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The Development of Orphan Drugs; A Financial and Ethical Decision

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Abstract

This paper explores the decision faced by a firm to invest in an orphan drug development project. Two primary areas of concern are considered: financial and ethical. In order to properly understand these two areas, the paper first summarizes the current development landscape for non-orphan and orphan drugs. Once the basic development structure is established, a discussion regarding the differences in the Net Present Value equation for a non-orphan and orphan product may occur. Once the differences in the financial decision are established, the paper will discuss the ethical considerations surrounding drug development and drug pricing. The combination of the financial model and the ethical guidelines for drug pricing form the argument for an increase in social corporate responsibility in the drug development industry to increase treatment accessibility for patients of rare diseases.

I. Introduction

The private nature of medicine in the United States has created an environment in which companies are responsible for developing new treatments for the general public. While the health of a society is a public good, the development of treatment options is the responsibility of the private sector. In order to protect public health, the United States government regulates pharmaceutical developers through the Food and Drug Administration ("FDA"). For a company to sell a drug in the United States, they must obtain marketing approval from the FDA. Marketing approval means a company is authorized to sell and advertise the drug as treatment for a specific condition. If the company discovers an approved drug can treat additional conditions, the company undergoes another application for marketing approval for the condition. While the process of approval ensures only safe and effective drugs are sold in the United States, it raises the costs and time needed to develop a drug. As development costs increase, the government has implemented incentive programs for the development of drugs which may have low profit potential due to small patient populations. The small patient populations for these drugs, called orphan drugs, limit the potential revenue of the drug which discourages companies from researching them. To properly examine the market, Section II of this paper will detail the drug development process with costs and time measurements for each stage. Section III will detail the effect of incentives to develop orphan drugs. Once the overall framework of the orphan drug development process is detailed, Section IV will discuss the methods used to model the financial situation for both orphan and non-orphan drugs. The conclusions of the financial models will be discussed in Section V. Sections VI and VII will examine the ethical decisions a pharmaceutical company faces in development and determining the appropriate price to charge for a medication. This paper will examine how the government incentives the development of

treatments for rare diseases, financial factors influencing the business decision, and the ethics behind developing drugs for rare diseases.

II. Drug Development Process

In order to market and sell a drug to treat a disease in the United States, the company must obtain marketing approval for the drug from the FDA. In order to obtain approval, the drug must be put through a rigorous testing process of clinical trials leading to the final application. Before the drug begins clinical trials for marketing approval, the application for a drug must be established. As drug development is a risky and expensive investment, a company wants to be as confident as possible that the drug has a chance to treat a condition. Preclinical trials consist of animal testing to show the drugs basic interaction with living entities (Umscheid, Margolis, & Grossman, Sep. 2011). Once the drug has been shown to be reasonably safe for human consumption, the company submits an investigative new drug application ("IND") to receive approval to begin human testing.

The initial phase of human testing is conducted on healthy test subjects to determine the maximum tolerated dose ("MTD") and the severity of side effects (Umscheid, Margolis, & Grossman, Sep. 2011). The purpose of these trials is to confirm the results of pre-clinical testing before the drug is given to individuals who are affected by the condition which it treats. Phase I trials simply demonstrate the drug is safe for human consumption and begin to measure adverse side effects. Instead of providing the drug to patients suffering for the targeted condition, the drug is administered to healthy individuals to observe the effects. The Phase I trial size for non-orphan drugs is generally 65 patients per trial (Jayasundara, et al., January 2019). These trials are small as they simply show the general safety of a new drug. For non-orphan drugs, a company conducts 1.06 phase I trials on average per approved non-orphan drug. This average indicates

that most companies conduct one Phase I trial over the course of one to two years. Additionally, companies have an average cost of $38,500 per patient in the trial (Jayasundara, et al., January 2019). On average, companies will spend around $2.5 million on their phase I clinical trial. It is important to note, that this number, alongside all future clinical cost numbers, is simply the direct costs in for conducting the clinical trial. The company will incur additional administration costs related to operating a business alongside the clinical costs.

Phase II trials are the beginning of testing on patients suffering from the targeted condition. Once a Phase I trial has shown the drug is safe for human consumption, Phase II trials are used to begin measuring treatment efficiency and safety for patients. As patients for the drug have different health condition than the healthy test subjects of Phase I, testing the side effects and safety in depth is needed. A successful Phase II trial will show the drug is safe for patients to use and begin to demonstrate the efficacy of the treatment (Umscheid, Margolis, & Grossman, Sep. 2011). These trials have a larger number of participants than Phase I in order to show that the drug can treat the disease. On average, non-orphan drugs have 235 patients per Phase II trial (Jayasundara, et al., January 2019). Similarly, to Phase I trials, an average of 1.05 Phase II trials are conducted per approved non-orphan drug. An average Phase II trial will take place over 2 years and cost $40,000 per patient. This leads to a total average cost of $9.4 million dollars for a Phase II trial. If the adverse side effects outweigh the benefits of the treatment, or there is no correlation between the medicine and health improvement, the company may decide to conduct further Phase II testing or abandon the project.

Once a company successfully completes Phase II trials, they may conduct Phase III trials. The purpose of Phase III trials is to conclusively show the treatment is safe and effective in treating patients. Not only do the trials need to confirm the drug is safe for patient use, Phase III

trials must also conclusively show the drug is effective. If the drug is the first to treat the specific condition, it merely needs to demonstrate it is more effective than no treatment. However, if a treatment option already exists for the condition, the Phase III trial must show that the new drug is better in some way than existing options (Umscheid, Margolis, & Grossman, Sep. 2011). On average, non-orphan drugs have 698 patients per Phase III trials and conduct 3.5 Phase III trials per approved drug (Jayasundara, et al., January 2019). An average Phase III trial lasts for just over two years and costs $42,000 per patient for a total average cost of $29.3 million per Phase III trial. As a company will likely conduct at least three Phase III trials, they may expect to pay at least $90 million in Phase III clinical costs.

