The Orphan Drug Act: Its Implementation and Impact on Rare Disease Patient

by

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Dedication

This thesis is dedicated to my loving brother-in-law, Nagaraju Minda, who encouraged and motivated me all the time to complete this thesis. I also dedicate this thesis to my parents, who made my dreams come true with their immense support and hard work in helping me to complete my master's. I am grateful to have you as my parents.

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It is a pleasure to pay tribute to my family Danaiah, Tulasidevi, Srinivas, Nagaraju, Abhisha, and Lakshmi for their support and motivation in completing my master's degree successfully. Finally, I would like to thank my friend who motivated me to do thesis and helped me all the way in completing the thesis.

Abstract

On January 4, 1983, the Orphan Drug Act was signed into law. Over the past twenty years there has been a considerable increase in the development of pharmaceutical drugs for treating rare diseases, primarily due to the passage of this act. Several incentives are provided by the Orphan Drug Act of 1983 to encourage the development of drugs for treating rare diseases. These drugs are referred as Orphan Products. To find the extent of success of the Orphan Drug Act, an electronic survey was conducted by using Google docs. Responses to the survey were recorded anonymously, and results of the survey suggest that most of the members believe that there is progress in the development of drugs for treating patients with rare diseases after the implementation of the Orphan Drug Act and some of them believe that most of the drugs for treating rare diseases are in the pipeline and still need to be marketed.

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Chapter 1: Introduction

The major health concerns today in the United States are rare disorders. Congress has defined a “rare disease or condition” as one that affects less than 200,000 people in the United States, or one that “affects more than 200,000 in United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug” (Rogoyski, 2006). About 20 million Americans are suffering from these rare disorders, which might be of 6,000 types, including genetic disorders as well as cancers (Pulsinelli, 1999). Every year around 250 new rare diseases and conditions are seen in United States (Wastfelt, Fadeel, & Henter, 2006). Orphan drugs are those that have been developed for treating these rare diseases. Rare diseases and neglected diseases are called as Orphan diseases (Randhawa, 2006). In the European Union a disease is said to be an orphan disease if it affects fewer than 5 in 10,000 people, and the limit of incidence of orphan disease in Japan is 4 in 10,000 people and 1 or 2 in 10,000 people in Australia (Denis, Simoens, Fostier, Mergaert, & Cleemput, 2009). Different countries have their own definition for orphan diseases.

Due to the low incidence of orphan diseases and a lack of awareness among people, the knowledge and study of these diseases are bounded, and its narrow application limits the pharmaceutical companies from developing drugs for these rare diseases as they have small markets. Hence the research and development of the orphan drugs has become very costly; these diseases were orphaned (Sharma, Jacob, Tandon, & Kumar, 2010). This is also partially due to the lack of support, or no one to conduct research on the orphan medication and perform the

essential examining to acquire the necessary acceptance from the Food and Drug Administration (FDA) (Rohde, 2000).

The executive director of the National Organization for Rare Diseases (NORD), which is a patient-consumer oriented health association, stated that it is difficult to motivate sponsors to develop products related to rare disease and conditions. Even though Narcolepsy and Multiple Sclerosis affect more than 200,000 patients, NORD is struggling to find sponsors to promote drugs to these disorders (Gibbons, 1990).

The findings of the Congressional, which are included as a preamble in the Orphan Drug Act of 1983 have summarized and reflected all of these concerns as a motivation stating that: (Field & Boat, 2010)

Congress finds that (Orphan Drug Act, 1983):

(1) "there are many conditions and diseases such as Huntington's disease, Myoclonus, ALS (Lou Gehrig's disease), Tourette syndrome, and Muscular dystrophy which affect such a small number of individuals residing in the United States that the diseases and conditions are considered rare in the United States;
(2) Adequate drugs for many of such diseases and conditions have not been developed;
(3) Drugs for these diseases and conditions are commonly referred to as "orphan drugs";
(4) Because so few individuals are affected by any one rare disease and 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;

(5) There is a reason to believe that some promising orphan drugs will not be developed unless changes are made in the applicable Federal laws to reduce the cost of developing such drugs and to provide financial incentives to develop such drugs and;

(6) It is in the public interest to provide such changes and incentives for the development of orphan drugs."

Chapter 2: Background

The orphan drug problem is due to the FDA's expensive and complex approval process. Before 1960, the drug approval process was a simple process that required only that drug manufacturers demonstrate that the drugs were safe and labeled accurately. At the end of the 1950s and the beginning of the 1960s, use of Thalidomide resulted in tragic birth defects. This led to the passing of the Kefauver-Harris amendments in 1962 to the Federal Food Drug and Cosmetic Act. These amendments state that all drugs, before getting market approval, must be proved safe and effective through accurate and controlled studies (Katz, 2004). Thus changes in the drug approval process occurred and helped in the formation of new drug approval process.

In order to bring a drug from the laboratory to the pharmacy, several steps are required by the FDA. After a drug with a potential therapeutic effect has been identified, it must be first tested in animals to demonstrate both safety and efficacy. This is a time-consuming process. After passing through these pre-clinical studies, the drug has to pass through several steps to test in humans, again to demonstrate safety and efficacy. In some cases, even post-marketing surveillance is required. After passing all these steps and hurdles, pharmaceutical companies have to compile the information and submit it to the FDA for approval. Today the FDA is demanding additional information at each step. In order to conduct all these steps and submit suitable reports to the FDA, a huge investment and effort are required. Apart from this, it is also very important to find a suitable drug candidate. Thus, development of a drug by the pharmaceutical company is a very expensive and time-consuming process (Mahajan & Gupta, 2010).

Most of the drugs developed by the pharmaceutical companies are used for treating conditions that affect many people. The investment incurred in the manufacturing of these drugs

can be recovered from them. As most of those drugs are patentable, profits can be enhanced by selling them without generic competition. In addition, these drugs are having a large market value to recover the investment in the development of drugs now estimated to be $802 million (Vernon, Golec, & Dimasi, 2010).

