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Indie Illness: An Evaluation of the Orphan Drug Act

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INDIE ILLNESS: AN EVALUATION OF THE ORPHAN DRUG ACT

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DEDICATION

This thesis is dedicated to everyone who let me talk to them about orphan drugs in the last year, that was really cool of you!

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I would like to thank the FDA for responding quickly to my Freedom of Information Act request for orphan drug applications.

ABSTRACT
NICHOLAS CASTELLANOS: Indie Illness: An Evaluation of the Orphan Drug Act
(Under the direction of Dr. Joshua Hendrickson)

The purpose of this study is to evaluate the Orphan Drug Act of 1983 by subtracting the cost of incentives for drug development from the estimated value created by each drug in the form of quality-adjusted life-year gains. Data regarding costs of incentives is retrieved from the FDA as well as a report released by the National Organization for Rare Disorders. Data regarding value created by each drug is retrieved from a Freedom of Information Act request to the FDA, the CEA registry, and a report released by the US Department of Health and Human Sciences. Sufficient data was available for a total of 16 drugs. The net average value created for the data set was $44.04 billion assuming 100% treatment scenario and $4.336 billion assuming 10% treatment scenario. It is unclear whether the calculations performed in this study are indicative of the Orphan Drug Designation program as a whole as the criteria for inclusion of data in this study was nonrandom. More research is needed to determine a representative data sample for orphan drugs in order to evaluate the Orphan Drug Act more fully.

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LIST OF ABBREVIATIONS

QALY	quality adjusted life years
QALYG	quality adjusted life year gains
VSL	value of a statistical life
VSLY	value of a statistical life year
Prev	prevalence
IVC	ideal value created
RVC	real value created
NIVC	net ideal value created
NRVC	net real value created
PATC	preliminary added orphan tax credit
CATC	current added orphan tax credit
ODATC	total average orphan tax credit
NODATC	total average non orphan tax credit
TE	total FDA expenditure per drug
AF	application fee

INTRODUCTION

There are currently over 7,000 rare diseases affecting a total of 30 million Americans. A rare disease is defined as one for which the total disease prevalence does not exceed 200,000 Americans. Additionally, rare diseases may be constituted by a subset of a non rare disease given that the subset classification is medically plausible. Orphan drugs are defined as those drugs developed for the treatment of rare diseases. Orphan drugs may be indicated for the treatment of both rare and non rare diseases, and many orphan drugs carry multiple indications (Office of the Commissioner, 2020).

The Orphan Drug Act of 1983 was passed as an incentive for the development of additional orphan drugs, and prior to the passage of the Orphan Drug Act, an average of only two orphan drugs were developed each year (Mikami, 2017). The Orphan Drug Act in its current form provides incentives in the form of 25% tax credits on qualified human clinical trials, application and program fee waivers, and up to seven years additional exclusivity (Office of the Commissioner, 2020).

This study seeks to evaluate the Orphan Drug Act by calculating the value created by each orphan drug in the form of life year benefits and subtracting from that value the costs incurred by the FDA in the form of incentives for drug development.

Data regarding prevalence for each orphan indication is retrieved via a Freedom of Information Act request to the FDA. Information on the quality adjusted life years gained from each drug is obtained using the CEA registry search engine. The dollar value of a statistical human life year as calculated by the US Department of Health and

Human Sciences is used in this study. Estimates of average orphan drug tax credits are calculated using data from the National Organization of Rare Disorders. The value of a drug application fee with clinical data waiver is obtained from the FDA website.

To calculate the net value created by each drug the sum of the average tax orphan tax credit and application fee waiver is subtracted from each indication prevalence multiplied by the quality-adjusted life-years gained from the associated drug and the value of a statistical life year.

Background

Modern medicine has changed the narrative on many of the most common diseases. A routine infection can now be treated with any of a slate of antibiotics. For example, new diabetes treatments are constantly being developed to suit the varied needs and preferences of diabetic Americans. The free market has been responsible for a large portion of medical innovation, but this economic mechanism works best for large patient populations. 37.3 million Americans, or one out of every ten, has diabetes and $327 billion dollars are spent in medical costs on diabetes in America each year (Centers for Disease Control and Prevention, 2022). This represents a huge market that invites constant research and development because new treatments that are developed will always have a market for buyers, and pharmaceutical companies will always be able to recoup their investments. The problem is that many illnesses affect only a small number of people. Treatments still require billions of dollars to be developed, even if their target market is less than 50,000 people, and this is where the FDA steps in to bridge the gap between American needs and pharmaceutical incentives to provide a broad spectrum of treatments for a broad spectrum of health problems.

In America, rare diseases are defined as those affecting fewer than 200,000 people. The drugs created to treat these diseases are referred to as orphan drugs (Office of the Commissioner, 2020). There are over 7,000 rare diseases affecting over 30 million Americans, or roughly one in every ten Americans, but prior to 1983, only 38 orphan drugs had been approved by the FDA (Office of the Commissioner, 2020; National

Organization for Rare Disorders, 2021). The story of the Orphan Drug Act of 1983, which forever changed the economic environment in which orphan drugs are developed, actually began in the late 1950s.

Thalidomide, a medication for treating nausea in pregnant women, became extremely popular in the late 1950s, but it was not until the early 1960s that this medication was found to have also caused severe birth defects in over ten thousand children (Kim et al., 2011). Suffice to say, the whole debacle turned a lot of eyes towards how the FDA approached medication quality and safety approvals. Ultimately, this led to the 1962 Kefauver-Harris amendments to the Food, Drug, and Cosmetic Act of 1938, which strengthened the FDA's approach to clinical trials and required drug developers to submit an Investigational New Drug Notice on any new molecules they were investigating (Mikami, 2017). This was of course, a very important step toward a world where one can trust a medication indicated for nausea in pregnant women to not cause birth defects in those same pregnant women, but it had an unintended impact on the way pharmaceutical companies approached the viability of new molecules. Suddenly, it became significantly more expensive (by way of increased trials, and application costs) to investigate new drugs, and so the pharmaceutical companies assigned drugs for rare diseases to the category of "low commercial priority," and only ten orphan drugs were approved in the entire decade leading up to the passage of the 1983 Orphan Drug Act (Mikami, 2017).

