WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

A Review: Global Orphan Drug Market

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ABSTRACT:

Orphan drug Market has seen atremendous growth in last 2 decades.There has beena paradigm shift in the pharma or biopharmaceutical market with focus on research and development for unmet medical / clinical needs , investing resources in developing drug stotreat rareclinical condition sthus targeting small poolof patients. More than7000 diseases (Gaucher disease,Pompe disease) have been given the designation of beingrare.The introduction of well define dandsoundregulatory framework,especially the Orphan Drug Act,1983 in the USA playedapivotrole to achieve the same.Thoughthere are sever alhurdles during or phandrug development ranging from economical constraintstoin sufficient clinical information.Wecan seesevera lstrategic program sand steps including mergers and acquisitions,association between the pharmaplayers and academic institutions with the aim to developne worphan drug molecules.Orphan drug market look spoisednow,having all the potential lto grabalarger share in the pharmamarket in the future.

Keywords: Orphan drugs ,Orphan drug act ,Gaucher disease,Pompe disease.

Introduction:

Background : This term was coined to describe active pharmaceutical in gradients that were developed for treating are medical in dications (orphandiseases).Orphan drugs never garnered interest or attention from pharmaceutical industryas they encompassed very small population and returns on investments were low until Orphan Drug Act (ODA), 1983 was passed in United States and later various countries enacted similar laws. It was major break through that encouraged several Pharmacompaniest of or mulate drugs for rare diseases. “Orphan Disease or Rare Disease ”is one affecting as maller portion of people and the reasons may or may not be genetically controlled [1,2,3].

Definitions by Several Nations:

Orphan drug is ”A drug to treat or cure rare medical conditions (orphandiseases) affectingless than 200 ,000 people ”as per US lawunder Orphan Drug Act.

Orphan drug is ”A drug for acondition ,disease or clinical mani festation affecting 5 or less in 10,000 citizens (0.05%) ”as per European law About 6,000 to 8,000 orphan diseases have been identified by EURORDIS (European Organization for Rare Diseases).

Orphan drug is “A drug which treats any medical condition or disease with not more than 50,000 cases (0.04%) and that has no other medical treatment available ”as per Japanese law.

Orphan drug is “One that treatsr are medical conditions and is no tintended for use in more than 2000 patient sayear by vaccine or invivodi agnostic “ as per Australian law.

Orphan drug is ”One that treatsr are disease with a patients number in gbetween Australian and United States definition ”as per Can adian law.

Orphan drug is ”One that treatsr are disorders/disease if it is prevalentin 1:10,000 people ”as per Taiwan law.

Orphan drug is “one that treata disease affecting less than 20,000 people ”as per Korean law [2, 4,5,6,7]

Some of the familiar diseases with rareor orphan status are Alzheimer’s disease, ALS ,Crohn's disease, Hodgkin's disease,Parkinson’s,leukemia (many forms) ,multiples cler osis, Huntington's disease ,sicklecell disease, muscular dystrophy,myasthenia gravis and spinal cord injury.

All disorders due to genetic defects in development (like spina bifida,Turner's syndrome, Klinefelter's syndrome,cleft lip and palate)and deficient enzymes (like cystic fibrosis, respiratory distress syndrome,Gaucher's disease,hemophilia),are considered or orphan diseases.

Some not so familiaror lesser known diseases are:

1.Juberg Marsidi syndrome-a genetic childhood disorder leading to severe mentalreta rdation, abnormal bone growth causing disfiguration of the head and body and loss of hearing.

2.Hermansky-pudlak syndrome-group of genetically heterogeneous disorders which share the clinical findings of oculocutaneou salbinism, platelet storage pool deficiency and ceroid lipofuscinosis.

3.Werdnig Hoffman disease- afatal, fetal disease similar to amyotrophic lateral sclerosis (ALS).

4.Omenn's syndrome- absence of mature B and T cells, children being born with late-stage ALS –like symptoms.

5.Fabry's disease- an X-linked lysosomal –storagedisorder due to deficiency of galactosidase A.

