A Critique of the Drug Development System in Relation to Orphan Drugs

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On my honor as a University Student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments

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Research and development in the United States is typically dependent upon both government funding and private investments. Government funding finances the exploratory science behind drug development and private investments finance manufacturing processes and clinical research (Field et al., 2010). Because pharmaceutical companies are commercial enterprises, they tend to focus their resources on the highest potential markets in order to obtain the greatest financial returns (Crompton, 2007). This means centralizing efforts to produce drugs that treat chronic conditions that affect many people, and making minor, yet patentable, variations to existing drugs with no realized added value to the drug (Gøtzsche, 2018). If a disease affects a limited number of patients, then therapeutic products for that disease may never be fully developed as the cost of private investment cannot be recovered. It has been found that pharmaceutical companies have possessed therapeutic drugs with promising benefits to rare diseases, but because these drugs were not patentable or the costs to develop were too high relative to the commercial demands these life-altering drugs were orphaned, that is, left undeveloped (Yin, 2008). The current system consequently promotes innovation in more profitable market sectors rather than incentivizing the study and development of therapeutic drugs for diseases for which a marketed drug may not exist. These pharmaceuticals that are commercially underdeveloped due to limited potential for profitability are known as orphan drugs (National Cancer Institute, 2011).

Orphan drugs treat rare diseases which are classified as diseases that affect less than 200,000 Americans (Yin, 2008). However, with the prevalence of over 5,000 rare diseases, over 20-25 million patients are struggling to get the medical intervention they need (Commissioner, 2019). In the 1980's, a grass roots coalition of patients and advocacy groups was formed to lobby

government officials and Department of Health and Human Services organizations to join the fight for recognition of rare diseases within the realm of pharmaceutical innovation (Commissioner, 2019). Subsequently, in 1983, Congress passed The Orphan Drug Act (ODA) to provide incentives for pharmaceutical industry investments in treatments for these rare diseases (Field et al., 2010). Throughout my research I will discuss how the political and economic structure of the pharmaceutical industry is inadequate in driving innovation. Orphan drugs by their very nature encourage us to think about what innovation is supported and what drug therapeutics are produced when profit is considered more important than public health. I will discuss the biopolitical problems that orphan drugs pose as well as the successes, failures, and what's next in the progression of the Orphan Drug Act.

The History of Pharmaceutical Development in the Realm of Rare Diseases

Standards are an important part of the development of modern medicine. These standards are otherwise known as guidelines or protocols that influence the conduct of stakeholders in the pharmaceutical industry. Standards in the drug development process tend to act in conflicting ways. They facilitate the creation of networks that combine technical, economic, and social activity, but they also close off certain policy and technological progress for therapeutics that do not necessarily fit into the highly regulated network of drug development (Novas, 2010). In the twentieth century, states began to actively develop a range of standards and guidelines in the fields of food and drug consumption, to protect the public health of the nation (Timmermans & Berg, 2003). This led to the creation of the United States Food and Drug Administration (FDA) in 1906 to ensure the safety and efficacy of medicinal goods before they were released into the public (Pediatrics, 1989). The FDA is the main health authority responsible for implementing rules and legislation in many industries including the pharmaceutical industry.

The regulations and practices associated with pharmaceuticals has been shaped by medical disasters, most notably with the drug Thalidomide. Thalidomide was discovered to treat morning sickness in pregnant women, but due to unforeseen chemical properties, it was found to cause severe birth defects. In the United States, this tragedy led to the passage of the Kefauver-Harris Amendment that required pharmaceutical companies to provide more specific safety and efficacy data based on a significantly larger amount of research and clinical trials prior to the approval of the drug (Abraham, 2002). The implementation of this amendment and many others imposed a new regulatory standard regarding the approval of drugs in efforts to protect the public health, but it also amended the techno-economic network of drug development. The Kefauver-Harris Amendment increased both drug development costs and the time required to gain FDA approval for sale while also shortening the maximum lifespan for drug patents in the 1970's (Novas, 2010). This led pharmaceutical companies to focus on the production of drugs intended for larger patient populations and shorter-term medicinal use as these investments would yield greater returns. Such practices gave rise to the problem of orphan drugs, ultimately gaining recognition in the early 1970's. The orphan drug problem problematized the regulatory practices of the pharmaceutical industry in terms of, what was originally referred to as, "drugs of limited commercial value" (Novas, 2010).