In 1975, the FDA recognized the poor plight of "drugs of limited commercial value" and resolved that something should be done to remedy this. Unfortunately, upon examination of the issue, the FDA concluded that the reasons for this plight were too

varied and distinct for each illness and nothing could reasonably be done (Mikami, 2017). Ultimately, it turned out to be the grassroots efforts of actual patients of rare diseases that were the catalyst for government action. A patient support group for Huntington's disease (a rare disease impacting thirty thousand Americans) advocated for and ultimately founded the Congressional Commission for the Control of Huntington's Disease and Its Consequences, which reported that there were no viable drugs for Huntington's disease or many other rare diseases in 1977 (Center for Neurological Treatment & Research, 2014; Mikami, 2017). This led to a 1978 FDA interagency task force that finally decided some action was warranted, and identified the increased cost of FDA approval as the issue. They suggested a program where companies could repay the approval and application costs after getting marketing approval and were actually able to sell the medication. They also suggested a new FDA board that would advocate for the development of drugs for rare diseases on a mainly humanitarian basis (Mikami, 2017).

In 1980, a researcher and patient were unable to get 5-HTP, a treatment for myoclonus, which caused the researcher to have to synthesize it himself in his lab. They contacted their representative, congresswoman Elizabeth Holtzman, who proposed a bill that outlined government actions "to assist in the development of drugs for diseases and conditions of low incidence" (Mikami, 2017). The bill failed, but triggered a Los Angeles Times article that was seen by Maurice Kluggman, an ordinary American except for two important qualities. The first is that he had a rare form of cancer, which would have met the criteria for a rare disease. The second is that his brother, Jack Kluggman, was the star of a popular television program, Quincy M.E. This brought Jack Klugman to produce multiple episodes about the tragic fate of Americans suffering from rare diseases, and this

is seen by many as the major turning point in the fight for public opinion on orphan drugs in America (Mikami, 2017).

Around the same time, a mother of a child with tourettes, who was unable to get medication for her child because it was unavailable in America even though it had been approved in Canada, contacted her representative, Henry Waxman. Waxman had participated in the failed legislative attempt of 1980, but in 1981, Waxman submitted his own bill, which would ultimately become the 1983 Orphan Drug Act (Mikami, 2017).

The Orphan Drug Act defines rare diseases as those affecting fewer than two hundred thousand Americans, or those for which a pharmaceutical company could not reasonably expect to recoup their investment in the development of treatments (Office of the Commissioner, 2020). Pharmaceutical companies request orphan designations for drugs treating conditions that they believe to meet these criteria from the FDA. Designation is sought relatively early in the drug production process, as the benefits of the Orphan Drug Act impact the clinical trials during drug development. The benefits of orphan designation are as follows. First, the drug developers also receive a waiver for the user fees incurred by the drug application. Second, pharmaceutical companies developing orphan drugs receive tax credits for qualified human clinical testing. Third, drug developers are also eligible for potentially seven additional years of exclusivity for their orphan products (Office of the Commissioner, 2020).

The FDA expends a large amount of resources to approve, regulate, and investigate applications for new drugs. This process is expedited in part by the existence of user fees. The Prescription Drug User Fee Act of 1992 authorized the FDA “to collect fees from companies that produce certain human drug and biological products” in order

to help fund and expedite the actions and duties of the FDA (Center for Drug Evaluation and Research, 2022). Every five years the PDUFA must be reauthorized; it is currently authorized through September of 2022. The user fees are first broken down by whether or not additional clinical data with respect to safety is required. For orphan drugs, the majority are new molecules or formulations and therefore do require clinical testing with respect to safety. The application fee without clinical data required is $1,558,609, and with clinical data required it is $3,117,218 (Center for Drug Evaluation and Research, 2022). Program fees are also assessed for each pharmaceutical company. Each company is "required to pay the annual prescription drug program fee for each prescription drug product that is identified in such a human drug application approved" (Food and Drug Administration et al., 2020). In 2022, the program fees were set at $369,413 each year per drug product approved through the FDA (Center for Drug Evaluation and Research, 2022). The fee amounts change each year and are set such that application fees represent 20% of the FDA's revenue and program fees represent 80% of the total revenue (Food and Drug Administration, 2020). By virtue of orphan drug designation, participating pharmaceutical companies are not required to pay program fees or application fees corresponding to their drugs with orphan status.

The tax credit for qualified human clinical testing represents by far the greatest monetary benefit for companies producing orphan drugs. In 2017, the tax credit was halved from 50% to 25% of qualified human clinical testing (Knowledge Ecology International, 2021). All drug research is eligible for some amount of tax credit through research and development tax credits, but there are key differences between R&D tax credits and those set out in the Orphan Drug Act. Under orphan drug tax credits,

contractor costs can be claimed at 100% instead of the R&D 65%. Companies are also eligible to recoup 25% of qualified research expenses under the orphan designation compared to the 10% of research and development covered under the R&D tax credit. Lastly, clinical trials that occur outside the U.S. are eligible for tax credits under orphan designation while they are excluded under normal R&D regulations (Barka, 2022). The orphan drug tax credits also extend to human clinical trials, which can represent a large chunk of the overall costs of drug development, and are excluded from R&D tax credits.

Orphan drugs are also eligible for an additional seven years of exclusivity under the Orphan Drug Act, but this part of the program is not always relevant. The orphan drug exclusivity is given in addition to and runs concurrently with the patent exclusivity that all drugs received by nature of being the product of research and innovation. The patent for pharmaceutical drugs lasts for 20 years and begins at the drugs invention. Additionally, the Hatch-Waxman act of 1984 increased the patent term for new chemical entities by the number of years that the drug is reviewed plus half of the time that the drug is in preclinical trials, and the FDA Modernization Act of 1997 extended the exclusivity period of pediatric drugs by six months (Biotechnology Industry Organization et al., 2015).