6.Lambert- Eaton myasthenic syndrome- anautoimmune disease of peripheral cholinergic system resulting in muscle weakness due to impaired acetylcholine release.

"Ribose-5- phosphate is omerase deficiency "is regardedas ther are stgenetic disease with only one patient so far . A disease may be rarein one part but still be common in another part of the world. More than 55 million people are estimated to bediag no sedwithsomeraremedical conditions in EU and in the US. Globally ,there are roughly 7000 rare disorders [7,8,9,10,11]

Challenges Before 1983:

In theearly eighties Pharmaceutical Industry considered large pool of patients as a great source of generating evenues . Orphan drugs were side lined or kept out of picture merely due to risk involved due to following reasons:

Financially Driven:

- High investments on R & D
- Lower Returns on Investments due to pricing policies due to smaller market size
- Fewer tax waivers

RegulatoryDriven:

- Longer duration for drug approval (lengthy pathways & stringent protocols.
- Lack of global harmonization on orphan drug development front .

Clinically Driven:

- Insufficient information and data about rare medical conditions.
- Problems faced in assessing clinical authenticity and cost analysis
- In appropriate and insufficient end points for predicting results
- Lack of appropriated iagnostictools / systems

Only 38 approved active pharmaceutical ingredients made to list for treating rare medical conditions [3,12,13,14,15,16]

After 1983 : A Boon To Orphan Drug Market.

Orphan Drug Act , 1983 was passed by United States with the aim to promote orphan drug development in order to treat the neglected rare and incurable diseases . The idea was to modify the law spertaining to preand post approval pathways for orphan drugs . Post ODA , other countries like European Union , Japan , Australia came up with similar norms and guidelines to increase the profit ability of pharma industry.

Contribution by government organizations on be half of ODD include (that are viable for both research and commercial purposes):

- Greater Tax exemptions
- Improved patent protection
- Longer market exclusivity period.
- Monetary subsidy on Clinical research, favourable reimbursements
- Fewer patients needed in phase III clinical trial
- Government owned enterprises involved in R & D
- Premium in Pricing Policy and lower marketing cost
- Off-label usage & expansion to mainstream clinical in dications[1,17,18,19,20]

Market Research Analyst Shalini Dewant old Med Ad News Daily,

"Market exclusivity has played acrucialrole in the success of the orphan drug market . Currently , as Asian pharmaceutical markets are growing , the opportunities for orphan drugs in Asia are also growing . In next five years , the orphan drugs market will experience steady growth in emerging markets ,mostly Asia. The increase is a pro for global orphan drugs market as it is encouraging manufacturers to invest In the research and development of new orphan drugs."[20.

Countries with Robust Regulatory Framework:

1.United States(1983): ODA (Orphan Drug Act)was passed on January 1983 by Congress,
Office of Orphan Products Development (OOPD) works under US-FDA (Food & Drug Administration).US governing body offers 7 years of market exclusivity.More than 400 drugs have been approveds of ar and close 2000 drugs are designated.[20]
2.Japan (1993): Regulatory guidelines under MHLW/OPSR offer a period of 10 years of market exclusivity and several tax in centives and approval via fasttrack pathway.
3.Australia(1997): Governing bodies worked together with USFDA to establish the policies.
4.European Union (2000): The EU's legislation (141/2000 EC) is watched by the Committee on Orphan Medicinal Products of the European Medicines Agency (EMA). It offers 10 years of marketexclusivityrightsandhas68approvedorphandrugstoitscredit.Otherbenefitsinclude partialfeewaiverforfilingprocessandsupplementaryprotectioncertificate(SPU).
5. . Taiwan (2010): Rare Disease and Orphan Drug Act was passed and there have been 159 diseases classified as rare ones and 77 drugs approved for orphan category [6,21,22,23,24].