Once a company is satisfied with their Phase III trials results, they may submit a New Drug Application ("NDA") to the FDA for marketing approval. An NDA carries a two million dollar application fee and takes a year for the FDA to process (Jayasundara, et al., January 2019). The application submits the findings of all clinical trials conducted to the FDA's Center for Drug Evaluation and Research and when approved the company is permitted to market and sell the drug (Umscheid, Margolis, & Grossman, Sep. 2011). As part of approval, the FDA may require the company to conduct additional Phase IV trials post-approval to expand the patient base, most commonly for approval to treat children (Umscheid, Margolis, & Grossman, Sep. 2011). While Phase IV trials cause a company to incur additional development costs and are not uncommon, as they occur post approval and have high cost variance, they are not included in this paper's discussion of development.

Once the company has received marketing approval, they have exclusive rights to sell the drug until their patent runs out, unless granted additional exclusivity. Patents provide exclusivity for 20 years from the patent application date. Companies generally patent their drug early in the

development process to prevent competitors from developing the same drug. Once their exclusivity expires, a competitor may submit an Abbreviated New Drug Application ("ANDA") to sell a generic version of the drug. The first company to submit an ANDA receives 180 days of market exclusivity for generic versions. This encourages generic versions to apply as soon as possible at the end of a patent or market exclusivity (FDA, 2015). Once a generic competitor exists, a company faces competition which may significantly impact their profits due to price competition and lost customers. However, patients may be hesitant to switch due to name brand recognition and familiarity with the original product (Tenn & Wendling, May 2014). Due to this, it is in the company's best financial interests to reach the market as quickly as possible to maximize the time of patent protection to recoup development costs. The company must balance the desire to reach the market quickly with the need to conduct thorough testing to ensure a quality product.

At each phase of clinical trials, the trial may have inconclusive results, or find results which indicate the drug may be unsafe or ineffective. If results which show the drug is unsafe are found, the company must either alter the drug and conduct another clinical trial with the new version or abandon the project. The best-case scenario for a development setback is simply an increase in development costs, and at worst, prior investments becoming sunk costs due to project abandonment. The potential for failure in development is relatively high. For non-orphan drugs, there is only a 10.4% chance of a drug starting the clinical process making it to market (Jayasundara, et al., January 2019). Perhaps most telling is the only 32.4% chance of making it from Phase II to Phase III for non-orphan drugs (Jayasundara, et al., January 2019). Due to the significantly higher clinical costs of Phase III trials, companies who found mediocre success in Phase II may be hesitant to invest further. If the results from Phase II are weak, a company may

decide to abandon the project, or decide to conduct additional small-scale trials before advancing to large scale Phase III trials. As a company must apply to market the drug with conclusive data which shows the drug is safe to use, and treats a condition efficiently, they are likely to conduct multiple Phase III trials to ensure adequate supporting data exists. Although the additional trials are expensive, failed applications will lead to delays and additional trials. These delays will lower the amount of time a company enjoys market exclusivity under patent protection.

As drug development is generally undertaken by financially motivated companies, if the development and sale of a drug is not profitable, they are unlikely to pursue it. As rare diseases have significantly smaller patient populations, the development costs of a treatment will become harder to recoup. If a company wished to develop an orphan drug for a rare disease, they would either need significantly lower development costs, or higher prices to make up for a smaller patient population. In order to promote investment into the development of orphan drugs to treat rare diseases, The Orphan Drug Act of 1983 ("ODA") was created (Orphan Drug Act of 1983). The ODA defines a rare disease as one which "affects less than 200,000 persons in the United States," or "affects more than 200,000 persons but has no expectation of sales of the drug recouping the development costs". Since showing a patient population is under 200,000 individuals is significantly easier than demonstrating a lack of financial viability, most orphan drug applications target the patient count of their disease to qualify for orphan status (Office of Orphan Products Development, 2017). Additionally, orphan drugs must treat diseases which lack pharmaceutical treatment options (Orphan Drug Act of 1983).

Although they possess much smaller patient populations, research for medicine which addresses rare diseases is needed for public health. Although each disease has a low number of patients, when the approximately seven thousand diseases are combined, they account for 25

million patients in the United States alone (Valdez, Ouyang, & Bolen, 2016). If no drugs were developed for rare diseases, a significant portion of the population would face inadequate healthcare. Once treatment is developed for these diseases, they may increase the life expectancy by significant amounts (Lichtenberg, 2001). For example, in the case of cystic fibrosis, a disease with 26,000 patients, research which developed treatment brought the life expectancy from 6 months in the early 20th century to 42.7 years currently (Hussain, Hussain, Malik, Patel, & Chittivelu, 2018). Developments of this form enable thousands of individuals who were likely to die as children, to finish college, find jobs, and live relatively normal adult lives. The ODA aims to encourage private investment in research for drugs which treat these diseases. Alongside the ODA, private organizations may work to raise funds for the research and awareness of a specific rare disease. Due to the variance across diseases, and lack of data on the results of these efforts, they are not included in the general discussion of pharmaceutical development.

In order to receive Orphan drug designation, a company must file an application with the FDA for their drug. If the FDA decides to award the drug the orphan status, the company is eligible for research tax credit of 50% of development costs, grants, waivers of application fees, smaller clinical trials, and easier access to patients and doctors (Orphan Drug Act of 1983). Additionally, the ODA guarantees orphan drugs 7 years of market exclusivity in addition to standard patent protection upon FDA approval (Orphan Drug Act of 1983). When researching an orphan drug, a company is guaranteeing their product will enjoy a market without competition. In contrast, many non-orphan drugs are entering markets which already have at least one treatment option. Although the new drug must be an improvement over existing treatments, competition will still exist. The combination of cost breaks and market protection enable companies to invest in the development of orphan drugs with lower costs and risk. Ideally, this

will lower the price charged for the medicine as there are less costs to be recouped. However, the guaranteed 7 years of market exclusivity may encourage companies to gouge the price of the drug without the threat of competition. Additionally, once exclusivity expires, competitors may be unlikely to submit ANDAs as the market is much smaller than a non-orphan drug. Tenn and Wendling conclusively showed that generic competitors decide to enter markets based off the amount profit they can expect (Tenn & Wendling, May 2014). While potentially high prices for orphan drugs may be attractive to generic producers, the relatively small market size is likely to discourage investment as there are less potential revenue streams.