It takes an average of 12.5 years for a drug to go through all the clinical testing and approval processes required to move from drug discovery to marketing approval (Biotechnology Industry Organization et al., 2015). The up to seven years of orphan designation associated exclusivity runs from the point of marketing approval, which means that in the average case, orphan exclusivity runs for 19.5 years after drug discovery compared to the patent that runs for 20 years (Biotechnology Industry

Organization et al., 2015). The orphan drug exclusivity can still be useful to pharmaceutical companies because orphan drug clinical testing takes longer than non orphan drug clinical testing, and if the clinical testing runs significantly longer than the average, the orphan designation associated exclusivity provides additional security that the pharmaceutical company will have enough time to recoup its investment.

In 2018, 503 drugs had gained orphan status and subsequent approval. Out of that group, 217 no longer had either patent protection or exclusivity from their orphan designation. Of that 217, only 116 actually faced generic competition (IQVIA Institute for Human Data Science et al., 2018). Orphan drugs are already in a market where profitability can be tricky to attain, and so it makes sense that competing developers would not always be incentivized to produce generic versions of orphan drugs. Additionally, the exclusivity stemming from the orphan designation only lasted longer than patent protection in 60 drugs, which represents 12% of cases (IQVIA Institute for Human Data Science et al., 2018). This is not to say that the additional period of exclusivity is useless or meaningless in regards to developer incentives and market deterrents, but it is important to understand the limited impacts of the extended exclusivity when actually worked out in the real world.

Drug developers are also able to gain orphan status for their drugs and targeted illnesses even when the disease's prevalence exceeds 200,000 Americans by establishing an orphan subset. The subset must, however, be medically plausible, which means that drug use would be appropriate within the proposed orphan subset, but inappropriate outside the subset due to mechanism of action, toxicity, cost, or some other reason (Food and Drug Administration, 2013). Pharmaceutical companies can also gain separate

approvals and orphan designations for the same drug, if the drug is indicated in the treatment of multiple rare diseases (Food and Drug Administration, 2013). If the same drug under a different formulation, for example, is to gain an additional orphan designation, the drug manufacturer must demonstrate clinical superiority somehow (Food and Drug Administration, 2013). Lastly, drugs can receive orphan status, while also being indicated and approved for use in non orphan diseases (Food and Drug Administration, 2013).

The Orphan Drug Act is carried out by the FDA's Office of Orphan Product Development. The OOPD has an annual budget of $29,099,000. This money is used to fund between 12 and 18 grant awards annually as well as to provide support and funding for existing projects (Office of Orphan Products Development, 2018). The OOPD carries out five roles under the FDA: the Humanitarian Use Device program, the Rare Pediatric Disease program, the Orphan Products Grants program, the Pediatric Device Consortia grants program, as well as the core role of designating and approving orphan drugs (Office of Orphan Products Development, 2018). The Orphan Products Grants program has funded 600 clinical trials, leading to 60 approvals of orphan products, which represent 10% of all orphan drug approvals. In recent years, the capacity for the OOPD to fund additional grants has decreased as the cost of conducting clinical trials has increased much faster than the rate of medical inflation over all (Office of Orphan Products Development, 2018).

The Orphan Drug Act in America is regarded by many as a successful piece of legislation, and Orphan drugs now account for about one third of all newly approved

drugs each year (Mikami, 2017). The Orphan Drug Act has inspired similar legislation in Japan, Singapore, Australia, as well as Europe (Mikami, 2017).

The quality adjusted life year (QALY) is a measure of a drug's efficacy, and is used in cost effectiveness analyses to determine the added overall health benefit associated with a drug's use. The use of QALYs was not widespread until the 1960s, and the practice got its start in calculations of the cost of nuclear shelters divided by the lives that could be saved by sucha shelter (Spencer et al., 2022). In 1965, president Johnson encouraged the Department of Health to take advantage of systems developed by the Department of Defense, which led to the incorporation of the QALY into the healthcare system of America (Spencer et al., 2022). The use of QALY is widespread in the UK through the National Institute for Clinical Excellence, but the use of QALY is banned in America for use in regards to Medicare coverage; however, the American Institute for Clinical and Economic Review still advises coverage for Medicaid and commercial health plans as well as pharmacy benefit managers (Kirkdale et al., 2010; Smith, 2019).

The QALY can be calculated by multiplying the health utility by the number of years of life expectancy (Spencer et al., 2022). Health utility is a quantity that varies between 0, meaning dead, and 1, meaning perfect health or cured. Values between 0 and 1 denote different qualities of life in a linear scale. Under the QALY system, ten years of life lived at 0.1 health utility is equal to one year of life lived at perfect health or a health utility value of 1.

The QALY is assessed via a number of means depending on the organization conducting the cost effectiveness analysis. The UK's National Institute for Clinical Excellence uses the EuroQol EQ-5D questionnaire to assess QALY. The EQ-5D includes

questions about daily activities, pain, depression and anxiety, self care, and mobility among others. The patient's answers are converted to one of 243 distinct health states that each correspond to a different numerical value for health utility between 0 and 1 (Kirkdale et al., 2010). Another way of assessing QALY is through a Time Trade Off Questionnaire. The TTO includes questions where patients are asked to identify preferences about theoretical health states and life expectancies:

> "Imagine that you are told that you have 10 years left to live. In connection with this you are also told that you can choose to live these 10 years in your current health state or that you can choose to give up some life years to live for a shorter period in full health. Indicate with a cross on the line the number of years in full health that you think is of equal value to 10 years in your current health state (Kirkdale et al., 2010)."

Once the change QALY for a given illness and a given treatment plan is assessed, the cost of the treatment is divided by the total change in QALY to come up with the cost per QALY afforded by that particular treatment. The cost per QALY is used by various bodies to determine whether a given treatment is cost effective enough to be covered.

