

## Benefits of the Orphan Drug Act for Rare Disease Treatments

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A great number of people suffer from obscure and unknown diseases for which there have been few attempts to create treatments prior to the Orphan Drug Act of 1983. Today, the Act has helped improve the quality of life of many afflicted individuals and has enabled multiple companies to achieve financial success for creating treatments to combat rare diseases. Our analysis focuses on how the ODA has helped lower barrier of entry to orphan drug research and development with the effect of making orphan drugs economically feasible for companies involved. Based on the health needs of rare disease patients and our analysis of the marketability of orphan drugs, companies are advised to pursue orphan drugs research for not only ethical reasons but financial ones.

### INTRODUCTION

The Orphan Drug Act (ODA) classifies a rare disease as one that afflicts less than 200,000 patients (under 7.5:10000) in the United States.<sup>1</sup> It is estimated that around 5000-8000 rare conditions exist in the United States and Europe, and a total of approximately 25 million individuals suffer from these diseases.<sup>12</sup> Despite the benefits the ODA has provided, there have been questions in regards to whether pharmaceutical companies have actively pursued these treatments.<sup>3</sup> Some argue that society in general is morally obligated to help address the healthcare needs of all individuals, especially those afflicted by rare diseases.<sup>4</sup> On the other hand, there are those who argue against this research due to limited clinical trial volunteers, insufficient knowledge of disease mechanisms and lack of valid biomarkers available for study.<sup>1</sup>

Lack of blood and tissue samples is cited as a barrier into rare disease research. As a result, several advocacy organizations have established a centralized repository into which rare disease patients can donate such samples.<sup>2</sup> These repositories have been crucial in promoting the research of various rare conditions, thereby enabling rapid gene discovery and speeding up the development of targeted therapy. One such example of a successful effort is demonstrated by the establishment of a blood and tissue bank for pseudoxanthoma elasticum (PXE), a rare connective tissue disorder. This repository provided samples for PXE research that ultimately led to the discovery of the causative mutation in the ABCG6 gene.<sup>5</sup> Also, increasing the efficiency of the discovery and development processes lowers overall costs. Hence, non-profit organizations can leverage incentives into rare disease research by developing blood and tissue repositories, which in turn benefits the pharmaceutical firm financially.

The ODA was established in 1983 to provide incentives for pharmaceutical firms to conduct research for and commercialize drugs aimed at treating rare “orphan diseases.” Prior to the enactment of ODA, only a handful of disease had available therapeutics.<sup>6</sup> As of 2009, an estimated 2,116 drugs had received orphan drug designation.<sup>7</sup>

### ODA INCENTIVES

In order to address the financial disincentives of pursuing orphan drug development, the ODA was implemented to provide multiple incentives to offset the costs of developing

orphan drugs and entice the pharmaceutical industry to conduct rare disease research. For instance, if a company develops a product (drug or biologic) approved by the FDA for a rare disease, the company is given seven years of sole commercialization rights for the product.<sup>1</sup> This timeframe gives the company a monopolistic opportunity to make a profit that would be unavailable in other drug markets. In the interest of innovating already-occupied rare disease space, however, the FDA allows for competition from any other product that can demonstrate clinical superiority for treating the same condition.<sup>1</sup> Other incentives for enticing research into rare diseases include regulatory fee waivers for orphan products, a 50% tax credit on clinical research upon designation, availability of grant funding towards private corporations and academic institutions for clinical research, regulatory assistance, and an expedited review process.<sup>1</sup>

### FINANCIAL MODEL: ESTIMATES AND ASSUMPTIONS

In order to demonstrate the financial restraints pharmaceutical companies perceive in orphan drug research and development, and to provide a baseline for comparison against the benefits provided by the ODA, a financial model has been constructed based on the research of Joseph DiMasi, showing the estimated value of rare disease research has added to the industry.<sup>8</sup> The first part of the model is constructed to exclude provisions in the ODA and shows the typical expenditures an average pharmaceutical entity incurs while bringing a drug from initial research to marketing. The second part of the model incorporates the incentives the ODA provides and the resulting financial benefits, showing how with such incentives the cost of rare disease R&D can be significantly reduced.

