Shifting of Pharmaceutical Companies Towards Orphan Drug Market: A Trend Analysis

By

Khshboo

Dissertation submitted for the partial fulfillment of the

MBA Hospital and Health Management

Academic year, 2015-2017

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INSTITUTE OF HEALTH
MANAGEMENT RESEARCH
(WHO Collaborating Centre for District Health System Based on Primary Health Care)

IIHMR UNIVERSITY

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The Candidate has successfully carried out the study designated to her during internship training and her approach to the study has been sincere, scientific, and analytical.

The Internship is in fulfillment of the course requirements.

I wish her all success in all her future endeavors.

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May 5, 2017

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This is to certify that Khushboo (15390) has served in our organization from February 06 ,2017 to May 05, 2017. She was working as Knowledge Management- Intern on contractual role and based at New Delhi office.

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May 5th, 2017

Sumeet Madaan
Human Resources Specialist

ZS Associates India Private Limited GURGAON HR

THE IIHMR UNIVERSITY, JAIPUR

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This is to certify that the dissertation titled "**Shifting of Pharmaceutical Companies towards Orphan Drug Market: A Trend Analysis**" submitted by **Dr. Khushboo** Enrollment No. IIHMR-U/01/2015-17/0294 under the supervision of **Dr. Sandesh Sharma** for the award of MBA in Hospital and Health Management of the University carried out during the period from 6th February 2017to 5th May 2017. This embodies my original work and has not formed the basis for the award of any degree, diploma associate ship, fellowship, titles in this or any other Institute or other similar institution of higher learning.

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CERTIFICATE BY SCHOLAR

This is to certify that all ethical issues have been considered while collecting data for my dissertation titled "**Shifting of Pharmaceutical Companies towards Orphan Drug Market: A Trend Analysis**"

Khushboo

Signature

ABSTRACT

Shifting of Pharmaceutical Companies towards Orphan Drug Market: A Trend Analysis

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ZS Associates, Gurgaon
Guided by Dr. Sandesh Sharma

Keywords: orphan drugs, orphan diseases, Orphan Drug Act, market capitalization, mergers and acquisitions, orphan drug approval, US orphan drug market

BACKGROUND

Rare/Orphan diseases are a large, complex, and heterogeneous group of conditions with a few similarities affecting a total of 350 million patients worldwide. There are 6,000-8,000 identified known rare diseases and fewer than 500 have treatment. The etiology for these known rare diseases is linked to genetics in approximately 80% of the cases. Children make up 75% of all identified cases with 30% of those never reaching their fifth birthday.
With only a limited number of the population affected by a rare disease, the justification for investing considerable funds for clinical studies by the pharmaceutical industry has always been a challenge and a real barrier to innovation. The introduction of the Orphan Drug Act (ODA) for the US in 1983, has been the catalysts for many reformatory changes. Also, due to curtail in the mass market of patients, the pharma industry will be encouraged to look at rare diseases as an opportunity.

The present study helps to know the trend in the number of new orphan drugs approval by FDA during 2010-2016. The shift of various pharma companies, which are segregated based on their market capital, towards orphan drug market and, the number of mergers and acquisitions that has happened during this time span.

METODOLOGY

Aim

To get an overview of US orphan drug market figuring out the driving factors responsible for the shift of the pharma companies towards this unchartered area of therapeutics

Objectives

- To study and analyze the trends in orphan drugs approval

- To categorize the orphan drug manufacturer based on market capitalization and analyze the orphan market dynamics
- To analyze the trends of mergers and acquisitions amongst pharmaceutical companies

Study design and Tools

a) Type of study: Systematic review of literature. Desk research was undertaken
b) Geographical scope: US. First to launch the orphan drug act to enable pharma companies to shift in this area
c) Time frame of the study: The study is based on the pharma companies with orphan drugs approval by FDA during the period between 2010-2016.
d) Type of data: Publicly available secondary research data sources were deployed

RESULTS

Through this study, it was analyzed that the percentage sales of orphan drug market are increasing with every succeeding year. The shifting of mid and small cap pharmaceutical industry has also been noticed besides the drifting of large companies. Also, it was assessed that the big industries have started acquiring the mid and small companies. This has resulted in increase in the overall value of the firm, better financial planning, diversification of the scope of operation, better research and development and reduced competition. Boost to the shift of pharmaceutical companies in this domain was observed after the enactment of orphan drug act by FDA which offered many incentives to the companies, thereby, influencing many companies for the shift in this area. Other factors include less competition as orphan market is still not been accepted by many firms due to great uncertainty associated with it.

CONCLUSION

The number of pharmaceutical industries have started expanding their pipeline in orphan market by smart utilization of technologies, but, still for many rare diseases medications

are unavailable, which shows that there is need of right planning as well as understanding for their risk and benefits.

ACKNOWLEDGEMENT

This thesis would have been an insurmountable task without the support, guidance and encouragement that I have been fortunate enough to receive from many people.

I would like to express my gratitude to my Project Manager – Ms. Sherin Alex (Consultant at ZS) for having great vision and for patiently guiding me through this project despite her busy workload. Sincere thanks are also due to Mr. Vaibhav Kumar my co-mentor (Associate Consultant at ZS), for his invaluable insights and suggestions at our daily review meetings.

I am very grateful to have Ms. Akanksha Anil Aggarwal as my mentor in the organization as her knowledge and advice has always steered me along the right path. I would like to thank my PD Manager Ms. Nidhi Grover who has provided me with a lot of insight into how KM operates and helped me get a better understanding of my career path within ZS. I would also like to express my sincere gratitude to everyone in the KM team for making the office a fun and welcoming place.

I am very thankful to Dr. Sandesh Sharma, my guide at IIHMR University, for his constant support, guidance and patience throughout the internship and thesis presentations. He has expertly molded and designed my crude work into a finished thesis that can withstand scrutiny. Thank you, sir.

Finally, I would like to thank IIHMR University for providing me with an amazing opportunity and for making it an experience worth cherishing for a lifetime. I could not have asked for a more interesting and wonderful bunch of classmates than the 20th batch. It is always a pleasure when our paths cross.

Thank you.

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ABBREVIATION

1. BLA	:	Biological License Application
2. bn	:	Billion
3. CBER	:	Center for Biologics evaluation and Research
4. CDER	:	Center for Research Evaluation and Research
5. CPAG	:	Clinical Priorities Advisory Group
6. DHHS	:	Department of Health and Human Services
7. DSM	:	Data and Safety Monitoring
8. FDA	:	Food and Drug administration
9. GMP	:	Good Manufacturing Practice
10. M&A	:	Mergers and Acquisitions
11. NBE	:	New Biological Entities
12. NDA	:	New Drug approval
13. NHLBI	:	National Heart, Lung and Blood Institute
14. NIAMS	:	National Institute of Allergies and infectious Diseases
15. NICHD	:	National Institute of Child health and Development
16. NIDDK	:	National Institute of Diabetes and Digestive and"Kidney
Diseases		
17. NIH	:	National Institute of Health
18. NINDS	:	National Institute of Neurological Disorders & Stroke
19. NME	:	New Molecular Entities
20. OD	:	Orphan Drugs
21. ODA	:	Orphan Drug Act
22. ODD	:	Orphan Drug Designation
23. ODTC	:	Orphan Drug Tax Credit
24. OOPD	:	Office of Orphan Products and Development
25. ORD	:	Office of Rare Diseases
26. PDUFA	:	Prescription Drug User Fee Act
27. R&D	:	Research and Development
28. RDC	:	Rare Disease Centre
29. RDCRN	:	Rare Diseases Clinical Research Network
30. US	:	United States

1. INTRODUCTION

Innovation has always been the rib-cage of the pharmaceutical industry. Numerous lifesaving drugs have been produced, by various pharma companies, having remedial action for several medical demands. Many diseases, particularly acute disorders, are now treatable or can be managed effectively [(1)]. According to the report of Pharmaceutical Commerce the worldwide market for pharmaceuticals is projected to grow from around $1 trillion in 2015 to $1.12 trillion by 2022, representing an annual growth rate of 4.9 percent [(2)]. It has been seen that utilization of medicines has boosted up with the time by various factors, including a rapidly aging world population and an associated rise in chronic diseases, increased urbanization and higher incomes, greater government expenditure on healthcare and growing demand for more effective treatments.

Despite technological improvement and large R&D investments, the number of new drug applications (NMEs and NBEs) approved per year by FDA are comparatively low. Interestingly, one of the emerging trend is shift from primary care blockbuster, a popular drug that generates an annual sale of at least $1bn, mindset to specialty products which can help to treat rare diseases.

Orphan/Rare diseases are a large, complex, and heterogeneous group of conditions with a few similarities affecting a total of 350 million patients worldwide which is about 10 percent of the U.S population. There are around 6,000-8,000 identified known rare diseases and to a surprise, fewer than 500 have any kind of treatment. The etiology for these known rare diseases is associated to genetics in approximately 80% of the cases. Children comprise of 75% of all identified cases with 30% of those never reaching their fifth birthday [(3)].

The term "rare disease or condition" means any disease or condition which [(4)]:

- Affects less than 200,000 persons in the United States or
- Affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing a drug for such disease or condition will be recovered from sales in the United States of such drug

Heavy burden was laid on the companies due to decrease in the new innovations in conventional pharmaceutical market to modulate their existing contribution and search new patient population within a niche market area. Also, on visualizing the scenario of traditional pharma companies, it was revealed that patents of some of the profitable

medicines began to expire, cheap generic drugs started taking over the market, decreased number of drugs in pipeline and the strict regulatory guidelines.

Due to halt in the opportunities in disease areas addressing the mass market of patients, the pharma industry will be inspired to look at rare diseases as an opportunity to create a base for themselves in field within healthcare having limited treatment options and extensive clinical unmet needs.

Overall pharmaceutical industry has started spending billions of dollars in establishing therapies for rare diseases, which appeared to be less fascinating to the predominate drug inventor, however, now mark the way toward a new era of innovational therapies and big profits. After analyzing the existing plot, many companies shifted money to rare-disease drugs as due to less number of entrants, this market is facing limited competition. Orphan drugs may help pharma companies to decrease the effect of loss of revenue caused by patent expiries of blockbuster drugs. The new business model of orphan drugs could offer an integrated healthcare solution that allow the pharma companies to develop newer areas of therapeutics, diagnosis, treatment, monitoring and patient support. Incentives for drug development administered by government as well as support from the FDA, are a further leap for the companies developing orphan drugs. Evolution of orphan drugs, for treatment of rare diseases, could bring on a new age of pharmaceutical companies that will be smaller in size, requiring less resources and having a focused product portfolio and strategic intent. The nature of rare disease with its limited patient population will also encourage a much closer alignment between clinical trials, patient advocacy groups and the end user clinician, who will most likely be the key opinion leader for the treatment [(5)].