The incremental cost effectiveness ratio is equal to the difference in cost of the new treatment relative to whatever treatment would be used otherwise divided by the difference in QALY afforded by the new treatment relative to the QALY afforded by the default treatment (National Council on Disability, 2019). ICER is another metric that closely resembles cost per QALY and is also used in cost effectiveness analyses to determine whether a given treatment is worth funding.

The American College of Cardiology and American Heart Association regards ICER less than $50,000 per QALY as high value, ICER between $50,000 and $150,000 per QALY as intermediate value, and ICER greater than $150,000 per QALY as low value (Dubois, 2016).

The UK's National Institute for Clinical Excellence will generally approve treatments with a cost per QALY of up to 30,000 pounds per QALY (Kirkdale et al., 2010). This converts to $39,437 per QALY.

America's Institute for Clinical and Economic Review values one QALY at between $50,000 and $150,000 (Smith, 2019).

In a literature review by Azimi and Welch, various cost effectiveness analyses were evaluated to determine general consensus on an appropriate value for a QALY. They found that below a value of $61,500 per QALY every cost effectiveness analysis surveyed judged the treatments to be worth it. Between $61,500 and $166,000 per QALY there was disagreement among cost effectiveness analyses (Azimi et al. 1998).

In 2018, CVS Caremark announced a new policy to allow pharmacy benefit managers to exclude any drug with a cost per QALY greater than $100,000 per QALY from their formularies; this action was taken with hopes that drug manufacturers would lower prices in order to remain competitive (National Council on Disability, 2019).

Literature Review

Pharmaceutical companies that produce orphan drugs, do so for small patient populations, and as a consequence, charge extremely high prices for these life saving medications. The average orphan drug costs five times more than the average non-orphan drug per year, costing patients $150,854 and $33,654 per year respectively, with data based on the mean values for the top 100 orphan and non orphan drugs in the US in 2018 (Chambers, 2020). As rare diseases continue to gain treatment options, there has also been a shift in the medical economy towards the thirty million Americans suffering from rare diseases. In 2021, 24.9% of U.S. prescription drug spending was on orphan drugs (Chua et al., 2021). Other reasons contribute to the lucrative nature of orphan drugs, including the nature of rare diseases. Most rare diseases are chronic and have a genetic component, which ensures that the patient population for most orphan drugs is life long. Additionally, 85-90% of known rare diseases are life threatening or serious, which means that small patient populations can be reliably charged high prices because of low price elasticity on the part of patients (Haffner, 2006).

In general, drug prices are set by pharmaceutical companies on a combination of the consumer's ability to pay and the desire to recoup research and development costs. However, the small market for orphan drugs means that pharmaceutical companies set prices with a greater emphasis on earning back research and development costs from a small number of patients, with decreased attention paid to consumer ability to pay (Srivastava, 2019). This combined with a low competition environment and high patient

need for the medications leads to an orphan drug market marked by such extreme price increases.

The market environment is not the only notable difference between orphan and non orphan drugs. The production process and associated costs also show divergence. Clinical testing of pharmaceutical drugs involves three stages of clinical testing. Phase 1 generally tests the safety and unintended side effects of a drug, which also helps to determine the optimal dose and timing. Phase 2 is the exploratory phase of clinical testing and uses biomarkers as the chief marker of efficacy. Phase 3 relies on more long term clinical outcomes, and is generally more costly than Phase 2 (Pateras et al., 2021). Each phase represents a different standard for continuation of development for pharmaceutical companies. 13.8% of drugs entering Phase 1 ever achieve marketing approval, which is the final step of approval for pharmaceutical drugs in America. Additionally, 35.1% of drugs entering Phase 2, and 59% of drugs entering Phase 3 ever achieve marketing approval (Wouters et al., 2020).

Orphan drugs, by definition, are created for small patient populations, which can make developing human clinical trials more difficult. One such extreme example is Adagen. Adagen treats severe combined immunodeficiency syndrome involving adenosine deaminase and only affects a total of 14 people in America. As a result, the clinical trial for Adagen involved only 8 people (Haffner, 2006). The average clinical study duration for orphan drugs is twice that for non orphan drugs. Additionally, orphan drugs have a lower mean number of subjects than non orphan drugs for phases two and three of human clinical trials (Jayasundara et al., 2019).

Even if the patient population is large enough for more typical clinical trials, as is the case the majority of the time, patient populations are generally dispersed over a wide range geographically, which can lend difficulty to the coordination of clinical trials. One drug suffering from this problem had to be approved by 62 different institutional review boards over a large number of hospitals just to ensure the sample population was large enough for statistically significant results (Haffner, 2006).

For orphan drugs, Phase 1 trials are usually not required; additionally the second and third phases can be combined if the patient population is sufficiently low (Srivastava, 2019). Additionally, there is often no requirement for a placebo arm in orphan drug trials (Srivastava, 2019). Because the orphan drug designation has such a large impact on the nature of human clinical testing, the application for orphan designation is generally submitted before the Investigational New Drug application, although it can be submitted at any point before the marketing application (Srivastava, 2019).

Jayasundara et al. (2019) investigated the costs of development for orphan vs non orphan drugs throughout the process of human clinical testing, by comparing the data on 100 random orphan drugs with 100 random non orphan drugs. The out of pocket clinical costs per approved orphan drug was 0.57 times the out-of-pocket clinical costs per approved non orphan drug, amounting to $166 million and $291 million per approved drug respectively (Jayasundara et al., 2019). The out of pocket clinical costs were capitalized at 10.5% per annum, resulting in capitalized out of pocket costs for orphan drugs at 0.71 times that of non orphan drugs, amounting to $291 million and $412 million respectively (Jayasundara et al., 2019). 74 out of 100 orphan drugs investigated were new molecular entities, compared to 54 out of 100 non orphan drugs. The term “new

molecular entity" refers to drugs for which the active moiety has not been approved previously by the FDA, as opposed to new chemical entities, for which the active moiety has been previously approved. When only considering new molecular entities, the capitalized costs for human clinical testing for orphan drugs was 0.50 times that of non orphan drugs, amounting to $242 million and $489 million respectively (Jayasundara et al., 2019). A number of factors contribute to this difference. First, the orphan drug clinical trials included significantly fewer subjects for the second and third phases, despite an estimated 2.5 times increased costs per patient for orphan drug trials. The capitalized difference in costs was lower than the uncapitalized difference in part because of the increased trial duration seen in orphan drug human clinical trials (Jayasundara et al., 2019).

