Review Article

Review on Orphan Drugs

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ABSTRACT

This paper surrounds innovation as socially constructed and posits a model for innovation policy based on Mode 2 knowledge production (Gibbons et al 1984), where scientific peer review is replaced by merit review demanded by accountability to a wider social, economic and political sphere. The paper looks at scientific research into rare diseases and the strategies being adopted by biotechnology companies. The paper then introduces the EU Orphan Drug Regulation (2000) and raises concerns about the pharmaceutical industries' use of publicly funded research and patent protection. Other barriers to patients actually receiving new treatments, even if they get as far as production, are raised in the final section.

Keywords: Innovation, rare diseases, patents, Mode 2, orphan drug[1].

INTRODUCTION

An orphan drug is a pharmaceutical agent that has been developed specifically to treat a rare medical condition, the condition itself being referred to as an orphan disease. In the US and EU it is easier to gain marketing approval for an orphan drug, and there may be other financial incentives, such as extended exclusivity periods, all intended to encourage the development of drugs which might otherwise lack a sufficient profit motive. The assignment of orphan status to a disease and to any drugs developed to treat it is a matter of public policy in many countries, and has resulted in medical breakthroughs that may not have otherwise been achieved due to the economics of drug research and development.

An orphan or rare disease may be defined, in United States of America (USA), one that affects less than 200,000 people in the US or one that affects greater than 200,000 people but for which there is no expectation that the cost of the development of the drug and making it available will be recovered from sales of that drug to poor affected population[1].The orphan diseases, affect only a small numbers of people, are generally neglected by doctors viz Fabry's disease, alveolar echinococcosis, variant renal cancer, high myopia, endometrial cancer and tobacco addiction[2]. The designation of orphan disease varies in different countries depending upon the ratios viz. EU: 5 per 10,000 individuals, USA: 7.5 per 10,000 individuals, Japan: 4 per 10,000 individuals, Australia: 1 per 10,000 individuals[3]. Almost 5,000 to 8,000 distinct rare diseases (Table 1) exist today, affecting 6% to 8% of the population in the European Union. Symptoms of some rare diseases may appear at birth or in childhood, including infantile spinal muscular atrophy, lysosomal storage disorders, patent ductus arteriosus (PDA), familial adenomatous polyposis (FAP) and cystic fibrosis. A few rare diseases are the result of infections (bacterial or viral) and allergies, or are due to degenerative and proliferative causes. Medical and scientific knowledge about such is lacking. Every week approximately five new diseases are explained in the medical literature[2].

Table 1: List of some orphan diseases[2]

Acrocephalosynylia	Acrodermatitis	Budd-Chiari Syndrome	Behcet Syndrome
Addison Disease	Adie Syndrome	Carcinoma256, Walker	Bowen's Disease
Alagille Syndrome	Amylose	Charcot-MarieTooth Disease	Brown-Sequard Syndrome
AmyotrophLateral Sclerosis	Angelman Syndrome	Chiari-Frommel Syndrome	Burkitt Lymphoma
Angiolymphoid HyperplasiawithEosinophilia	Arnold-Chiari Malformation	ColonicPseudo Obstruction	Caroli Disease
Arthritis,Juvenile Rheumatoid	Asperger Syndrome	Craniofacial Dysostosis	Chediak-Higashi Syndrome

What Is the Size and Nature of Disease Burden?

Patients with a rare disease may suffer significantly from many complaints over a long period of time and may have a low quality of life. Unfortunately there are not many epidemiological data and data on the burden of disease recorded for rare diseases due to several factors. Examples of rare diseases are discussed to give an impression of the burden of disease for patients. Factors like lack of information, lack of knowledge on natural history, lack of (early) diagnosis, lack of appropriate medical care, absence of pharmacological interventions or under use of medication will have an important impact on the burden of many rare diseases in future. Likely future factors that have an impact on burden of disease. There are many factors that currently have an impact on the burden of disease and will likely also have an impact in future[3].

Lack of knowledge and training

About 1300 rare diseases are medically well described. All other rare diseases do not have an appropriate medical description. Medical doctors are not trained in rare diseases and lack experience. General practitioners and medical doctors do not know and cannot be expected to know the symptoms of the many rare disorders. However, they need to develop a sense of urgency that the specific patient with the unfamiliar symptoms and complaints should be referred to a specialist.