However, investing on medicine for a disease which has comparatively fewer patients is nothing less than breaking a rock. Since every orphan disease has low prevalence and in many cases the etiology, pathogenesis, course of action or whether the disease manifests differently in people with different risk factors or genetic profiles is not known. Above all, enough number of patients to participate in clinical trials, which is required by Food and Drug Administration (FDA) to grant approval to the rare disease therapy, has always been a challenge and pose a hurdle to innovation. In case the biopharmaceutical developers can overcome this road roller, post this arises a serious trouble in redeeming the investments which is required to discover, develop, and deliver the therapy because the patient population is less. With only a limited number of the population affected by a rare disease,

the justification for investing substantial funds for clinical studies by the pharmaceutical industry has always been a challenge and a real barrier to innovation.

All these hindrances were overthrown with the advent of Orphan Drug Act (ODA) by the US in 1983, which had made many reformatory changes in the domain of orphan drug market. Prior to the existence of Orphan Drug Act, FDA approved only 34 medicines that were recognized for orphan diseases [(6)].

ODA established incentives to promote innovation, one of which was the creation of the ODTC, which is designed to promote investment in R&D on orphan drug market advancement. Specifically, the ODTC allows developers to receive a tax credit for the clinical trial costs associated with potential new orphan drugs. This has been the catalyst for recent R&D investment, by reducing some of the inherent risk in developing an orphan drug, this change in public policy sought to offer hope to millions of patients.

Several approaches have emerged such as some large companies for example Pfizer, GSK, Amgen etc., are collaborating with small and medium-sized enterprise (SME's) that specialize in a specific therapeutic area, others are establishing a rare diseases business arm as a core part of their organizational structure. Many are doing both.

Moving into rare diseases will provide an opportunity to pharma companies to diversify and begin to move away from developing drugs for the mass market indications. These niche areas are desired due to the potential for companies to gain the first mover advantage and the ability to establish themselves as the market leaders.

Today's pharmaceutical business model, by contrast, is focused increasingly on rare diseases, where the low volume of prescriptions must be countered by high unit costs to ensure a return on investment [(7)]. The worldwide OD sales is projected to grow from around $124 billion in 2017 to $209 billion by 2022, representing compound annual growth rate (CAGR) of 11.1 percent [(8)].

In this study, the Novel drugs approvals (with respect to OD), by FDA during the cross-sectional period of 7 years (2010-2016) are studied. Also, this study categorizes the pharmaceutical industry, whose Orphan products were approved during this tenure (2010-2016), into large, mid, and small depending upon their market capitalization to know which type of pharmaceutical industry is more inclined towards treatment of rare diseases. It has been observed that the viable way for large Pharma to bolster pipelines, expand market

growth prospects, and address the challenges of fast- approaching patent expirations is through mergers and acquisitions.

2. OBJECTIVE

- To study and analyze the trends in orphan drugs approval
- To categorize the orphan drug manufacturer based on market capitalization and analyze the orphan market dynamics
- To analyze the trends of mergers and acquisitions amongst pharmaceutical companies

3. MATERIALS AND METHODS

3.1 Study design

A non-systematic review of literature has been applied in this research to study the trend of orphan drug approval in U.S

3.2 Study Duration

The study is based on orphan drugs approval in the time duration of 2010-2016 to predict the trend in the coming years

3.3 Data Collection

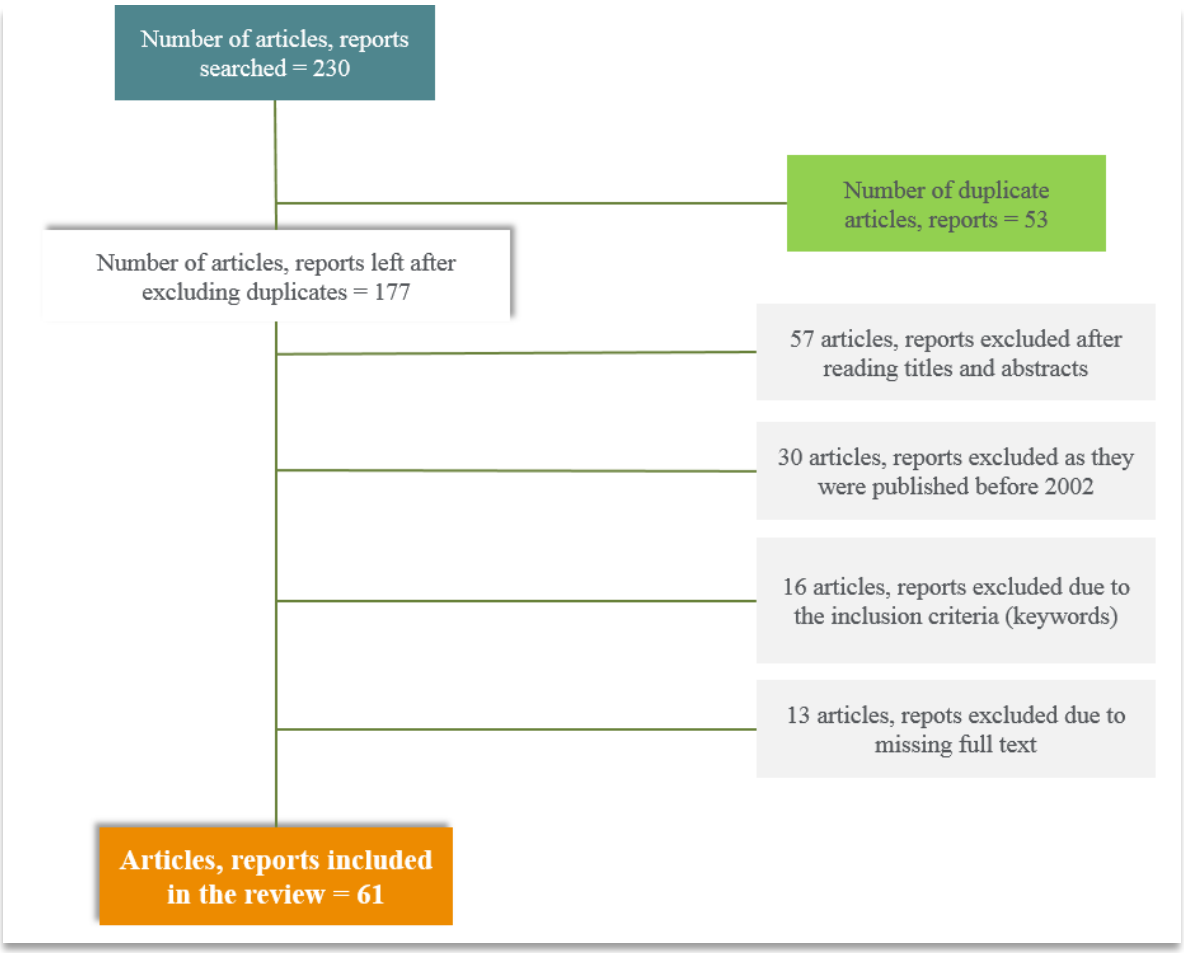
Secondary Research is conducted. The data gathered from various sources is compared and analyzed. The data are collected from:

- Internal Data such as previous researches from various published sources and written submission from interested parties was considered
- Government statistics and information from government agencies like FDA
- Different sources like articles from journals, reports from research centers and electronic databases that includes Research Gate, PubMed Central, BioMed Central, ScopeMed, Oxford Journals, British Medical Journals and International journal of health sciences and research

3.4 **Sample**

The data is obtained for the USA. The selection criteria for taking this country is, it is the first country to launch Orphan drug act, which has a great role in diverting attention of pharma companies in this domain.

3.5 Sample Size



Keywords (inclusion criteria): Orphan drugs, orphan diseases, orphan drug act, market capitalization, mergers and acquisitions, orphan drug approval, US orphan drug market, FDA

Exclusion Criteria: Articles and reports on medicinal products approval and reimbursement process in the USA and Europe were excluded.

The sample size contains **61** relevant articles, journals, projects, and papers published.

4. REVIEW OF LITERATURE

A literature search was performed to identify published studies related to the Orphan drug market. The search was limited to full paper articles published in English. However, this review gives a broad reflection of substantial research performed across different countries. The review of literature provides the in-depth description of the various components, such as OD approval process, segregation of pharma companies on market capital basis, mergers, and acquisitions of the pharma companies, based upon which the study result is analyzed.

4.1 Worldwide prevalence

According to WHO- there may be as many as 7,000- 8,000 rare diseases. Most of them have genetic basis. A rough estimate would be that one out of 15 persons worldwide could be affected by a rare ("orphan") disease that makes the total to around 400 million people worldwide, of whom 30 million are in Europe and 25-30 million in the United States. Rare diseases are serious chronic diseases, and may be life-threatening [9]. Till date, only 5% of rare diseases have approved treatment [6].

This estimate has been used by the rare disease community for several decades to highlight, though the individual diseases may be rare, the total number of people with a rare disease is large.

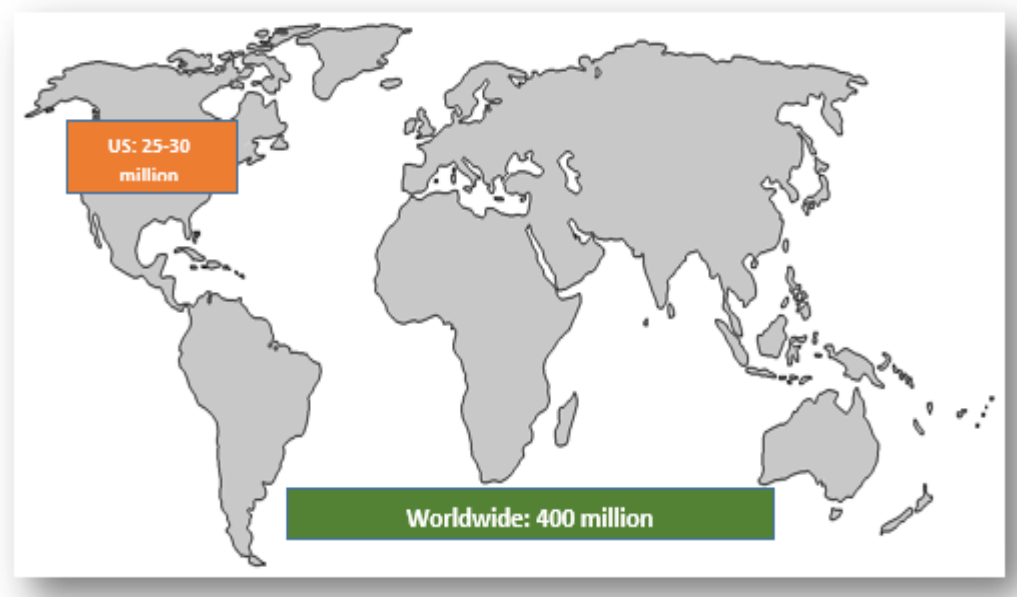


Figure 4.1 Prevalence of Orphan diseases worldwide and in US

4.2 Scenario in US

In the United States, only some specific types of rare diseases are diagnosed when a person is diagnosed. These include certain infectious diseases, birth defects, and cancers etc. As, most rare diseases are not tracked, it is hard to determine the exact number of rare diseases or how many people are affected. In the United States, over 400 products have been approved as therapy for more than 200 rare disease indications [(9)]. In addition, the establishment of various (research) programmes and networks has also helped in advance understanding and diagnosis of rare diseases. The U.S. National Institutes of Health was launched, with the aim of fostering international collaboration in rare diseases research. However, despite these positive developments, the burden of rare diseases continues to persist.