But the scenario is different in the case of diseases that affect very few people. The market for these drugs is extremely low, and there is no belief in the manufacturers of these drugs that they can recover the cost incurred in drug manufacturing. In addition to this, there are complications in the development process of these drugs because there is difficulty in designing effective clinical trial protocols for these drugs. The problem on the recovery of cost incurred in developing and manufacturing is further aggravated by the fact that, as many of the drugs are already known to have a positive effect for the rare diseases, they are not eligible either to develop as a product or to obtain a patent. Hence, pharmaceutical companies are not willing to invest a huge amount of money in developing products for rare diseases. These are also vulnerable for competition in the market without patent protection. These drugs have no assurance in the market and, moreover, they have limited market value. But still the only reason to develop these drugs is for public service (Villa, Amelia, & Reich, 2008). So, the drugs that are used for treating rare diseases and conditions are called “orphan” drugs, as the pharmaceutical companies are reluctant to adopt them and take them through the drug approval process.

Even though these individual diseases are rare, in aggregate they are affecting 10 to 20 million people in the United States. Hence, in the beginning of 1980, Congress took interest in resolving the problems related to orphan drugs. This resulted in passing the Orphan Drug Act of 1983. The major driving force in bringing the Orphan Drug Act was the NORD, which was led by Abbey Meyers. The passage of the Orphan Drug Act was finally catalyzed by the huge public

outcry in response to the broadcasting of an episode of *Quincy* in 1981. This episode was the story of a boy suffering with Tourette syndrome, which is a classic orphan disease (Pulsinelli, 1999).

2.1 History

Even though for decades there has been interest with the problems concerning the inadequate resources and incentives in the development of orphan products, it has been less than a decade since there have been a specific legislative provisions and attention for these problems. To deal with the problems related to patients with rare disease and resources needed for developing products, the first systematic attempt made was voluntarily initiated by DHEW (Department of Health, Education and Welfare), which is an Interagency Committee on Drugs of Limited Commercial Value. This information was seen on an informal basis by the FDA who later sponsored this committee in 1974. In 1975 Interagency Committee stated in its interim report regarding the problems of patients and proposed various important administrative mechanisms which were potentially useful on economic basis (Haffner, 1991).

As a result of this, in March 1978 a new group was formed voluntarily that included members and representatives from within and outside the agency and pharmaceutical industries. Special awareness had been created by the following achievements by this time:

- In 1977, a chapter was dedicated to the issue of "drugs of little commercial use" in an Office of Technology Assessment (OTA) Report to the Congress stating that these problems existed for a long time and did not receive proper attention and moreover patient needs were not met as there was no systematic study.

- In 1977, Secretary of HEW proposed for the formation of a body in response to the report for the control of Huntington's disease.
- In 1977, an appeal was made by the professional staff at the executive office of the White House, requesting the Pharmaceutical Manufacturers Association (PMA) to consider incentives in the development of orphan products.
- Later in 1978, a survey was done by the PMA to investigate what its firms were doing with orphan products.
- In the late 1970s and early 1980s, Congress modified in drug reform legislation by addressing questions about whether to include orphan drugs through Federal production or industry persuasion.

As a result of all these efforts, in March 1982, the Orphan Products Board was established by the secretary of DHEW in the Department Of Health and Human Services for coordinating federal policies and efforts, and in May 1982, the Office of Orphan Products Development was established by the FDA (Haffner, 1991). Finally on January 4, 1983, the Orphan Drug Act was passed to promote the development and marketing of orphan drugs for treating rare diseases and conditions.

Though the availability of orphan drugs for treating rare diseases and conditions is a worldwide problem, the success of the Orphan Drug Act in the United States had received universal recognition, and many important international events were initiated by this act. FDA officials had facilitated and worked with the officials of Japan and the European Union in designing Orphan Drug legislations to benefit patients of their jurisdiction (Haffner, 1998). The following are the legislations made by the officials of Japan and the European Union:

- In 1993, Japan passed its Orphan Drug Legislation.
- In 1993, a draft proposal was submitted for a European Parliament Council Regulation on Orphan Medicinal Products to the parliament in Brussels.
- In Korea, under the Ministry of Health and Social Affairs, researchers at the Korea Institute of Health and Social Affairs started developing approaches for supplying orphan products in Korea.
- In Australia, efforts were taken by the Australian Department of Health and Family Services Therapeutic Goods Administration for improving access to Orphan Drugs.

2.2 Incentives of the Orphan Drug Act

Various kinds of incentives were provided by the Orphan Drug Act for the manufacturers of orphan drugs, which includes market exclusivity for sponsors, tax incentives, and research grants. The most motivating incentive of the Orphan Drug Act was the seven years of market exclusivity for the manufacturers of that product (Haffner M. E, 1997). Without this market exclusivity, there might be heavy competition from the generic versions of the drug. Market exclusivity for the second application was granted by the FDA for the same sponsor for the same drug but with the different use.

Tax credits up to 50% may be claimed by the manufacturers for conducting clinical research on the designated orphan drugs. Tax credits were extended permanently by the Congress in 1997. These provisions of the tax were administered by the Internal Revenue Service. The Research Grant program was another incentive for developing orphan products, which was administered by the Office of Orphan Product Development (OOPD) in which researchers may compete for research grants for conducting clinical trials in order to support the approval of the orphan drugs. The main objective of this program was to fund the clinical

research that helps in the approval of unapproved drugs or for the approved products which were experiencing unapproved use in spite of their promising results in treating rare diseases and conditions.

Assistance in the development of protocol for research and study design may be requested by the manufacturers for getting an expedited review and approval by the FDA. After requesting assistance in the protocol, a formal review was conducted by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) (Villarreal, 2001).