The struggle for legislative action began when Sharon Dobkin and Dr. Melvin Van Woert realized that they were unable to find a commercial sponsorship or a government agency that was willing to conduct trials for the approval of L-5HP, a therapeutic that was promising in the treatment of myoclonus, due to the economic implications (Asbury, 1992). Their efforts led to the introduction of a bill in Congress and subsequent Congressional hearings in 1981. During this time, groups of patients who suffered from myoclonus, Tourette's syndrome, Huntington's

disease, Wilson's disease, and many others detailed accounts of how the pharmaceutical industry and existing drug regulations served to marginalize the needs of the rare disease population (Asbury, 1992). After a lengthy hearing process, The Orphan Drug Act was passed in 1983 and provided companies with tax credit equal to 50% of clinical trial expenses, 7-year market exclusivity for orphan drugs, assistance with the FDA application process, and a grant program for research of rare diseases (Yin, 2008). Although the ODA is deemed to be one of the most successful pieces of legislation in the realm of healthcare by some, it is not without its fair share of problems (Haffner, 2006).

Biopolitical Nature of Orphan Drugs

In the discussion surrounding the development of therapeutics, Michel Foucault's concept of biopolitics can be used to present and analyze the power relationships that exist between a variety of stakeholders. The stakeholders in this industry include patient organizations, clinicians, pharmaceutical and biotechnology companies, and health authorities. Biopolitics refers to the political rationality of social, environmental, cultural, economic, and geographic conditions that may restrict or advance the health of humans (Rose, 2001). More generally, biopolitics refers to the questions of how the biological lives of humans should be governed. Foucault claims that ever since the creation of biological power there have been entities that have resisted it (Foucault, 1978). In the case of drug development, many deem biopolitical intervention as highly necessary to govern human life, yet there are also resistance movements that stand in firm opposition, such as the case of the orphan drug movement. The orphan drug movement acknowledges the necessity of intervention, but questions what incentives should be imposed to accurately attack the problem of unmet needs for small patient populations. The struggles that exist in the development of drugs can be split into the supply and

demand of pharmaceuticals. The supply of pharmaceuticals refers to the drug development process and which illnesses are targeted as being a market of interest for the government or pharmaceutical companies. The demand side refers to pricing, access to medicines, and who is responsible for paying for the medicine (Novas, 2010). The issue with orphan drugs is biopolitical because it deals with the drug development for a specific patient population while also raising questions about the access to therapeutics. These struggles are significant because they include questions about the administration of someone's life in relation to investment choices of pharmaceutical companies (Novas, 2010). For this reason, the drug development system, specifically orphan drugs and The Orphan Drug Act should be heavily critiqued.

The Orphan Drug Act is regarded by some as one of the most successful pieces of health-related legislation to ever be put into effect (Yin, 2008). The two main incentives of income tax credits and market exclusivity successfully increased the number of orphan drugs on the market that were targeted to treat small patient populations. This increase in the development of orphan drugs spurred the growth of the biotechnology industry as it incentivized start-ups to focus their attention on rare diseases (Novas, 2010). As the industry expanded, orphan products became more diverse as drugs, biologics, and medical devices were all developed. Furthermore, the adoption of the ODA in the United States has led to similar pieces of legislation in other countries such as Singapore, Japan, Australia, and the European Union (Novas, 2015).

While The Orphan Drug Act is generally viewed as beneficial, it fails to address a number of problems in the pharmaceutical industry. The ODA led to the development of many therapeutics, but less than 10% of patients with rare diseases are treated (Rhee, 2015). Of the drugs that have been produced, many are still inaccessible due to high costs. Orphan drugs in some cases are proving to be profitable ventures and companies are raising their prices to ensure

profitability. Some believe that the incentives may not be enough for pharmaceutical companies to focus their efforts on rare diseases rather than commercially lucrative areas (Rhee, 2015). The policy has been used by companies to take advantage of various tax, policy, monetary, and political incentives that were not originally intended (Tribble, 2017).

Responses to the Orphan Drug Act

Successes of the ODA

In response to the failure of pharmaceutical companies to value public health over profit, The Orphan Drug Act provided legal and economic incentives to develop treatment for rare diseases and has been successful in some aspects. In the decade prior to 1983, only 10 drugs were approved and marketed for treatment of rare diseases, and only 36 therapeutics had ever been produced (Yin, 2008). As of 2018, 780 drugs have been approved for approximately 250 different rare diseases indicating a positive trend in the development of these drugs (Szydlo, 2018). However, it is important to note that this expansion in the development of rare drugs would not have been possible if patient organizations had not drawn attention to their severe underrepresentation in the industry. Inspired by such groups, the pharmaceutical industry continues to make positive changes. For instance, in 2018 the FDA approved over 90 therapeutics for rare diseases which was the highest since the ODA was passed (Szydlo, 2018). Putting ethics aside for the moment, it is clear to see that the ODA spurred innovation in the sense that more therapeutics were developed. The ODA was able to successfully improve the public health of many who were originally left out of the flawed drug development system.