According to the National Institutes of Health (NIH), an orphan disease is defined as a condition that affects fewer than 200,000 people nationwide. This includes diseases as familiar as cystic fibrosis, Lou Gehrig's disease and Tourette's syndrome and as unfamiliar as Hamburger disease, Job syndrome, acromegaly etc. Some diseases have patient populations of fewer than a hundred. By and large, however, they affect as many as 25 million Americans, and that makes the diseases, and finding treatments for them, a severe public health concern [(4)].

An orphan drug is defined in the 1984 amendments of the U.S. Orphan Drug Act (ODA) as a drug intended to treat a condition affecting fewer than 200,000 persons in the United States, or which will not be profitable within 7 years following approval by the FDA [(6)].

In a study by J.K. Aronson (2006) on rare diseases and orphan drugs, state that the word orphan comes from the Greek word orphanos, a child who has lost one parent or both, or an adult who has lost a child, whereas in modern English the word orphan is most commonly used in its original Greek sense, but metaphorical meanings have also emerged. An orphan vehicle, for example, is a discontinued model, and an orphan is a line of type that begins a new paragraph at the bottom of a column or page. This study, defined Orphan diseases as the one that are neglected by doctors and are used to designate the diseases that only affect small number of individuals. An orphan drug can be defined as one that is used to treat an orphan disease [(7)].

4.3 Problems faced by patients with rare diseases

Due to the exceptional nature of the rare diseases the patient has to face great difficulties as the condition of the sufferer is not easily correlated with the other familiar conditions.

Problems of patients [10,11].

i. Difficulty in obtaining an accurate diagnosis
ii. Limited treatment options available
iii. Little or no research being done on the disease
iv. Difficulty finding physicians or treatment centers with experience in treating a rare disease
v. Treatments that are generally more expensive than those for common diseases
vi. Reimbursement issues related to private insurance, Medicare, and Medicaid
vii. Difficulty accessing medical, social, or financial services or assistance because those making the decisions are not familiar with the disease
viii. Feelings of isolation and of having been abandoned or "orphaned" by healthcare system

In a study by Arrigo Schieppati et al (2008) to assess the impact of rare diseases on community and public health, around 1800 questionnaires were mailed to organizations dealing with rare diseases and it was analyzed that in 25% of the patients, 5–30 years had elapsed from the time of first symptoms to the correct diagnosis, 40% of the patients were diagnosed incorrectly (before final diagnosis) and the others had no diagnosis, 16% of the patients had to undergo surgery due to incorrect diagnosis, 33% did not receive appropriate medical treatment and 10% were given psychological care on the assumption that symptoms were psychosomatic. 25% of the respondents travelled to another region to obtain a confirmatory diagnosis and 2% travelled abroad. Also, it was recorded that the method of communicating the diagnosis was unsatisfactory. The study concluded that despite limitations to the methods, appropriate information and medical expertise on rare diseases are often insufficient and access to care is difficult which leads to increased risk of medical complications and late sequelae [12].

Another study conducted by Karolina Budych et al (2012) on 107 subjects to assess the impact of patient physician interaction in rare diseases and it was observed in 36% cases the patient had more knowledge about the disease than physician, in 54% cases physician and patient take mutual decision on any treatment, in 6% cases physician takes all decisions and

in 4% cases patient takes decisions all alone thereby, showing that people with rare diseases often face challenges, due to the low prevalence and the resulting lack of knowledge of their healthcare providers [13].

4.4 Overview of Global Pharmaceutical market:

The pharmaceutical industry is the part of the healthcare sector that deals with medications. The industry comprises different subfields pertaining to the development, production, and marketing of medications. These interdependent subfields consist of drug manufacturers, drug marketers, and biotechnology companies [14].

4.4.1 Overview of pharmaceutical industry:

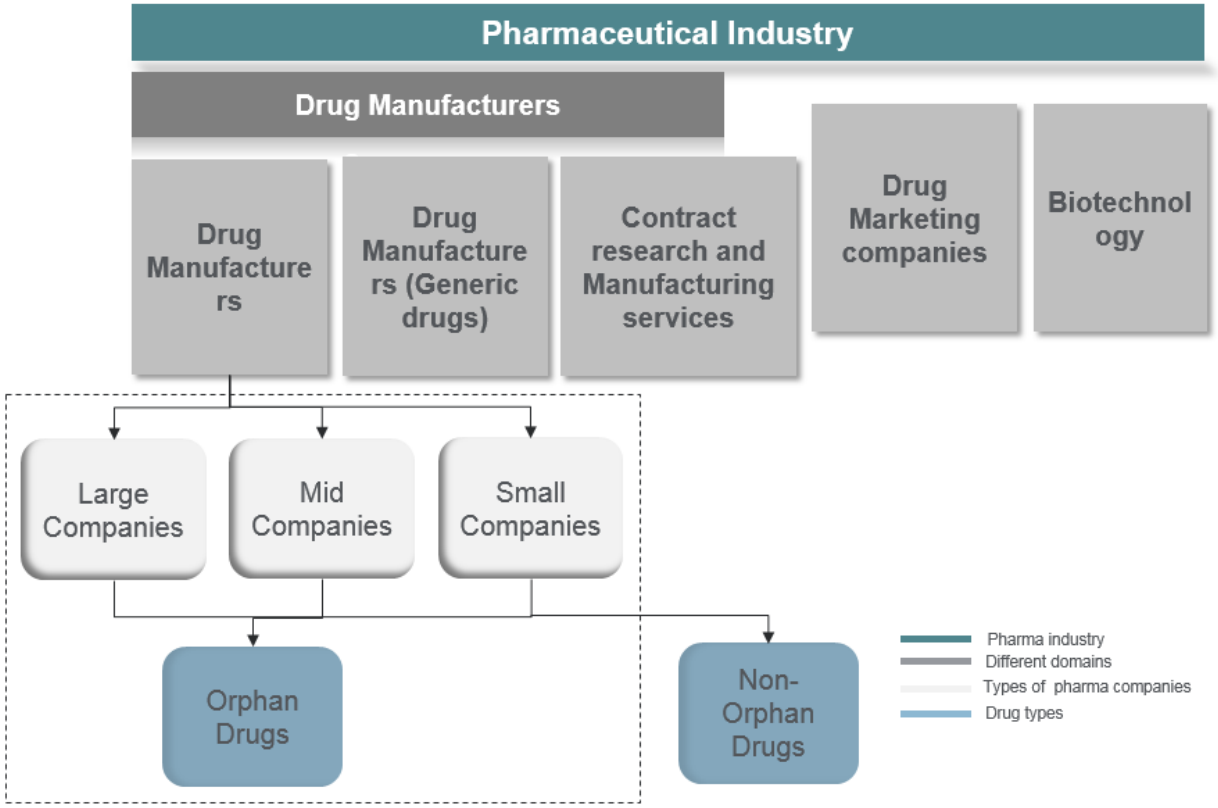


Figure 4.2 Overview of global pharmaceutical industry

Source: Market Realist

Drug manufacturing: It includes the companies that are involved in manufacturing various formulations, such as generic drugs, which are the off-patented, cost-effective, low price drugs and patented drugs that are developed by companies through in-house research.

Drug marketing: Helps in increasing the market reach of drugs.

Biotechnology and R&D: Pharmaceutical companies are either dependent on their in-house R&D centers, or they rely on biotechnology companies to provide them with licenses to manufacture patented products.

4.4.2 Regulatory bodies

The pharmaceutical companies have to follow the policies set by regulatory bodies. These bodies monitor not only manufacturers, but also drug sellers and prescribing physicians [15].

Figure 4.3 Pharmaceutical industry regulators
Source: Market Realist

4.4.3 Worldwide sale of orphan drugs

The worldwide sale of orphan drugs has shown an increase over the span of years. It is estimated to be 16.4% of the total prescription sales in 2016. Orphan drugs are set to account for 21.4% of global prescription sales in 2022 showing an upsurge in the total orphan drug market [8]. Prescription drugs are those drugs that are taken for reasons or in ways or amounts not intended by a doctor or taken by someone other than the person for whom they are prescribed [16].

4.5 Overview of the US Pharmaceutical market

According to Global Business Report (2015), The U.S.-based pharmaceutical industry conducts most of the world's R&D in pharmaceuticals. In 2012, of the approximately $137 billion spent globally on pharmaceutical R&D, around $50 billion was from the United States [17]. Globally, the pharmaceutical market has reached nearly $1 trillion in revenues,

of which the United States has generated more than 40%. The annual Medicines report, from the IMS Institute for Healthcare Informatics, 2016 states that the US sales has reached $424.8bn and the year over growth rate was 8.5% [18].

According to evaluate Pharma report, of the top 100 drugs in the US the average cost per patient per year for an orphan drug was $140,443 in 2016, compared with $27,756 for a non-orphan [8].

The regulatory body in US is FDA which ensure that the entire drug development process safeguards both innovation as well as health.

A study by Thomson Reuters (2013) to assess the increased focus of pharmaceutical company on rare diseases and increase in investment in R&D by various companies, analyzed that due to good return on investment in Orphan drugs market the pharmaceutical industry are undergoing a transformative approach to drug therapy and, companies investing in rare diseases have been able to maximize the sales potential of existing drugs by relocating them into additional rare diseases [19].

In another study by Karen Finn (2013) on changing focus of pharma companies found that the interest of pharmaceutical industry in developing Orphan Drugs has been increasing rapidly over years and this approach seems to persist in the near future [20].

Mark Kessel in his study (2011), to know the problems faced by pharmaceuticals working in OD market, observed that pharmaceutical companies have entered OD market, and some, like Pfizer, have even created specific business units which focused exclusively on orphan diseases to help make up for the imminent loss of revenues associated with their other drugs that are facing patent expiry. Also, this study states that these firms will have to build drug development competence for rare disease indications and marketing infrastructure for niche populations [21].

Another study by Shilpi Kumari et al (2013) to know the trends in the development of Orphan Drugs, found that major multinational pharmaceutical companies are investing in the field of rare diseases and the increase in number 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 outpouring in development of orphan drugs by various companies [22].