Lack of information

Dissemination of information is a key issue in the field of rare diseases. Without information diagnosis and treatment cannot be improved, research will not continue, the patients are not empowered and there is no right usage of clinical resources. The lack of information was an important reason for the development of the EU community action programme on rare diseases (1999-2003).

Diagnosis

Important factors that contribute to the burden of disease of rare disorders are issues on diagnosis. For several genetic diseases the diagnosis can be made via enzymological methods or molecular biology tools. However, for many of these diseases no diagnostic tools exist due to a lack of research on the cause of these diseases. In these cases the diagnosis may be only clinical. Ancillary investigations are then used to exclude other diseases. The absence of a diagnosis or late diagnosis may lead to an unnecessary deterioration of the patient's condition. The time period between the first symptoms of a patient and the final diagnosis varies enormously. In a study, in which 44 Dutch patient associations representing at least 600 rare diseases filled in a questionnaire, it appeared that the diagnosis of the diseases was made in 27% of the cases within 3 months. This time period was partly due to the fact that babies died very soon after they were born. In 38% of the cases diagnosis took more than 2 years. A medical specialist in 70% of the cases made the diagnosis.23 In another study of the Genetic Interest Group (UK) representing 600 families with a genetic rare disease it was indicated that 75% of the diagnoses took on average 6 months. In 30% of the cases diagnosis took more than 2 years and in 15% more than 6 years.23 It was mentioned that the diagnosis of a patient with neurofibromatosis even took 15 years.24 In a Danish study with 100 patients with a specific form of neurofibromatosis (also called Von Recklinghausen disease) it appeared that the diagnosis took on average 20 years(!).25 Although Von Recklinghausen disease is characterized by a very wide variability of its clinical expression, a doctor well acquainted with the disease can diagnose the majority of patients after physical examination. The wide variation of the clinical expression, the tumour risks and the totally unpredictable evolution of the disease require regular monitoring of NF1 patients. Therefore early diagnosis is important. In a study from EURORDIS (EurordisCare®) several aspects concerning diagnosis were compared for six rare diseases in seventeen European countries.26 Screening methods (prenatal and preimplantation), delay between disease presentation and confirmative diagnosis and availability of diagnosis centres for Crohn's disease, cystic fibrosis, Duchenne muscular dystrophy, Marfan syndrome, Prader Willi syndrome and tuberous sclerosis were considered. A North-south gradient was seen revealing a higher density of screening centres in southern Europe. Significant delays between initial symptoms and confirmative diagnosis were noted. These delays vary from one disease to another but also from one country to another. For example the diagnosis for Prader-Willi syndrome was much more rapid in Austria (within weeks) than in France (from some weeks up to 10 years). The main problems underlying such a late diagnosis are due to ignorance of the physician, absence of centres of expertise, unavailability of techniques for diagnosis and/or no insight in the natural history of the disease. Recently a

high-level, independent Expert Group, which had been invited by the European commission to discuss a number of issues relating to human medical genetic testing has recommended among others that an EU-wide network for diagnostic testing of rare genetic diseases be created and financially supported as a matter of urgency. Furthermore they recommend that an EU-level incentive system for the systematic development of genetic tests for rare diseases be created and that EU member states introduce universal neonatal screening as a priority for rare but serious diseases for which treatment is the effects of (early) diagnosis are nicely illustrated with the rare disease PKU. Classical phenylketonuria (PKU) is an inherited metabolic disease that is characterized by an inability of the body to utilize the essential amino acid, phenylalanine. This is due to a deficiency of the enzyme phenylalanine hydroxylase. This enzyme normally converts phenylalanine to another amino acid tyrosine. Without this enzyme, phenylalanine and other biochemical products accumulate in the blood and body tissues. Through a mechanism that is not well understood, the excess phenylalanine is toxic to the central nervous system. This results in mental retardation and other neurological problems when treatment is not started within the first few weeks of life. When a very strict diet is begun early and is well-maintained, affected children can expect normal development and a normal life span.18 Because of the very positive outcome when children are treated early and well, newborn screening for PKU is carried out in most developed countries. The incidence of PKU in Europe is about 1 in 12,000. Prevention of the burden of disease of this disease has been seen as being that important that PKU has been included in screening programs of several countries to be sure that early diagnosis can lead to early intervention.