Altered standards for clinical testing coupled with financial incentives from the FDA has led to a huge increase in the production of orphan drugs in recent years. In 2015, 21 new orphan drugs were approved by the FDA, representing 47% of new approvals. The proportion decreased to 40% of new approvals in 2016 and only 29% of approvals in 2020, but this still represents a comparatively large portion of drug approvals when considering the small associated patient populations (Tribble, 2017). As a result of this steady flow of new orphan drug development, there has been a huge improvement in prognosis for patients suffering from rare diseases. Before the Orphan Drug Act was passed in 1983, the rate of deaths from rare diseases was growing at a rate of 2% per year relative to only 1.2% for other diseases. Between 1983 and 1993, deaths from rare diseases actually declined at a rate of 3.1% compared to deaths from other

diseases continuing to increase at a rate of 1.3% per year (Biotechnology Industry Organization et al., 2015).

Despite this, 95% of Americans with rare diseases were still without options for treatment as of 2018 (Gerry, 2018). Out of 7,000 rare diseases, only 289 have at least one treatment option available (Biotechnology Industry Organization et al., 2015). However, 33% of marketing applications sent to the FDA are for orphan drugs, and 35% of Phase 3 trials are also for drugs with orphan designations (Wehrwein, 2021).

This discrepancy in part stems from the type of orphan drugs that become especially successful. Some diseases draw the majority of new development. For example, there were 30 different drugs available for hemophilia in 2021 (Wehrwein, 2021). Seven out of the ten top selling drugs in America have at least one orphan designation (Socal et al., 2020). Drugs already approved for non-rare diseases must still go through the approval process for additional indications, including rare diseases. They are also still eligible for the benefits associated with orphan drugs.

In a study by Socal et al., out of 86 orphan drugs, for which researchers were able to obtain prevalence data, there was an average of 2.7 orphan indications per drug (Socal et al., 2020). Of this sample, 21 drugs, or 24.4% had combined patient populations between each indication that amounted to more than the 200 thousand population threshold set out by the FDA as a definition for rare diseases (Socal et al., 2020). Additionally, 18 drugs, or 20.9%, had at least one non orphan approval, which automatically increases the total patient population significantly beyond the orphan threshold (Socal et al., 2020). In 2017, there were 70 orphan drugs that first gained approval for mass market use and only subsequently gained orphan designations and

benefits (Tribble, 2017). One notable example is Botox, which started out only indicated for treatment of eye muscle spasms and now is indicated for treatment of three rare diseases (Tribble, 2017). Another example of orphan drugs contradicting the idea behind the Orphan Drug Act is Amgen's Repatha. In 2015, Amgen Inc. achieved approval for two designations on the same day. The first was a rare disease, homozygous familial hypercholesterolemia, which affects only 300 people. The second was uncontrolled levels of LDL cholesterol, which affects over 11 million people (Tribble, 2017).

As a result of this lopsided economy, only 38.6% of spending on orphan drugs is actually for orphan indications (Chua et al., 2021). The non orphan spending is either directed towards indications for non-rare diseases or in many cases towards off-label indications. In a study by Kesselheim et al. on three of the four top selling orphan drugs in 2012, lidocaine patches, modafinil, and cinacalcet, the rate of orphan on label uses rose at rates of 3.12, 0.24, and .03 patients per month respectively. This was much lower than the rate of non orphan off label uses that rose at rates of 14.6, 1.45, and 1.58 patients per month respectively, which shows that while drugs can receive orphan indications, often the off-label use exceeds the on-label orphan use (Kesselheim et al., 2012).

Pharmaceutical companies that produce orphan drugs often apply for and receive additional orphan indications. It is important to note that orphan drugs are only *eligible* to receive *up to* seven years in marketing exclusivity, and it is at the discretion of the FDA to decide how many years of marketing exclusivity to give with each orphan designation. However, drugs are eligible for additional years of market exclusivity with additional orphan designations. Orphan drugs that received a second orphan designation on average received 4.7 additional years of marketing exclusivity (Padula et al., 2018). The third

orphan designation resulted in an average of 3.1 additional years of marketing exclusivity (Padula et al., 2018). The fourth and fifth orphan designations were associated with an average increase of 2.7 and 2.9 additional years of exclusivity, respectively (Padula et al., 2018).

In a study conducted by the National Organization for Rare Disorders, the average cost of development of orphan drugs as well as the impact of the orphan designation associated tax credit was calculated in 2015. The average out-of-pocket cost of preclinical trials for drug development was $233 million for established drug developers. The out of pocket costs for phase one, two, and three of clinical trials were $126 million, $123 million, and $176 million, respectively (Biotechnology Industry Organization et al., 2015). All drug development is eligible for some form of tax credit from the government in the form of research and development tax credits. A pharmaceutical company producing an orphan drug will take advantage of both research and development and orphan drug tax credits at different stages of drug development. The research and development tax credit is applied to preclinical testing, and the orphan drug tax credit is applied to human clinical testing. When calculating the value of the tax credit, the time value of money as well as the company's cost of capital were taken into account to come up with the present value of the tax credit to the pharmaceutical company. The average present value of the research and development tax credit was $11.3 million, and the average present value of the total orphan drug tax credit was $138.8 million (Biotechnology Industry Organization et al., 2015). In the non-orphan drug scenario, the orphan drug tax credit is unavailable, but out of pocket costs for human clinical testing are still eligible for the research and development tax credit. The value of the increased

research and development tax credit was calculated to be one tenth of the value of the lost orphan drug tax credit; the total present value of the research and development tax credit for non-orphan drugs was calculated to be $28 million. It is important to note that this study was conducted in 2015, which was two years *before* the orphan drug tax credit was reduced from 50% to 25% of qualified human clinical testing. The average present value of out of pocket costs for drug development, including research and preclinical as well as clinical testing, was calculated to be $466.3 million. The net out of pocket costs for orphan drug development after tax credits was calculated to be $316.1 million, and the net out of pocket costs for non-orphan drug development after tax credits was calculated to be $438.3 million (Biotechnology Industry Organization et al., 2015).

