Bioengineering Independent Study Project Final Report

BE 498 Spring 2018

Project Title:

The Orphan Drug Act – Effect on Innovation and Unintended Consequences

Faculty Advisor
Prof Abby Alpert
# Table of Contents

1. The Orphan Drug Act – Overview ........................................................................................................... 3
   1.1 Background ....................................................................................................................................... 3
   1.2 Qualifications ................................................................................................................................. 4
   1.3 Incentives ...................................................................................................................................... 5

2. Objectives and Methods .......................................................................................................................... 7

3. Success of the Act ...................................................................................................................................... 7

4. Unintended Consequences ..................................................................................................................... 9
   4.1 Overview ....................................................................................................................................... 9
   4.2 ‘Salami-Slicing’ ............................................................................................................................ 10
   4.3 Multiple Orphan Indications .......................................................................................................... 12
   4.4 Mass Market to Orphan (Repurposed Orphan Drugs) ............................................................... 13

5. Orphan Drug Pricing, Access and Reimbursement .............................................................................. 15
   5.1 Orphan vs. Non-Orphan Drug Pricing ......................................................................................... 15
   5.2 Orphan Drug Pricing Distribution ............................................................................................... 15
   5.3 Orphan Drug Spending and Volume ............................................................................................. 16
   5.4 Reimbursement ............................................................................................................................. 17

6. Conclusion: Should changes be made? .................................................................................................. 19

References ..................................................................................................................................................... 21
The Orphan Drug Act – Effect on Innovation and Unintended Consequences
Samantha Carter
Independent study project, BE498, Spring 2018
Advisor: Professor Abby Alpert
Health Care Management, The Wharton School

The Orphan Drug Act, passed in 1983 to provide incentives for the development of treatments for rare diseases, has been recognized as one of the most successful legislations in the United States. As of January 2018, the FDA has granted almost 4,500 orphan drug designations and has approved 489 orphan drugs since the passage of the act. Despite the act’s success, there has been growing concern that drugs that are not “true orphans” are being granted orphan designations and benefitting from incentives and regulatory resources that might be better focused elsewhere. These practices include the division of common diseases into smaller patient subsets to qualify for orphan status and the expansion of orphan drugs to patient populations outside of those they were originally intended for, often resulting in significant revenue potential. Ultimately, the growth in orphan drugs and the various paths by which they are gaining approval requires the maintenance of a difficult balance between incentivizing innovators, maintaining patient access and ensuring affordability to patients. Any changes to the Orphan Drug Act should limit government support, in the form of taxes or reduced market exclusivity, for orphan drugs once they exceed certain profit thresholds since the original intent of the act was to encourage the development of drugs with limited economic potential.
1. The Orphan Drug Act – Overview

1.1 Background

Rare diseases are serious, chronic illnesses that can limit life expectancy and significantly impact quality of life. Approximately 7,000 rare diseases have been identified, and the National Institutes of Health (NIH) estimates that between 25 and 30 million people in the United States suffer from them.¹ There are many challenges faced by individuals and caregivers affected by rare diseases. It is difficult for patients to receive appropriate diagnosis and care due to the low awareness of rare diseases and limited access to medical expertise, diagnostic testing and treatments.⁴ The lack of knowledge surrounding these diseases makes it difficult for patients to receive an accurate and timely diagnosis. There is a limited number of rare disease specialists, and on average, patients visit 7.3 physicians and often experience symptoms for 4.8 years before receiving a diagnosis.¹ In addition, approximately 60% of rare disease patients and caregivers have provided physicians with information on their condition.¹

In the late 1970s and early 1980s, there was a growing awareness of the high unmet need for the treatment of diseases affecting small patient populations. The Kefauver-Harris Drug Amendment to the Federal Food, Drug, and Cosmetic Act was passed in 1962 and its requirements resulted in increased costs of drug development. Prior to drug approval, manufacturers were required to provide proof of the drug’s safety and effectiveness. In addition, the amendment required drug advertisements to disclose accurate information regarding side effects and ensured that inexpensive generic drugs were no longer marketed as expensive “breakthrough” medications under new trade names.¹ As a result of increased drug development costs, manufacturers focused on the development of treatments for chronic diseases that affected larger patient populations. Therapies for diseases affecting smaller patient populations were not
being developed due to the expectation that the investment required to develop these drugs would not be recovered.

