. Furthermore, an interesting pattern of receptor redundancy was observed, with several GPCRs having affinity for the same ligand (34). The functional importance of the previously undetected receptors will need to be addressed in future studies.

Zaprinast as an agonist for GPR35:

In other studies, Yasuhito Taniguchi *et al*. found that zaprinast, a well-known cyclic guanosine monophosphate-specific phosphodiesterase inhibitor, acted as an agonist for a G protein-coupled receptor, GPR35 (36). The G protein-coupled receptors (GPCRs) are a large family of cell surface receptors that account for over

30% of current drug targets (37). Sequencing of the human genome has led to the discovery of novel GPCRs, and many of them are orphan receptors for which the natural ligands have not yet been identified. To determine the biological functions of these orphan GPCRs, identification of their natural ligands is the first step. However, despite extensive attempts at receptor–ligand pairing, a number of GPCRs are still orphan receptors (36). GPR35 (38) is one of these orphan GPCRs. Although chromosomal mapping and the expression of GPR35 in a number of human tissues have been investigated in previous studies (38-40), little is known about this receptor. The observations obtained in this study strongly suggest that zaprinast acts as an agonist for GPR35.

Roles of the apelin system (41)**:**

Dennis K. Lee *et al*. previously reported the roles of the apelin system. The apelin receptor was initially classed as an orphan G-protein-coupled receptor, and little was known about its physiological functions until apelin, the endogenous ligand, was identified. Now, roles have been established for the apelin system in lowering blood pressure, as a potent cardiac inotrope, in modulating pituitary hormone release and food and water intake, in stress activation, and as a novel adipokine that is excreted from fat cells and regulates insulin. Given its broad array of physiological roles, apelin has attracted much interest as a target for novel therapeutic research and drug design. Already, we have insight into the physiological significance of this system, which details roles in blood-pressure modulation, regulation of the adipoinsular axis, stress, hypothalamic regulation of adrenal hormones, food intake, water balance, thermoregulation, and as one of the most potent endogenous cardiac inotropes. With these and future discoveries, apelin and its receptor provide attractive targets for the development of novel therapeutic compounds and excellent examples of the therapeutic potential of orphan GPCRs.

Orphan Drug Act (1)**:**

The pharmaceutical industry has, over the years, provided a considerable number of therapeutic and diagnostic agents as a public service for patients with rare diseases. In many cases, all or most of the research leading to development of these agents was conducted by investigators under Government or private grants. This, of course, does not lessen the contributions of drug companies in seeking marketing licenses, developing finished dosage forms, and distributing the products. In some cases, drug companies have performed a considerable amount of research themselves. Understandably, they cannot be expected to divert much of their

resources away from the study of drugs for common diseases. Therefore, all groups that investigated the orphan drug problem concluded that special incentives were needed to stimulate research on and development of these drugs. Such incentives are provided, to a considerable degree, by the Orphan Drug Act. The act was signed into law by the President on Jan. 4, 1983. An earlier version had been introduced in the Congress by former Representative Elizabeth Holtzman. The present act was passed largely through the efforts of Representative Henry A. Waxman, Chairman of the House Subcommittee on Health and the Environment.

Provisions of the orphan drug act (1)**:**

The act defines an orphan drug as a drug or biologic intended for a disease or condition which occurs so infrequently in the United States that there is no reasonable expectation that the cost of developing the drug and making it available will be recovered from sales in the United States. Examples of rare diseases given in the act include Huntington's disease, amyotrophic lateral sclerosis, Tourette syndrome, and muscular dystrophy. Among these examples, the disorder with the highest prevalence is Tourette syndrome, with an estimated prevalence in the United States, for the full-blown syndrome, of 100,000 patients. The Orphan Drug Act provides four incentives for drug companies:

1. A tax credit of 50 percent for the expenses of the clinical trials performed prior to marketing approval. This credit, together with the normal deduction for the remainder of the clinical expenses, amounts to about 73 cents' return per dollar spent. The tax credit is permitted only for clinical testing conducted in the United States unless there is an insufficient testing population in this country.
2. A 7-year exclusive marketing license for unpatentable drugs. During this period, the Food and Drug Administration (FDA) cannot approve another marketing application for the same drug for the same orphan use. The exclusivity applies only to the specific orphan indication. If another firm develops the same drug for a common-disease indication or for a different orphan indication, approval will also be granted to that firm. It should be noted that exclusivity continues only so long as the firm can supply the needs of the US population with the orphan disease. Should a firm charge a high price unjustified by the costs of development, so that few patients can afford the drug, or, in the case of a complex biological, should a firm be unable to manufacture enough of the product, then approval will be granted to other manufacturers.
3. Protocol assistance: Under this provision, the FDA must provide, on request, written advice to a sponsor of an orphan drug on the studies (animal and clinical) needed for marketing approval.

4. Grants and contracts: The act permits the Congress to appropriate $4 million per year for grants or contracts to support clinical trials of orphan drugs. The act authorizes such appropriations only for fiscal years 1983-85. The grants and contracts may be awarded to private entities or individuals.

Discussion

Rare diseases and orphan drugs have been boons to applied pharmaceutical research. It stimulated tremendous growth of biotech industry. A recent study by the Tufts Center for the Study of Drug Development found that from 1983 to 1992 the biotech industry secured 19 percent of all orphan drug approvals; 76 percent of such approvals went to pharmaceutical companies. By 2001 biotech's share had grown to 41 percent. Of the 10 best-selling biotech drugs worldwide in 2001, five were originally approved as orphan drugs, and three more were approved for orphan indications in addition to their original use. The orphan indication afforded their developers seven years of marketing exclusivity. Indeed, the biggest moneymaking orphan products helped to launch some of the major players in the biotech industry, including Amgen and Genentech. Sometimes, orphan drugs are so costly, that many patients, who need to buy them, go bankrupt. One such example is Cerezyme of Genzyme. The drug which is an enzyme-replacement therapy for Gaucher disease, is the world's most expensive medicine. Still, most companies that produce orphan drugs have formal or informal programs for providing drugs free to indigent patients, but they hardly ever make public the number of patients they accommodate or what such patients must do to qualify. In the end, the high cost of orphan drugs probably has to be addressed as part of the bigger problem of high drug costs in general. The FDA itself is in no position to insist that costs come down for orphan drugs or any others. It has no authority over pricing.

Orphan drugs can be potential source of profit. In 1988 Lars-Uno Larsson, a former Bristol-Myers Squibb executive, founded Swedish Orphan International in Stockholm. According to him, the Orphan Drug Act made it possible to earn modest but sufficient returns on drugs for rare diseases. Now with affiliates around the world, Swedish Orphan has developed a number of products and inspired others to establish similar companies. According to John Bullion, a former venture capitalist and now the CEO of Orphan Medical, a Minnesota-based company with half a dozen approved orphan products, you can make very good money with a $10-million product, (orphan drug product) but you need several of them (2). With a concerted effort, academics, nonprofit organizations, and industrial groups can

work together to develop the equipment, technologies, and assays needed for investigating orphan drugs.

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