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Trends in Development of Orphan Drugs - A Review

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Abstract

Orphan drugs are pharmaceutical agents that treat rare medical condition known as orphan or rare disease. According to U.S Rare Disease Act of 2002, any disease that affects less than 200,000 patients or 1 in 1500 is termed as a rare disease [1-3]. European Union defines rare disease as a life threatening or chronically debilitating disease which is of such low prevalence that special efforts are needed to address it." It should affect 1 in 2000 persons [2,3]. European Union definition for rare disease also includes some tropical diseases found in developing countries [3]. There are around 5000-8000 rare diseases reported, out of which only 10% have cures [4]. According to the European Organisation for Rare Disease (EURORDIS) 80% of rare diseases are genetic in nature [5].

Literature Review

Orphan/Rare diseases

Lysosomal Storage Disease (LSD) is a rare disease condition, which is currently gaining a lot of attention, and hence research on it is being pursued. Fabry Disease, Pompe Disease, Mucopolysaccharide (MPS1, MPS2, MPS3, MPS4) is different known LSD diseases [6]. Tay-sachs was the first disorder to be described in 1881, Gaucher disease in 1882 and Fabry in 1898. Pompe Disease has a frequency of 1 in 40,000. Fabry disease, MPS I, MPSII (hunter), MPSIV (Morquio syndrome) have frequency of 1:117000, 1:100000, 1:150000, 1:700000, respectively. In India, there are around 33 million patients with around 6000-8000 rare diseases conditions, mostly genetic in nature [6-9]. Some diseases like Madras Motor Neuron Disease and Kyasanur Forest Disease are limited to India. Most of the rare diseases are missing from the classification of rare diseases in the International Classification of Diseases 10 (ICD10), and those which are present are mostly misclassified [10]. It results in the negligence of morbidity and mortality due to rare diseases by Health Information Systems. Therefore to bring a fair representation of rare diseases, a partnership has been established by Orphanet with WHO (World Health Organization). Orphanet has established a database of phenotypes indexed with ICD10 codes, MIM (Mendalian Inheritance in Man) which recodes and gives information on genetic disorders and genes, the mode of inheritance, the age of onset and the class of prevalence based upon all published expert classifications are collected and represented [10,11].

Trends in development of medicines for treatment of orphan/rare diseases

In the United States, the Orphan Drug Act (ODA) was passed in 1983.This Act provided clinical trial incentives to pharmaceutical companies and also gave them market exclusivity for 7 years. These incentives resulted in more focussed attention of pharmaceutical towards research in the area of rare diseases [8]. Following the same policy as the United States, Singapore (1991), Japan (1993) and Europe (2000) passed laws with aim to promote research and development in the field of rare diseases [12,13]. European Union provides market exclusivity to sell orphan drug for 10 years. Other countries like South Korea, New Zealand, and India are also planning to pass laws specific to rare diseases [2]. Before ODA was passed, FDA approved only 38 drugs with status of orphan drugs, but after passage of ODA that numbers increased significantly. Until May 2010, FDA had approved 353 orphan drugs. Among all the approvals by the FDA, orphan drug approvals contributed 17% from 1984 to 1988; which almost doubled to 31% between 2004 and 2008.Cancers are the most common category of rare diseases, which account for 36% of orphan drug approvals by the FDA between 2000 and 2006. In 2007 USA and European Union took a decision of common application procedure for orphan drugs, so as to make easier and less time consuming for pharmaceutical companies to apply for Orphan drug approvals in both the regions [3]. Table 1 represents the comparison of US and EU legislations regarding orphan drugs.

Many national institutes have come up with aim to identify different rare diseases. Institutes like National Organisation for Rare Disorder (NORD) and European Organisation for Rare Disorder (EURORDIS) collect data on various rare diseases reported. Rare disease day is observed every year in which different pharmaceutical companies, various government organisations like LSDSS (Lysosomal Storage Disorder Support Society), patients and doctors come on a common platform to know about latest happenings and research going on in the field of rare diseases [2].