1.2 Qualifications

The Orphan Drug Act was passed in 1983 to provide incentives for drug manufacturers to develop treatments for rare diseases. A “rare disease” was first defined as one that “occurs so infrequently in the United States that 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 the sales in the United States of such drug.”¹ This original definition focused on whether a disease was rare enough to result in market neglect. Congress amended the act in 1984 due to the difficulty of objectively determining which drugs were qualified under this definition as well as the reluctance of drug sponsors to submit applications for orphan drug designation due to the lack of certainty provided by the definition.⁵ A “rare disease” was redefined as one that affects less than 200,000 people in the United States or affects greater than 200,000 people but offers no reasonable expectation that the cost of development and making available a drug for the disease will be recovered from sales.¹ The current definition incorporates the prevalence of a disease as well as its commercial viability and provides drug sponsors with much more predictability regarding the orphan drug designation process, resulting in an increase in the number of applications for orphan drug designation.⁵ The prevalence-based component of the definition dictated most orphan drug designation, with only three therapies receiving orphan drug designation due to a prevalence of greater than 200,000 people and commercial non-viability as of January 2017.¹ Other amendments of the act include the extension of marketing exclusivity to both patentable and unpatentable drugs in 1985 and the requirement of sponsors to apply for orphan designation prior to applying for marketing approval in 1988.¹
1.3 Incentives

The three primary incentives of the Orphan Drug Act are seven years of marketing exclusivity, tax incentives and clinical research subsidies. The seven-year market exclusivity is granted for approved orphan drugs. During the period of exclusivity, which begins on the date of marketing approval, the FDA will not grant market authorization for another drug for the same orphan indication unless the product is demonstrated to be clinically superior. This exception applies for drugs that demonstrate superiority in clinical trials, such as a lower occurrence of side effects, easier administration of the drug or increased safety or efficacy, with a “substantial portion” of the population indicated for the original drug. The market exclusivity is a substantial incentive due to its superiority to typical market exclusivity and traditional IP patent protection granted to products. Typically, five years of market exclusivity is granted for a new chemical entity approved by the FDA. In addition, drug patents protect a particular structure or compound and, therefore, are not as protective as grants of market exclusivity, which protect the use of the drug. The market exclusivity is guaranteed for seven years after market approval of the drug while a patent lasts for twenty years and can be granted at any point during the development of a drug, which is typically long before the drug enters clinical trials. Although the period of patent protection is longer, drug development and clinical trials can occupy a large portion of the twenty-year period before the drug reaches the market. Therefore, the seven year market exclusivity provided by the act is a very attractive incentive.

Another incentive provided by the act is tax credits that contribute to reducing the cost of orphan drug development. The Orphan Drug Tax Credit (ODTC) is granted to sponsors after orphan designation is issued and allows for the collection of a tax credit for U.S. clinical trial costs incurred on the orphan indication. The tax credit, which was initially 50%, has recently
been lowered to 25% due to the Tax Cuts and Jobs Act. One estimate from the National Organization for Rare Disorders (NORD) is that 33% less orphan drugs would be developed if the ODTC were not an incentive of the act.¹

The Orphan Product Grant program provides funding for clinical research on new therapies to treat and/or diagnose rare diseases.¹ In addition to lowering the cost of drug development, receiving a grant makes gaining marketing authorization more likely. From a pool of over $20 million per year, the clinical research subsidies can reach approximately $500,000 per year and are renewable for up to four years.⁷,⁸ As of January 2017, the Office of Orphan Products Development (OOPD) reviewed 2,200 applications of the 2,500 received, funded over 590 studies and helped 60 products gain marketing approval.¹ In addition to grants, technical assistance is provided for the development and execution of clinical trials, resulting in shorter development timelines. The FDA helps orphan drug sponsors to establish clinical trials that will be acceptable with a small patient population available for testing. The FDA’s suggestions allow orphan drugs to reach the market much faster than non-orphan drugs.⁵