A study by Igho j Onakpoya (2015) on 74 OD to assess effectiveness, safety, and cost of orphan drugs, concluded that 73% demonstrate moderate quality of evidence. 85% showed significant clinical effects, but serious adverse events were reported in 86.5%. Their annual costs were between £726 and £378 000. There was a significant inverse relationship between disease prevalence and annual costs [23].

4.5.1 Timeline of Orphan drugs

The timeline give the detail description of the OD market in the chronological order since when the ODA has not been passed till date and even the future perspectives in OD market (56)

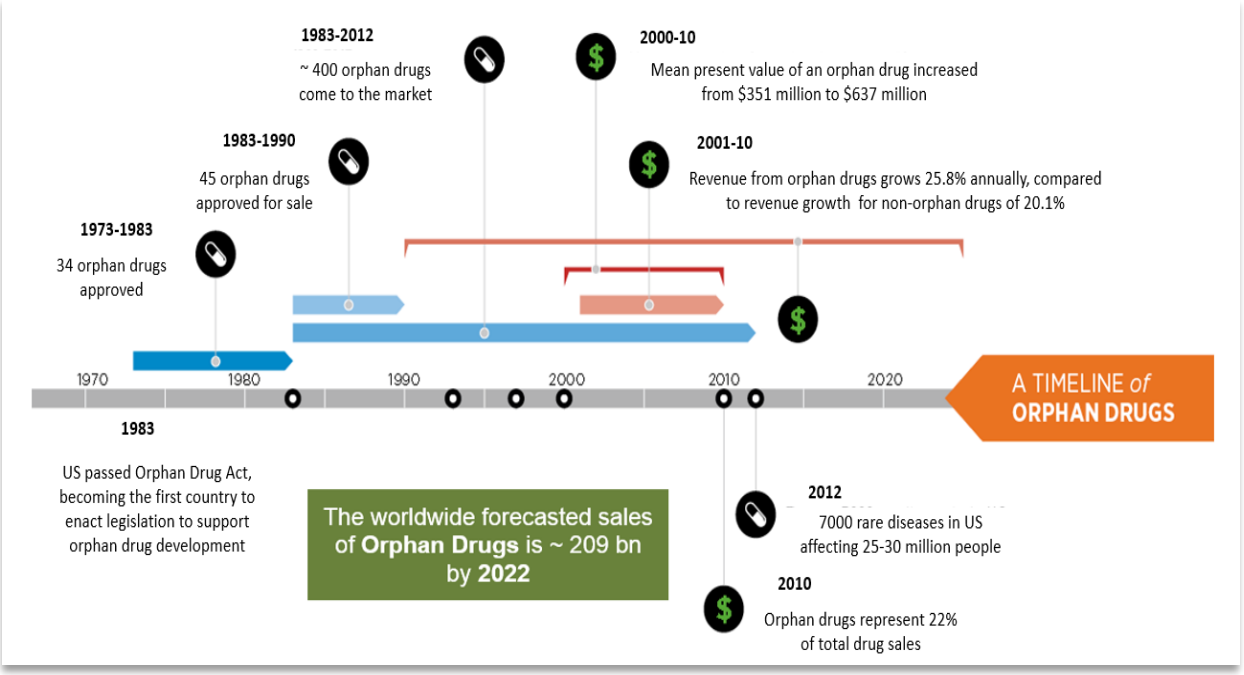


Figure 4.4: Timeline of Orphan Drugs
Source: Pamplin, 2013

Timeline illustrates that a great improvement is seen in the orphan drug market starting from the enactment of Orphan Drug Act, 1983, before which only 34 orphan drugs were available in the market. The timeline also show that the OD market is contributing a higher portion of revenue as compared to the non-orphan drugs. Also, the percentage of sales of OD is increasing as the time lapse indicating that many pharmaceutical companies are trying to enrich portfolio by investigating in several new opportunities, like OD market, contrary to the traditional business model.

4.5.2 Orphan Drug Act

The Orphan Drug Act seeks to protect Orphan Drugs, that is, drugs that need to be adopted by a pharmaceutical company if they are to be brought to market. Due to a few individuals are affected by any one rare disease or condition, a pharmaceutical company which develops an orphan drug may reasonably expect the drug to generate relatively small sales in comparison to the cost of developing the drug and consequently to incur a financial loss as a result of which promising orphan drugs will not be developed unless changes are made in the applicable Federal laws to reduce the costs of developing such drugs and to provide financial incentives to develop such drugs[24, 25]. Incentives for the development of orphan drugs has a great impact on public interest

The Orphan Drug Act is recognized as one of the most successful legislation actions of the United States. Prior to its enactment, only 34 products which treat rare diseases were approved. The ODA significantly increased the annual flow of new clinical trials, spurred innovation in novel drug technologies, as well as in personalized drugs and lead to the identification of numerous new disease types.

Novel Drugs encompasses the innovative products that serve previously unmet needs or otherwise significantly help to advance patient care and public health. These drugs have chemical structure that have never been approved before [26].

The multitude of orphan products now available and the consistent growth in the number of orphan designations demonstrates the ability of the ODA in stimulating research into rare diseases. Nonetheless, the ODA has numerous issues which permit specific orphan drugs, under relatively uncommon instances, to become highly profitable and/or treat patient populations more than 200,000. The issues surrounding orphan drugs will likely amplify as these essential and emotionally compelling pharmaceutical products occupy a greater place in healthcare budgets and within pharmaceutical product portfolios [27].

4.5.3 Orphan Drug designation and approval

The FDA Office of Orphan Products Development (OOPD) mission is to advance the evaluation and development of products (drugs, biologics, devices, or medical foods) that demonstrate promise for the diagnosis and/or treatment of rare diseases or conditions.

A. Eligibility:

A previously unapproved drug may be eligible for orphan drug status if it meets the definition of an orphan drug and is:

i. A previously unapproved drug

ii. A new orphan indication for an approved drug

iii. The "same drug" as one already approved but with a potential to be "clinically superior"

Sometimes, a drug may be granted orphan status when it is under development for only a subset of persons with a disease or condition, a demonstration that the subset is medically plausible. A medically plausible subset of a more common disease has been defined only in terms of a characteristic of the drug that would limit its use to just a segment of those afflicted. An example of a medically plausible subset is of a drug so toxic that only the most severely ill patients would use it (e.g. stage IV cancer), there would be too many risks for a less ill patient to use that therapy [28].

In a study by U.S. Department of Health and Human services on improvement in development of products for rare diseases due to incentives by OOPD, observed that the program has successfully enabled the development and marketing of over 600 drugs and biologic products for rare diseases since 1983. Also, it was found that, fewer than 10 products came to market before the launch of the program [10].

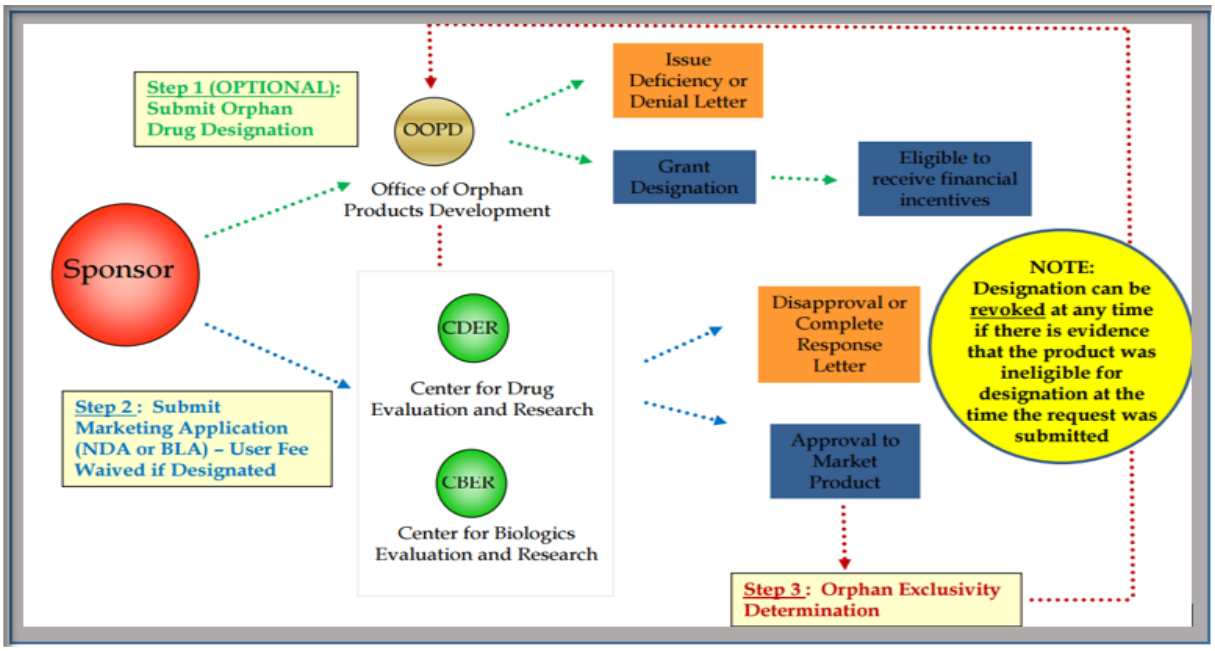


Figure 4.5: Orphan drug designation and authorization
Source: FDA

CDER/ CBER: is a focal point for public inquiries regarding human drug products. It deals with various drug regulatory programs.

NDA (New drug application): An application to FDA for a license to market a new drug

BLA (Biologics license application): An application to FDA for a license to market a new biological product

Figure 4.6: Orphan drug designation request can be submitted during the pre-clinical and clinical development phases
Source: FDA

B. Requesting Orphan Designation

The sponsor must submit the request for orphan designation to OOPD before filing the NDA/BLA. After the grant of orphan designation by OOPD, a drug is said to have orphan status. In case of request for designation of a drug for the same indication as a previously designated product, the sponsor must submit their own data in support of their designation request.

C. Orphan Drug Status

Orphan status and FDA approval are not the same. In case the drug obtain the status of an orphan designation, however, the standard regulatory requirements and process for obtaining marketing approval does not get altered. Sponsors must establish safety and efficacy of a compound to treat a rare disease through adequate and well-controlled studies [(29)]

Repurposing of Products for Rare Diseases- These are the products that have received orphan status designation and are already market-approved for the treatment of some other diseases.

Sponsor of the OD send the request to the OOPD (secretary) to provide written recommendation for the investigation which is to be conducted before the drug is approved (under section 505) or licensed, if biological product (under section 351). The secretary promulgates the procedure based on information available. After this, sponsor request the secretary to designate the drug which is done before the submission of application under section 505 or 351. In case secretary finds that the drug should be investigated for rare disease

and its application is approved under section 505 or licensed under section 351, secretary give the drug ODD.