The FDA Office of Orphan Products Development (OOPD) provides incentives for sponsors to develop products for rare diseases. Humanitarian Use Device (HUD) program designates a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals in the United States per year [14]. The Orphan Products Grants Program provides funding for clinical research that tests the safety and efficacy of drugs, biologics, medical devices and medical foods in rare diseases or conditions. On the last day of February Rare Disease Day is coordinated at the

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	US	EU
Legal Basis	Orphan Drug Act, 1983	Regulation 141/2000/EC
Component Authority	FDA and Office of Orphan Products & Development	European Medicines Agency Committee for Orphan Medicinal Products
Tax incentives	50% of the clinical studies. Some written recommendations are provided by FDA for clinical and preclinical studies.	No uniform tax regulations exist in EU. Protocol assistance (free scientific advice) is provided by EMA for orphan drug development National measures of different
Fee reduction	No	Waiver for registration fee, Fee reduction for Pre and post-authorization activities (including marketing and authorization fee)
Authorization peculiarities	Fast-track procedure	Centralized procedure
Research grants	Yes	European framework programs and national funding

Source: a. Table adapted from Chapter - Principles of Orphan Drugs; Fundamentals of International Regulatory Affairs. http://www.granzer.biz/content/PrinciplesofOrphanDrugs.pdf. Page No:81-86
b. Garcia A, http://leda.law.harvard.edu/leda/data/621/Orphan_Drugs_RTF.html; March 2004
c. Holloway,P.; Pawlukowski,D, Fast Tracking Procedures and Orphan Drug Programs in the USA, EU and Australia, http://www.findlaw.com.au/articles/1525/fast-tracking-procedures-and-orphan-drug-programs-.aspx, Thomsan Reuters Australia; 2013

Table 1: A comparison of Orphan drug Legislation in USA and EU.

international level by EURORDIS and NORD in the US and other countries. The Rare Disease Day 2012 theme focused on solidarity, and the need for collaboration and mutual support in the field of rare diseases. Shire supported the Rare Disease Day 2012, a leading non-profit rare disease advocacy organization, in their Global Genes Project (Market Watch.htm). In India for the first time on February 28th, 2010 rare disease day was observed with support of LSD support society of India. In 2012, 29th February was observed as rare disease day and in India it was organised in Mumbai [2].

Tables 2 and 3 represent data on research and development being carried out in the field of rare diseases/orphan drugs and drugs which are in development pipeline respectively.

Methodology

Methodology includes systematic literature review with the aim to find out pharmaceutical companies which are leading at present in the rare disease market. The literature search revealed both MNC and biopharmaceutical companies are investing in developing drugs for rare diseases. Three companies Pfizer, Novartis and Shire, were identified which seems ahead of other companies in developing medicines and allocating resources for rare disease segment. A comparison between the numbers of drugs approved for these 3 companies, and the number of these drugs being awarded as orphan drugs status was made for the time period of 2007-2012. Further, to evaluate the trend of development of orphan drugs, the New Molecular Entities (NME) approved by US FDA as orphan drugs over a period of 6 years (2007-2012) were reviewed.

Results and Discussion

Figure 1 represents the total number of NME approved as orphan drugs over the period of 6 years (2007-2012) by USFDA. The numbers indicate that there is no clear trend in the number of NME approved as orphan drugs. In 2007, 7 NME were granted orphan drug status by FDA, in 2008 10 NME, while in 2009, 7 NME were granted orphan

Rare disease Name	Drug available	Marketing Authorization Holder
Alzheimer and Parkinson (special condition)	Exelon® [15]	Novartis
CCR5-tropic-HIV-1	Selzentry® [16]	Pfizer
Chronic Idiophatic Thrombocytopenia	Promacta® [17]	GSK
Chronic lymphocytic leukemia	Arzerra® [18]	GSK
Chronic Obstructive Pulmonary Disease (airflow obstruction)	Arcapta® [19]	Novartis
Cryoprinic Associated Periodic Syndrome	Ilaris® [20]	Novartis
Fabry disease	Replagal® [21] Fabrazyme® (Agalsidase beta)	Shire Genzyme
Gaucher disease	Vpriv® Cerezyme® (Imigluserase)	Shire Genzyme
Maroteaux-Lamy Syndrome (MPS VI)	Naglazyme® [22]	Biomarin
Mucopolysaccharidosis I (MPS I)	Aldurazyme® (laronidase)	Genzyme
Non-small cell lung cancer	Xalkori® [23]	Pfizer
Non transfusion dependent thalassemia	Exzade® [24]	Novartis
Pancreatic neuroendocrine tumours	Sutent® [25]	Pfizer
Phenylketonuria	Kuvan® [26]	Biomarin
Philadelphia Chromosome positive chronic MyloidLeukemia	Tasigna® [27]	Novartis
Pompe Disease	Mycozyme® and lumizyme® [28]	Genzyme
Primary Immune Thrombocytopenia	Rozrolimupab® [29]	Swedish Orphan Biovitrum
Restless leg syndrome	Horizant® [30]	GSK
Subependymal Giant Cell Astrocytomas	Afinitor® [31], Votubia® [32]	Novartis

Table 2: Research and Development going on in the field of rare diseases/Orphan drugs.