III. Success and Failure of the ODA

The ODA is unique as it is one of two U.S. polices which stimulates private investment in R&D through supply-side subsidization (Yin, 2008). There are two obvious measures which may be used to determine the success of the ODA: 1) the change in the number of clinical trials for orphan drugs, and 2) the change in the number of approved orphan drugs. Since the ODA has been implemented, there has been a 69% increase in new clinical trials for well-known rare disease (Yin, 2008). Yin argues that the ODA was able to increase clinical research by lowering the upfront development costs of R&D. Yin's arguments are supported as the yearly requests for orphan drug designation continue to grow, quadrupling from 2000 to 2017 (Office of Orphan Products Development, 2017). While these measurements clearly indicate some form of success for the ODA, more complex factors which are harder measure may also be considered. Clinical trial numbers and approval numbers are both reported through the FDA making them easy to measure. However, they do not provide information regarding the efficiency of development, cost effectiveness, or measurements of patient accessibility to drugs after approval. While these

measurements are important to consider when discussing the success of the ODA, they are difficult to measure as they are not reported to the FDA.

Although the ODA also increased potential revenue through market exclusivity, lowering the risk of initial investment appears to motivate companies to increase research. After the implementation of the ODA, a significant observed difference between non-orphan drugs which historically have a measly 10.4% chance of making it to market, versus orphan drugs which have a 32.9% chance has occurred (Jayasundara, et al., January 2019). While the ODA does not have a specific policy which targets solely risk, the observed difference has changed companies' confidence levels in investment and should be considered.

Since the implementation of the ODA, the number of drugs which qualify for orphan status that received marketing approval has significantly increased. In the decade leading up to the ODA, under ten drugs which met the orphan requirements received marketing approval. Since 1983, over five hundred orphan drugs have received marketing approval. This indicates a significant shift in the industry; likely caused by the new incentives (Office of Orphan Products Development, 2017). Perhaps the most telling observable cost savers in action, are in the average trial size, and number of trials per phase per drug. Although orphan drugs on average have more Phase II trials, 2.56 versus the 1.05 of non-orphan drugs, they have significantly fewer Phase III trials, 1.93 versus 3.5 (Jayasundara, et al., January 2019). Due to Phase III trials significant size and duration, the tradeoff of additional Phase II for fewer Phase III is an attractive proposition. Additionally, both Phase II and III have smaller patient populations on average for orphan drugs. However, they cost roughly two and a half times more per patient, and each trial lasts a year longer on average (Jayasundara, et al., January 2019). Although the additional clinical costs due to trial duration are accounted for in the per patient cost, longer trials will still lead to additional

non-clinical trial costs, such as administration, and overhead, before revenue occurs. While developing a new pharmaceutical of any form remains expensive, the improved chance of an orphan drug successfully making it to market, increases the attractiveness of investing as the company is less likely to face unexpected development costs, delays in obtaining marketing approval, or project abandonment.

IV. Methodology of Financial Modeling

When a company either discovers or can purchase the rights to a new drug, they must decide if the drug will be worth the investment. A company must determine if they believe the investment will be profitable before they begin clinical trials. In order to accomplish this, the company must evaluate all future cash flows discounted over time to determine the potential profitability. The primary method used is the Net Present Value ("NPV") equation. The initial equation used is as follows:

$$NPV = \sum_{t=0}^{n} \frac{R_t}{(1+i)^t}$$

Where:

R=net cash flows during a single period *t*

i=discount rate

t=number of time periods

By summing the current value of each year of cash flows, the company can determine if the project is likely profitable. This equation may be applied effectively across multiple industries and provides a snapshot of an investment's value at a specific time through the calculation of the current value of future cash flows. For the purpose of drug development, the

equation informs a company if the future potential revenues outweigh the immediate development costs. When using an NPV model, the key decisions which must be made are determining the discount rate and predicting future cash flows. The discount rate should reflect the expected return on investment for shareholders financing the project. In general, an 11% discount rate reflects a modest return on investment. An NPV model using an 11% discount rate will be used as a starting point for this paper.

While an 11% discount rate may accurately reflect an acceptable return for most industries, drug development has a high element of risk with non-orphan drugs having a 10.4% success rate (Jayasundara, et al., January 2019). As risk of investment increases, investors may require a higher expected return. Across a survey of industry professionals, it was found that a significantly higher discount rate is used for drug development projects to account for the significant risk factor (Alacrita, 2018). The second NPV calculation this paper will use will have a 33% discount rate to account for the higher risk of investment in the industry.

In addition to simply using a higher discount rate to account for risk, a slightly modified equation should also be considered. A risk adjusted NPV ("rNPV") discounts each cash flow before multiplying them by the chance of the cash flow occurring before summing all flows. For a high-risk industry such as drug development, this allows the company to use a normal discount rate, 11% for this paper, while still considering risk. While the 33% discount rate model accounts for risk, it does not allow for specific adjustments per stage of development which reflect the risk facing the company at that point. As historical data exists reflecting the likelihood of a project advancing to the next development stage, specific risk rates are accessible. The following equation results from including risk:

$$rNPV = \sum_{t=0}^{n} r\left(\frac{R_t}{(1+i)^t}\right)$$

Where:

R=net cash flows during a single period *t*

i=discount rate

t=number of time periods

r=percent chance of the discounted cash flow occurring

A model using an 11% discount rate before adjusting for risk will be used to provide a third measurement which accounts for risk specific to the project. As non-orphan and orphan drugs face significantly different success rates, a risk adjusted model will provide a better evaluation of value which accounts for risk specific to each project.