Also, in case the application is approved or licensed the manufacturer have to notify secretary about any kind of discontinuance at least 1 year before discontinuance. The secretary then promulgate procedure for implementation.

Secretary may not approve another application for same drug for at least 7 years except when:

i. Holder of license or approved certificate is unable to provide sufficient quantities of drug
ii. The holder provides secretary in writing the consent for approval of other application or license before expiration of 7 years

D. Incentives

Orphan drugs are in great demand by patients with rare diseases. The ODA provides for granting special status, orphan drug designation, to a product to treat a rare disease or condition upon request of a sponsor. Once the product used for the treatment of rare disease or condition fulfill the eligibility criteria orphan drug designation is given to the drug. Orphan designation qualifies the sponsor of the product for [30]:

i. Seven-year marketing exclusivity to the first sponsor obtaining FDA approval of a designated drug
ii. Tax credit equal to 50% of clinical investigation expenses
iii. Exemption/Waiver of PDUFA application (filing) fees
iv. Assistance in the drug development process
v. Orphan Products Grant funding

Philip J. Vickers in his study (2013) on Orphan drugs analyzed that much improvement has been noticed after the Orphan Drug Act and the future for the development of drugs to treat rare diseases is bright. Also, the study observed that much improvement is seen in the rate of development of new therapeutic modalities in the treatment of rare genetic diseases [31].

In a study by Cara Toman (2016) on role of Orphan Drug Tax Credit in R&D of rare diseases, observed that since the creation of ODTC, more than 200 new OD have been approved by FDA, compared with only 34 approvals before the ODTC was enacted [32].

Incentives for orphan drug development

Table 4.1: Drivers in orphan drug market

R&D Drivers	Commercial Drivers
Tax credits	Favorable reimbursement
R&D grants	Fewer hurdles to approval
Waived FDA fees	Longer exclusivity
Shorter development timelines	Lower marketing costs
Greater regulatory success	Faster uptake
	Premium pricing

a) Drug development drivers of Orphan Drugs

Economic Value

The factors underlying the positive investment case for OD, which are related to product development, including the following [33,34]:

i. **Tax credits**: US OD regulation grants tax credit amounting to 50% of money spend on R&D.

ii. **R&D grants**: There is annual grant funding in US to address the costs of qualified clinical testing expenses. In addition, US regulations provide support to companies in protocol development and clinical study design. The FDA's grant program is to support clinical development of products used for rare diseases.
Phase 1 studies are eligible for up to $250,000 per year for up to 3 years. Phase 2 and 3 studies are eligible for up to $500,000 per year up to 4 years

iii. **Fee waivers**: FDA PDUFA filing or user fees are waived for companies with less than $ 50 million worldwide revenues. PDUFA fees for application requiring clinical data are currently ~ $ 2 million.

iv. **Favorable clinical development costs**: Besides, the cost benefits already mentioned, there is a strong evidence indicating that clinical development spend for OD is lower than that for non-orphan drugs. The average and median phase III clinical trial costs for OD are 46% and 64% that of non-orphan drugs, respectively. Practically, this could translate to phase III clinical trial costs for OD being one-quarter that of non-orphan drugs, when the 50% tax credit is taken into

consideration. Evidence of 6.6-fold difference in the number of clinical trial participants in the largest trails.

v. **Regular approval success**: It has been estimated that OD designation status is associated with the higher FDA first-cycle approval rates compared to non-orphan drugs.

vi. Efficient clinical development and regulatory approval timelines

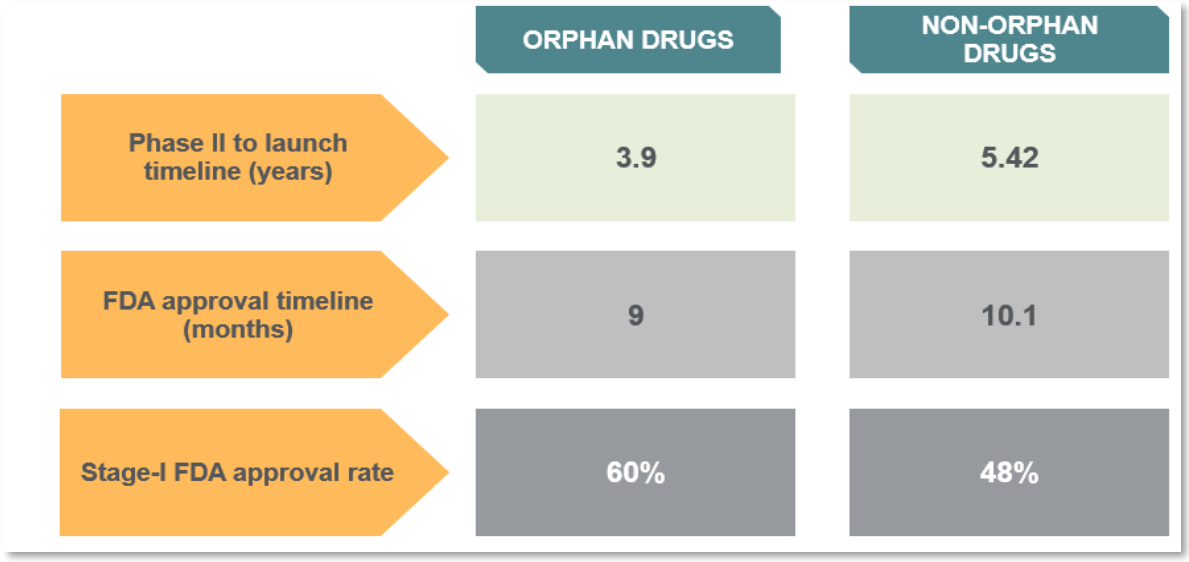


Figure 4.7: Orphan vs non-orphan development timelines and approval success

b) Commercialization drivers of Orphan drug

Economic value

The factors underlying the positive investment case for OD, which are related to commercialization, include the following:

i. **Market exclusivity**: US grant 7 years' market exclusivity from the date of approval. This market exclusivity benefit is incremental to patent exclusivity for drugs that are not patent-expired and can represent tremendous financial gains for the product.

ii. **Premium pricing**: Pricing pays an important role in driving the economic value of orphan drugs, given that there is an inverse correlation between price and prevalence.

iii. **Product use expansion through follow-on indications**: Some of the top selling OD are for single indication use, the revenue generating potential of OD is clearly enhanced by obtaining multiple follow-up indications, including additional orphan indication. An economically viable strategy for Biopharma R&D, which evaluated the present value of revenues of cohort of OD, indicate a correlation between multiple orphan indication and overall product value.

There are two additional factors that could be considered as commercialization drivers of OD economic value, albeit based more on directional evidence compared to the one discussed above- rapid market uptake and lower marketing costs (relative to non-orphan drugs)

E. Challenges in Orphan Drug development

There are various challenges faced by the pharmaceuticals companies during the development of Orphan drugs [35,36]:

i. Small size of rare disease populations is the biggest challenge to orphan drug development by far. Patients with these progressive, serious, life-limiting and life-threatening diseases are often geographically dispersed, due to which it become difficult to find sufficient patients who could reach the sites of clinical trial.

ii. Lack of expertise of the medical practitioners for the conditions that are seen so rarely. It often results in a consolidation of expertise at a single or few locations that may be troublesome for some patients to reach.

iii. Large, placebo-controlled, randomized trials or repetition of even small trials are not always feasible in small populations as seen in case of rare diseases. Thereby, restricting the possibility of study replication. Acceptability of clinical outcomes that serve as trial end points, regulatory flexibility in terms of the evidence required for drug approval, support groups and innovative statistical design is often used for orphan drug evaluation and approval.

iv. Another challenge in orphan drug development is that the natural history of rare diseases is often poorly or incompletely understood, which is considered as a valuable tool in learning how the disease progresses over time.

v. An additional, perhaps over-looked challenge to orphan drug development is the lack of advocacy or support groups for many rare diseases. Support groups are considered important for patients and families as they provide knowledge about the disease, guidance, and resources. Support groups identify interested patients that may be appropriate for new and ongoing clinical trials thereby, helping to advocate for research funding. These groups can also support patient-focused drug development efforts by listening patient and family concerns and perceptions of disease.

vi. Uncertainty of duration of treatment in case of orphan diseases

vii. Lack of appropriate end points results in difficulty in predicting the outcomes

In a study by Philip J. Vickers (2013) on challenges and opportunities in the treatment of rare diseases, observed that major challenges associated with the orphan diseases are the R&D in rare disease field due to the unique characteristics of rare disease patient population. Another challenge, according to the study is little knowledge about pathophysiology of disease and less number of patients available for clinical studies [(31)].

In another study by Aaron S. Kesselheim et al (2011) on all new orphan and non-orphan drugs approved between 2004-2010 to treat cancer to assess clinical testing dates, approved indications, and regulatory characteristics (regular vs accelerated review, advisory committee review, post-marketing commitments). The study also compared design features (randomization, blinding, primary end point) of pivotal trials supporting approval of orphan and non-orphan drugs and rates of adverse safety outcomes (deaths not attributed to disease progression, serious adverse events, dropouts) in pivotal trials, it was observed that 15 orphan and 12 non-orphan drugs were approved between January 1, 2004 and December 31, 2010. Pivotal trials of orphan drugs had smaller participant numbers (median, 96 [interquartile range {IQR}, 66-152] vs 290 [IQR, 185-394], patients exposed to the drug ($P < .001$) and were less likely to be randomized (30% vs 80%). The study indicated that there is a great difference in the blinding of Orphan and non-orphan pivotal trials, with orphan trials less likely to be double-blind (4% vs 33%). Primary study outcomes also varied, with orphan trials more likely to assess disease response (68% vs 27%) rather than overall survival (8% vs 27%). Serious adverse events in trials of orphan drugs were noticed compared to the trials of non-orphan drugs (48% vs 36%) [(37)].

A study conducted by W. Ansari (2016) to compare clinical trial attributes used in pivotal studies for both orphan and non-orphan oncology drugs approved between February 2013 and September 2015, found 14 trials for orphan drugs (54%) and 12 trials for non-orphan drugs (46%) approved to treat cancer diseases between February 2013 and September 2015 indicating that OD get approval easily compared to non-orphan drugs [38].

4.5.4 Clinical Trials

Clinical trials for drugs to be used for treatment of rare diseases also have to face ethical conduct, efficacy, and safety as other, non-orphan drugs. However, while performing trials of orphan drugs, investigators face many challenges that are not usually noticed in clinical trials on larger populations [38].