2.2.1 Overview of the Orphan Drug Act

In 1983 Congress passed the Orphan Drug Act to promote the development of drugs for rare diseases (Sharma et al., 2010). Prior to the legislation of this historical act, pharmaceutical companies had fewer incentives to invest money in developing products for rare diseases, which was unprofitable. This act was proposed in response to the small number of drugs that were approved in the U.S. in the years before it was enacted (Vazquez, Monguio, Szeinbach, & Visaria, 2008). This law provided three incentives: 1) providing 7 years of market exclusivity to sponsors for approved orphan drugs, 2) giving a tax credit of 50% for cost of conducting the clinical trial, and 3) providing federal grants for testing new therapies or diagnose required for approved orphan drugs. In addition to these incentives, the Congress added additional incentives for those pharmaceutical companies that were manufacturing products for rare diseases by making them free from the routine drug application or user fees that were charged by the FDA. Companies were eligible for faster review of their applications if they were developing products for treating life-threatening diseases. And most of the orphan drugs were used for treating life-threatening diseases.

2.2.2 Amendments to the Act 1983

Amendments were made to the act of 1983 in 1984, 1985, and 1988 (Pulsinelli, 1999). The 1985 amendment extended the rights of exclusivity to both patentable and unpatentable products, and the 1988 amendment states that sponsors need to apply for Orphan Designation before submitting an application for market approval. All reviews related to the acts were addressed to the FDA as it plays a major role in administering the acts. Within the FDA there was an office of Orphan Products Development, which awards small grants and administers the Orphan Drug Act. The funds granted by the FDA support clinical trials on effectiveness and safety of the orphan products used for treating rare diseases.

Finally the FDA released its regulation in 1992, which provides the standards and detailed procedures necessary to grant an orphan drug status to a drug and list the agency's commitment for providing the Orphan Drug Act incentives without enabling their misuse.

2.2.3 Orphan Drug Act of 1992

As most of the terms were left intentionally ambiguous by Congress, the FDA has made significant changes and regulations for shaping the Orphan Drug Act. The FDA stated that the main purpose of the Orphan Drug Act was to initiate innovation in developing the products for rare diseases and to make superior drugs available to the patients (Clissold, 1995). In order to achieve this stated purpose, the FDA has made several changes to the Orphan Drug Act.

The major significant change to the act was the incentive of market exclusivity. The act states that it should retain the market exclusivity property even if the population increases beyond 200,000, as it is necessary to protect the sponsor's good faith in investment.

The act also retained the provision that any company can gain the indicated designation by showing that it will not recoup investments. If a company wants to utilize this provision, they need to provide the following information to the FDA.

- They should provide all the data regarding the cost incurred and invested in the development and marketing process.
- They should explain all possible reasons for their investment.
- They should provide information regarding sales promotion by justifying the prices.
- They should give rights to the FDA for evaluating financial records.

2.3 Production of Orphan Drugs

As a result of the Orphan Drug Act, various new products were developed for treating rare diseases and conditions like cystic fibrosis, Gaucher's disease, people affected by HIV complications, hemophilia, and rare forms of cancer. After the implementation of the Orphan Drug Act, there was a rise in the Orphan Drug Designations and marketing approvals. The Orphan Drug Act of 1983 led the FDA approval for 322 orphan drugs between 1983 and 2007, whereas 1,793 Orphan Designations included 1,199 products. Before the enactment of the Orphan Drug Act, only 34 orphan products were marketed by the manufacturers. Of these, only 10 were developed by the pharmaceutical industries, and the remaining were funded and developed by the federal government (Asbury, 1991).The impact of the Orphan Drug Act on orphan drug designations are shown in Figure 1.

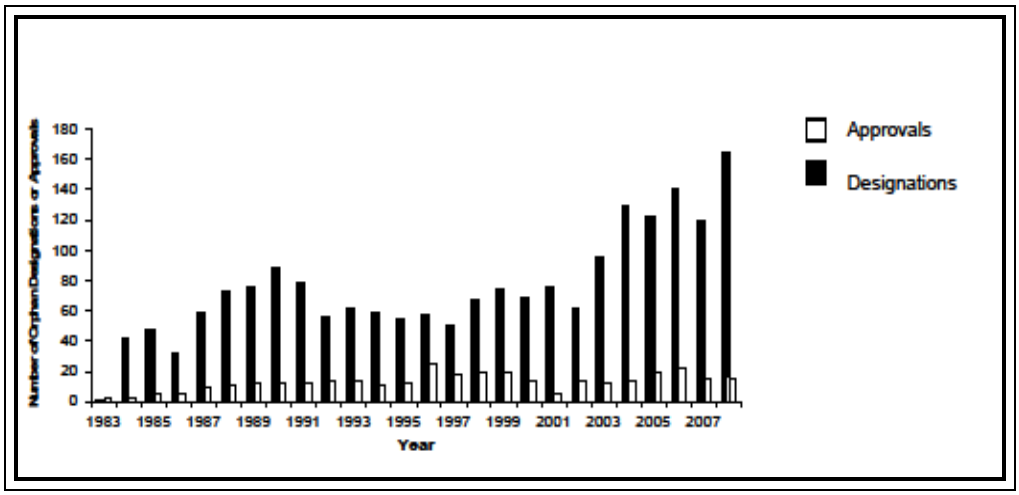

Figure 1. Graphical Representation Showing Impact of Orphan Drug Act on Orphan Drug Legislation

The Orphan Drug Act and the Development of Products for Rare Diseases; Thomas, Mathew T; US Food and Drug Administration; www.fda.gov; n.d.; 10 Jan. 2013.