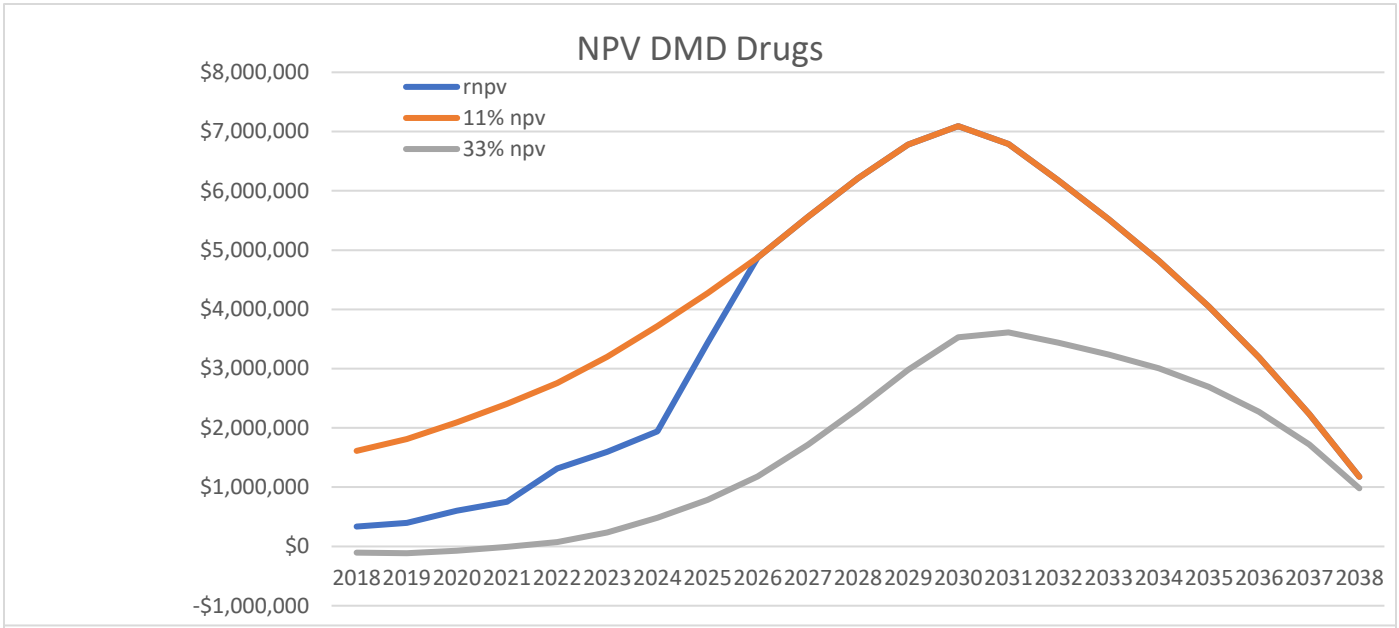
This paper will compare a risk adjusted 11% NPV model to standard 11% discount rate and 33% discount rate models to provide a complete overview of the NPV models between orphan and non-orphan drugs. A comparison of the three models will provide a well-rounded picture of the financial situation which must be evaluated. To adjust for risk, the probability of advancing to the next clinical trial stage from Jayasundara, et al. will be used. The cash flows for each year are based on the research of Jayasundara, et al. alongside market research for a potential small molecule drug with treatment indications for a non-orphan disease, congestive heart failure ("CHF"), and an orphan disease, Duchene muscle dystrophy ("DMD"). Although the end development product may have different dosage sizes, the same molecular entity would be used. By choosing specific drugs, determining potential revenue streams which are based on patient populations is possible. For congestive heart failure, a disease which has existing

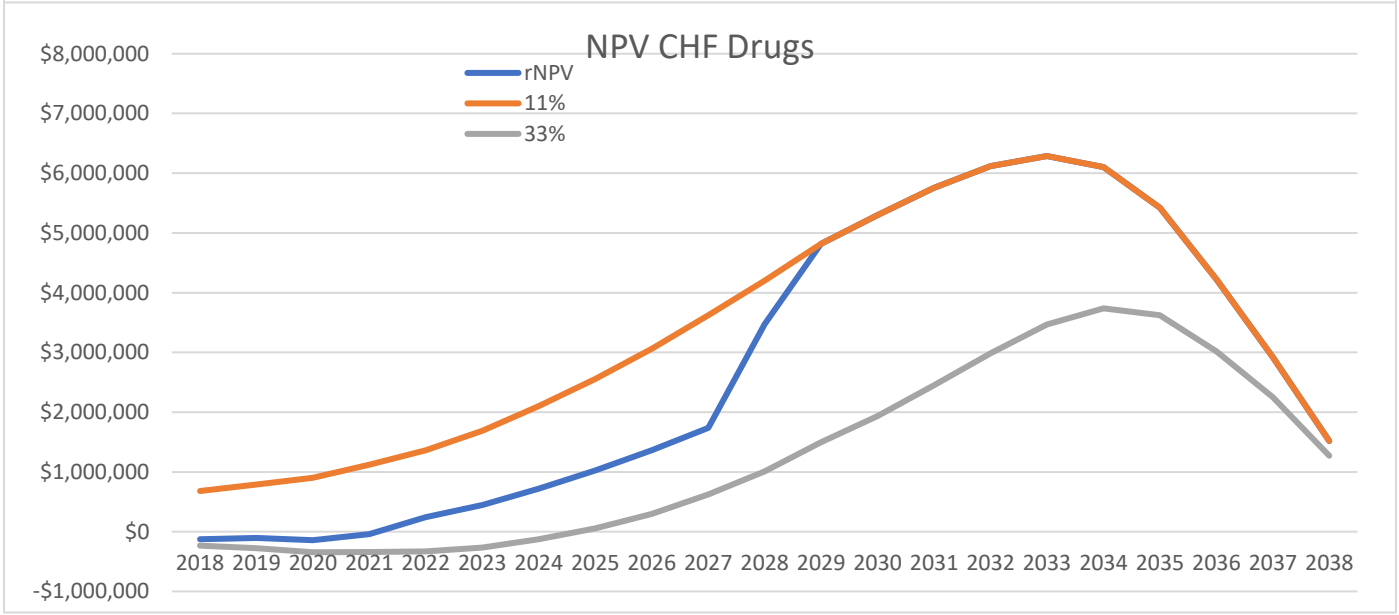
treatment options, the model assumes a new treatment would only be able to capture an 8% share (AstraZeneca, 2017) of the roughly 5.7 million patient market with a medication which costs patients $5,000 yearly (Center for Disease Control). For Duchene Muscle Dystrophy, the model assumes the company will be able to capture 60% of the 5,700 patients with a medication which costs patients $500,000 yearly (Center for Disease Control). The two models are clearly substantially different in how they determine potential revenue streams. However, CHF already has existing treatments with generic versions which breed competition and drive down price. Additionally, the presence of competitors prevents the potential drug from capturing as large of a market share. For DMD, if the company is the first to reach the market, they will enjoy market exclusivity allowing them to capture a large share of the market. The price charged for the drug is substantially higher but is the average between the two announced prices for products currently seeking approval for the condition (Grover, 2019) (Silverman, 2016). Due to the significant variance in both revenue and cost structures, the NPV models will allow for a simpler comparison of potential value to the company.