Disease	Drug	Company
Achondroplasia	BMN-111 [33]	Biomarin
Cushing Disease	SOM230 [34]	Novartis
Duchene Muscular dystrophy	HGT 4510 [35]	Shire
Fabry Disease	Amigal [36]	GSK
Homozygous familial Hypercholesterolemia	Kynamro [37] (Nipomersen)	Genzyme
Hunter syndrome	HGT 2310 [35]	Shire
Metachromatic Leukodystropy	HGT 1110 [35]	Shire
Pompe Disease	BMN-701 [38]	Biomarin
Sanfilippo A syndrome	HGT 1410 [35]	Shire
Transthyretin familial amyloid polyneuropathy	Tafamidis meglumine [39]	Pfizer

Table 3: Drugs in development pipeline.

drug status. In 2010, only 3 NME attained orphan drug status, whereas in 2011, 15 NME were approved as orphan drugs. The number again fell and only 6 NME were approved as orphan drugs by FDA in 2012. The comparative results of the 3 companies under study are represented in Figure 2. During the years 2007-2012, 75% of total approved drugs for Pfizer and Shire were granted orphan drug status. Pfizer's 6 out of total 8 approved drugs were granted orphan drug status, while Shire's 3 out of total 4 approved drugs were granted orphan drug status. Novartis

received USFDA approval for 21 drugs during this period and 10 drugs of these 21 were granted orphan drug status. As represented in Figure 1, there is no clear trend in the annual development of Orphan drugs but interestingly drugs approved for orphan diseases share a major part of the total number of drugs approved (as indicated in Figure 2, for 3 companies).

The three companies identified for this study have made a steady progress in recent years in the field of rare diseases. Shire was one of the companies, along with Genzyme which started research in the area of rare diseases. But at present MNCs like Pfizer and Novartis have entered the orphan drug market and have acquired huge share in this earlier neglected field. From 2009 onwards, big pharmaceutical companies account for 43% of total orphan drug approvals by FDA and claimed over 70% of market share, up from 56% in 2006, according to Business Communication Company (BCC) research (Market Forecasting). The success of Pfizer and Novartis as depicted in our study clearly indicates the growing interest of big pharmaceutical players in rare disease area. For getting the foothold in orphan disease area, MNC's have basically acquired small biotech companies involved in orphan drug development or have entered in a partnership with them [40]. Shire and Genzyme have Vipriv and Cerenzyme respectively in market for Gaucher treatment; despite this fact, Pfizer paid 60 million dollars to Protalixto acquire latter's Gaucher disease enzyme replacement therapy Taligurase Alfa [41]. Pfizer also acquired Fold Rx pharmaceuticals, whose main therapy area is developing drugs to treat diseases caused by protein misfolding [42]. Novartis is targeting orphan indications in cancer research. Its molecule Gleevec, first got approval for Chronic Myelogenous Leukemia (CML) and subsequently Gleevec was granted orphan drug status for gastrointestinal stromal tumors too. Till date, Gleevec has got 5 more approvals for different related indications. Presently Gleevac is giving revenues in $2.5 billion and is expected to increase up-to $4 billion with the growth rate of 10-12%.

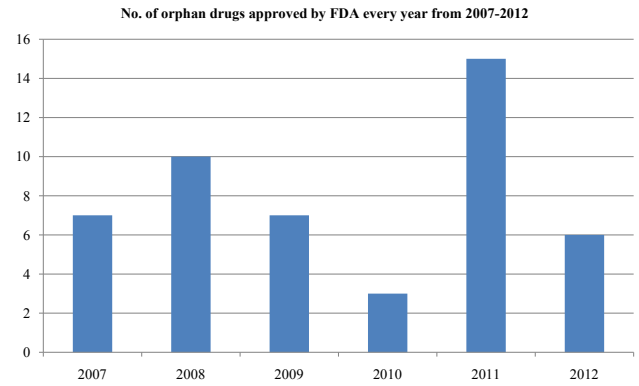

Figure 1: Orphan drugs approved by USFDA from 2007-2011.