For unestablished, premarket drug developers, the increased value of tax credits for orphan drugs relative to non orphan drugs was calculated to be $101.6 million, because premarket drug developers do not have the same ability to access tax credits before drug production (Biotechnology Industry Organization et al., 2015). Drug developers can apply the tax credit to the prior year or over a period of as much as 20 years to future taxes (Nuventra, 2022). This is especially useful for premarket drug developers, because they may not owe enough taxes prior to drug development to take advantage of the tax credits.

As previously discussed, the ultimate value provided by pharmaceutical drugs can be measured in QALYs. In new chemical entities approved by the FDA between 1997 and 2015, orphan drugs had a median QALY gain of 0.25, while non-orphan drugs had a median QALY gain of 0.05 (Chambers et al., 2020). Additionally, 45% of orphan drugs afforded a cost per QALY of at least $150,000 per QALY, while only 21% of non-orphan

drugs exceeded this threshold (Chambers et al., 2020). The median cost per QALY for orphan drugs in this period was $276,288 per QALY, while non-orphan drugs in this period had a median cost per QALY of $100,360 per QALY (Chambers et al., 2020).

Methodology and Results

It is important when evaluating government programs to understand whether or not the benefits created by the program outweigh the costs created by the program. When considering the value created by a program like the Orphan Drug Act, it is useful to determine the value created by the drugs themselves. Pharmaceutical drugs create value for American citizens in the form of health benefits, which can be estimated as quality-adjusted life-years. The value created by the Orphan Drug Act can therefore be estimated to be the total amount of quality-adjusted life-year benefits experienced by all patients taking orphan drugs. Because the FDA expends significant capital in incentivizing the creation of these benefits, it is also worthwhile to gain an estimate of what the costs are for the incentivization of each drug's development. The FDA expends dollar amounts for two of the three orphan drug benefits, user fee waivers and orphan tax credits, which can be estimated and added together to gain an estimated total cost per drug expended by the FDA. The net value created can then be understood to be the difference between the benefits and the costs associated with the program.

In order to determine the value created by each orphan drug in dollars, the prevalence of each indication is multiplied by the quality-adjusted life-year gains for each drug and the value of a statistical life year. The cost incurred by the FDA in incentivising each drug is calculated by adding the average added orphan tax credit to the value of a drug application with clinical data waiver. The net value created by each orphan drug is

calculated by subtracting the costs incurred by the FDA from the value created by each drug.

In order to determine the Value of a Statistical Life Year, this study relies on calculations performed by the US Department of Health and Human Services that released a report in 2016 providing guidelines for regulatory impact studies. Often, the value of a statistical life and the Value of a Statistical Life Year are chiefly relevant in cases where risk of fatality is altered somehow in order to assign monetary values to risk increases or risk reductions. The basis of the report was six studies on revealed preferences with the value of a statistical life report from $4.4 million to $14.2 million with a midpoint of $9.3 million in 2014 dollars (Robinson et al., 2016). To determine the value of an individual statistical life year, the total value was divided out across the life span and then a 3% discount rate was applied to future years, yielding a central estimate of $490 thousand in 2014 dollars per life year (Robinson et al., 2016). This value can be converted to $548 thousand in 2022 dollars per year.

Due to the 2017 modifications to the Orphan Drug Act, as well as the usage of 2022 user fee amounts, all dollar amounts that are not reported in 2022 dollars are converted to 2022 dollars for calculations performed in this study.

In order to calculate the Ideal Value Created by each orphan drug (IVC) for which data was obtained, the Value of a Statistical Life Year (VSLY) is multiplied by the Quality-Adjusted Life Year Gains (QALYG) associated with the drug and the total United States prevalence of the drug (Prev).

$$IVC = VSLY \times QALYG \times Prev$$

Because rare diseases are less common, it takes an average of 7.6 years for patients with rare diseases to receive the correct diagnosis (Biotechnology Industry Organization & National Organization for Rare Disorders, 2015). Furthermore, the treated population of rare diseases only represents on average 10% of the total prevalence of the disease due to a lack of public awareness regarding many rare diseases (IQVIA Institute for Human Data Science & National Organization for Rare Disorders, 2018). The estimated 10% treatment rate is converted to a factor of 0.1 for the purposes of this study. To calculate the Real Value Created by each drug (RVC), the Ideal Value Created is multiplied by a factor of 0.1 to account for inefficiencies in terms of diagnosis and treatment.

$$RVC = IVC \times 0.1$$

The main data used in this study was acquired from the FDA's Office of Orphan Medical Products. Scans of orphan designation applications were obtained via a freedom of information request submitted through the online FDA FOIA request form. In total, the orphan designation applications for 85 designation-drug combinations were obtained in redacted form. As a rule, orphan drug designation applications must include data regarding national prevalence in order to prove that the associated rare disease does not affect more than 200,000 Americans. The applications must also include calculations explaining and supporting the claimed prevalence data. The prevalence data, as well as drug name and indication, were obtained from each orphan designation application.

The basis for inclusion of different drug applications in the response to the Freedom of Information Act request was applications that the FDA already had prepared in response to other freedom of information requests. As a result, it is unlikely that the

data from the obtained 85 orphan designation applications are completely representative of orphan designation applications as a whole, as their inclusion was non random.