Additionally, the model assumes that each phase of clinical trials is successful. If a company were to have negative results from a clinical trial, the model would no longer be accurate due to additional costs and delays. While these delays would alter the model, adjusting the NPV to account for risk ensures the value returned by the model is adjusted for the potential failure. While the discount rate and risk functions adjust future cash flows to account for potential failures, additional research to compare the effect of failure across the two models to investigate if orphan drug development projects enjoy a more forgiving development process where failure has a smaller cost.

V. NPV Comparison

The below graphs summarize the comparisons of NPV for CHF and DMD.





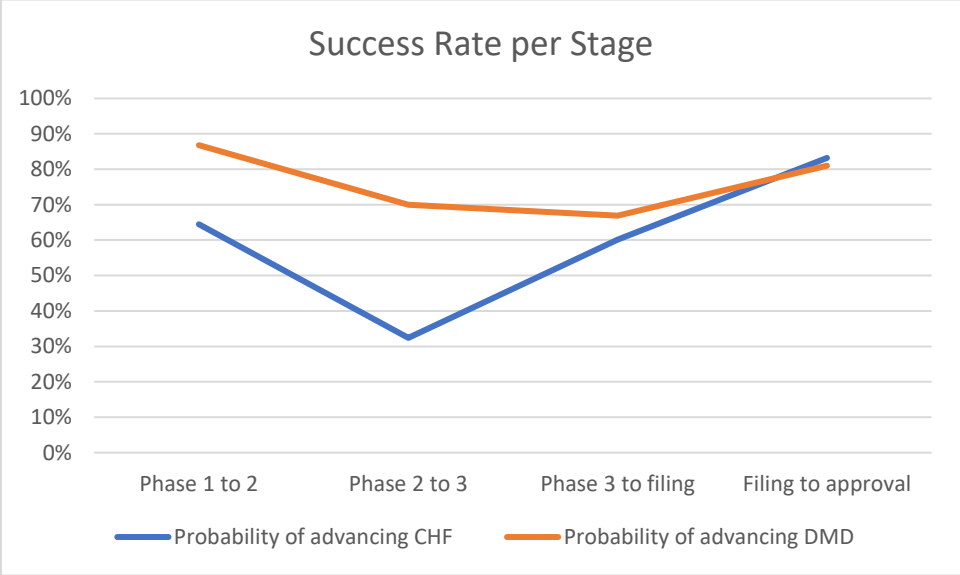
While NPV is used to evaluate the value of a project at a single point in time, graphing the NPV as the project continues enables a more complete understanding of the project. While the values at the beginning of the project may be compared, understanding how the value of the project is likely to progress will enable better comparisons. Additionally, it allows for discussion of the differences in value at different clinical stages and post market approval. In practical

application, understanding the future changes in value is important to make an informed decision. As discussed later, two of the models for CHF experience a dip in NPV in the first few years of the project. If a company had not examined the value moving forward, they would not be aware of this loss in value. In order to make a fully informed decision, the value moving forward is important in setting expectations.

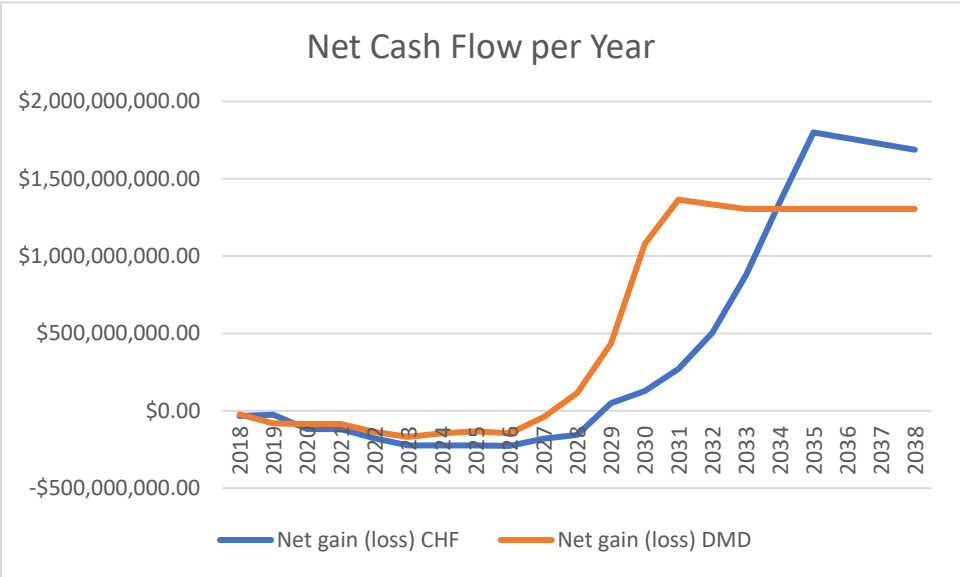
As rNPV is calculated with a discount rate of 11%, once the drug reaches the market all revenue is assumed to occur, so the risk no longer decreases cash streams and the value becomes equal to the 11% NPV model. Similarities between CHF and DMD quickly become clear. The general trend of each line is the same. All six lines peak around the year 2030 with a steeper slope leading up to peak revenue. The NPV decreases after this point as cash streams after the patent protection expires are not included due to unpredictability of generic actions. Although revenue is unlikely to completely disappear at this point, the additional variables complicate modeling.

The second significant observable pattern is a decrease in NPV for 33% discount models, and the rNPV model of CHF in the first few years. Generally, as positive cash flows become closer, and therefore less discounted, the NPV would be assumed to go up. However, the high cost of Phase III clinical trials outweighs the potential revenue as it also becomes less discounted. This does not occur in the 11% discount rate model as discount rates have an exponential effect over time. This means the lower interest rate will have a smaller effect on future cash streams relative to a higher discount rate. The question then becomes, why does the DMD rNPV model not experience an early dip in NPV? To determine this, the variables which may affect the value must be considered. In this case, the discount rate, 11%, is the same as the

CHF model, however, the two other variables, chance for success, and total cash flow, are different.