Another regulatory incentive is a waiver of the new drug application or “user” fees charged by the FDA. Exemption from these fees contributes to lower orphan drug development costs and allows patients to gain access to products sooner.¹ The user fees have risen significantly and are currently worth approximately $2.4 million.⁸ This incentive has especially benefitted small, start-up companies in their ability to finance research, but has also contributed to encouraging large companies to develop orphan drugs.²

Orphan drugs also undergo faster tracks to regulatory approval due to additional approvals, including priority review, accelerated approval and fast-track designation, that are often granted. Priority review is granted to therapies that serve as major advances in treatment or
provide a treatment for a condition that has no adequate alternate therapies. This status results in a review cycle of six months compared to a standard review time of ten months. Accelerated approval allows for earlier marketing of treatments that address an unmet need for a serious condition and is granted based on surrogate endpoint data, such as disease response or disease progression rather than a clinical endpoint like overall survival, that indicates the likelihood of clinical benefit. Finally, fast-track designation facilitates better collaboration between the agency and manufacturer throughout the development process as well as a more efficient review process.

2. Objectives and Methods

In this study, my goal was to analyze the extent to which the Orphan Drug Act has been used in a way that was not originally intended and the effect of these practices. In addition, I will analyze the effect of the Orphan Drug Act on drug pricing, reimbursement and healthcare costs. The FDA Orphan Drug Designations and Approvals database was used to study orphan drugs approved since the passage of the act in 1983 and to analyze their orphan indications and marketing approval dates. The Drugs@FDA database was used to obtain information on approved drug products and their approval history prior to orphan designation. In addition to databases, I used online research tools to generate written sources including reports, journal articles, periodicals and government documents.

3. Success of the Act

The Orphan Drug Act has been universally recognized as one of the most successful legislations in the United States. From the time that the Orphan Drug Act was passed in 1983 to
2018, a total of 489 orphan drugs have been approved in the United States. From 1967 to 1983, only 34 drugs approved by the FDA were for rare diseases, signifying the tremendous success of the act. Another estimate is that there were only 10 products brought to market by the pharmaceutical industry that would have met the orphan drug definition in the decade prior to the passage of the act. The success of the act is also demonstrated by the adoption of similar orphan drug legislation in key markets, including Japan in 1993, Australia in 1998 and the European Union in 2000.

From 1983 to 2018, there have been a total of 7,089 orphan drug designation requests, with 16 requests in 1983 and 715 in 2017. The number of applications for orphan drug designation has increased by 23% from 582 applications in 2016 to a new high of 715 in 2017. From 2002 to 2017, the percentage of applications accepted have ranged from a low of 57% in 2016 to a high of 99% in 2013.

As of January 2018, the FDA has granted almost 4,500 orphan drug designations since the passage of the act. Growth in the total number of orphan designations has varied from 7% and 12% between 2002 and 2017, with the high of 12% growth occurring between 2016 and 2017. The significant growth in the number of orphan designations demonstrates the act’s
success in stimulating research and innovation for diseases that otherwise would have no other
treatment. Of the 7,000 rare diseases currently identified, there are only treatments available for
5%, indicating the ongoing need for the development of therapeutic treatments. The Orphan
Drug Act provides hope to patients and caregivers who are affected by these rare diseases that
currently do not have available treatments.

![USA Cumulative Orphan Designations](chart.png)

Sources: EvaluatePharma 2017, FDA Orphan Drug Designations and Approvals Database

4. Unintended Consequences

4.1 Overview

As previously mentioned, from the time that the Orphan Drug Act was passed in 1983 to
2018, a total of 489 orphan drugs have been approved in the United States. There has been
growing concern that drugs that are not “true orphans” are being granted orphan designations and
benefitting from the incentives and regulatory resources that come along with this status when
they might be better focused elsewhere. Of the 489 orphan drugs, 322 are approved to treat a
single rare disease. 75 served the mass market first and were repurposed to treat a rare condition
and, therefore, to qualify for orphan indication. 102 have multiple orphan indications, meaning
that subsequent to their initial orphan approval, they were granted orphan approval for additional
therapeutic indications. In addition, as of January 2017, 34 drugs received orphan indication first
before later receiving a non-orphan indication. It is clear that many orphan drugs have both orphan and non-orphan indications, and regardless of which indication was received first, these drugs have been extended to the treatment of patient populations outside of those they were originally intended for.