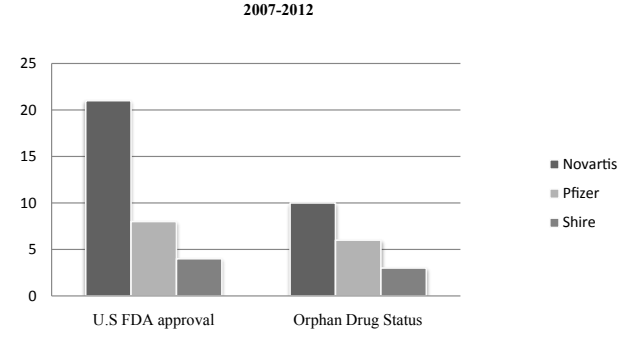

Figure 2: Comparison of Novartis, Pfizer and Shire; Total number of US FDA approved drugs vs. total number assigned Orphan Drug Status.

Sixty percent of the orphan drugs available in market at present are biotech products (monoclonal antibodies, interferons/interleukins, growth hormones, plasma products) [43]. With the diminishing pipeline of drugs and stiff competition, the big pharmaceutical companies have invested in rare disease field and most of their approved drugs are for rare diseases. Our study indicates the growing success of pharmaceutical companies in orphan disease area, but the study is limited in approach as only the US FDA approved drugs were studied. Moreover the rare diseases affecting the population in developing countries are out of scope of current study (Figures 1 and 2).

Future Prospects

Based on the model of fast track courts, the US Senator Kay Hagen has proposed fast track approach for orphan drugs in U.S Congress. The idea is to make provisions for more accelerated review of drugs meant for rare disease by FDA. His views are supported by Biotechnology Industry Organisation (BIO) and GSK. Though FDA has the provision of exemptions, many biotech companies feel that the criteria for using this flexibility is quite unclear as pointed out by BIO. Senator proposes that FDA should review orphan drug cases in the same way as it uses Accelerated Approval Program for AIDS and cancer treatment. According to Accelerated Approval Program, companies can conduct shorter clinical trials and it is based on measured effect of the drug rather than complete clinical results. According to BCC research, orphan drug market reached $84.9 billion in 2009, out of which cancer sector contributed for $30.6 billion. The market is expected to grow at a Compound Annual Growth Rate (CAGR) of nearly 6% to reach $112.1 billion and $49.7 billion for cancer orphan drugs by 2014. The U.S. accounted for 51% of the market in 2009 and is expected to grow at a CAGR of 8.9% to reach $65.9 billion by 2014 [44].

Conclusion

Our study indicates that major multinational pharmaceutical companies are investing in the field of rare diseases and the same pattern is expected to be followed by other pharmaceutical MNCs. The percentage of molecules granted orphan drug status, by FDA, suggest that pharmaceutical companies are diversifying into new therapy areas, which were ignored earlier. The incentives offered by ODA such as grants, market exclusivity and tax breaks seems to be a few important reasons for the recent surge in development of orphan drugs by various companies. The study is limited in its scope to US FDA approved drugs only. Though, there has been a considerable development in the area of orphan drugs and at face value it's a great achievement for pharmaceutical industry but, still for many rare diseases medication is unavailable, which shows that there is need of right strategy as well as understanding for their risk and benefits.

References

1. Aronson JK (2006) Rare diseases and orphan drugs. Br J Clin Pharmacol 61: 243-245.
2. Randhawa G (2006) Orphan Disease and Drugs. Indian Journal of Pharmacology 38: 171-176.
3. Aagard L (2011) Medical treatment of rare diseases must be put on the agenda. Orphan Drugs: Research and Reviews 1: 1-2.
4. The voice of 12,000 patients. Experiences and expectations of rare disease

patients on diagnosis and care in Europe. A report based on the EurordisCare2 and EurordisCare3 Surveys.