Disease management

Disease management of rare diseases can be divided as follows. For several (mono) genetic rare diseases prenatal and/or neonatal screening is possible.40 Prenatal screening is performed in clinical genetic centers or in other referral centers in many cases. The result of a prenatal screening test may ultimately lead to an abortion. Newborns are screened for certain metabolic defects in many countries. In this way early diagnosis of the defect can lead to early intervention, e.g. for PKU. In some ethnic groups (monogenetic) rare diseases are more frequent. This may also be caused by consanguineous marriages. Voluntary carrier screening programs for several rare disorders may be offered for couples to be informed as to whether they have a chance of getting an affected baby with a rare disease. Although prenatal and neonatal screening of rare inherited disorders is very important as a control strategy, several of those disorders do not present until the first one or two years of life (e.g. hemoglobin disorders, cystic fibrosis, lysosomal storage disorders). Thus studies that include follow-up from birth are needed to diagnose these diseases at an early stage to be able to prevent as much burden of disease as possible. For several specific diseases, like hemophilia, Gaucher disease and Pompe disease. There are centers of expertise in several regions in the world. Where the natural course of a rare disease may be followed, medical care may be improved, medication may be adjusted, possibilities of cost-effective treatment may be investigated and data may be collected. Several centres of expertise may have contacts all over Europe (and outside Europe) to discuss their data on a specific disease. Unfortunately for many rare diseases these centres are not present. This may be due to shortage of financial resources or lack of interest from researchers and/or clinicians. In some EU countries there are also national or regional centres who have specialised in cure and/or care for rare diseases in general, e.g. the Clinical Research Center for Rare Diseases ‘Aldo e Cele Daccò’ in Italy, the Center for Små Handicapgrupper in Denmark, Frambu in Norway and the Ågrenska Centre for Rare Disorders in Sweden. In the USA eight rare diseases clinical research networks were established recently. Information to patients and physicians is still a crucial issue in rare disease management. Basic knowledge about diseases, list of available drugs, lists of specialists or consultants specialized in a given disease, are still not widely available in the world. However, information in EU and USA is growing due to several organizations, like NORD, FDA, EMEA, ORPHANET and EURORDIS. Some of these efforts have been paid for via the European Framework programme and the Community Action on rare Diseases.

Table 2: Classification of orphan drugs[4]

Type	Detail	Expected profits	Available medication
I	Little / no commercial benefit	Poor	Inadequate
II	Commercial benefit	Good to excellent	Inadequate
III	For rare disease that can currently be treated	Variable	Adequate
IV	Unprofitable for a common disease	Poor	Inadequate
V	Orphan for both rare and common disease	Variable	Variable

European regulation defines orphan medicinal products as those for which it can be established that either intended for the diagnosis, prevention or treatment of a life-threatening or chronically unbearable condition affecting not more than five out of ten thousand people; or intended for the diagnosis, prevention or treatment of a life-threatening, seriously unbearable or serious and chronic condition and that, without incentives, they are unlikely to generate sufficient revenues to justify the necessary investments. Orphan drugs are defined as drugs intended to treat either a rare disease or a widespread disease where manufacturer cannot expect to make profits. Drugs and vaccine for tropical diseases are orphan drugs because patient sufferings from these diseases, although numbering tens of millions, are too poor to pay the price of medications. Vaccines are virtual orphans and also called economic orphans. The number of vaccines introduced in the market has decreased drastically in the recent years. The growth hormone (GH), earlier obtained from corpses, manufactured by recombinant technology is still classified as orphan drug in USA. The Orphan Drug Act USA defines an orphan drug as a drug or biological product for the diagnosis, treatment, or prevention of a rare disease or condition. Orphan drugs available to treat rare diseases are a heterogenous group. Table 2 represents a classification of five categories of orphan drugs based on their commercial potential and the availability of adequate treatment. Numbers of drugs have crossed from the type1 to type III categories over the period. These include Wilson's disease, which can be treated now a days with penicillamine, zinc & triethylenetetramine and rare bacterial diseases that can be treated with antimicrobials. Type I and III orphan drugs are usually the most difficult ones to find sponsors for if the drugs are known to have activity but are yet not marketed. These drugs can become profitable type V drugs if found to be effective in treating a common disease.

PURPOSE

The purpose of this inspection was to assess the implementation of the Orphan Drug Act of 1983 and its impact on industry and patients[5].