The ODA led to an increase in the supply of orphan drugs which inevitably stimulated the growth and diversity of the biotechnology industry. Many start-up biotechnology companies found that obtaining orphan drug designation was necessary to secure venture capital

investments and spur rapid growth of their firm (Novas, 2015). The 7-year market exclusivity, tax breaks for clinical trial related expenses, and general orphan drug designation finance current and future products as well as attract attention from larger pharmaceutical firms for potential acquisition deals. In fact, many biotech companies have been created for the sole purpose of research and development of orphan drugs because the sector that was once of "limited commercial value" is now a potentially profitable market sector.

Furthermore, with financial and legal help from the ODA, both pharmaceutical companies and biotechnology firms were permitted enough freedom to recycle, repurpose, and diversify previously discontinued therapeutics (Rhee, 2015). Orphan products now include traditional chemically based drugs, biologics, and medical devices (Rhee, 2015). This was a step forward in terms of valuing public health of marginalized groups instead of profit. In terms of progressing world public health, the ODA was highly impactful as it inspired other countries to recognize and intervene in the biopolitical problems surrounding rare diseases. Similar legislation was developed in Australia, Japan, Singapore, and the European Union using the ODA as a model (Novas, 2015). The Orphan Drug Act was instrumental in beginning the recognition and allocation of resources for smaller patient populations as evidenced. However, not all perceptions of the ODA are positive. Some of the existing flaws further problematize the current system of drug development and where value is placed in the pharmaceutical industry.

Existing Problems

Due to the flawed political and economic structure of the pharmaceutical industry there have been many unforeseen challenges and instances of abuse from both pharmaceutical or biotechnology firms and the FDA. One of the main outstanding issues of the ODA is that, to this day, 95 percent of rare diseases still have no treatment options, and those that have been

produced are among the most expensive (Rhee, 2015). For example, Genzyme, a small biotechnology company, proved the profitability of the orphan drug market with their therapeutic Cerezyme which is one of the most expensive drugs in the world (Novas, 2010). Cerezyme is used to treat Gaucher's disease and is marketed at prices as high as $400,000 per year (Novas, 2010). As Gaucher's disease is a life-long battle, this therapeutic treatment yields substantial revenue for Genzyme every year, but poses questions about accessibility as well as the true intentions of pharmaceutical companies. Genzyme is not alone in its profitability as orphan drugs now account for seven of the ten top-selling drugs of any kind (Tribble & Lupkin, 2017). After the passing of the act and, more recently, the dramatic increase in sales of orphan drugs, Kaiser Health News (KHN) launched an investigation to demonstrate the manipulation of drug makers to maximize their profits and to protect fruitful markets for their own benefit.

Many of the drugs that have been approved by the FDA for orphan drug status are not new therapeutics. At least 70 drugs that were first approved by the FDA for mass market use have since obtained orphan drug status meaning manufacturers received millions of dollars from the government as well as seven years of market exclusivity effectively creating a monopoly (Tribble & Lupkin, 2017). Market exclusivity restricts competitors from selling another version of the same drug at a potentially lower price to increase the accessibility. Exclusivity is a dominant pricing tool that companies regularly exploit. For instance, blockbuster drugs like cholesterol blocker, Crestor, cancer monoclonal antibody, Herceptin, and the primary rheumatoid arthritis drug, Humira, all have gained orphan status even as some of the highest grossing pharmaceuticals in the world (Tribble & Lupkin, 2017). More specifically, Genentech's cancer treatment, Avastin, that was originally approved for mass-market use has earned 11 orphan drug designations meaning it will operate as a monopoly until 2025 preventing other, less expensive

biosimilars from entering the market (Lupkin, 2018). Although these therapeutics are treating some rare diseases, they are receiving large amounts of funding from the government which could be allocated to more novel treatments.

KHN discovered that a third of the drugs that acquired orphan status were previously approved as mass-market drugs or drugs that obtained multiple orphan approvals (Tribble & Lupkin, 2017). While "repurposing" therapeutics does increase the amount of patient groups reached, many drug makers purposefully identify small patient populations to gain additional approvals. This process is known as "salami slicing". Dr. Martin Makary from Johns Hopkins School of Medicine stated, "By salami slicing the disease into small subgroups, it allows them to get orphan drug approval with all the government benefits and even some subsidies" (Tribble & Lupkin, 2017). The original intention of the ODA was to promote innovation for marginalized populations, and thus the repurposing drugs for the sole purpose of gaining market exclusivity to raise prices clearly does not align with the goals of the ODA. Drugs should be developed to bring the appropriate treatment to the right patients based on unfulfilled need, not based on the relative size of the patient population. All too often, patient groups are dismissed in the development process. Former FDA orphan drug director Haffner commented on drug makers taking advantage of the ODA saying, "It's the American way, I don't mean that in a nasty way. But we take advantage of what's in front of us" (Tribble, 2017). The drug development system is clearly flawed if the natural tendency of companies is to exploit health-care legislation.