A. Drawbacks of clinical trials includes:

i. Small size of the trial population due to spread of the population in a wider geographical area
ii. Problems of coordination in a multi-lingual and multi-cultural continent with a diversity of healthcare systems

Most of the OD are used to treat life-threatening conditions due to which they often receive a priority review, which is a mechanism used by the FDA to promote the scrutiny of the drugs which are expected to have greater effect on the treatment of a disease [39], moreover, the patients being enrolled in these clinical trials are smaller in number resulting in less amount of data available for the review. Therefore, the orphan drugs take comparatively less approval time than that of the non-orphan drugs.

Randomized, double-blind, placebo-controlled studies (i.e. the gold standard of clinical trials) are not always possible to conduct, so an alternative study designs are often required, in the setting of rare diseases. Also, to show adequacy in a study having very small number of patients, products might need to show a compelling treatment effect than the studies conducted on large population. As the patients suffering from rare diseases are less in number, so to recruit enough patients for investigations of an orphan drug, clinical trials often need to be conducted at multiple sites. Careful coordination and harmonization through national or international networks of centers or clinics is required at these multicenter. The Rare Diseases Act, signed into law in the United States in 2002, provided a legislative mandate to establish the ORD within the National Institutes of Health. The

ORD provides support for the RDCRN, consisting of 10 clinical research consortia and a Data and Technology Coordinating Center (Fig. 4.8).

The aim of the RDCRN is to facilitate team work amongst experts on multiple groups of rare diseases and create platforms for the association to identify biomarkers for disease risk, disease severity & activity and clinical outcome. These consortia also encourage the development of new approaches to diagnosis, prevention, and treatment of rare diseases. In addition, the ORD provides support for basic and clinical research on rare diseases and supports the activities of patient advocacy groups such as the Genetic Alliance and the National Organization for Rare Diseases [40].

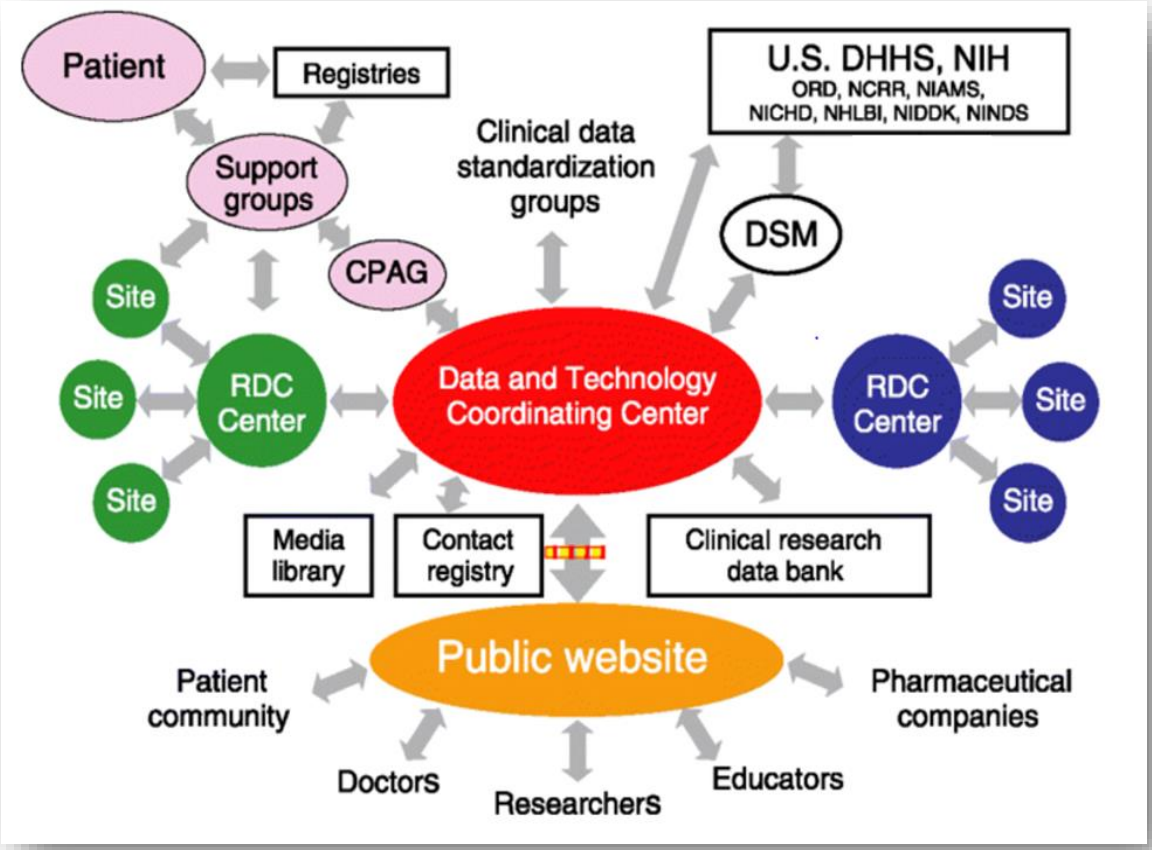


Figure 4.8: Organization of Rare Disease Clinical research Centre network in the US
Source: Journal of internal medicine

4.6 Classification of Pharmaceutical companies based on market capitalization

For the ease of understanding about, which segment of pharmaceutical industry is shifting towards the Orphan drug market, the pharma companies are categorized into large, mid, and small cap based on their market capitalization [41].

According to Economic Times, Market capitalization is the aggregate valuation of the company based on its current share price and the total number of outstanding stocks. It is calculated by multiplying the current market price of the company's share with the total outstanding shares of the company.

Table 4.2: Differentiation of pharma companies

Company Type	Characteristic (market capitalization)
Large-cap	Over $ 10 billions
Mid-cap	$ 2-10 billions
Small-cap	$ 300 million - $ 2 billion

4.7 Trends

With the lapse of time the sum and frequency of M&A have started rising. Many opportunities exist for smaller players, even in the emerging countries, to collaborate with multinational pharmaceutical companies provided that the technology platforms or specialty medicinal products are what the big pharma wants [42-44].

Merger and Acquisitions:

Mergers and acquisitions (M&A) is the area of corporate finances, management and strategy dealing with purchasing and/or joining with other companies. In a merger, two organizations join to become a new business unit, usually with a new name or the name incorporating both the firms, moreover, the companies involved are typically of similar size and stature. In an acquisition, on the other hand, one business buys a second and

generally smaller company is absorbed into the parent organization or run as a subsidiary [45], wherein the larger firm take hold of all the shares and products of the organization which has been acquired. M&A is the way being adopted by several firms to achieve exponential growth and to generate interest.

Pharmaceutical companies are trying to refine their portfolios. They have now realized that the greatest investment opportunity is in specialty areas, which will enable them to obtain enough revenue. Because of this, various larger companies acquire small biotech companies to catch hold of the assets that they have been unable to develop themselves. In addition to this, the trend of M&A is increasing as the big pharma want to integrate their portfolios to meet their strategic needs. They are targeting their efforts on those therapeutic areas where they feel they have greater strength and probability of succeeding.

In another study by Sonali Chatterjee et al (2016) to gauge the effect of mergers and acquisitions it was observed that M&A have long been a popular element of corporate strategy, it represents an important alternative for strategic expansion through external growth and is becoming popular due to their capacity to create additional revenues [46].
Karen Finn in his study (2013) on Mergers and Acquisitions found that establishing business units for rare diseases by collaborating with or acquiring SME's that are already established in this sector are also increasing, as seen in case of acquisition of Genzyme by Sanofi [20].
Makarand Jawadekar in his study (2017), to assess the trend of mergers and acquisitions in pharma industry, found that mergers and acquisitions is becoming a common trend for big pharma, wherein large companies that are losing the revenues due to the expiry of patented drugs are now getting motivated to buy companies with great revenue potential, if they have the cash to do so [47].

Some of the M&A that took place:

- Sanofi and Genzyme merger- The future of their M&A is also bright as the company plans to launch a new medicine every 6 months in the next 4 years. The acquisition of Genzyme was a real driver for Sanofi's transition from an old pharmaceutical giant based on chemistry and small molecules to a modern Biotech giant [48]

- Glaxo Smith Kline and Human (GSK) genome sciences (HGS), complete ownership of GSK on HGS has helped the firm to optimize R&D, commercial and manufacturing operations to advance its products most effectively and efficiently while securing the full potential long-term value of the assets [49]
- Amgen's acquisition of Onyx helped both the firm in expanding their pipelines [50]. The acquisition of Onyx has added many late-stage pipeline products of Onyx into Amgen's portfolio
- Shire Baxalta and NPS Pharmaceuticals acquisition- The acquisition enabled Shire to expand its portfolio in rare diseases. Shire has expertise in the field of gastrointestinal, ophthalmic, and neuroscience drugs [51]
- AbbVie and Pharmacyclics merger- AbbVie has been interested in reducing its dependence on a single drug. AbbVie purchase of Pharmacyclics will reduce its dependence on rheumatoid arthritis blockbuster Humira (adalimumab), whose patent expires next year [52].
- Alexion Pharmaceuticals Inc M&A with Synageva, has enabled the firm to enter high-priced rare diseases market. The willingness of Alexion to pay an impressive amount for Synageva demonstrates that the demand for large acquisitions in healthcare continues unabated. It also highlights the attraction of medicines for rare diseases that can command exceptionally high prices with little payer pushback because of the limited number of patients [53]
- Acquisition of Actelion by Johnson & Johnson, indicates that rare diseases are emerging as an alluring takeover target as these drugs face less pricing pressure [54]

5. DISCUSSION AND CONCLUSION

The shift of the pharmaceutical companies towards OD market is increasing progressively. Companies are entering into orphan vertical by expanding their product line. The availability of new drugs and biological products often means new treatment options for patients and advances in health care. For this reason, CDER supports innovation and plays an important role in supporting development of new drugs. The data for the orphan drugs was collected from the FDA site to observe the trend in approval [55-61].

I. Comparing worldwide sales of Orphan Drugs

In 2016, Orphan Drug sales ($114bn) increased to 12.2% as compared to 2015 ($101bn). By 2022 Orphan Drug sales (worldwide) are forecasted to reach $209bn. OD are expected to account for 21.4% of total prescription sales in 2022 (excluding generics), thereby up from 11.1% in 2010.