The value created by orphan drugs for individual consumers is measured in this study using quality-adjusted life-years (QALYs). Data regarding quality adjusted life years and price per quality adjusted life years were obtained through the Cost Effectiveness Analysis Registry of the Tufts Medical Center, which "is a comprehensive database of >10,000 cost-utility analyses on a wide variety of diseases and treatments published from 1976 to the present (Tufts Medical Center, 2018)."

The generic and brand names were obtained from each orphan application and were both searched via the methods section of the CEA registry search engine, which yielded results in the form of articles published by the National Center for Biotechnical Information. Quality-adjusted life-year data is presented as a relative value. In cases where another drug for the indication already exists and is commonly used to treat the rare disease, the Quality-Adjusted Life-Year Gains are reported relative to the Quality-Adjusted Life-Year gains of that preexisting treatment. In cases where such a drug does not exist, quality adjusted life year data is reported relative to best supportive care.

Data regarding cost effectiveness was available for 20 of the 85 drugs, for which applications were received from the FDA. Of that subset, data regarding raw quality adjusted life year gains was available for 16 drugs.

The QALY and prevalence values for each drug are reported in Table 1.

Table 1. Drug name, indication, indication prevalence, and drug efficacy

Drug	Indication	Prev	QALYG
Afatinib	EGFR-mutation positive NSCLC	24086	1.36
Xalkalori (crizotinib)	c-MET/ROS/ALK positive locally advanced/metastatic NSCLC	197205	2.68
Epidiolex (cannabidiol)	Lennox-Gastaut syndrome	82290	0.7
Esbriet (pirfenidone)	idiopathic pulmonary fibrosis	41990	3.318
Kalydeco (ivacaftor)	cystic fibrosis	30000	6.8
Nexavar (sorafenib)	renal cell carcinoma	162472	0.27
Ultomiris (ravulizumab-cwvz)	paroxysmal nocturnal hemoglobinuria	463	1.67
Riluzole	amyotrophic lateral schlerosis	22540	0.182
Somatropin	human growth hormone deficiency	14286	3.25
Somavert (pegvisomant)	acromegaly	18946	0.15
Stivarga (regorafenib)	metastatic/unresectable gastrointestinal stromal tumors	8506	0.42
Stivarga’ (regorafenib)	hepatocellular carcinoma	29968	0.18
Tafinlar (dabrafenib)	V600-positive stage IIb-IV melanoma (advanced/metastatic)	93913	0.1565
Tukysa (tucatinib)	HER2 positive breast cancer with brain metastases	19375	0.21
Actemra (tocilizumab)	juvenile ideopathic arthritis	24000	0.23
Natpara (recombinant parathyroid hormone)	hypoparathyroidism	66500	0.94

The value created by orphan drugs is achieved by incentives funded through the FDA to encourage development of orphan drugs. The FDA incentivizes orphan drug development through improved tax credits for qualified human clinical trials, application and program fee waivers, and up to seven years exclusivity.

The Total FDA Expenditure per drug (TE) is calculated by adding the Current Added Orphan Tax Credit to the application fee (AF) with clinical data.

$$TE = CATC + AF$$

In 2017, the orphan tax credit changed from 50% to 25% of qualified human clinical testing (Knowledge Ecology International, 2021). Because the Preliminary Added Orphan Tax Credit was calculated in 2015 based on 2015 policies, it must be multiplied by 0.5 to achieve the Current Added Orphan Tax Credit (CATC). The new tax credit will be used for calculations of value exchanged even for drugs for which the applications were submitted prior to 2017 because the purpose of this analysis is to determine the value of the orphan drug program going forward.

$$CATC = PATC \times 0.5$$

The Preliminary Added Orphan Tax Credit (PATC) is calculated by subtracting the average non-orphan total tax credit (NODATC) from the average orphan total tax credit (ODATC).

$$PATC = ODATC - NODATC$$

The Net Real Value Created (NRVC) and Net Ideal Value Created (NIVC) for a given drug are calculated by subtracting the Total FDA Expenditure for the drug from the Real Value Created and Ideal Value Created, respectively.

$$NIVC = IVC - TE$$

$$NRVC = RVC - TE$$

The cost expended by the FDA through application and program fee waivers was determined through the FDA's website. The application and program fees are updated annually, so 2022 fees were obtained and are used in this analysis. The application fees for drugs where clinical data is required are used in this analysis and amount to $3,117,218 per drug application (AF) (Center for Drug Evaluation and Research, 2022). The FDA waives this fee for orphan designated drugs, and so it can be counted as an expense on the part of the FDA in order to encourage orphan drug production. For the purposes of this study, the program fee waiver will not be included as it is an annual fee accrued for each drug a pharmaceutical company is currently producing and it represents a very small portion of the benefits provided by the FDA.

The cost expended by the FDA through tax credits for qualified human clinical testing were estimated based on data from the National Organization for Rare Disorders report: "Impact of the Orphan Drug Tax Credit on Treatments for Rare Diseases." Because orphan drug tax credits cannot be doubly applied to expenses also used for research and development tax credits, the value of the orphan drug tax credits is reported as the difference in tax credit between a scenario with only research and development tax credits and a scenario with both research and development as well as orphan drug tax credits applied to different expenses. These values were calculated separately for established and non-established drug developers; although for the purposes of this analysis, the established drug developer estimate will be used.

The research and development tax credit for orphan drugs amounts to an average of $11.3 million when used in conjunction with the orphan drug tax credit, which amounts to an average of $138.3 million; both values are reported as a present value using a 5% discount rate. The total average tax credit for the orphan drug scenario (ODATC) is therefore $149.6 million. In the non orphan drug scenario, where only the research and development tax credit may be applied, the average total present value tax credit is valued at $28.0 million (NODATC), also calculated with a discount rate of 5% (Biotechnology Industry Organization & National Organization for Rare Disorders, 2015).