BACKGROUND

The increased focus on rare diseases started in part because of the stimulus provided by the Orphan Drug Act (ODA) in the U.S. and similar Acts in other regions of the world. These Acts, coupled with high-profile philanthropic funding, shone a new light on orphan diseases and encouraged investment in R&D for a number of these debilitating conditions. As scientific understanding of rare diseases improves, the pharmaceutical industry is undergoing a transformative approach to drug therapy .The Thomson Reuters analysis shows that orphan drugs address a high unmet medical need and so benefit from a pricing structure that makes them commercially attractive to pharmaceutical companies. Case in point, the orphan oncology drug Rituxan (generic: Rituximab) is the world's second most profitable drug, just behind mainstream blockbuster Lipitor (generic as of November 2011), and is expected to garner more than $150 billion in revenue over its lifetime, the majority of which is for orphan indications. Current estimates from the National Institutes of Health and the European Organization for Rare Diseases indicate that there are approximately 7,000 rare diseases worldwide and that the recognized number of such diseases rises at the rate of approximately 250 per annum. Although each disease may only affect a small group, ranging from a handful up to 200,000 patients, collectively they affect tens of millions of people in North America alone. A shared, global desire to address the unmet treatment needs of rare diseases led to the 1983 U.S. Orphan Drug Act, as well as similar Acts in 1991 in Singapore, 1993 in Japan, 1997 in Australia and in 2000 by the European Union. These Acts stimulated orphan drug research around the world, offering pharmaceutical companies potentially profitable incentives to focus on rare diseases. The last decade has been the most productive period in orphan drug development, both in designations and approvals. This period of tremendous growth has also coincided with an increased focus on precision medicine. Orphan drugs are targeted at diseases of very high unmet medical need and therefore can receive rapid approval and high levels of

reimbursement. As the data from Thomson Reuters suggests, this can make them commercially attractive for pharmaceutical companies. Through careful analysis of the economics and investment case for orphan drug development and commercialization, this report shows that while orphan drugs target much smaller populations than traditional mainstream drugs, the high cost of therapy and attractive developmental drivers, such as government incentives, smaller and shorter clinical trials, extended exclusivity and high rates of regulatory success, have made top orphan drugs as equally viable as their non-orphan peers[6].

METHODOLOGY

We reviewed a database from FDA that contains information on all designations and approvals from 1983 to 2000. We interviewed regulatory affairs staff and other representatives from a purposeful sample of 36 biotechnology and pharmaceutical companies. We focused on companies that received multiple orphan designations. We also interviewed representatives from 37 patient advocacy groups, stratified into two groups--those for which orphan products were in development or on the market and those for which no orphan products were in development or on the market. We conducted a *Orphan Drug Regulations* . December 29, 1992 and 21 CFR Part 316 et seq. The FDA defined three criteria for establishing clinical superiority. Focus group with FDA staff and consulted with drug policy experts and representatives from trade groups. We also reviewed relevant literature. We conducted this inspection in accordance with the *Quality Standards for Inspections* issued by the President's Council on Integrity and Efficiency.

The U.S. Orphan Drug Act (1983)

Patient groups, without effective treatments for their conditions, provided the impetus for the formation of the National Organisation for Rare Disorders (NORD) which, with the help of the media, lobbied the Federal government to assist in the development of treatments for rare diseases. This culminated in the passage of the US Orphan Drug Act of 1983 (see Crompton 2001). There appears to be an unanswered question as to whether the Act encourages innovation and if so, at what cost (Rhode, 2000). Pharmaceutical companies follow the economic model based on the law of supply and demand (Rohde, 2000), focusing resources on the largest markets in order to achieve the greatest returns. Even if there was an indication that a compound could be used in a treatment for an orphan disease it was difficult to find a company that would take the research forward due to the cost of clinical trials and production. The mass marketplace became the driver of innovation in product development (Rohde, 2000). Recognising that unless incentives were provided the market would continue to operate on the economic model US sufferers of minority diseases used the power of mass lobbying and the media in pushing the Act, with its economic and regulatory incentives, through Congress. The passage of the Act was opposed by the pharmaceutical industry, which preferred a relaxing of FDA approval to more legislation. The Act was opposed by the US tax department, due to the potential costs of tax credits (Crompton 2001). However the Act was passed at the final hour. The Act, upon FDA approval of an orphan drug designation, allows a tax credit of up to 50% of clinical trials with assistance in protocol design (especially useful to SMEs), government grants and contracts for clinical trials and an exclusive marketing right of seven years from the date of FDA marketing approval. These incentives were intended to encourage innovation and are particularly attractive in chronic disease R&D, as drug provision will be long-term providing a steady income stream. Concerns have been raised about abuse of the system and that private industry has profited by public research, thereby making the public pay twice – once for the research and again for what is perceived to be an overpriced product. Changes in policy and many debates about possible changes to the OD Act have created uncertainty in the industry as to whether, after perhaps years of development, the rules may change. This uncertainty may retard development: 16 'It is ironic that the very process of looking for a way to curb abuses in a statute designed to foster innovation, could deter that innovation.'(Rhode, 2000, p.138).