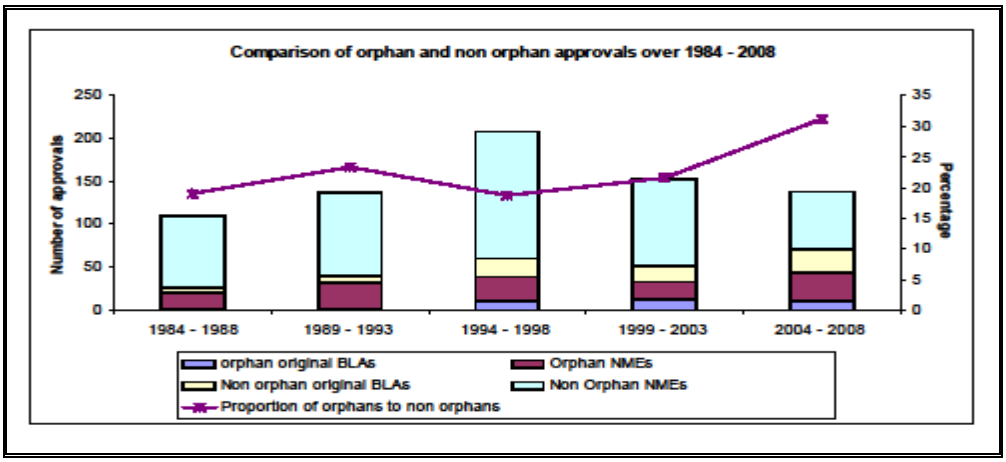

Figure 2. Comparison of Orphan and Non-Orphan Approvals Over 1984-2008

The Orphan Drug Act and the Development of Products for Rare Diseases; Thomas, Mathew T; US Food and Drug Administration; www.fda.gov; n.d.; 10 Jan. 2013.

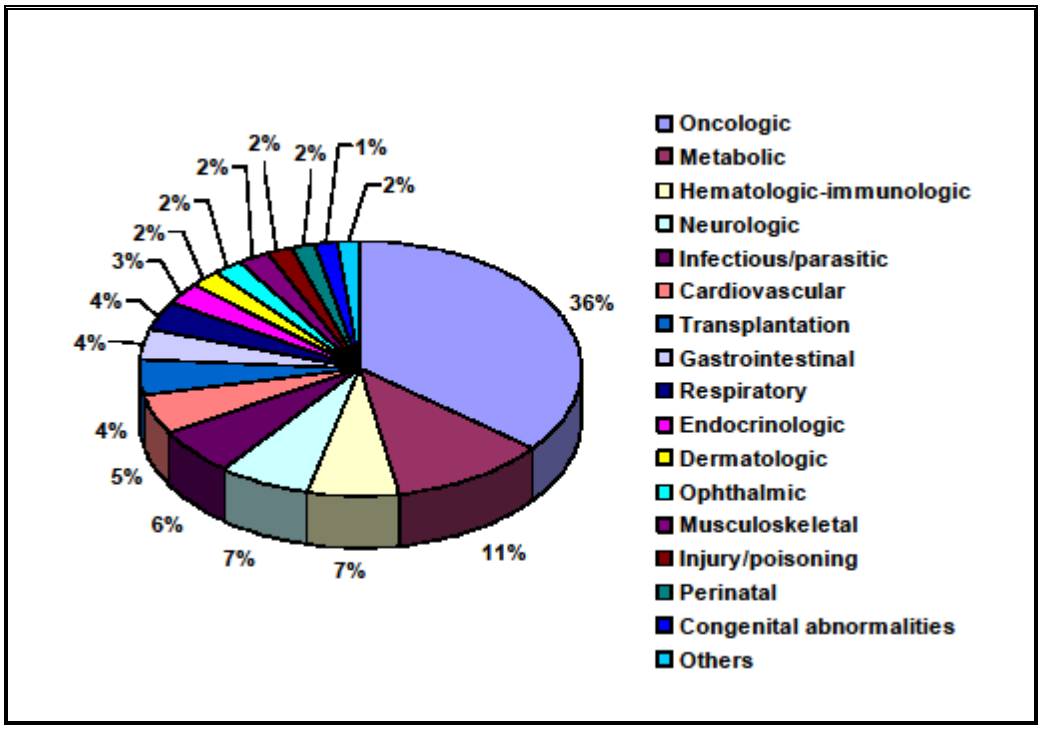

Figure 3. Distribution of Orphan Drugs According to Therapeutic Class

Figure 3. The Orphan Drug Act and the Development of Products for Rare Diseases; Thomas, Mathew T; US Food and Drug Administration; www.fda.gov; n.d.; 10 Jan. 2013.

Due to the increase in the development of drugs for rare diseases, 85% of these drugs were being used for treating serious and life-threatening conditions. The largest numbers of orphan designations were for the rare forms of cancer, which includes ovarian cancer and hairy cell leukemia (Haffner, Whitley, & Moses, 2002). Even though some of the products were developed for single occurrence disease, most of the rare diseases were chronic. About 50% of the approved orphan drugs are for pediatric use.

2.4 Policy Issues and Concerns

Even though the Orphan Drug Act succeeded in the development of products for rare diseases, there were problems in the administration of the act. The major criticism was that it provided excessive profits for the drugs, which were not truly orphans and were highly profitable. Several amendments were made by the Congress over the years in an attempt to prevent the companies from making excessive profits by using orphan drug status. As the Orphan Drug Act was mostly based on the market-oriented strategies in promoting the development of orphan drugs, some critics argued that it resulted in the overpricing of drugs. They stated that over pricing of drugs limited the use of drugs by the patients, particularly people without health insurance coverage. In response to these arguments, some of the analysts stated that any amendments to the incentives of the Orphan Drug Act might result in suppressing research on the development of orphan drugs, which may lead to the development of fewer drugs for treating rare diseases and conditions in the long run (Thamer, Brennan, & Semansky, 1998).