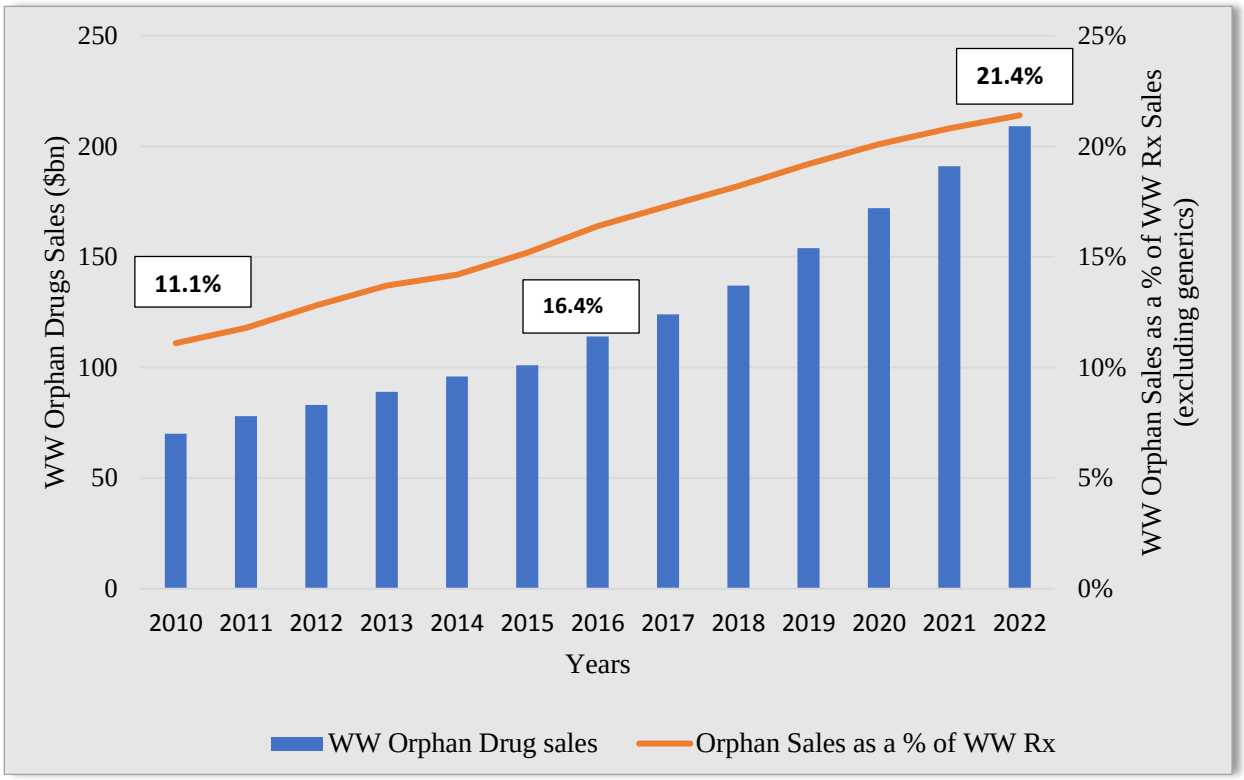


Figure 5.1: Worldwide Orphan Drug sales and share of prescription drug market (2010-16)

The worldwide Orphan Drugs sales in 2010 was $70bn and in 2016 was $114bn highlighting an increase in sale at the rate of 8.64% during a span of 7 years. The forecasted sales in 2022 is $209bn which is estimated to escalate at the rate of 10.85% when compared to sales in 2016.

Overall, orphan drug market shows a consistent increase in terms of sales and revenue during the period of 12 years, 2010-2022.

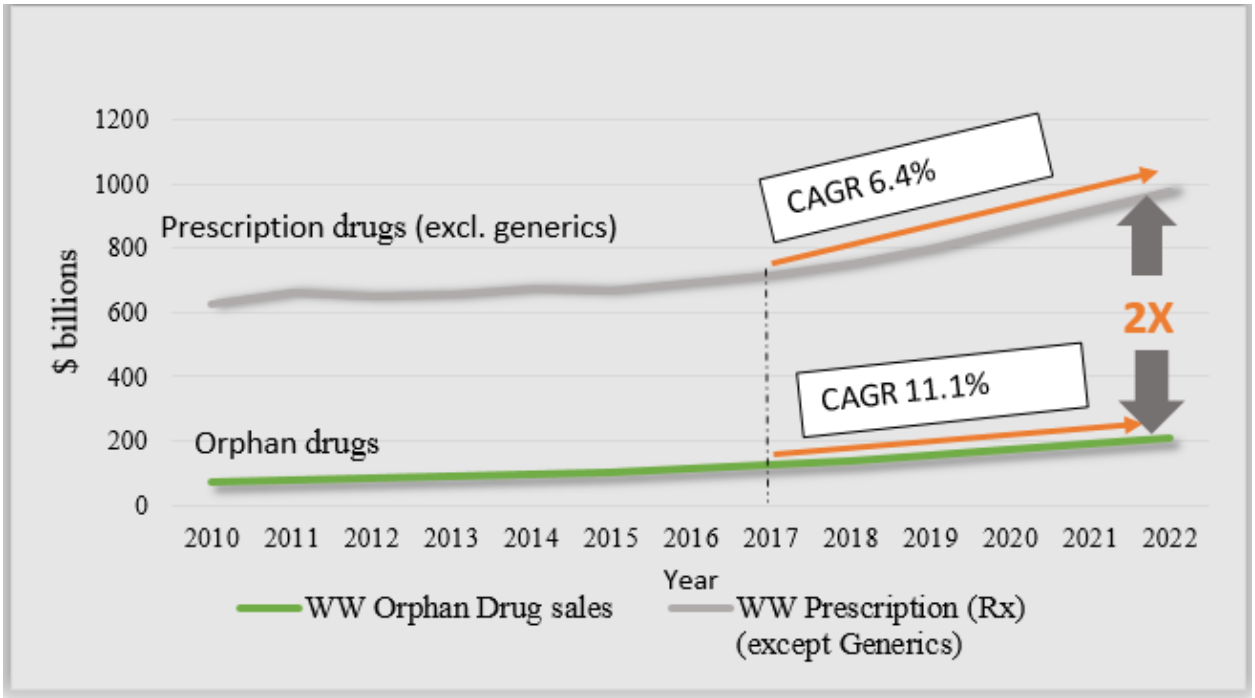


Figure 5.2: Graph depicting forecasted worldwide change in CAGR of prescription drugs and Orphan drugs (2017-2022)

Prescription drugs: These are the drugs that are not available without the doctor's advice

The compound annual growth rate (CAGR) of OD for 5 years (2017-22) is calculated to be 11.1% while that of the prescription drugs for the same duration is 6.4%, which is almost half of the Orphan Drugs.

Implication:

CAGR of Orphan Drugs is projected to be double of that of prescription drugs, indicating there is preeminent scope in this domain. This is one of the prominent factor for pharma companies to invest in this field rather than solely investing in traditional drugs. As indicated in graph 5.1, OD market has shown a steady growth over the years suggesting that the growth in OD market will have a favorable impact on the overall pharmaceutical revenue growth.

II. Percentage of Orphan drugs approval from total approvals granted in the period of 2010-2016

Plotted graph shows a gradual increase in the number of OD approval through the years. 2015 shows highest number of OD approvals, while 2010 has lowest number of OD

approvals. The percentage of approvals has increased with the progressing years, however year 2016 is an exception to this as it shows a decline of 6% when compared to the previous year.

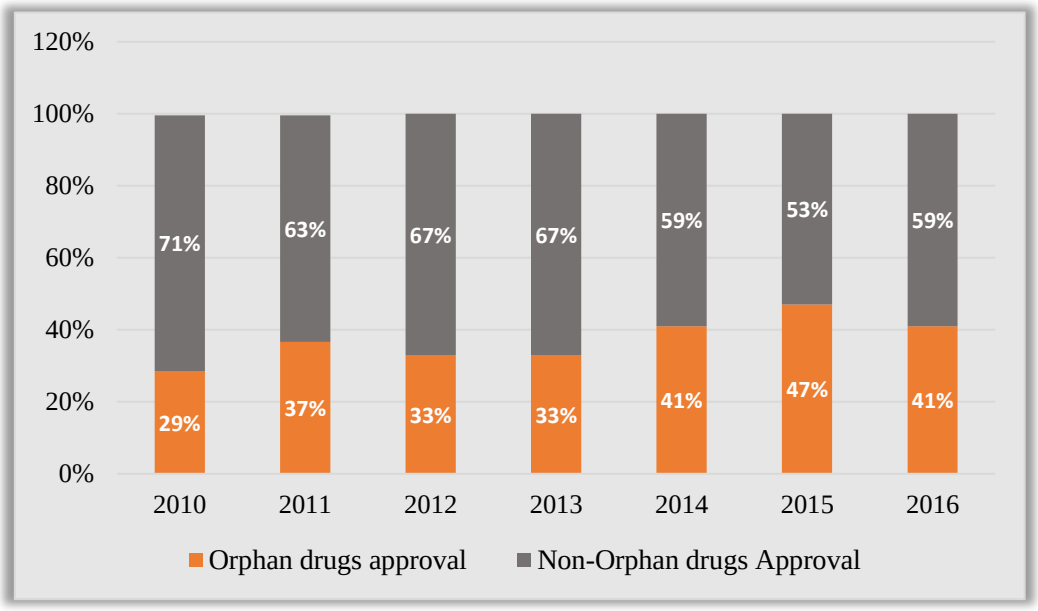


Figure 5.3: Graph showing the percentage of orphan drugs approval as a percentage of Novel Drug Approval during the years

Novel Drugs are those, that have never been approved before

Implication:

The pharmaceutical companies have started filing more number of applications for approval of OD. Also, the approval process for OD is comparatively less stringent than other drugs. To promote the development and review of drugs, CDER used number of regulatory programs including fast track, breakthrough therapy and priority review and accelerated approval.

- **Fast Track**- Drugs that can treat unmet medical needs
- **Breakthrough Therapy**- A drug with preliminary clinical evidence demonstrating that it may result in substantial improvement on at least one clinically significant endpoint over available therapies
- **Priority Review**- A drug is given a priority review if there is potential to provide a significant advance in existing medical care

- **Accelerated approval**- Early approval based on markers that predict a reasonable benefit, with more testing to confirm clinical benefit after approval

III. Categorization of pharmaceutical companies

Not only blooming pharma companies have deflected themselves towards the OD market but also emergence of medium and small size organization in this segment is noticed. The pharma companies that have started to spread their branches in OD market, have been broadly classified into large cap, mid cap and small cap depending upon the market capital.