The EU Orphan Drug Regulation (2000)

The US Orphan Drug Act (1983) with its incentives, both financial and regulatory, has led to 837 medicinal products being awarded orphan drug status. At the end of 1997, 152 orphan products had obtained marketing approval. These products are now being used by over eight million patients (Reider, 2000). The 1983 Act is widely regarded as one of the most successful pieces of health-related legislation enacted so far in the USA, fostering the creation and growth of many small to medium sized biotechnology companies. These successes could potentially be repeated in the UK under the European

Orphan Drug Regulation which became fully operational in May 2000 under pressure from the EU Parliament (Torrent-Farnell, 2001). The regulation provides incentives for drug manufacturers to invest in orphan drug R&D. Regulation 847/2000 stipulates the rules under which orphan drug status may be given in order to receive these incentives. Compliance to these rules requires detailed documentation and solid scientific evidence, ergo non-contradictory to known scientific understanding. For example applicants have to prove a product is: 'Intended for the diagnosis, prevention or treatment of a life threatening or chronically debilitating condition affecting not more than 5:10,000 persons.' Further proof is required that, without the Orphan Drug incentives, a product would be unlikely to generate sufficient returns to justify R&D and marketing investments. A comparison of the OD legislations of the EU, US, Japan and Australia.

Table 3: National orphan drug regulations

Country code	EU	US	Japan
Year	2000	1983	1993
Prevalence per 10,000	<5	<7.5	<4.2
Protocol Assistance	80% Reduction	Yes	Yes
Fees Waiver	50% Reduction	Yes	c35% reduction
Market Exclusivity	10*	7	10
Research Grant	No**	Yes-FDA	Max 50% p.a.#
Tax credit	Up to Member State	50%	% decided by KIKO

* This may be reduced to 6 years if OD criteria is no longer met, or OD becomes excessively profitable. There are no grants available from EMEA or COMP but economic help is available from Member states or EU institutions (e.g. VIth Framework Programme). # This is subject to part repayment if sales reach more than 100m Yen? Australia is presently reviewing its OD procedures so these may change – results expected July 2002.

Adapted from Management Forum (2001)

The costs of developing medicinal products for the treatment of rare (orphan) diseases are disproportionately high in relation to the volume of products likely to be sold, since there are few sufferers needing treatment. However the costs of developing drugs is disputed. The R&D strategies of the large UK pharmaceutical companies appear to be driven by the 'big hits' (such as cancer and heart disease) and do not include orphan drug or rare disease research, due to a perceived lack of potential profit (Crompton 2001). Some research is already funded by member states, through public research laboratories and academic institutions, complemented by charities. 'The challenge of rare diseases is great because it's an area that few actors have paid attention to, either from a discovery point of view or development process' Andrea Rappagliosi: VP Health Policy and Government Relations, Serono International (2000) EPPOSI (2000). However this funding is not enough to pay for the clinical trials, manufacturing, patent, marketing and regulatory costs necessary to make therapies available for rare diseases. It normally requires the resources of the pharmaceutical and biotechnology industry, with the added backing of venture capitalists (in some cases) to take promising projects forward. There was a firm commitment by the European Commission that patients suffering from rare diseases should be entitled to the same quality (of safety and efficacy) as other patients in the EU, hence the high scientific and ethical standards of the Regulation. Patient representation, in a new patient driven approach, was deemed paramount and patient representatives were included in a continuous dialogue with all other interested parties. One of the aims of the regulation was to boost research, development and innovation in novel drug developments, with particular attention to emerging biotechnology derived products (Torrent- Farnell, 2001).