After the enactment of the Orphan Drug Act in 1983, several amendments were considered to the Act on different occasions. By the end of 1980s and at the beginning of 1990s, amendments which were proposed to the Orphan Drug Act had addressed concerns that the orphan products that were developed with federal assistance gained higher profits for the pharmaceutical companies. These proposed changes also included sales cap provisions, but the amendment was not passed as some of the analysts stated that these amendments might damage the incentives and success of the act (Levitt & Kelsey, 1993).

The goals of the Orphan Drug Act were perverted by many industries by still sticking to the initial drug law. Several techniques were used by the sponsors of the orphan products for misusing the Orphan Drug Act (Arno, Bonuck, & Devis, 1995). One of these common

techniques was applying for orphan drug designation and market exclusivity by the sponsors for a narrow indication even though wide range off-label market for other indications exist or may be likely to develop. Another common technique used by the sponsors was applying orphan drug designation for those drugs that were hardly modified versions of the orphan drugs that already existed and had only slight improvements in the therapeutic action. Also patient subgroups were formed by dividing the patient population so that 200,000 patient limits could be avoided. Sponsors of the manufacturing companies were stacking seven-year market exclusivity for the drugs on the top of each other for indications, which differ very negligibly. Table 1 shows the list of companies applying for multiple orphan drug designations.

Table 1

Companies Applying for Multiple Drug Designations

S.NO	**Drug**	**Company**	**Orphan Drug Designation**.
1	Clindamycin	Upjohn Company	i. To prevent AIDS - associated PCP. ii. To treat AIDS-associated PCP.
2	Pentamidine isethionate	Fujisawa Pharmaceutical	i. To treat PCP. ii. To prevent PCP.
3.	Rifabutin	Adria loboratories, Inc.	i. To prevent disseminated MAC. ii. To treat disseminated MAC.
4.	Dapsone USP	Jacobus pharmaceutical.	i. To prevent PCP. ii. To treat PCP.
5.	HIV immune globulin	North American Biologicals.	i. To treat AIDS. ii. To treat HIV infected women and their children.

Abbreviations:

PCP — Pneumocystis carinii pneumonia

MAC — Mycobacterium avium complex

HIV — Human immunodeficiency virus

AIDS — Acquired immunodeficiency syndrome

2.5 Purpose of Study

The purpose of this project is to find whether the Orphan Drugs Act and its implementation is really satisfying the needs of the rare disease patients by surveying the various rare disease patient advocacy groups and to determine the impact of the Orphan Drug Act on the treatment of patients with the disease for which they advocate.

Chapter 3: Research Design and Methodology

3.1 Sample Population

This research was conducted to determine whether the Orphan Drug Act was really satisfying the needs of the people. A well designed electronic device was developed to answer this research question. The population of interest in this study was the survey members of the NORD. The Vice president of Communications of NORD was asked to forward the survey to all the members of the organization.

3.2 Development of Survey Questions

The survey questions were developed for surveying the various organizations representing the particular rare disease in NORD. The survey questions were also framed to answer the research question of whether the Orphan Drug Legislation was really satisfying the needs of the rare disease patients.

3.3 Human Subject Protection

Prior to conducting the research survey, I submitted an application for Review and Approval to conduct research or survey involving human subjects to the College of Health and Human Services Human Subjects Review Committee (CHHS-HSRC) at Eastern Michigan University. The CHHS-HSRC approved the study to conduct the survey on February 04, 2013 (Appendix A: College of Health and Human Services Human Subjects Review Committee Approval Letter).

All the potential participants were informed clearly about the purpose of the study, procedure for responding to the survey, voluntariness and withdrawal, protecting the rights of the

participant, and contact information by means of the Online Survey Consent Form (Appendix B: Survey Completion Request or Online Survey Consent Form or Email Survey).

The informed consent form or Online Survey Consent Form was mailed electronically along with the survey to Mary Dunkle, Vice President for Communications of NORD, and she forwarded the Consent form to the Organizations of NORD. By filling out the survey, the participant agreed to the conditions of the Online Survey Consent Form.

3.4 Method of Data Collection

I have conducted the computer-based survey using Google docs.

The survey instrument (Appendix B: Survey), including the email survey consent form, was sent to the Mary Dunkle, following the approval of CHHS-HSRC. The survey instrument included the consent form and two mandatory questions to be answered before the subjects took the short online survey. The purpose of two mandatory questions was to ensure that the potential participant read the consent form and voluntarily agreed to take the survey. Then, it directed the participant to the survey (Appendix C: Survey). After completing the 6 questions regarding the Orphan Drug Act, the participant was directed to click the “submit” button, which submitted their anonymous answers to the investigator.

Chapter 4: Analysis and Presentation of Data

A total of 14 responses were recorded for the survey regarding the Orphan Drug Act. The survey was answered by executive directors, volunteers, and patients of the NORD. Results of the survey likely suggest that new products to treat the rare diseases are now available in the markets which were not available before implementation of the Orphan Drug Act 1983, while some of them reported that they have not seen any progress in the treatment of the rare diseases. Tables 2-4 present the tabulations of responses recorded.

Question 1:

What rare disease patient group does your organization advocate for or support?

The purpose of this question was to know which rare disease patient organization they are serving. Eleven responses were recorded to this question, which includes the following:

(a) Ataxia

(b) Mitochondrial Disorder

(c) Congenital Hyperinsulinism International

(d) Gaucher disease

(e) Organic Acidemias

(f) Pulmonary Hypertension Association

(g) Primary immune deficiency and Narcolepsy

(h) Niemann-pick types A, B, and C

(i) CIDP

(j) American Porphyria Foundation

(k) Cold Auto Inflammatory Syndrome

Question 2:

What is the size of the population in the U.S, with this rare disease?

Members of the organization were asked to select one of the following options: (a) <1000, (b) 1000-10,000, (c) > 10,000.