Most of the figures used to generate this model are taken from DiMasi’s research, US Census information, and FDA guidelines for the fiscal year of 2010. However, the model also incorporates the following assumptions. The first is that pre-tax clinical costs stay constant regardless of whether the company pursues an orphan drug or not. While this assumption is not completely accurate, it provides a fair assessment for the difference between common and rare disease treatment costs. Second, it was assumed that the developed treatment must be taken regularly and for an extended period of time. Third, 15 years of the 20-year lifespan of patents were

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assumed to be spent performing R&D and clinical trials.<sup>8</sup> Fourth, it was assumed that three of the five remaining years will be spent recouping costs so that the company has time to make some money before the drug becomes generic. In the scenario with ODA incentives, the amount of years to break even has been increased to seven, and as a result, the company needs four years to recoup costs. A similar situation is assumed in the third model, but pre-clinical costs are waived because the orphan drug has been used for another disease.

### FINANCIAL MODEL: AN AVERAGE TREATMENT

Historically, pharmaceutical research and development has proven to be costly and lengthy. The difficulty in achieving profitability alone is enough to drive away drug developers from investing in orphan drugs, as rare diseases by definition affect less than 200,000 people in the US and thus constitute smaller markets and lower potential revenue. Consider the following dilemma: clinical trials to test general drug candidates require, on average, anywhere from 350 to 4000 people<sup>9</sup>, while rare diseases such as Penta X Syndrome<sup>10</sup>, Chromosome Ring 18 Syndrome<sup>11</sup>, or Niemann Pick Type C afflict less than 2000 patients each.<sup>12</sup> This reveals an important problem regarding rare disease research, one which requires drug developers to forgo profit as their primary objective and instead focus more on the health needs of rare disease patients, something a profit-based company would be unlikely to do.

To further illustrate why orphan drug R&D could be financially unattractive, we examine a simplified expenditure model (Table 1). DiMasi et al estimated the pre-tax total cost of drug development to be \$802 million, with \$335 million for preclinical testing, and \$467 million for clinical trials, is expended for every approved drug.<sup>8</sup> Assuming a 15 year discovery process, a tax rate of 35%<sup>13</sup>, and FY10 FDA fees<sup>14</sup>, we have determined a preliminary figure of roughly \$1.09 billion to bring a prospective drug to market.

In order to ensure profitability before patent expiration, it is in the drug developing company's best interest to recoup the costs as quickly as possible. We have chosen three years for the purpose of this approximation. The model will assess the costs required of each patient if the drug is taken by 80% of total patients, with the exception of Penta X Syndrome (since the disease has such low number of reported cases, 11, we assumed that all of those people will be treated); results of the cost per patient per year are represented in Table 2.

Niemann Pick Type C has a prevalence of about 1 in 150,000 people<sup>12</sup>, which in a population of 300 million translates to about 2000 patients in the United States. Chromosome Ring 18 Syndrome and Penta X Syndrome are even rarer; only 50 and 11 cases respectively, have been diagnosed since the 1960s in the United States. Given that the median income per household in the US is \$50,233<sup>15</sup>, the financial cost of treatment for these diseases represents a significant portion of a household's annual earnings. Without financial relief, these drugs could cost a patient anywhere from \$226,000 to \$33 million in order for a company to recoup development costs. The positive effect on company image that an investment in philanthropic projects would bring would not outweigh the massive financial burden a company would have to impose

on itself.

### INDUSTRY ADVANCES WITH THE INTRODUCTION OF THE ODA

Since the inception of ODA, many patients suffering from rare diseases have gained access to therapeutic products that would otherwise be unattainable. Additionally, the ODA has helped drug developers overcome adversities in research and development of orphan drugs by funding clinical trials, expediting approval processes, and providing guidance in protocol design. The ODA has also resulted in major cost savings across the healthcare industry. For example, infant botulism has a prevalence of 80 – 100 per year in the US and is considered an ultra rare disease. In 1991, the California Department of Health Services created Botulism Immune Globulin (BIG) for treatment of infant botulism. It cost approximately \$10.6 million (2005 dollars) to bring Botulism Immune Globulin from discovery, through development and licensure and into market; the FDA OOPD provided \$1.9 million, and FDA-approved pre-licensure cost recovery fees provided an additional \$1.8 million.<sup>16</sup> To date, this therapeutic has resulted in more than 30 years of avoided hospital stay and more than \$50 million of avoided hospital costs.<sup>16</sup> Such indirect costs could not have been realized without the provided incentives.

The ODA has attracted tremendous intellectual power and economic commitment into rare disease research and development. As a direct result of the ODA, the cost of drug R&D is less of a hurdle due to unprofitability, as was the case with many life-saving therapeutics.<sup>17</sup> Since it is estimated that in the US, 1 out of 10 persons is afflicted by a type of rare disease (NORD), the health and social impact of orphan drugs cannot be underestimated. Without the ODA, millions of patients within the United States and around the globe would lack access to any treatment.