AUSTRALIAN ORPHAN DRUGS ACT

The Australian orphan drugs policy was set up in 1997. This orphan drugs program aims to ensure the availability of a greater range of treatments for rare diseases and allows the Australian Therapeutic Goods Administration (TGA) to use information from the US Food and Drug Administration (FDA) Orphan Drugs Program as part of the Australian evaluation process. To be eligible for designation as an orphan drug the product must not have been rejected on safety grounds by the TGA, the Food and Drug Administration of the United States of America (FDA), the Medicines and Healthcare Products Regulatory Agency of the United Kingdom (MHRA), the Therapeutic Products Directorate of Canada (TPD), the Medical Products Agency of Sweden (MPA), the Medicines Evaluation Board of the Netherlands (MEB) or the European Medicines Agency (EMEA) for use for the disease in

question. Orphan designation is intended for drugs which aim to treat diseases with a prevalence of 2000 patients or less in the Australian population (18 million)/ a maximal of twelve to per ten thousand. Another alternative criterion which leads to orphan designation consists in combining the fact that the drug is not commercially available, when used in the patient population it is indicated for. Once orphan designation is granted, the TGA waives the evaluation fees, thus removing a major obstacle to making these crucial drugs available. A distinct evaluation pathway for processing orphan drugs is also set up. One of the programme's important purposes is the possibility of making drugs available to treat leprosy and trachoma which affect the aboriginal population. The main characteristic of the Australian Orphan Drugs Program is that it is based upon a close collaboration of the TGA with the US FDA. The Australian programme takes into account the FDA's orphan drugs evaluations. Additional criteria are also established for identifying and evaluating orphan drugs in Australia which have not been evaluated in the USA or do not meet the US criteria. The main characteristics of the orphan drug policy in Australia are: A legal framework for orphan drug designation; Waiver of application and evaluation and no annual registration fees; Five-year exclusivity.

Table 4: Some orphan designated drugs across Australia in year 2010

Afamelanotide	***Ex vivo* cultured adult human mesenchymal stem cells**	**Romidepsin**
Bosentan	Human hepatitis B immunoglobulin	Sunitinib malate
C 1 esterase inhibitor	Immunoglobulin - antithymocyte (rabbit)	Tadalafil
Catumaxomab	Mycophenolic acid	Terlipressin acetate
Duodopa (levodopa/carbidopa)	Octreotide	Tobramycin
Everolimus	Peginterferon alfa-2b and ribavirin	Vandetanib

EUROPEAN ORPHAN DRUG ACT

Efforts have been jointly made at national and European levels by industry and health authority, European Medicines Evaluation Agency (EMEA), in order to offer the incentives required to stimulate the development of orphan drugs. The goal was to rapidly make available for rare diseases, drugs with a level of quality equivalent to that required for any other drug. A policy was implemented much later I Europe than in the USA. The reason lies mainly in the fact that its territory is split-up and its competencies as regard to health are scattered. Since 1 January 1995, with the new system of EU marketing authorisation that is valid for the whole territory and the free circulation that goes with it, Europe can be considered now as a territory with a population of about 377 million inhabitants that is a population greater than that of the United States where a common regulation is enforced. On 16 December 1999, the European Parliament and the Council adopted regulation (CE) No. 141/2000 on orphan drugs. The goals were to encourage the pharmaceutical and biotechnological industry to develop and market orphan drugs, create a Committee of Orphan Medicinal Products (COMP) within the European Medicines Evaluation Agency (EMEA). This committee is responsible for studying the applications for orphan designation and to advise and assist the Commission in discussions on orphan drugs. The COMP consists of persons appointed by the European Member States, and 3 are appointed by the European Commission to liaise with the Committee of Propriety Medicinal Products (CPMP) responsible for scientific evaluation of medicinal products within EMEA as well as three representatives of patient associations. The participation of patient representatives in the COMP has been very positive for the process of developing therapies for rare diseases in Europe. Companies with an orphan designation for a medicinal product benefit from incentives such as: Protocol assistance (scientific advice for orphan medicines during the product development phase) Direct access to centralised marketing authorisation 10-year marketing exclusivity Financial incentives (fee reductions or exemptions) National incentives detailed in an inventory made available by the European Commission. Since 1 February 2009, orphan medicinal products are eligible for the following level of fee reductions: Full reduction for protocol assistance and follow-up Full reduction for pre-authorisation inspections, 50% reduction for new applications for marketing authorisation to applicants other than small and medium-sized enterprises; Full reduction for new applications for marketing authorisation only to small and medium-sized enterprises; Full reduction for post

authorisation activities including annual fees only to small and medium sized enterprises in the first year after granting a marketing authorization. According to European regulation No. 141/2000, only drugs for human use can be designated as orphan drugs. Therefore it does not concern veterinary medicines, medical devices, nutritional supplements and dietary products. Drugs designated as orphan are entered in the Community register for Orphan Medicinal Product.