- **Large cap pharma company**- Company with a market capitalization value of more than $10 billion
- **Mid-cap pharma company**- Company with a market capitalization value between $2-10 billion
- **Small cap pharma company**- Company with a market capitalization value of less than $2 billion

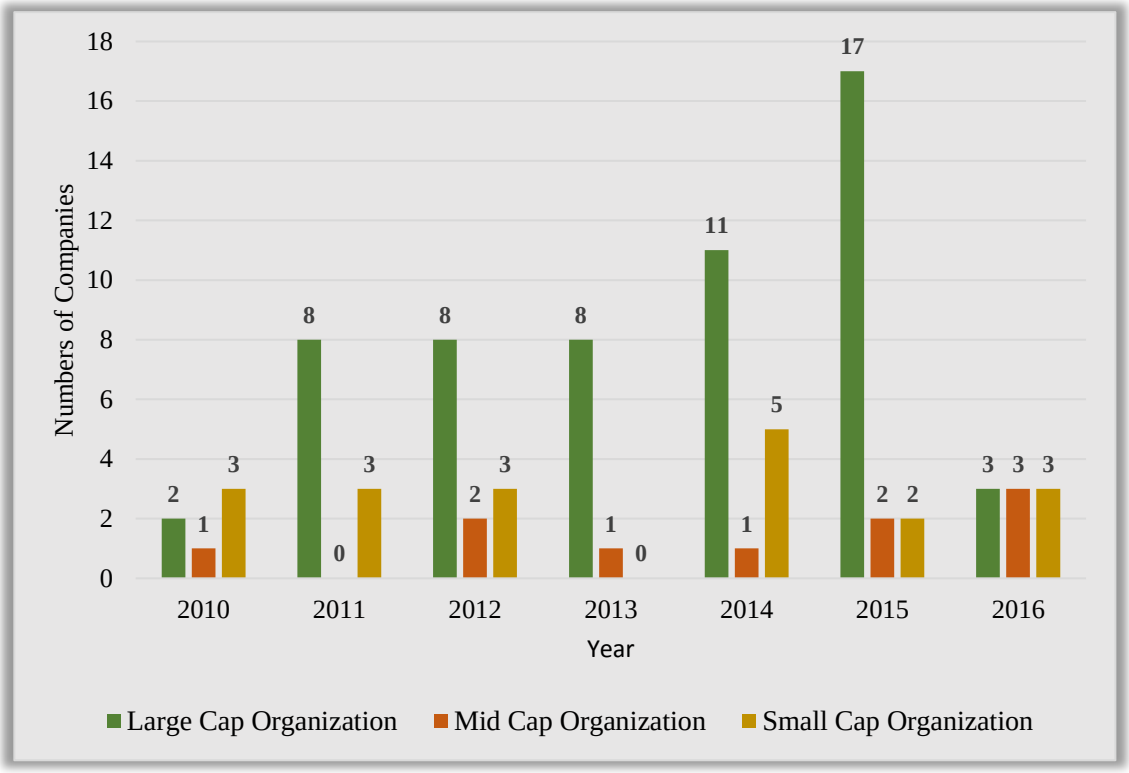


Figure 5.4: Segregation of large, mid, and small cap pharmaceutical companies with Orphan Drug approval during 2010-2016

The graph shows that the number of large cap organizations have shown an increase throughout the time span of 2010-2015 with maximum increase in 2015. However, contrary to this, large cap organizations experienced a sudden decline in 2016, reason being that the FDA granted approval to five drugs which industry watchers had expected to be approved in 2016, pushing up the numbers for 2015. Also, in 2016, FDA delayed the approval of several medicines of large cap firms, until companies got their plants in compliance with the agency's current Good Manufacturing Practices (cGMP) standards.
Year 2016 have shown a lift in OD approvals by mid cap companies compared to the preceding years, pointing that mid pharma companies have started venturing in this area.

Implication:

Big (large cap) Pharma Company's interest in OD development is clearly on rise. But now**,** with the advancing years the mid and small cap pharma companies have also started realizing the abundance of scope in Orphan vertical and some have started switching towards it.

IV. Mergers and Acquisitions in the Orphan Drug market

M&A has aided large Pharma companies to bring the reformatory changes as well as minimize the competition. M&A is used as a means by the firms to bolster their core competence and work out strategic position as a global player. To be effective, companies have to look for strengthening their expertise and reducing their extra burden in the departments they are not competent in, this may sometimes be the best or only option to bring in adequate revenue and to survive in global competition.

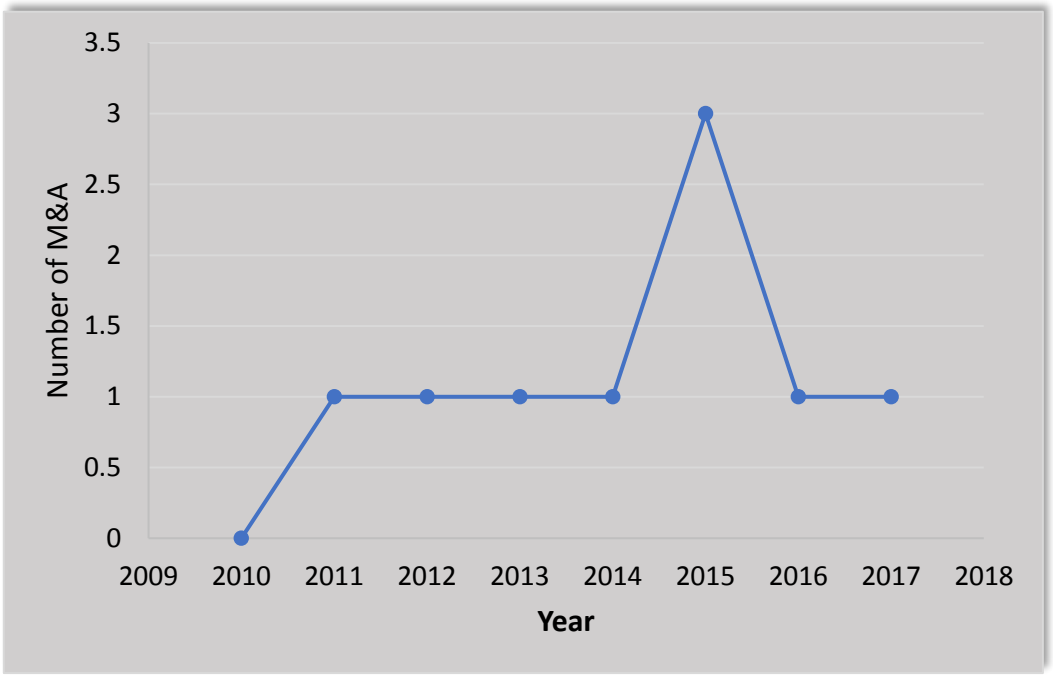


Figure 5.5: Total numbers of Mergers and Acquisitions in Orphan vertical

The graph shows the total number of M&A that took place in OD market. It depicts that 2015 is the year of maximum acquisition. No acquisition occurred during 2010.

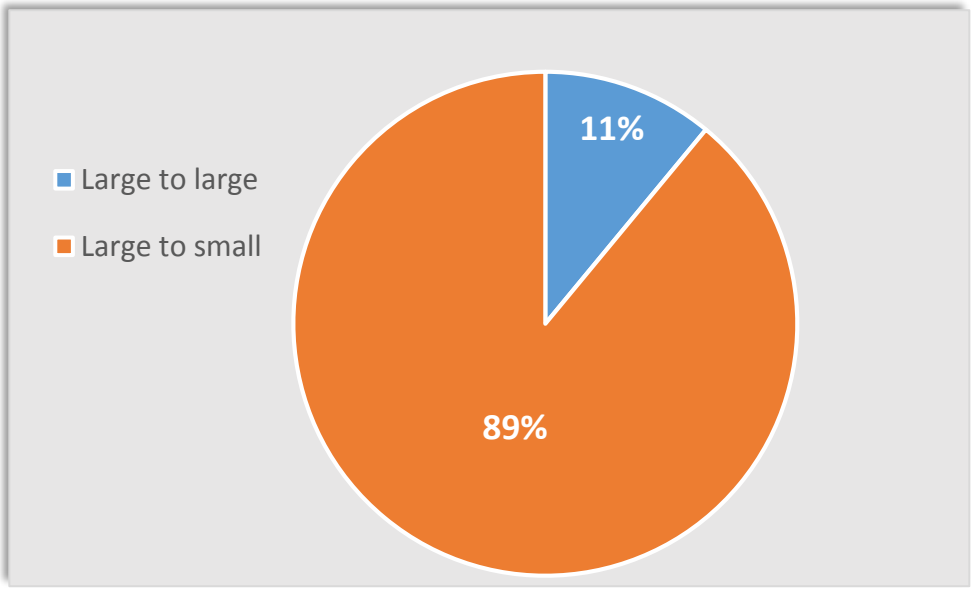


Figure 5.6: Percentage of intersectoral Merger and Acquisition

This above graph shows that maximum number of acquisition took place between large and small cap firms. Following M&A takes place during 2010-16

Table 5.1: Mergers and Acquisitions

Year	Purchaser		Target	
	Company	Type	Company	Type
2011	Sanofi	Large cap	Genzyme Corporation	Small cap
2012	GlaxoSmithKline	Large cap	Human Genome Science	Small cap
2013	Amgen	Large cap	Onyx Pharmaceuticals	Small cap
2015	Roche	Large cap	Genentech	Small cap
2015	Shire	Large cap	NPS Pharmaceuticals	Small cap
2015	AbbVie	Large cap	Pharmacyclics	Small cap
2015	Alexion pharmaceuticals	Large cap	Synageva Biopharma	Small cap
2016	Shire	Large cap	Baxalta	Small cap
2017	Johnson & Johnson	Large cap	Actelion	Large cap

Implications:

- The overall value of the firm, after M&A increases and they work more efficiently
- It leads to better financial planning and control
- The amalgamated company will have their operation higher than each individual company
- The growth of the combination is better than the individual firm
- Diversification of scope of operation
- Better R&D
- Reduced competition

Through this study, it is assessed that large-cap pharmaceutical companies have started spending in the field of rare diseases and the similar arrangement is forecasted to be followed by other large as well as mid and small cap pharmaceutical organizations. The percentage of molecules granted orphan drug status, by FDA, suggests that pharmaceutical companies are diversifying into new therapy area, which was ignored earlier. Economic drivers such as tax credits, grants, waived FDA fees, reduced timelines for clinical development and higher probability of regulatory approval, coupled with commercial drivers such as premium pricing, faster uptake, lower marketing costs and longer market exclusivity, further fuel the economic power of orphan drug development. The study is limited in its scope to US FDA approved drugs only. Though, pharmaceutical industry has

a history of achieving high value and will continue to outweigh challenges with innovative scientists and wise utilization of technologies, but, still for many rare diseases medications are unavailable, which shows that there is need of right planning as well as understanding for their risk and benefits.

6. LIMITATIONS

- **Lack of information**: The study has included the overview of US orphan drug market as the data of other areas is not available.
- **Confidentiality**: As per ZS policy, sharing any data from paid sources and databases used by ZS is strictly forbidden and is considered grounds for immediate termination of employment. Several insights could have been added to this document and existing insights could have been further expanded upon in the absence of this policy. ZS confidentiality policy has not been violated in any way during the preparation and final presentation of this document.
- **Secondary research**: As information and insights were obtained from secondary search, it is advisable to check for any updates, modifications or discontinuations to laws, systems, processes, and stakeholders mentioned in this report before making any recommendations.

7. ETHICAL CONSIDERATION

This study is based on secondary/desk research and uses data from publicly available sources, thus, there are no associated ethical considerations for this study

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