5. (2005) Rare diseases: Understanding this public health priority. European Organization for Rare Diseases (EURORDIS).
6. http://Www.Lsdss.Org/Lsd_Diesese.Html
7. (2013) Orphan Drug Act. U.S. Food and Drug Administration.
8. (2012) Novartis works for patients with rare diseases.
9. Devi RR (2012) Rare disorders hurt millions. Accessed September 23, 2013.
10. Hamosh A, Scott AF, Amberger J, Bocchini C, Valle D, et al. (2002) Online Mendelian Inheritance in Man (OMIM), a knowledgebase of human genes and genetic disorders. Nucleic Acids Res 30: 52-55.
11. Rath A, Ayme S, Bellet B (2010) Classification of rare diseases: a worldwide effort to contribute to the International Classification of Diseases. Orphanet J Rare Dis 5: O21.
12. Gericke CA, Riesberg A, Busse R (2005) Ethical issues in funding orphan drug research and development. J Med Ethics 31: 164-168.
13. Meyers AS (1997) Orphan drugs: The current situation in the United States, Europe, and Asia. Therapeutic Innovation & Regulatory Science 31: 101-104.
14. (2013) Developing products for rare diseases & condition. U.S. Food and Drug Administration.
15. http://parkinsons-disease.emedtv.com/parkinsons-disease-articles.html
16. (2007) Selzentry approval marks big win for Pfizer. Fiercebiotech.
17. (2011) FDA grants full approval for PROMACTA® (eltrombopag) for treatment of rare blood disorder.
18. (2009) FDA extends review of ARZERRA™ (Ofatumumab).
19. (2011) Novartis receives FDA approval for Arcapta(TM) Neohaler(TM), a novel once-daily bronchodilator for chronic obstructive pulmonary disease.
20. New biological therapy Ilaris approved in US to treat children and adults with CAPS, a serious life-long auto-inflammatory disease. Accessed February 9, 2013.
21. Shire targets fourth quarter filing of BLA for REPLAGAL® for Fabry disease with USFDA. Accessed February 12, 2013.
22. Naglazyme® (Galsulfase) For MPS VI. Accessed February 9, 2013.
23. Herper M (2011) Pfizer wins approval for Xalkori, lung cancer drug that heralds age of expensive, personalized medicines. Accessed February 15, 2013.
24. Exzade approved for use in non transfusion dependent Thalassemia. Accessed February 18, 2013.
25. (2011) FDA approves sutent for rare type of pancreatic cancer. American Gastroenterological Association. Accessed February 15, 2013.
26. Kuvan (SapropterinDihydrochloride) tablets for PKU. Accessed February 15, 2013.
27. Hareyan M (2007) Tasigna receives FDA approval - hope to chronic myeloid leukemia. Novartis, Emaxhealth. Accessed February 15, 2013.
28. Dooren J (2010) FDA approves Genzyme's Lumizyme to treat Pompe disease. ADVFN. Accessed February 13, 2013.
29. Symphogen and Swedish Orphan Biovitrum receive U.S. Orphan Drug Designation for Rozrolimupab in ITP. Accessed February 10, 2013.
30. GlaxoSmithKline and XenoPort receive FDA approval for Horizant™. Accessed February 13, 2013.
31. Bochner H (2010) Novartis drug Afinitor® approved by FDA as first medication for children and adults with a benign brain tumor associated with tuberous sclerosis. Accessed February 25, 2013.
32. Riley N (2011) Novartis receives EU approval for Votubia®, the first medication to treat children and adults with SEGA associated with TSC. Accessed February 11, 2013.
33. BMN-111: CNP for Achondroplasia. Biomarin Pipeline. Accessed February 15, 2013.
34. Vanderham G (2010) Novartis drug SOM230 is first medical therapy to show efficacy in a Phase III trial in Cushing's disease, a debilitating hormonal disorder. Accessed February 27, 2013.
35. Shire: Our Pipeline. Accessed February 13, 2013.
36. GlaxoSmithKline and Amicus Therapeutics commence second phase III study of Amigal™ for Fabry disease. Accessed February13, 2013.
37. Genzyme and Isis Announce Submission of European Marketing Authorization Application for Mipomersen (Kynamro®). Accessed March 15, 2013.
38. BMN-701: IGF2-GAA for Pompe disease. Accessed February 22, 2013.
39. FDA accepts NDA for Tafamidis Meglumine. Accessed February 23, 2013.
40. Ratner M (2010) Pfizer Stakes A Claim In A Plant Cell-Made Biopharmaceutical. Nat Biotechnol 28: 107-108.
41. Ariyanchira S (2010) Big Pharma Steps into Orphan Drug Market. Genetic Engineering & Biotechnology News. Accessed February 7, 2013.
42. Ariyanchira S (2010) Biomarket Trends: Orphan Drug Arena Driven By Biologics. Genetic Engineering and Biotechnology News.
43. Riordan M (2013) A Refined Approach to Selecting and Developing Orphan Products. Putnam Associates Inflection Point: Putnam Prospective Orphan Drugs. Putnam Associates. Accessed February 28, 2013.
44. Global Markets for Orphan Drugs. BCC Research Market Forecasting. Accessed February 11, 2013.