Availability of orphan drugs in Europe:
The granting of marketing approval does not mean the drug is available throughout all the European countries. The marketing approval holder must decide in advance on its commercial status within every country and the drug will then go through numerous steps in each country in order to condition its management. Drugs which are exclusively used in hospitals are, following positive mention by the Commission, registered on the list of admitted products for the community. They price nothing. Despite joint efforts, the heterogeneous approaches among countries make patients access to orphan drugs more complex. Several orphan drug designation have been given for rare diseases (Table 5 shows a few among that) since the regulations framed in Europe and entered in Community register for Orphan Medicinal Products.

Table 5: Few Orphan diseases for which the orphan products designated in Europe during 2010

Hepatocellular Carcinoma	Primary Myelofibrosis	Cystic Fibrosis
Acute Myeloid Leukaemia	Post-Essentia Thrombocytha Myelofibrosis	PrimaryBiliary Cirrhosis
Ovarian Cancer	Medulloblastoa	Glioma
MantleCell Lymphoma	Idiopathic Pulmonary Fibrosis	Low-Flow Priapism
Acute Myeloid Leukaemia	Perinatal Asphyxia	Rhodopsin-Linked Retinitis Pigmentosa
Post-Polycythaemia Vera Myelofibrosis	Acute MyeloiLeukamia	Mucopolysaccharidosis, Type IIIA (Sanfilippo A Syndrome)

ORPHAN DRUG ACT IN INDIAN PERSPECTIVE

The established and developed countries have captures the importance of orphan drug regulation offering several incentives along with fast approval process for the pharmaceutical manufacturers. The developing countries like India would be affected a lot during third world war with rare disease. Need for such an act is evident, initiative from the Indian Pharmacists and the Government to implement such Laws would strengthen the health infrastructure, manufacturers and provide relief to the numerous rare disease sufferers across the country. A group of pharmacologists at a conference held by the Indian Drugs Manufactures Association (IDMA) in 2001, requested the Indian Government to establish the Orphan Drug Act in India. If such legislation could be implemented, it will be a benefit not only to pharmaceutical and biotechnological Industry but will also bring relief to the unlisted very possibly large groups of rare disease sufferers, in the country. The national orphan drug regulation should offer lucrative incentive, economic outcome and market exclusivity rights to the rare drug manufacturer to enjoy the reasonable profit and interest for investment in the R&D of rare drugs.

Examples of rare diseases
Several rare diseases are actually known to the general public. Examples of more known rare diseases are cystic fibrosis, sarcoidosis, haemophilia, phenylketonuria (PKU) and severe acute respiratory syndrome (SARS). Examples of general unknown disorders are e.g. primary ciliary dyskinesia, Darier disease, erythropoietic protoporphyria, Smith-Lemli-Opitz syndrome, Usher syndrome and alkaptonuria. Sometimes, rare diseases are especially frequent within a region or within a specific ethnic group. For example thalassaemia is rare in Northern Europe and more frequent in the Mediterranean area. Gaucher disease is more frequent within the Ashkenazi Jewish population (with a carrier frequency of 1:13). Diseases may be called rare in a specific area (e.g. Western Europe) whereas it is not rare in other areas of the world. Examples of these diseases are infectious diseases like tuberculosis and malaria. Rare diseases can also migrate from one part to another part of the world. For example haemoglobinopathies like thalassemia and sickle cell anaemia, but also tuberculosis, are migrating through Europe. Examples of groups of rare diseases are e.g. neuromuscular diseases, inborn errors of metabolism (like lysosomal storage disorders,

peroxisomal disorders and mitochondrial disorders), several chromosomal disorders, rare forms of cancer, etc. Priority Medicines for Europe and the World.

What Are They?