The success rate per year, compared to the rNPV gives insight into why a dip occurs between 2019 and 2020 for CHF. In the model, this is the time which the company transitions between Phase I and II clinical trials. This transition substantially increases the chance of the high cost Phase III clinical trials happening. For DMD, the transition was not as impactful due to the higher success rates and lower Phase III costs.



Examining the cash flows of the two models highlights a second key difference which affects the development process. While the CHF model has a higher peak revenue, it takes longer to ramp to peak revenue but enjoys a significantly higher peak revenue. The DMD model recognizes revenue earlier but has a lower peak revenue. Additionally, the DMD model rampageps to its peak revenue faster than the CHF model. The ramping occurs faster due to the lack of competition in the DMD space. As orphan drugs are definitionally entering a market without competition, they are likely to capture a significant portion of the market quickly. Mass market non-orphan drugs, including a medication for CHF, may be entering markets with treatment options already available. Even if the new medication is objectively better, the patient population will still experience delays in transitioning between medications leading to a slower growth rate. Perhaps the most important aspect of cash flows is the observation that while treating significantly fewer patients, 0.75% of the CHF model, the DMD model expects a peak revenue equal to 71.34% of the CHF models peak revenue. The difference in patient number is made up be a significant price differential. Sections VI. and VII. will address the ethical decision made to price the drug this way. If the drugs were priced the same, the DMD option would not be competitive with the CHF model due to significantly lower revenue.

The final aspect to consider is the values of each calculation. Both 33% discount rate models begin with negative values, while the 11% models both begin with positive values. The rNPV model for CHF begins negative, while the DMD rNPV model begins positive. The increased chance of successfully reaching the market, 34% for DMD versus 10% for CHF, leads a higher rNPV for DMD as the future revenue streams retain more value in the discounting process. As development continues and future revenue becomes more likely, the CHF rNPV model quickly recovers to a positive value. Overall, DMD appears to be a better investment due

to a higher peak NPV alongside positive initial NPV values. While the financial model provides one aspect of the decision-making process, a core aspect, price, needs to be considered from an ethical point of view in order to fully understand the development decision and orphan drug market.

VI. Corporate Social Responsibility in Pharmaceutical Developers

Although a company is likely to primarily consider the financial aspect of the drug development decision, ethical factors should also be considered to make a complete business decision informed not only by money. While considering simply the financial aspect of the decision is perhaps standard, considering all aspects of the decision is necessary to fit within a goal of finding another way of doing business. Ethics in drug development is a particularly touchy issue as in many cases development decisions are directly impacting patients' lives. As a company is pursuing a life changing medicine, consideration regarding how the decision whether to develop, clinical trials, and eventually the price charged, will affect patient wellbeing is necessary. Corporate social responsibility ("CSR"), is the practice of ensuring corporate actions are focused on the betterment of all stakeholders through enabling of all impacted parties to influence the decisions of the company, not just the shareholders and board members of the company. This practice will likely shift the focus of a company from profit potential, to acting in a way which creates the greatest value for the company, its investors, and the patients it treats.

CSR provides a framework which enables a company's motivation behind an investment decision to be mapped. The motivation may fall into three different categories; Ethical, Economic, or Legal (Bruyaka, et al., 2013). Orphan drugs developed for economic reasons are generally companies which developed a technology which "happened to be applicable to treat rare diseases" (Bruyaka, et al., 2013) or larger established firms which acquire a smaller

company developing an orphan drug once the investment appears profitable due to clinical trial success. Legally motivated companies develop orphan drugs due to arrangements with the government. Solely legally motivated actions in the orphan drug space are not observed in the United States due to the structure of the ODA. However, some European firms have entered into arrangements with the government to develop certain drugs (Bruyaka, et al., 2013). Ethically driven decisions are more often seen in companies founded for the purpose of finding a cure for a specific rare disease, or companies deciding to operate at a loss to ensure a treatment option remains on the market for a rare disease (Bruyaka, et al., 2013). While each motivation, legal, ethical, and economic, could theoretically exist as the sole motivation of a company, practically, companies will likely balance all three in their decision-making process. However, the examination companies which ignore one or both sections may provide insight into the value of the ignored section.

Perhaps the most dangerous position to public health a company can hold, is a company motivated by financial and legal incentives, while ignoring ethical motivations. On example of this is Bristol-Myers ownership of the drug Taxol, which treats ovarian cancer. Bristol-Myers acquired exclusive rights to the drug, alongside an orphan designation granting additional protection, from the National Cancer Institute ("NCI") in a partnership deal aimed at increasing the speed at which the drug would become available. Although the NCI invested tens of millions of dollars to develop the drug, the profits from the sale of the drug will go to a private company. Additionally, if Taxol was later shown to also treat another form of cancer which brought the total patient base over 200,000, Bristol-Myers would retain market exclusivity under the ODA (Newman, 1992). This enables Bristol-Myers to enjoy significant profits with minimal risk. Once a drug obtains an orphan designation, it can continue to acquire additional orphan

designation for other rare diseases regardless of total patient population treated by the drug. Companies can find subsections of disease which fit under the 200,000 patient requirement, acquire multiple orphan designations, and benefit from the ODA incentives while having a total patient population of over 200,000 patients (Newman, 1992). The second potential issue is companies applying for orphan designation for drugs which are financially viable without the benefits of the ODA. This action draws limited resources, such as grants, away from treatments which will not be developed without them (Yin, 2008).

On the flipside, drugs motivated by a combination of ethical and legal factors may do significant good, but not sustain a business or provide returns for investors. However, in some cases, a larger company may be able to absorb significant costs in order to provide treatment. An example of this is Merck & Co.'s partnership with government organizations to donate as much ivermectin as needed to eradicate river blindness. The company has continued to donate treatments to push to eradicate the disease over the decades. Instead of attempting to profit through the sale of the drug, Merck decided to pursue partnerships with government agencies which would provide treatment to impoverished communities in Africa (The World Bank, 2014). This decision enabled massive progress towards the eradication of river blindness through the donations of Merck. While Merck could absorb the cost of donating the drug, a smaller company may be unable to maintain their financial position while donating their product. A well-intentioned company may charge low prices or even give their drug away for free at the expense of the financial obligations. While high pharmaceutical prices and profits can become controversial, as discussed in the following section of this paper, ignoring the financial obligations of the firm is mismanagement and marginalizes the shareholders of a company.