In 2017 alone, 37 new orphan drugs were approved, 5 of which were approved for more than one orphan indication and 3 of which served the mass market prior to orphan designation. A total of 15 drugs gained multiple orphan indication status, and 13 drugs, previously with multiple indications, gained one or more additional indications.

### Orphan Drug Breakdown

![Orphan Drug Breakdown Chart]

**Sources:** FDA Orphan Drug Designations and Approvals Database, Drugs@FDA: FDA Approved Drug Products Database

**4.2 ‘Salami-Slicing’**

The number of recognized rare diseases has been increasing and continues to do so as a result of scientific advances and a growing emphasis on the adoption of precision medicine. Scientific advancements in genetics and molecular biology and the use of biomarkers have allowed for the segmentation of diseases into more specific and smaller patient populations. For example, 40-80% of non-small cell lung cancer patients have epidermal growth factor receptor
(EGFR) mutations, which allows for the segmentation of the patient population into a smaller EGFR population with approximately 75 to 150 thousand patients per year. This practice of dividing common diseases into small subsets in order to qualify for orphan status is often referred to as ‘salami-slicing’.

The growing number of orphan designations over the past decade has been accompanied by an increase in orphan-designated drugs that target biomarker-defined disease subsets of common diseases. A biomarker-defined subset is defined as “any drug approved based on its efficacy in a subset of a more prevalent disease characterized by a particular genetic variant or other specified diagnostic test.”\textsuperscript{8} From 2009 to 2015, 16% of the drugs with orphan designations were for rare subsets of prevalent diseases split by predictive biomarkers.\textsuperscript{1} In addition, of these orphan drugs that target biomarker-defined subsets, 85% had oncology indications. This demonstrates that most biomarker-defined orphan drugs relate to oncologic indications. In this time period, of the 39 orphan drugs approved for oncology indications, 11 or 28% were for biomarker-derived disease subsets.

Ultimately, analyses have shown that orphan drugs for treatment of biomarker-defined patient subgroups have resulted in the addition of new indications and/or significant off-label uses after approval.\textsuperscript{12} Therefore, concerns stem from the idea that manufacturers are seeking orphan approval to benefit from the incentives with the intention of ultimately gaining additional indications and expanding the patient populations reached by the drug. Despite these concerns, ‘salami-slicing’ does have a beneficial effect. This practice serves as a model for precision medicine because the division of diseases into smaller patient populations allows for earlier intervention and improved patient outcomes through more predictive and targeted treatment.\textsuperscript{4}
4.3 Multiple Orphan Indications

The majority of orphan drug designations are granted or denied based on the prevalence of the disease for which the drug is intended. The same drug can receive more than one orphan designation for different therapeutic indications, all of which have a different disease prevalence, but each indication must be shown to be a distinct medical entity. For each indication, a separate, independent clinical trial must be carried out. In addition, a separate market authorization and a separate reimbursement approval are required for each indication.\textsuperscript{4}

Studies have found that orphan drugs with multiple orphan indications are associated with higher prices, indicating that the combined prevalence of all the indications does not influence pricing.\textsuperscript{11} Orphan drug prices are often set based on the prevalence of the drug’s first indication since prices are unlikely to be reviewed for subsequent approvals in other orphan indications.\textsuperscript{11} Because orphan drugs with multiple orphan indications reach a significantly larger patient population and have higher prices, they are more likely to become sufficiently profitable. As a result they often become “blockbuster drugs”, indicating that they generate annual sales of at least $1 billion.\textsuperscript{7} The high profitability of these orphan drugs has caused questions regarding the extent to which they deserve orphan incentives since the original intent of the Orphan Drug Act was to encourage the development of drugs with limited economic potential.

The top ten selling orphan drugs in the U.S. in 2016 by sales and their associated number of orphan indications are demonstrated in the table below. Of these ten orphan drugs, eight have more than one orphan indication. Imbruvica (ibrutinib) has ten orphan indications and Gleevec (imatinib mesylate) has nine orphan indications. Both of these drugs are oncology therapies. Gleevec’s orphan indications include chronic myeloid leukemia (CML), Philadelphia-positive (Ph+) acute lymphoblastic leukemia (ALL) and gastrointestinal stromal tumor, which each affect
fewer than 200,000 patients per year. The first approved indication for CML in 2001 accounts for about 90% of all patients treated with the drug, while the other indications only account for 10% of the patients. In addition, the price of the drug upon its initial approval for CML was approximately $30,000 per year. By 2012, after seven additional orphan approvals, the price increased by more than three times to $92,000 per year. This demonstrates the strong economic potential of orphan drugs with multiple orphan indications.