Rare disease = one affecting fewer than 200,000 people in the US 6000 8000 rare diseases affecting 7% of population 4 out of 5 have a genetic basis 70 75% have a prevalence of < 100,000 people Orphan drug = one that has been developed to treat a rare disease More than 2200 molecules designated as orphan drugs 30 40% are for rare cancers 362 approved drugs since 1983.

Orphan Drug Development and Regulatory Challenges

- Large heterogeneity in disease pathophysiology
- Poorly understood natural histories and progression
- Few patients are available conducting clinical trials
- Uncertain appropriate duration of treatment
- Lack appropriate endpoints that predict outcomes
- Large heterogeneity in treatment effects
- Require compromise, innovation and trade-offs
- Make difficult decisions in absence of ideal information
- Extract most amount of knowledge from least amount of information.

Case for Rare Disease and Orphan Drug Trends

- Licensing deals (ex: Pfizer and Protalix)
- Mergers (ex: Sanofi and Genzyme)
- Label extension strategies (ex: EPO for anemia in CRF)
- Government roadmaps (ex: EMA and NIH)
- Dedicated industry units (ex: GSK and Pfizer).

Categories of Rare Diseases and Orphan Drugs

NME for as yet untreated people with rare disease Example: alglucosidase alfa for Pompe disease (~ 1:40000?)

Exogenous source of lysosomal enzyme acid alpha-glucosidase (GAA) Muscle weakness, enlarged hearts, difficulty walking Drug for common disease Drug for rare disease (“re-purpose”) Example: sildenafil for pulmonary hypertension (~ 1:50*?)

Selective inhibitor of phosphodiesterase type 5 (cardiac biomarkers)

SOB, chest pain, tachycardia, ankle/leg swelling Drug for rare disease Drug for common disease Example: canakinumab for Muckel-Wells syndrome (~ 1:2000?)

Anti-interleukin-1 beta monoclonal antibody (protein biomarkers)

Fever, rash, conjunctivitis, swollen joints, hearing loss, renal failure.

FINDINGS AND OBSERVATIONS

Lipitor, used to prevent heart disease and lower high cholesterol, is the largest revenue generating drug globally. It generated an estimated $197 billion for Pfizer over its lifetime. The second largest revenue-generating drug is Rituxan, which has garnered significant sales for the treatment of two rare (orphan) diseases: chronic lymphocytic leukemia and non-Hodgkin’s lymphoma, as well as for the non-orphan indication rheumatoid arthritis. Figure 1 lists the top 10 drugs globally, ranked by overall lifetime revenue potential.

Table 6: Approximate Sales of Orphan Drugs with ODE Expirations in 2011

Drugs with Orphan Exclusivity in the U.S. Expiring in 2011	Active Ingredient	Orphan Indication
SENSIPA R	Cinacalet hydrochloride	Hyper parathyroidism
VIDAZA	Azacitidine	Myelodysplastic syndrome
ACETADTE	Acetylcysteie	Acetaminophen overdose
CLOLA R	Clofarabine	Acute lymphoblastic leukemia
TINDAMX	Tinidazole	Bacterial vaginosis and trichomoniasis
VENTAVI S	Iloprost	1ClassIII Primary Pulmonary arterial hypertension
NUTRESTE	Glutamine	Used with growth hormone and indicated for congenital short bowel
APOKYN	Apomorphie Hydrochlorie	Parkinson's disease and associations with the disease
LUVERIS	lutropin alfa	Fertility medication for infertile rhypogonadotropic hypgonadal (LHdefici)
MEMBRANEBLUE	Trypan blue	Dye used for staining membranes during eye surgery
PENTATE CALCIUM TRISODIUM	Pentate calcium trisodium	Treatment of internal contamination of plutonium, americium or curium
PENTET1ATE ZINC TRISODIUM	Pentetate zinc trisodium	Treatment of internal contamination of plutonium, americium or curium

CONCLUSIONS

The success of orphan drug designation for neglected rare diseases shows that companies using orphan drug programs can generate profits and recoup their R&D investments even with relatively small markets in the developed world. The orphan drug designation mainly encourages investments and initiatives by small science-oriented companies. In general, orphan drugs have been developed by small biotech firms focused on niche markets or by academic investigators combining solid scientific expertise in a specific medical area with good entrepreneurial skills. The orphan drug designation should be promoted in various countries, not having their regulations for such categories of diseases, to promote the treatment for sufferers with rare diseases.

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