A combination of ethical, legal and economic motivations for developing an orphan drug will lead to a company which develops orphan drugs in order to satisfy previously unmet patient needs by taking advantage of legislative incentives to create value for their investors (Bruyaka, et al., 2013). Ideally, a company would be able to perfectly balance their motivations and perfectly maximize value for all shareholders. Practically, a company may struggle to balance their financial obligations to investors, and their obligation to patients as the creators of treatment options. In order to behave in a socially responsible manner, a company should follow some basic guidelines. As previously discussed, a company must evaluate the development costs alongside future revenue to accurately communicate with investors regarding potential returns. By providing evaluation of net yearly cash flows, the risk of each stage, and the net present value of the investment, the company is likely to maximize the value for shareholders through maximized transparency enabling informed investment decisions. For legal motivations, the company should ensure it uses legislative incentives to develop orphan drugs not only legally, but also responsibly. In order to use the ODA responsibly, companies should only apply for orphan designation if they would be unable to develop the drug without the incentives in order to match the original reasoning behind the ODA. The ODA was implemented to enable the development of drugs which would otherwise be neglected. To simplify applications, a strict patient count requirement was implemented. If a company is attempting to be socially responsible, the practice of slicing the drug into smaller sections to qualify for the orphan designation through patient count should not be undertaken. The practice of sectioning the drug to manipulate the orphan drug system enables a company to access resources intended for a specific purpose, the development of drugs which are not feasible to develop without the incentives, which are funded by the population of the country through taxes. The practice of

manipulating the system to qualify financially feasible projects for unneeded incentives to maximize the firms value ignores the firm's obligation to society and the patients to responsibly manufacture and develop medication. If the firm wishes to acquire orphan status for drugs which would treat more than 200,000 patients as they need the incentives for financial feasibility, they should work with the FDA to acquire designation through the "affects more than 200,000 persons but has no expectation of sales of the drug recouping the development costs" clause in the ODA. By operating within the intended process of the ODA, a company will recognize its obligation to society to responsibly use the resources offered.

VII. Ethical Pricing Practices

A primary concern regarding the balance between ethical and financial motivations in the CSR model for orphan drug developers is pricing. A company must charge enough for their drug to ensure the long-term financial security of the company, and to fulfill their obligations to investors. In the case of large firms such as Merck, financial stability may be maintained while donating significant amounts of drugs. Merck could have decided to sell the river blindness medication to the World Health Organization and other NGO's but instead decided to donate it. While the expect revenue from selling the medication was small, Merck is a company committed to developing and providing invaluable medication on a global scale. As an nearly 100 year old company with over $9 billion in yearly sales at the time, the donation of one of their products to those in need did not significantly impact their obligation to shareholders. Merck has continued to thrive as a company, reporting over $4 billion in profit for 2018, while continuing to fund need based donations of medicine globally. While Merck is a prime example of a company finding a balance between social contribution and financial security, a smaller less established pharmaceutical firm should be wary of emulating Merck's example.

If a company is considering the donation of a product to aid those in need, they must evaluate the impact of the donation on their obligation to shareholders. For a small or new pharmaceutical firm, the donation of a drug may hurt their long-term financial security and ignore their obligation to shareholders. Additionally, while the short-term benefits to the patients of donation may be high, if the company fails to stay in business, the long-term implications for the patients may be negative. The following example demonstrates the potential long-term downside of a company failing succeed long-term.

A well-known ignoring its obligation to the patient in the orphan drug sector is that of Martin Shkreli and his company Turing Pharmaceuticals. Turing Pharmaceutical's purchased the rights to Daraprim, a treatment for toxoplasmosis which affects some individuals with HIV, and immediately raised the price from $13.50 to $750 per pill. Although Daraprim was out of patent, it only served a patient base of around 12,000 patients which makes it very similar to orphan drugs and had not attracted generic competition. Turing was able to confidently increase its price, as the relatively small market was not attractive to generic competitors, even though the drug was long out of patent protection (Carrier, Levidow, & Kesselheim, 2017). Additionally, Turing changed the distribution method to significantly increase the difficulty of acquiring samples for potential competitors (Carrier, Levidow, & Kesselheim, 2017). Carrier, Levidow, & Kesselheim argue that not only was this practice unethical, it also broke antitrust laws made to protect consumers. The actions of Turing were met with general outrage from patients, the general populace, and Presidential candidates. Clearly motivated by financial factors, Turing is an example of why ethical motivations are needed. Additionally, it reflects the need for an ethically motivated company to maintain its financial position to ensure continued control over their drug. If a company is seeking to minimize the cost to the patient, it is in the patient's long-

term interest for the cost to be high enough to maintain the company's financial position. While low costs or donations may benefit the patient in the short-term, long-term affects should be primarily considered in pricing decisions.

The need for a minimum price which an ethically motivated company should charge to remain in business is simple and unlikely to be met with opposition. The difficult part of ethical pricing is determining the maximum ethical price. A primarily ethically motivated company may argue that the highest ethical price is equal to the minimum price a company may charge to recoup development costs, cover yearly operating costs, and enable future development for long term security. If this fits with a company's mission, charging a minimum price is ethical and socially responsible. However, many companies exist as financially motivated companies who develop drugs to make money. How should a financially motivated company determine what price to charge? From a purely financial aspect, a company should attempt to maximize its long-term financial security and profits (Gordon, 1948). For the orphan drug market, this strategy is likely to lead to prices which maximize profits while ignoring the obligation a company has to its patients. Basic economic theory states that profit is maximized where the marginal revenue of producing and selling an additional unit is equal to the additional cost of selling the unit. However, the model assumes that the market is competitive. As demand is likely to be relatively inelastic, and the number of firms in the market for a specific drug is low, the basic rule does not adequately explain the decision. Market exclusivity, through the ODA, gives a drug developer a monopoly for the first seven years on the market. Additionally, since orphan drugs are by definition providing treatment for a condition which did not previously have a treatment option, the demand for the drug is likely to be inelastic due to heavy patient reliance (McGuire, Jabon, & Faseruk, 2014). These market conditions indicate a company can charge almost any price to

maximize their profits without significant risk of losing patients. Charging high prices to maximize profits is ethically problematic as it ignores any obligation to the patients to provide treatment options in a way which is accessible and valuable. High prices, particularly in the case of life saving medications, may force individuals to decide between massive debt, and death. If a company in the orphan drug sector is considering the obligation they have to a patient, they will necessarily need to ignore the maximum short-term profit potential and instead focus solely on long-term financial security. This position enables a company to consider the needs of the patients, while maintaining their financial position and fulfilling the responsibility to their shareholders. If a company takes this position, they must clearly communicate their position and motivations to shareholders for full transparency.