Contribution by Health Authorities / Research Organizations:

1. Groups advocating Patient ‘s Right: National Organization for Rare Disorder (NORD) , Global Genes Project (GGP), Children's Rare Disease Network (CRDN), Zellweger Baby Support Network (ZPSN), EURORDIS (European Organization for Rare Diseases)[20,25].
2. Research Organizations: Center for Orphan Drug Research at Minnesota University ,The Keck Graduate Institute of Applied Sciences Center for Rare Disease Therapies (CRDT) , The Center for Rare and Neglected Diseases at the University of Notre Dame, the Manton Center for Orphan Disease Research at Children’s Hospital in Boston and Raymond and Ruth Perelman School of Medicine at the University of Pennsylvania[21,25,26].
“Orphan Diseases & Orphan Drug Development” has an Orphan Status in India?

- Lagging Behind: India lacks concrete and robust regulatory guidelines for rare diseases though between 6000 and 8000 rare clinical indications have been designated in such a populous nation so far.
- The Hindu in April 2012 reported, “Taking the lower limit of global prevalence estimate, populous nations like India and China should have more than 70 million rare disease cases each.”
- February 28, 2010: “Rare Disease Day” was observed / recognized for the first time in New Delhi, India.
- It’s High Time: India must act now and come up with a well defined framework / legal policies to support and encourage pharmaceutical players which will eventually allay the sufferings of patients diagnosed with rare disease. It’s the need of the hour.
- Relevant actions that are needed: Indian governing bodies can intervene by launching several programs including awareness drive / campaign and encouraging a feasible alliance between the industrial players and academic institutions [23, 27, 28, 29].

Recent advancements: Monetary Achievements [1,12,17,23,30,31

- Unprecedented Approval & Designations alloted: Between January 1983 and May 2010, there were approval of 353 orphan drugs & orphan designations to 2,116 compounds and approximately 200 designated orphan diseases became treatable.
- Monetary Evaluation: Globally, orphan drug market was valued at $84.9 billion in 2009 and close to $86 billion in 2012.
- Products that ruled: Biological products covered 64.3% of the orphan drug market with sales up from $51.4 billion in 2008 to $54.6 billion in 2009.
- Largest revenue generators: Oncology division had the largest revenues in 2009, $30.6 billion, compassing 36% of the market.
- Most Expensive Dug so far that achieved unimaginable revenues: In 2010, Solaris (most expensive drug; for blood disease paroxysmal nocturnal haemoglobinuria), brought in $541 million for Alexion Pharmaceuticals
- Oncology is the biggest disease category for new orphan drugs; close to 40 percent of today’s orphans are used to treat cancer. Roche’s Rituxan (Top Selling Orphan Drug) belongs to oncology caregory
- Some of the Money spinners in the year 2012 are Rituxan/MabThera , Gleevec , Copaxone , Velcade with sales between $2.2B and $7.2B despite small pool of patients for such rare clinical manifestations

Strategically Positioning Drugs for Sales growth[7,16,24,32]:

- Adding non-orphan drug status to orphan drugs
- Adding secondary orphan indication to a previously marketed orphan drug.
- Transitioning from non orphan indication to a secondary rare clinical manifestation for a particular drug.

- Supplementary protection certificate (especially in EU) like for Glivec till 2016, thus giving additional time to generate revenues despite expiration of market exclusivity in 2011

High Pricing of Orphan Drug. Why? [27, 28, 33]

Monopoly: Due to Market Exclusive Rights.

Lack of Alternatives: In Health care sector for rare diseases.

Patients & Insurance Companies: Have limited scope for negotiation.

Recovery of R&D investment: From relatively small pool of patients suffering from rare diseases. Orphan V/s Non Orphan Drugs [16, 17]

A comparative work suggests that duration of clinical trials are relatively shorter and filing work have more success rate in case of orphan drug class. R&D costs are also less due to fee waivers and other tax incentives. Orphan drugs are an integral part of the pharmaceutical market with 22% share and are equally potent to non orphan drugs in terms of generating revenues (CAGR between 2001 and 2010 was 25.8% for orphan class and 20.1% for non orphan class of drugs). Market research reports suggest that CAGR (2010 – 2030) of orphan drugs will continue to outrun its competitor and hence are worth such huge investments.