Pharmaceutical companies are not alone in their abuse of the system. The Food and Drug Administration should also be held accountable for their failures. The Government Accessibility Office (GAO) revealed that FDA reviewers did not validate the size of the target patient population but instead trusted what the drug makers claimed in their application for orphan drug

status (Lupkin, 2018). In fact, of the 148 records the GAO reviewed, 26 applications obtained orphan status even though there was missing information (Lupkin, 2018). This disregard and haphazard effort by the FDA is concerning. Many therapeutics did not receive adequate scrutiny to ensure the safety and efficacy of the drugs being produced. Due to the unintended problems surrounding the ODA it is important for the FDA to alter relevant policies to promote fairness and equity while eliminating the exploitation of drug makers.

What's to Come?

The existing problems with The Orphan Drug Act are not lost on the FDA. In 2017, the FDA Commissioner Scott Gottlieb mentioned that he wants to ensure that the financial incentives are granted "in a way that's consistent with the manner Congress intended" when the ODA was originally passed (Tribble, 2017). The Food and Drug Administration admitted to faults on their own account as well as acknowledged that drug makers may be abusing the ODA. The next step for the FDA in ensuring that patient groups are at the center of the conversation is to modernize the act and respond to improper use of this legislation. The first proposed intervention was to eliminate the backlog of drug applications that are seeking to obtain orphan drug status (Tribble, 2017). While the applications remain idle, patients are suffering with little hope and minimal access to therapeutics.

The second intervention point proposed was to mandate that pharmaceutical or biotechnology companies provide strict data detailing that their medicine is clinically superior to those that already exist before obtaining market exclusivity (Tribble, 2017). All drugs undergoing the approval process should receive sufficient scrutiny to ensure funds and efforts are being pointed in the right direction. The FDA is working to add this clause to The Orphan Drug

Act after lawsuits were filed by Depomed, Eagle Pharmaceuticals, and United Therapeutics claiming their drugs were denied orphan drug status because they had not proved clinical superiority even though this was not a clause in the original ODA (Tribble, 2017). Again, all efforts should be focused on providing patient groups with the safest and most effective therapeutics rather than sorting through applications of companies attempting to find a loophole in the legislation for monetary gain.

The third intervention point discussed closing the loophole in the context of pediatric orphan drugs. Currently, manufacturers may skip pediatric testing requirements when developing a mass-market drug for rare diseases in children due to inadequate specification in the act (Tribble, 2017). Closing the loophole will require all drugs approved for common adult diseases to also undergo pediatric testing as children deserve access to safe and effective medicine. All three interventions and the modernization plan proposed is in an effort to increase competition and decrease drug prices as the market for rare diseases is a monopoly in some cases (Tribble, 2017).

Although the Food and Drug Administration is attempting to close loopholes and amend the ODA so companies will not be able to take advantage of the act, there should be more of a focus on patient organizations. The voices of patient organizations are still rarely considered in the early stages of drug production even though their voices were the ones that began the movement for the production of orphan drugs. With patients in the conversation with health care officials and pharmaceutical companies, orphan drugs present some of the most novel and unique opportunities in medicine to treat some of the most detrimental diseases.

Conclusion

Since the creation of the FDA and regulations relating to drug development, small patient populations have been underrepresented in a system that promotes profit over public health. The Orphan Drug Act was passed in 1983 in an attempt to reconfigure the political and economic structure and standards of drug development. The Orphan Drug Act has served to increase the number of treatments available to people with rare diseases and spur similar models of legislation in other countries, but it has also promoted manipulation and exploitation of the legal and economic incentives from drug makers to make more money than they would in a typical, competitive market. The problems encountered with drug development both historically and currently are biopolitical in nature as they deal directly with the use of politics to govern the quality of human life. The biopolitical struggles associated with orphan drugs will continue to grow if no action is taken to promote the individual lives of patients over profitability. As companies continue to produce more drugs for rare diseases, questions surrounding providing expensive treatments to small patient populations while still trying to finance health care needs for the general population will only increase. It is important to criticize the system of drug development, with an emphasis on orphan drugs, because these questions refer to regulating an economically significant sector while acting upon the health of the public.

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