While social responsibility may control a company's prices, evaluating the problem of high prices in the case of inelastic demand from an ethical point of view is also valuable. The most applicable ethical system may be a form of utilitarianism. A company should seek to set a price which maximizes the public utility. A potential cost structure for a new drug is charging a price which reflects the value generated for the patients. Arguably, this will create equal value for the patient, while allowing a company to profit in a controlled manner. For orphan drugs, this structure poses a problem. As the drugs are likely to be highly impactful in patient's lives, attaching a monetary value to the medicine is almost impossible. For example, Novartis, a Swiss pharmaceutical manufacture, recently announced the price of their life saving orphan drug, Zolgensma, at $2.1 million. In announcing the innovative medication, Novartis argued that the significant price was justifiable as it was significantly lower than the $4-$5 million the company deemed it was worth to patients (Thomas, 2019). If a medicine will add decades to a patient's life, is it ethical for a company to charge millions of dollars? Does life have a monetary value?

Although this approach may be useful for less extreme conditions where medicine is only generating a small benefit for the patient, for life changing medicines, assigning a monetary value to determine price becomes difficult and ignores the company's obligation to the patient. When discuss the price of medication, attempts to justify price with the value generated for the patient fall short due to the intangible value of human life. The case of pricing lifesaving medication shows the downfall of utilitarian ethics as a method to price medication. The value of the medication is potentially priceless which may lead to a profit seeking company arguing that an incredibly high price is ethical. If this argument is there only price justification, they do not have a strong ethical argument. As this paper is focused on socially responsible corporations, determining a strict guideline for solely financially motivated companies is outside its scope. Creating an ethical argument which justifies high prices for medication is difficult as higher than necessary prices ignore a company's obligation to the patient and society. This is irrelevant to a profit seeking company, however, if facing public critique, the company will struggle to defend their price model. While public critique does not determine ethics, the company may lower prices to improve their public image. For a company striving to be a well-rounded socially responsible organization, the same difficulties will arise if they try to determine the maximum ethical price that recognizes their obligation to the patient.

Instead of attempting to determine the maximum price a socially responsible pharmaceutical company could charge, examining if a company should charge higher than the minimum price is a better approach. The minimum price should provide the company with the revenue necessary to recoup development costs, fulfill investor obligations, and enable future development. In the case of large companies who discover an application for an existing non-orphan drug to treat a rare disease, the company should carefully consider how to price the drug.

In the case of Pfizer, they market the drug sildenafil citrate as both Viagra, to treat erectile disfunction, and Revatio, to treat pulmonary arterial hypertension ("PAH"). Revatio costs nearly 6 times as much as Viagra even though they are the same drug (Simoens, 2011). Revatio, which treats a rare disease, serves a significantly smaller market with less competition. This allows Pfizer to significantly markup the price for the same compound. In order to market sildenafil citrate as a treatment for PAH, Pfizer needed to conduct additional clinical trials as part of an additional application. They may argue that the price of Revatio is higher to recoup the development costs. Although this stance is logical for a profit driven company, a socially responsible corporation may choose to include the development costs for the small market, in the mass market version. The practice of cross-subsidization to lower prices for smaller patient populations closely follows the example of Merck & Co., Inc.'s donation of medication. A socially responsible company should consider pricing an orphan and non-orphan version of the drug the same to fulfill their obligation to all patients. In order to accomplish this, the company will need to alter their price model to consider the two development projects under the same set of costs. While the financial models presented earlier in the paper reflect a decision between two options, socially responsible companies should consider the combination of the two programs to maximize the benefit created for society. The price for the mass market version will shift higher, however, drastic price cuts for the orphan version may be possible. Outside of the orphan drug discussion, companies striving for social responsibility may consider pricing model changes which help provide treatment to individuals who struggle to access or afford it.

While a single company may practice cross subsidization, for significant changes to occur, the structure of the industry would need to change. The government may construct policy which enables patients who struggle to afford pharmaceutical treatments to access the

medications they need. While the Affordable Care Act of 2010 targeted increased access to treatment for everyone, a targeted policy may be implemented for pharmaceuticals. In the case of orphan drugs, refinement of the current legislation to ensure all patients of the condition have access to the drug through price controls may be needed. This refinement would fit the original spirit of the ODA to increase the treatment options available for those suffering from rare conditions. While government reform may be the ultimate driving force to ensure patients receive the necessary care, the discussion of large-scale policy changes would require additional research beyond the scope of this paper as such changes require significant study of potential economic impact and ramifications.

VIII. Conclusions

This paper has shown the financial structures which encourage companies to develop orphan drugs, and the ethical consideration necessary for such a company to become not only financially successful, but also socially responsible. If a company has discovered a drug which may treat a rare disease, they first must determine the viability of the drug from a financial aspect. If the company is unable to show the financial viability of their product, they may struggle to attract investors or funding to develop their product. This is also applicable to larger companies as they decide whether to pursue a new project. While the financial viability of a development project is important, the ethical decisions which a company must make are equally important and vital to building adequate financial models. As potential revenue is vital to determining the viability of a project, ensuring the projected price fulfills both financial obligations and obligations to the patient will enable the development project to begin and progress in a socially responsible manner. A socially responsible company will only price their

drugs as high as needed to be a financially viable project and only use legislative incentives that they need to develop their drug.

Although companies may decide to act in a socially responsible manner, the privatization of healthcare in a capitalist market leads to profit focused decisions. If healthcare is to become more affordable and accessible in the United States, especially for rare diseases, a shift towards the publicization of healthcare is necessary. Unless a company decides to act in a socially responsible manner, the structures in place do not create a system which encourages socially responsible development of drugs which are accessible for individuals suffering from rare diseases. If healthcare continually shifts towards becoming a public good, corporate social responsibility may increase along with affordable treatment options.

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