Projections on Future Orphan Drug Market [1,3,8,12,17,30,24,34]

- Biotech orphan drug market is projected to grow at a 6.9% CAGR to reach $76.2 billion by 2014, mostly interferons, monoclonal antibodies.
- Revenues for cancer-related orphan drugs are expected to grow at a CAGR of 10% to reach $49.7 billion in 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.
- The total market value for orphan drugs is expected to hit $112 billion in 2017 after increasing at a five-year compound annual growth rate of 5.4 percent.
- Globally, sales of orphan drugs are expected to touch $127 billion in 2018.
- Novartis will hopefully retain its position as world leaders in orphan drug company in 2018, with expected sales of $11.8 billion.
- Kyprolis (company: Onyx Pharmaceuticals) for multiple myeloma, which was the most promising new orphan drug in 2012, with U.S. sales in 2017 expected to reach $897 million

Hurdles in Assessing / Analyzing the Future of Global Orphan Drug Market [16, 28, 33, 35]

- Difficulty in obtaining the sales information for rare clinical indications Problems faced in assessing the patient's percentage that are undergoing treatment
- Market accessibility varies across borders (regions , nations) for orphan drugs
- Variations in mode of payment (by patients or insurance companies) among nations
- Threats from drugs under development

Pharma & Biopharmaceutical Players with their Orphan Drug Molecules:

1. Pfizer – Sutent for Pancreatic endocrine tumors
2. Genzyme - Mycozyme and Lumizyme for Pompe Disease
3. Novartis – Exelon for Alzheimer & Parkinson special indications
4. Glaxo smithkline – Promacta for Chronic Idiophatic Thrombocytopenia
5. Biomarin – Kuvan for phenylketonuira
6. Shire – Vpriv for Gaucher Disease
7. Swedish orphan biovitrum – Rozrolimupab for Primary immune thrombocytopenia
8. Bristol-Myers Squibb – Yervoy for Metastatic Melanoma
9. Roche – Zelboraf for Metastatic Melanoma
10. Apo Pharma – Ferriprox for Thalassemia

Some of the Orphan Drugs (their Marketers) with expired market exclusive rights :

1. Avonex (Biogen)
2. Betaseron (Novartis & Bayer)
3. Epogen (Amgen)

4. Cerezyme (Genzyme)
5. Rituxan (Genentech)
6. Enbrel (Immunex) [1, 2, 13, 14, 17, 27]

Future Trend: Major Role of key Players & other Factors:

- Biogenerics: Future of the orphan drug market depends heavily upon biogenerics, as biologics account for more 50% of the orphan drug market due to lesser generic versions after patent expiration.
- Awareness among Asian countries: Governing organization is becoming more aware of the importance of orphan drugs which will increase the market share of orphan drugs.
- Pharmacogenomics: Role model in paradigm shift in patient care. Shift from large pool to small group of patients especially with the aid of nuclear cloning and cell & gene therapy (therapeutic cloning).
- Orphan Drugs to outshine Mainstream Drugs : Increase in orphan drug approvals are suggestive that the CAGR of launched orphan drugs will be more than that of the non-orphan drugs in next 3 decades mainly due biological orphan drug class. Orphan drugs offer a greater return on investment than non-orphan drugs [1,4,13,17,27,30,34].

CONCLUSION :

Estimation and projections by several market research firms suggest that the future the orphan drug market has no stopping and will continue to have double digit compound annual growth rate. Big pharma players are realizing the potential of orphan drug market. Orphan drugs especially (oncology division) are playing a pivotal role in generating revenues and proving as gold mines for the investors. Currently, these big companies hold the majority of the market share (53%) while biotech firms hold 37% of market share. Remaining percentage is with midsized to small pharma companies. Biotech and small pharmaceutical companies are playing rather pivotal role in investing during the early stages of orphan drug development. Big pharmaceutical companies are entering at a later development stage and are choosing to collaborate with biotech companies rather than start new drug development program targeting an orphan disease which has been a boon for biotech companies, which often struggle with inadequate funding. And the future lies with precision medication to improve the life of millions who suffer from rare medical conditions.

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