The purpose of this question was to find out the size of the population with that rare disease in the United States. According to the results from Table 2, the following results were reported:

- Twenty-nine percent of the members reported that the size of population with rare diseases (congenital hyperinsulinism international, Gaucher disease) in the United States was less than 1000.
- Fourteen percent of the members reported that the size of the population with rare disease (Organic Acidemias) in the United States was in the range of 1,000-10,000.
- Fifty percent of the members reported that the size of population with rare diseases (ataxia, mitochondrial disorder, pulmonary hypertension association, primary immune deficiency and narcolepsy, Niemann-pick types A, B and C, CIDP, and American Porphyria Foundation) in the United States was greater than 10,000.

Table 2

Survey Responses Regarding the Population

Response	**Frequency**	**Percent (%)**
<1000	4	29%
1000-10,000	2	14%
>10,000	7	50%

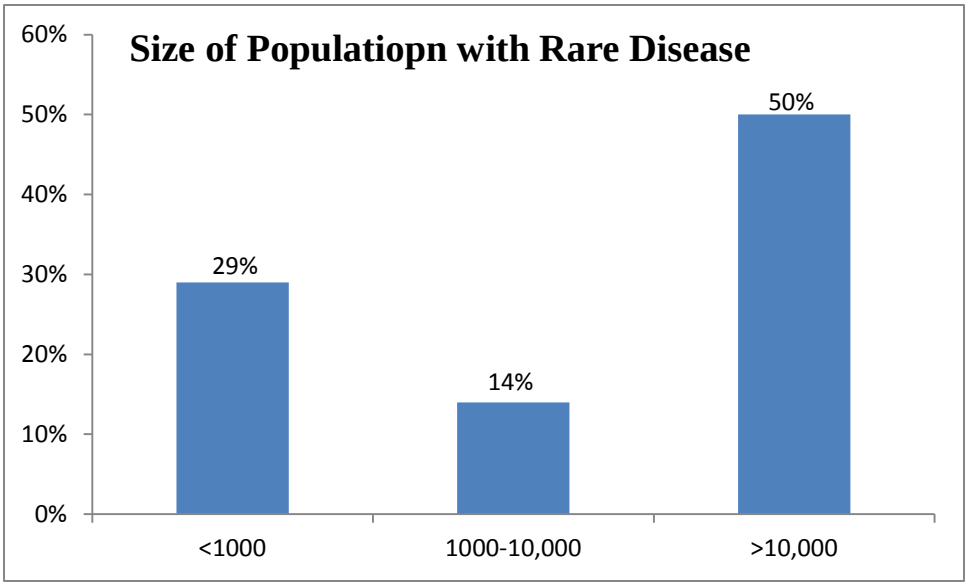

Figure 4. Graphical Presentation of the Size of Population With the Rare Disease

Question: 3

How long has your organization been in existence?

Members of the organization were asked to select one of the following options: (a) 0-5 years, (b) 6-10 years, (c) >10 years.

The purpose of this question was to find out length of the existence of the organization. From the results of Table 3, the following was reported:

- Twenty-one percent of the members (Gaucher disease) reported that their organization has been in existence for 0-5 years.
- Fourteen percent of the members (mitochondrial disorder, congenital hyperinsulinism international) reported that their organization has been in existence for 6-10 years.

- Fifty-seven percent of the members (ataxia, pulmonary hypertension association, primary immune deficiency, narcolepsy, Niemann-pick types A, B and C, CIDP, American Porphyria Foundation, and organic acidemias).

Table 3

Survey Response Regarding the Existence of the Organization

Response	Frequency	Percent (%)
0-5 years	3	21
5- 10 years	2	14
>10 years	8	57

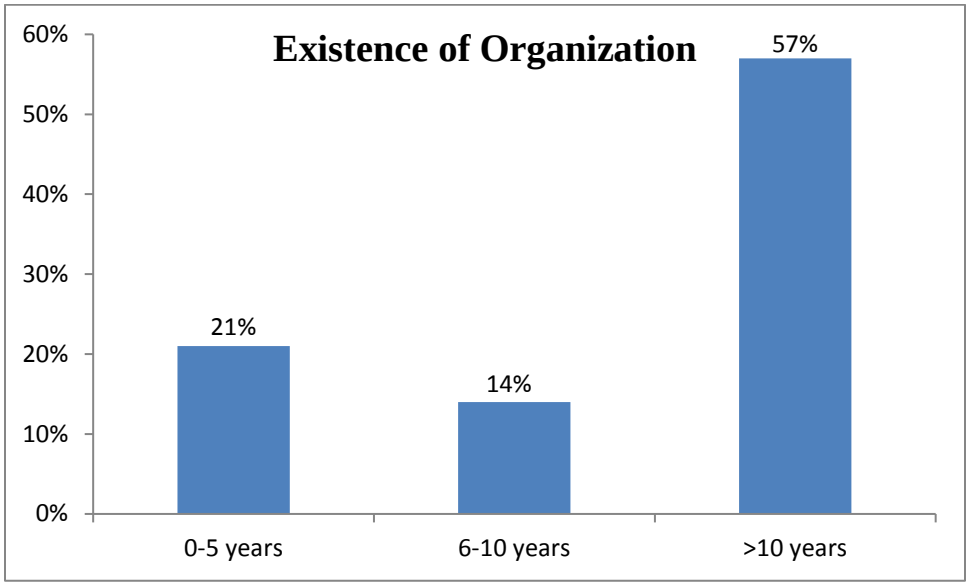

Figure 5. Graphical Representation of Existence of an Organization

Question: 4

Are you familiar with Orphan Drug Act?

Members of the organization were asked to select either yes or no.

The purpose of this question was to find out whether the members of the organization were familiar with the Orphan Drug Act.

- Ninety-three percent of members reported that they were familiar with the Orphan Drug Act.

Question: 5

Do you feel your patients/members have benefited from the Orphan Drug Act?