The coinciding of the first wave of biotech company formation in the late 1970's and the FDA's enactment of the ODA shows that the ODA generated interest in many biotech start-ups to pursue orphan drugs. Amgen, Genentech and Genzyme, some of the largest biotech companies, were all founded on the prospect of developing an orphan product.<sup>18</sup>

### FINANCIAL MODEL: ORPHAN DRUG TREATMENT

Table 1 illustrates the financial benefits brought forth by ODA and how costs of orphan drug R&D are reduced significantly. For rare disease, in particular, the incentives provided by the ODA reduce cost of each orphan medication per patient by an estimated 31% (Table 3). This suggests that the ODA incentives provide more flexibility for drug pricing than would have ordinarily been available.

Companies such as Novartis and Genzyme have begun focusing their research efforts on common biochemical pathways, themes, or similarities that could potentially result in therapeutics that treat a multitude of rare diseases. This means that products could eventually have multiple drug designations, which could greatly reduce meaningless expenditures on dead-end research for similar disorders.

For example, Zavesca, developed by Actelion, was originally approved for treatment of Gaucher's Disease Type 1, a

lysosomal storage disease. Recently, it has been approved in Europe to treat Niemann Pick Type C, a related lysosomal storage disorder. In addition to Gaucher's Disease Type 1 and Niemann Pick Type C, Zavesca is being evaluated for its therapeutic efficacy in Cystic Fibrosis, and may soon be approved for its third indication.

Similarly, Novartis' Pasireotide has been shown to significantly improve patients with Cushing's disease, Acromegaly, and Carinoid Tumors, all of which involve tumors affecting the pituitary gland. Bayer's Nexavar has already gained approval for treating Renal Cell Carcinoma, Hepatocellular Carcinoma, and is in Phase II trials for Melanoma.

Commercializing an existing drug for a second indication costs substantially less. The pre-clinical costs are eliminated because the drug has already been developed, so the only expense that is taxed is that of clinical trials. By the end of clinical trials, the patent for such recycled drug would have most likely expired, and the drug developer would only have the seven-year market exclusivity as the window of opportunity to make profit. With the assumption that it requires four years to recoup the cost of R&D and clinical trials, and three more years to make profit, we estimate that Niemann Pick Type C would cost \$85,738.28 per patient per year, Chromosome Ring 18 syndrome would cost \$3,429,531.25 per patient per year, and Penta X Syndrome would cost \$12,471,022.73 per patient per year.

## PUBLIC-PRIVATE PARTNERSHIPS

One alternative to the ODA that has been utilized to encourage orphan drug development and benefit rare disease patients is the forming of public-private partnerships. These types of partnerships have successfully been used in the past to channel industry funds into rare disease research.<sup>4</sup> An example of this case is demonstrated by the treatment of African onchocerciasis (river blindness).

Beginning in 1987, Merck and Co. decided to donate an unlimited supply Mectizan at no cost with the intention to eradicate onchocerciasis in poor African nations.<sup>19</sup> Following the donation by Merck and Co., community-directed treatment programs were implemented in order to effectively distribute and administer one to two doses of Mectizan per patient annually.<sup>19</sup> Since the onset of therapy, Merck has donated 2.5 billion tablets (valued at \$3.9 billion) to 80 million people afflicted by onchocerciasis.<sup>20</sup> In addition to drug costs, Merck's investment into its Mectizan donation program is currently valued at \$35 million. These investments along with the aid of government programs have prevented approximately 40,000 cases of river blindness, thereby providing poor African nations with 7.5 million years of productive adult labor.<sup>20</sup>

The Merck case successfully demonstrates how public-private partnerships can benefit patients suffering from a rare disease. This goodwill approach has improved Merck's corporate image, attracted top quality employees and inspired other pharmaceutical companies to follow. Nonetheless, it is not a financially viable option for most of the pharmaceutical industry as it involves a significant amount of investment on the company's part, requiring significant fiscal strength to

take on such a charitable initiative.

## CONCLUSION

The enactment of the ODA in 1983 has facilitated the creation of over 230 orphan drugs.<sup>7</sup> It has significantly reduced treatment cost and increased the time frame for drug developers to recoup cost through incentives. Collaborations have been made between public and private sectors to increase public awareness of rare disease and help lower the barrier of entry to orphan drug development. In the disorders presented earlier as examples, the estimated cost per patient per year was reduced by over 30% of what the drug would traditionally cost. When both drug developers and individuals afflicted with rare disease benefit from orphan drug development, it is both logical and advisable for drug developers to participate in orphan drug R&D. Analysis of research and financial data show that it is possible to recoup cost and make profit on orphan drugs, and has led to hope being brought to millions of rare disease patients.

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