<table>
<thead>
<tr>
<th>Rank</th>
<th>Product</th>
<th>Generic Name</th>
<th>USA Sales ($m)</th>
<th>Number of orphan indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Revlimid</td>
<td>lenalidomide</td>
<td>4,417</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>Rituxan</td>
<td>rituximab</td>
<td>3,970</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>Copaxone</td>
<td>glatiramer acetate</td>
<td>3,257</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>Opdivo</td>
<td>nivolumab</td>
<td>2,664</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>Avonex</td>
<td>interferon beta-1a</td>
<td>1,675</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>Imbruvica</td>
<td>ibrutinib</td>
<td>1,580</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>Sensipar</td>
<td>cinacalcet hydrochloride</td>
<td>1,240</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>Gleevec</td>
<td>imatinib mesylate</td>
<td>1,214</td>
<td>9</td>
</tr>
<tr>
<td>9</td>
<td>Velcade</td>
<td>bortezomib</td>
<td>1,133</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>Xyrem</td>
<td>sodium oxybate</td>
<td>1,114</td>
<td>2</td>
</tr>
</tbody>
</table>

Sources: EvaluatePharma 2017

4.4 Mass Market to Orphan (Repurposed Orphan Drugs)

Pharmaceutical companies also repurpose drugs for common diseases toward treating a rare disease so that they can benefit from orphan drug incentives. Examples of repurposed drugs include sildenafil and ibuprofen. Sildenafil achieved blockbuster sales through its initial indication of erectile dysfunction and later received orphan approval for pulmonary arterial hypertension. Ibuprofen, originally used for the treatment of inflammatory joint disorders, was subsequently granted orphan approval for patent ductus arteriosus. Another example of a repurposed drug is Humira (adalimumab), which was initially approved for the treatment of rheumatoid arthritis in 2002. Subsequent to its initial non-orphan indication, Humira received
approval for several other indications, including five orphan approvals. Of the $13.6 billion in total sales in 2016, the drug’s orphan indications only accounted for 3.8%.

Studies suggest that repurposed orphan drugs are associated with lower prices since their prices are often determined by the price of its initial indication for a common disease. These lower prices would make sense due to the difference in economic viability between repurposed orphan drugs and new orphan drugs. Repurposed drugs do not require novel R&D or a high level of investment to market the drug; therefore, it is argued that the lack of economic viability that is implied when a drug is granted orphan approval does not apply for repurposed drugs. If lower prices were associated with all repurposed orphan drugs, criticism from the medical community regarding high prices would not exist, and instead there would be more appreciation for the discovery of new indications for existing drugs to treat rare diseases.

Emflaza (deflazacort) is one example of a repurposed drug that does not signify the supposedly low prices associated with repurposed orphan drugs. Emflaza is a corticosteroid drug that received orphan approval for the treatment of Duchenne muscular dystrophy (DMD) in February 2017. Before its orphan approval, deflazacort had been used as an anti-inflammatory and immunosuppressant for decades. In addition to its mass market use, 7-9% of U.S. patients used the drug off-label for the treatment of DMD. When Marathon Pharmaceuticals set the annual list price of its newly approved orphan drug at $89,000, the company received strong criticism from the DMD community since the generic version of the drug cost less than $2,000 annually. Less than a week after Marathon announced the orphan approval, the company decided to “pause” the marketing process and meet with any interested groups before moving forward with commercialization. The company, however, ended up selling its rights to Emflaza to PTC Therapeutics for $140 million in cash and stock, and the new drug price has not been set yet.
5. Orphan Drug Pricing, Access and Reimbursement