Members of the organization were asked to select one of the following options: (a) Yes, new products to treat this rare disease are now available that were not available before the implementation of the Orphan Drug Act in 1983; (b) Yes, new products to treat this rare disease are in development but not yet marketed; and (c) No, I have not seen any progress in the treatment of this rare disease.

The purpose of this question was to find out whether the members of the organization had seen any improvement in the development of drugs for rare diseases after the implementation of the Orphan Drug Act.

- Fifty-seven percent of the members reported that new products to treat rare diseases are now available in the market that were not available before the implementation of Orphan Drug Act in 1983.
- Seven percent of the members reported that new products to treat rare diseases are in development but not yet marketed.
- Twenty-nine percent of the members reported that they did not see any progress in the treatment of the rare diseases.

Table 4

Response Regarding the Implementation of Act

Response	Frequency	Percent (%)
a	8	57%
b	1	7%
c	4	29%

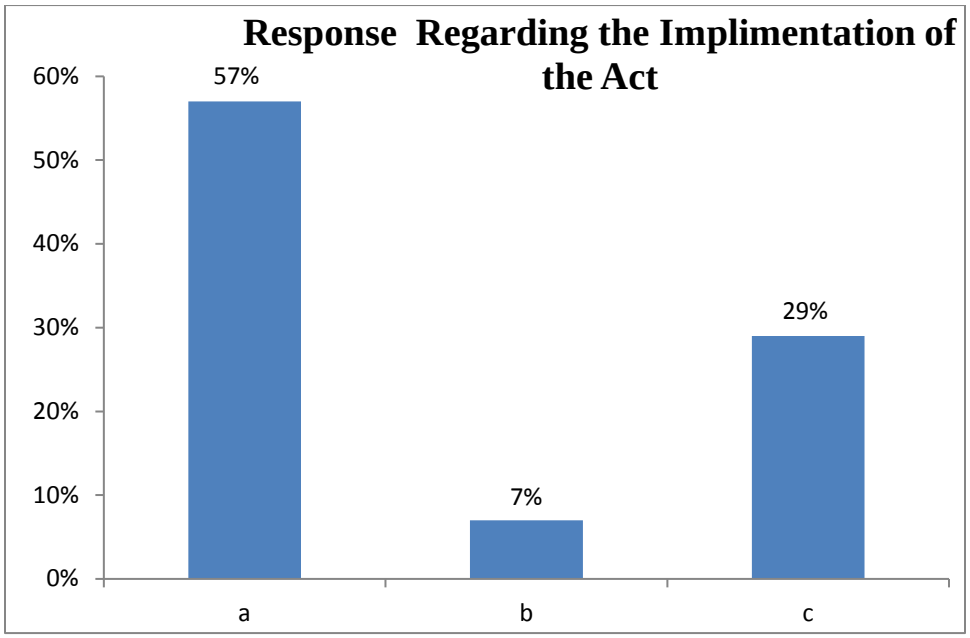

Figure 6. Graphical Representation Regarding the Implementation of the Act

Chapter 5: Discussion and Conclusion

5.1 Discussion

In my study, the survey was limited to the patient disease organizations, which were listed in the NORD. The sample population who responded to the survey may not be the representative sample population. Therefore, the results of the survey were limited by the responses of the respondent population. The survey instrument was posted on the e-news of the NORD. One might get more responses if survey questionnaire was emailed to the executive director of the organization directly. And one of the reasons for the low response rate might be that most of the members were not aware of the survey questionnaire in the e-news, which was posted on the bottom of the page. Also people who feel that Orphan Drug Act had satisfied the needs of the rare disease patients might not have felt it necessary to respond to this survey.

Several different forms of surveys were available. Surveys by email were inexpensive, but the response rates to surveys were quite low, typically from 5-20% (Sharma, 2006). Surveys as research may be vulnerable to bias. The wording of a question can influence the outcome a great deal. Mail survey questionnaires were typically short and simple and usually contained closed ended questions. And mail surveys response rates were usually limited and there was no guarantee that that people would respond to the mail survey. The response rate and the representativeness of the sample to its population would validate the mail survey (Chen, 1996). A difference between the characteristics of the sample and its population was due to different circumstances. This difference was termed as bias by researchers. In survey-based research, for almost any survey project, a proportion of subjects will choose not to participate (Hager, Wilson, Pollak, & Rooney, 2003). It was found from the studies that a significant difference exists between the respondents and non-respondents in attitudes and behavior towards some issues

(Brennan & Hoek, 1992). This might affect the results significantly and may have an effect in interpreting the results. The response rate can be increased by offering incentives to the people who answer the survey questionnaire.

This survey surprisingly found a large percentage of respondents who were not satisfied with the Orphan Drug Act. It was likely that these results were highly influenced by the low rate of response. Perhaps respondents who were less satisfied were more likely to respond to a survey (Mazor et al., 2002). In this study, respondents who believed that there was no progress in the development of drugs for rare diseases after the implementation of Orphan Drug Act might more likely respond to the survey and this might be the reason for larger percentage of respondents showing dissatisfaction with the Act.

The ideas of my research question might be better tested by directly sending the questionnaire of the entire sample as a friendly reminder to them. However, working through a third party, such as the NORD, limited on the ability to directly contact the subject pool as well as controlled follow-up reminders.

5.2 Suggestions for future research

According to this study, it was suggested that there were still concerns among the respondents regarding the progress in the development of drugs for rare diseases even after the implementation of the Orphan Drug Act. A similar study can be conducted targeting a large number of rare disease patient organizations but not working through a third party such as the NORD, which would validate the conclusions derived. The validity of the study can be further enhanced by regular follow-up and attracting the organizations to answer the survey by providing small incentives. By conducting the study directly among different rare disease patient

organizations and with the executive medical directors, more broad responses can be recorded which can provide many comments regarding progress in the development of drugs for rare diseases after the implementation of the Orphan Drug Act.