The difference between the two tax credits is the Preliminary Added Orphan Tax Credit and amounts to $145.7 million in 2022 dollars. After adjusting for current policy, calculations yield a Current Added Orphan Tax Credit of $72.85 million in 2022 dollars. The Total FDA Expenditure per drug is the combination of Current Added Orphan Tax Credit and Application Fees, which amounts to $75,967,218 per drug indication, which is reported in Table 2, along with the Ideal Value Created and Real Value Created as well as the Net Ideal Value Created and Net Real Value Created for each drug.

Table 2. Drug name, Ideal and Real Value Created, Net Ideal and Real Value Created

Drug	IVC (billions)	RVC (billions)	NIVC (billions)	NRVC (billions)
Afatinib	17.95	1.795	17.87	1.719
Xalkalori (crizotinib)	289.6	28.96	289.52	28.88
Epidiolex (cannabidiol)	31.57	3.157	31.49	3.081
Esbriet (pirfenidone)	76.35	7.635	76.27	7.559
Kalydeco (ivacaftor)	111.8	11.18	111.72	11.10
Nexavar (sorafenib)	24.04	2.404	23.96	2.328
Ultomiris (Ravulizumab-CWVZ)	.4237	.04237	.3477	-.0336
Riluzole	2.248	.2248	2.172	.1488
Somatropin	25.44	2.544	25.36	2.468
Somavert (pegvisomant)	1.557	.1557	1.481	.0797
Stivarga (regorafenib)	1.958	.1958	1.882	.1198
Stivarga' (regorafenib)	2.956	.2956	2.880	.2196
Tafinlar (dabrafenib)	80.54	8.054	80.46	7.978
Tukysa (tucatinib)	2.230	.2230	2.154	.1470
Actemra (tocilizumab)	3.025	.3025	2.949	.2265
Natpara (recombinant parathyroid hormone)	34.26	3.426	34.18	3.350
Average	44.12	4.412	44.04	4.336
Total	705.95	70.595	704.70	69.371

The drug with the largest net value created is ivacaftor, the brand name for which is Kalydeco. Ivacaftor is designated to treat cystic fibrosis, which is an autosomal recessive disorder that impacts mucus production in airways (Shteinberg et al., 2021). Ivacaftor treats cystic fibrosis by altering activity of the cystic fibrosis transmembrane conductance regulator, which is the protein impacted by the cystic fibrosis gene (Condren et al., 2013). Cystic fibrosis has an estimated prevalence of 30,000 Americans, and ivacaftor usage results in an average gain of 6.8 quality adjusted life years in cystic fibrosis patients (Wherry, 2020). Ivacaftor has a net ideal value created of $111.72 billion and a net real value created of $11.10 billion.

The one drug included in the study with a negative net real value created is ravulizumab-cwyz, the brand name for which is Ultomiris. Ravulizumab-cwyz is designated to treat paroxysmal nocturnal hemoglobinuria, which is a disease of bone marrow failure that results in low blood cell counts and blood cell blockage of veins and arteries (Brodsky, 2014). Paroxysmal nocturnal hemoglobinuria has a prevalence of 463 Americans, and ravulizumab-cwyz usage results in an average gain of 1.67 quality adjusted life years (O'Connell et al., 2020). Ravulizumab-cwyz has a net ideal value created of $.3477 billion and a net real value created of negative $.0336 billion.

The average net ideal value created for the 16 drugs included in this study is $44.04 billion, and the average net real value created is $4.336 billion dollars.

Conclusion

This study set out to evaluate the Orphan Drug Act by calculating the value created by drugs, the development of which was facilitated by incentives associated with the Orphan Drug Act. The drug applications for 86 drugs were retrieved from the FDA via a freedom of information request, and the prevalence data for each rare disease indication was recorded. The generic and brand names for each drug were then searched on the CEA registry search engine, and QALY data was available for 16 drug indication pairs. The value of a statistical life year was calculated using estimates performed by the US Department of Health and Human Services. The value of a statistical life year was multiplied by the quality adjusted life year gains associated with each drug and the prevalence of the drug indication to calculate an estimated value created by each drug's development.

The net value created by each drug was calculated by subtracting the costs expended by the FDA in funding orphan drug incentives from the value created by each drug. The costs expended by the FDA for each drug consist of application fee waivers and tax credits. The data for application fees with clinical data required in 2022 was retrieved from the FDA website. The average orphan tax credit was calculated by adjusting data from a study conducted by the National Organization for Rare Disorders to the new, lower tax credit for 2022. The average tax credit was added to the application fee waiver to calculate the average cost expended by the FDA in incentivizing orphan drug development.

The average net value created for the data set was $44.04 billion assuming 100% of the disease population is treated and $4.336 billion assuming 10% of the disease population is treated. A back of the envelope calculation, extrapolating from these average values, yields an estimated total net value created by the Orphan Drug Act of $45.76 trillion assuming 100% treatment for every orphan drug and $4.505 trillion assuming an average of 10% of each disease population is treated (IQVIA Institute for Human Data Science, 2020). It is unclear how relevant these estimates are as the inclusion for drugs in this study was doubly nonrandom. Furthermore, sufficient data was only available for 16 out of an estimated 1039 drug indication pairs (IQVIA Institute for Human Data Science, 2020). The first degree of nonrandomness comes from the FDA's response to the Freedom of Information Act request. The criteria for inclusion in the response to the Freedom of Information Act request was that the FDA has already gathered and redacted the application files in response to other freedom of information requests. The second degree of nonrandomness comes from the availability of quality adjusted life year data. Data regarding quality adjusted life years was not available for 70 out of 86 drug indication pairs on the CEA registry. It is unclear whether these limitations imply the estimates performed here would be an overestimate or an underestimate of the actual values.

Chief limitations in this study were the availability of application data from the FDA as well as the existence of quality adjusted life year data on a minority of orphan drugs. Future research should explore ways of either collecting data on a larger sample of orphan drugs or ensuring that the data used is random and representative of the whole sample. Given time and resource limitations, these hurdles were unable to be surmounted

in the conduction of this study. However, the calculations performed in this study provide a basis and beginning estimate for the range of values created by orphan drugs and their relationship to the costs of incentives provided by the FDA.

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