5.1 Orphan vs. Non-Orphan Drug Pricing

In 2016, the average retail cost per patient per year for an orphan drug was estimated to be $140,443, compared to an average of $27,756 for non-orphan drugs.\(^3\) Average prices have increased each year for both orphan and non-orphan drugs since 2012. From 2012 to 2016, average drug pricing had a compound annual growth rate of 4.8% for orphan drugs and 10.44% for non-orphan drugs.\(^3\) In addition, the median price differential between orphan and non-orphan drugs has dropped from 9.8 in 2012 to 5.5 in 2016.\(^3\) The median price of orphan drugs has increased by a factor of 1.3, from $64,099 in 2012 to $83,883 in 2016 while the median price of non-orphan drugs has increased by a factor of 2.3, from $6,543 in 2012 to $15,239 in 2016.\(^3\) This data demonstrates the significantly higher prices of orphan drugs compared to non-orphan drugs; however, it is evident that non-orphan drug pricing has experienced greater growth than orphan drugs between 2012 and 2016, resulting in a decrease in the median price differential.

5.2 Orphan Drug Pricing Distribution

There is a wide variation in annual cost per patient for orphan drugs. Of the 335 approved orphan drugs as of January 2017, 22.4% of orphan drugs are priced at less than $6,000 per patient per year. The highest percentage of orphan drugs, 36.7%, are priced between $6,000 and
$50,000. Only 1.2% of orphan drugs are priced at greater than $500,000 per patient per year, and these drugs account for 1.7% of the $36.1 billion in total orphan drug sales in 2016 due to the relatively small number of patients using these treatments.

5.3 Orphan Drug Spending and Volume

Of the $450 billion in total drug sales in the United States in 2016, only $36.1 billion (7.9%) was attributed to orphan drugs. 58.5% of spending was for non-orphan traditional drugs and 33.6% was for non-orphan specialty drugs. Specialty drugs are defined by QuintilesIMS as “those which treat chronic, complex or rare diseases and which have a minimum of four out of seven of [specified] additional characteristics,” which include having a list price greater than $6,000 per year, requiring administration by another individual, requiring special handling in the supply chain and having significant side effects that require additional monitoring. In addition, of the total volume of drugs used in 2016, orphan drugs only accounted for 0.3% due to small patient populations. The orphan drug share of total volume peaked at 0.6% in 2003 and declined to 0.3% in 2016. Therefore, it can be concluded that orphan drugs currently do not account for a significant portion of healthcare spending in the United States.
5.4 Reimbursement

Historically, high orphan drug prices have not been associated with limited access to insurance coverage because, due to small patient populations, high prices would not have a significant impact on overall budgets and insurance premiums.\(^{12}\) It is also widely recognized that orphan drug prices on a per-patient basis need to be high to allow innovators to achieve reasonable profits. However, in a changing environment defined by an increase in orphan drug approvals, “often contingent on less-than-robust evidence, and coupled with rising pricing and frequent expansion beyond original orphan indications,” private payers are becoming concerned.\(^{12}\) As stated earlier, orphan drugs are currently not a significant portion of health care spending in the United States. However, the changing orphan drug landscape has caused concern regarding its future impact on the health care budget and has already affected reimbursement for some orphan drugs. Recent surveys have found that two-thirds of leaders at seven private insurers have been monitoring the orphan drug pipeline and that most private payers do not know the most appropriate way to assess the cost-effectiveness of orphan drugs.\(^{12}\)

The high prices of orphan drugs often result in their inability to meet commonly accepted cost-effectiveness thresholds used to value other treatments.\(^{12}\) The appropriate method of assessing the cost-effectiveness and value of orphan treatments is often discussed in an ethical...
context. Arguments revolve around whether they should be assessed using the same standards as other treatments or if the characteristics of rare diseases should allow for a deviation from the traditional methods of economic valuation. This often boils down to a question of fairness. Some ethicists and health economists argue that the primary goal of health insurance and the health care system is to utilize available resources in a way that maximizes the health of the entire population and, therefore, that the use of resources for orphan treatments that do not meet cost-effectiveness thresholds ultimately takes resources away from other patients who would benefit more. The opposing argument is that the goal of the health system is to ensure that all patients have an equal opportunity to benefit from health care, even if this means that spending results in less health gain for the entire population. This is often accompanied by the value of “fair innings,” which argues that, all else being equal, resources should be prioritized for younger individuals who have not been given the chance to live a full life due to an illness. Justifications for this view in regards to rare diseases include the fact that they often result in severe disability or very limited life expectancy, many affect infants and young children and supportive care is often the extent to which treatment options exist. Rare conditions like these have a significant impact on patients as well as their families and caregivers. Ultimately, a balance needs to be maintained between these two conflicting views of fairness. Many ethicists do argue, however, that treatments for very rare diseases deserve some premium, though not one that is unlimited.12