5.3 Conclusion

The objective of the study was to find whether the Orphan Drug Act was really satisfying the needs of the rare disease patients by surveying the membership organizations of NORD. Based on the responses to the survey questions it was evident that most of the members in the organization were familiar with the Orphan Drug Act. However, from the literature review it was proven that among the health laws passed in the late twentieth century, the Orphan Drug Act was one of the most successful laws and had a direct impact on bringing orphan drugs to the market and making them available for treatment of rare diseases. There had been a considerable increase in the number of orphan drug approvals and orphan drug designations after the enactment of the Orphan Drug Act of 1983. Incentives offered by the government for developing products for rare diseases developed hope among the rare disease patients, which was greater than anticipated with the success of the Orphan Drug Act, and continues to encourage the manufacturers of the orphan drugs. The Orphan Drug Act has great impact in the United States on public health. From the results of the survey it was found that members of the organization likely believe that new products were available in the market after the implementation of the Orphan Drug Act in 1983 and the products were in the pipeline and yet to be marketed. In this study, the survey was limited to the members of the organizations who were included in the NORD. The results of the survey were limited to the responses given by the respondent population. The results of the study can be validated by conducting a study directly targeting large populations and by having regular follow-up.

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Appendix A: College of Health and Human Services Human Subjects Review Committee Approval Letter

Dear Venkatesh,

Congratulations! After careful review, your proposal and the requested revisions "The Orphan Drug Act: Its implementation and impact on rare disease patients." has been approved by the College of Health and Human Services Human Subjects Review Committee. You may insert the dates of approval on the consent form as “from February 4, 2013 to February 3, 2014."

We stress that you do not stray from your proposed plan.

Good luck with your research effort.

Sincerely,

Gretchen Dahl Reeves, PhD

Chair, CHHS-HSRC

Appendix B: Survey Completion Request or Online Survey Consent Form

Title of the Survey:

The Orphan Drug Act: Its implementation and impact on rare disease patients.

Dear Organization Director,

As part of my master's thesis, I would like to request your participation in a survey research.

As a member of the NORD, you are being asked to participate in a survey concerning the Orphan Drug Act to find whether the Orphan Drug Act and its legislation is really meeting the needs of the rare disease patients.

Your participation is voluntary and you may choose not to participate. If you decide to participate in this research survey, you may withdraw at anytime. Your participation and individual responses will be kept anonymous. There are no direct benefits associated with your participation, but your input is valued. There is no known risk involved in your participation.

As a researcher I respect your rights to privacy and I hold in the utmost respect your responses to this survey and I will keep your survey results confidential. I am not collecting any kind of personal identifiable information or personal health information during the course of this survey.

The data will be collected via the online survey (Google Docs) and the results of the survey will be held by me. I will hold the data on a password protected personal laptop; there is no access to anyone. I will be protecting the laptop from theft and the word document containing email list for survey is both encrypted and password protected. The folder on my laptop

(password protected) containing the results of the survey will be deleted upon the submission of the dissertation and the password protected document containing email list for survey will be deleted upon the completion of survey.

I will be sending the survey to potential participants by using Google docs and the survey tool or document or form containing emails will be deleted forever upon the analysis of results. Privacy Policy of Google http://www.google.com/intl/en/policies/privacy/

I have taken all reasonable measures to protect your identity and responses. However, email and the internet are not 100% secure, so it is also suggested that you clear the browser history to protect your privacy after completing the survey.

This survey (6 questions) will take you approximately 5 to 10 minutes to complete. There is no known risk involved with your participation.

Link:
https://docs.google.com/spreadsheet/viewform?formkey=dEZKZjNUc1F1Y21wWmw0Y1QwOG9TYUE6MQ

By clicking on the link above, you are indicating that:

- You have read above information.
- You voluntarily agree to participate.

I can provide the results of the survey information at the completion of the study, if you are interested. There is no direct benefit in your participation but your input is valued and I hope you will respond. If you have any questions or concerns about the study, I encourage you to

contact Irwin Martin Ph.D., Associate Professor, College of Health and Human Services, Marshall Building, imartin2@emich.edu.

"This research protocol and informed consent document has been reviewed and approved by the Eastern Michigan University Human Subjects Review Committee for use from February 04, 2013 to February 03, 2014. If you have questions about the approval process, please contact "Gretchen Reeves, PhD, 734-487-3236, greeves@emich.edu", Chair, College of Health and Human Services Human Subjects Review Committee.

Thank you,

VENKATESH BURLA,

Masters student,

College of Health and Human Services.

Appendix C: Survey

Title of the Survey:

The Orphan Drug Act: Its implementation and impact on rare disease patients.

1. What rare disease patient group does your organization advocate or offer support?
2. What is the size of the population in U.S with this rare disease?
    (a) <1000
    (b) 1000-10, 000
    (c) >10, 000
3. How long has your organization been in this existence?
    (a) 0-5 years
    (b) 6-10 years
    (c) >10 years
4. Are you familiar with Orphan Drug Act? Yes/no.
5. Do you feel your patients/members have benefited from the Orphan Drug Act?
    (a) Yes For, new products to treat this rare disease are now available that weren't available before implementation of the Orphan Drug Act in 1983.
    (b) Yes, new products to treat this rare disease are in development but not yet marketed.
    (c) No, I have not seen any progress in the treatment of this rare disease.
6. Please state your position in your organization.
    (a) Executive Director
    (b) Medical Director
    (c) Other Staff Member

(d) Volunteer

7. Please feel free to provide any comments you might have on the Orphan Drug Act.

Appendix D: News letter was posted on the website of NORD

Master's Degree Candidate Conducting Survey on Orphan Drug Act

A graduate student at Eastern Michigan University is conducting a survey for his master's degree project regarding the Orphan Drug Act and how helpful it has been to rare disease patients. A letter from the student, with a link to his survey, may be viewed here.