The effect of high orphan drug prices on reimbursement has been demonstrated by Medicaid, the largest single insurer of children in the United States, which has adopted prior authorization policies for orphan drugs in some states. For example, for a new orphan drug for the treatment of cystic fibrosis, Arkansas Medicaid required patients to first prove that older, less expensive treatments did not provide sufficient benefit. It has been argued that these prior
authorization policies are not consistent with the laws that require Medicaid to provide access to any medically necessary drug whose manufacturer is part of the Medicaid drug rebate program.12

Reimbursement issues can also be seen with the orphan drug Spinraza (nusinersen). Spinraza was approved by the FDA in December 2016 and has orphan indications for use in all types of spinal muscular atrophy (SMA). It is delivered through intrathecal injections (into the spinal canal) and four loading doses followed by maintenance doses every four months are required.12 Biogen, a Boston biotechnology company, set the list price of Spinraza at $125,000 per injection, which amounts to a first-year cost of $750,000 and $375,000 in subsequent years. These prices do not cover other costs, such as physician and facility fees, that are associated with the administration of the drug. Payer responses to these high prices have varied. National payers, Anthem of Indianapolis and Humana of Louisville, Kentucky, only provide coverage for patients with the most severe form of the disease (Type 1 SMA) and require monitoring every six months to ensure that the drug is working in order to continue treatment. Another insurer, Aetna, provides reimbursement for all types of SMA except Type 4 and does not require any monitoring. UnitedHealth Group of Hopkins, Minnesota covers Spinraza for all but Type 4 of SMA as well, but requires ongoing monitoring to demonstrate sustained improvement in order to continue therapy. The type of proof drugmakers are required to provide includes improvement in symptoms, motor milestones and avoidance of invasive ventilation.12

6. Conclusion: Should changes be made?

The growth in orphan drugs and the various paths by which they are gaining approval requires the maintenance of a difficult balance between incentivizing innovators, maintaining patient access and ensuring affordability to patients. Any changes to the Orphan Drug Act should not reduce the incentives granted upon orphan designation to ensure that the level of orphan drug
development is not negatively impacted. Instead, changes should be focused toward orphan drugs that exceed certain profit thresholds. In other words, it should be a priority to address drugs that receive orphan approval and later expand to other patient populations through additional orphan indications or off-label use. If not for the high prices associated with these drugs, the practices of expanding existing orphan drugs for use by other patient populations and ‘salami-slicing’ diseases into smaller subsets would be beneficial since they ultimately result in an increase in available treatments and encourage the adoption of precision medicine. Therefore, changes should only limit government support for drugs once they extend their profits beyond a threshold since the original intent of the Orphan Drug Act was to encourage the development of drugs with limited economic potential. This allows for the maintenance of a balance between protecting the initial intent of the act and preventing the discouragement of drug companies to develop orphan drugs. These changes can be implemented through taxes or reduced market exclusivity. For example, in Japan, pharmaceutical companies must pay a 1% sales tax on orphan drugs that generate annual profits greater than 100 million yen. The taxes stay in place until government subsidies that were provided upon orphan designation are repaid. This ensures that manufacturers continue to have limited investment risk and allows for government costs to be recovered and used toward other drugs. Another consideration would be to reduce market exclusivity for treatments once they reach certain profit thresholds in order to encourage increased competition and pressure to lower prices. Although the Orphan Drug Act would benefit from some changes, these changes would target specific circumstances and thereby would not impact the overall success of the act.
References


9. FDA Orphan Drug Designations and Approvals Database


13. “About FDA: Total Number of Orphan Drug Designation Requests Received in the Month.” *Accessdata.fda.gov*,

15. Drugs@FDA: FDA Approved Drug Products Database

