Sociotechnical Construction of Biosimilars in the United States

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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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Introduction

Biosimilars have been proposed by many as a possible solution to drug accessibility and affordability. This stems from the expectation that they will have a similar groundbreaking impact on the overall American health care system as generic small molecules. This is an ongoing conversation in the United States with the Food and Drug Administration redefining insulin as a biologic rather than a small molecule in March. This would allow for future biosimilar insulins and interchangeable insulins to enter the market and therefore reduce the financial burden on patients. However, this problem is not simply a one-dimensional technical problem. Proponents of biosimilars advocate for their ability to improve both quality and affordability of healthcare. However, ethical concerns exist regarding their expedited regulatory processes which may introduce safety and efficacy risks to the patient. The effects of biosimilars on society is a wicked problem that has been extensively studied by others within the realm of science, technology, and society. Much research into drug affordability and availability has been centered on the origin of this sociotechnical problem, the development of biosimilars, and future improvements to the integration of biosimilars onto the market. This sociotechnical analysis of the impact of biosimilars in the United States will aim to answer the following research questions via social construction of technology:

- How can the expansion of biosimilars address drug affordability and accessibility?
- Can expedited regulatory approval processes and drug interchangeability be morally justified, given potential for increased risks to patient?
- Could biosimilar expansion in the United States mirror similar successes seen in Europe?
- How do legislative and political differences between the European Union and the United States affect the potential of biosimilars?

Literature Review

The origin of drug availability and affordability can essentially be studied by analyzing the ethical and moral issues surrounding patenting of medicine. Sterckx (2005) studies the ethical question of drug patents, particularly whether or not they are morally justifiable. The author presents their analysis by investigating natural rights, distributive justice, and utilitarian arguments. The overall analysis is framed with the perspective that drug patents are evolving away from their initial humanitarian nature. An argument for reevaluating drug patenting is made in order to return to the ultimate goal of benefitting society and expanding accessibility to medicine. Crespi (2005) analyzes the ethical and legal dilemmas surrounding patenting of biologic materials and processes. The author presents the rationale and justification of both pro- and anti-patent arguments from the perspective of a patent professional. Each argument is framed with regards to the key stakeholders which include research scientists, governmental bodies, and health care organizations. A comparison study is also made between the United States and Europe regarding the role of patent law in the development of biomedicine.

The impact of biosimilars emerging onto the pharmaceutical market is the primary focus of this research study and has thus been evaluated extensively. Boccia et al. (2017) investigate the potential for biosimilars to address health care reform in the United States. The authors evaluate the current impact of biosimilar expansion on accessibility, affordability, and quality of health care. This evaluation is framed with regards to the goals of the Affordable Care Act, which sought to expand health care coverage, lower costs, and improve quality of care. Morton, Stern, and Stern (2018) investigate the effects of the entry of biosimilars onto the pharmaceutical market, with a focus on prices and market shares. The authors stage their analysis to predict the impact and success of biosimilars in the United States over next several years. This analysis was carried out

by investigating how market features and public policies influence product penetration and competition. Zhai, Sapatwari, and Kesselheim (2019) investigate the slow rollout of biosimilars onto the market since the Biologics Price Competition and Innovation Act of 2009 was passed. The authors focus on the lack of the lack of success biosimilars have seen in the United States by examining the current landscape of the pharmaceutical market, anti-competitive tactics employed by patent-holders, and ethical barriers to wide-spread adoption of biosimilars.

There are many current pitfalls and downsides to current biosimilar development that may be addressed to improve their societal impact. Diependaele, Cockbain, and Sterckx (2018) present an argument against the adoption of biosimilars. They argue that biosimilars are not the solution to improving costs and accessibility of health care. The authors present their argument via an analysis of the current regulatory pathway for biosimilars in the United States and the European Union. Potential solutions to the shortcomings of current biosimilar development are also presented. Hemphill (2020) reviews the current pitfalls of the regulatory processes in the United States. The author particularly focuses on areas of improvement regarding the interchangeability of biosimilars and incentives for second-to-market drugs. The arguments for these improvements are investigated with the aim of facilitating price competition for the benefit of the patient. Jones (2005) presents an argument against the overregulation of pharmaceutical drug development. The argument particularly focuses on the unnecessary and superfluous nature of phase III clinical trials. The author argues that including pharmaceutical companies in the development of regulatory clinical trials will establish a more efficient drug development process to minimize cost to the consumer.

Rathore and Bhargava (2020) provide an overview of the current status of biosimilar development in developed economies across the world, including the United States, the European

Union, Japan, Canada, and South Korea. The innate complexity of biotherapeutics and their dominance over drug pipelines of pharmaceutical companies have created unsustainable healthcare costs in many of these developed nations. The authors investigate the rise of biosimilars as a potential solution to address drug affordability. The regulatory processes for approval of biosimilars is of particular focus in this analysis. Furthermore, the authors provide comparisons between the current state of biosimilars in each development economy studied, including the United States, Europe, South Korea, Canada, and Japan. Moorkens et al. (2017) provide an overview of current biosimilar policies across Europe. The authors focus on drug availability, affordability, quality, and policies to promote their growth. The overview is framed with regards to the European Medicines Agency and its goal in establishing a sustainable yet competitive biologics market.

STS Frameworks/Methodology

The main frameworks used to study this wicked problem will be social construction of technology, with artefactual politics and actant-network theory as supporting frameworks. Social construction of technology will aid in defining the various stakeholders present in this complex sociotechnical system. Artefactual politics will aid in analyzing the power and authority biosimilars hold in society. The interplay between each of these stakeholders will then be investigated through actant-network theory.

Due to the high quantity of stakeholders in this sociotechnical system, it is important to study the associated social construction. Social construction of technology analyzes the interdependence of social and technical elements by considering technologies as social constructs. There is much interpretational flexibility in the differing social groups involved in this system. Pharmaceutical companies and government legislators may have entirely different rationale behind

pursuing biosimilars, leading to differing interpretations of the technology. The variability in interpretation is important to analyze to not only analyze the effectiveness of biosimilars in improving drug affordability and availability, but to determine key limitations that must be overcome in the United States to achieve their full potential in improving the American healthcare system.

The implementation of biosimilars onto the pharmaceutical market may be seen as an infringement on intellectual property rights and the free market. Therefore, it incorporates politics into this sociotechnical system that may greatly differ when switching perspective. These artefactual politics heavily influence the social order, decision making, and deployment of biosimilars. Pharmaceutical companies, regulatory agencies, and medical professionals together make up the social order of healthcare in the United States. As owners of intellectual capital, pharmaceutical companies are typically the sole decision makers. Finally, deployment of novel biosimilars is entirely dependent on cooperation between each of these stakeholders.

As part of the social construction of this system, key important actant-network interactions are worth investigating. In particular, it is especially important to analyze the interplay between human and nonhuman actants. Actant-network theory analyzes the role of different social or technical groups within the sociotechnical network. Besides biosimilars themselves, other important nonhuman actants include legislation and medical prescriptions. Legislation holds significant power as it determines the legality and specifications of what constitutes a biosimilar. Furthermore, medical prescriptions are the final barrier to biosimilar treatments for patients and directly elevate the position of power for medical professionals within the established social order. Each of the stakeholders listed previously are important relevant social groups that together cooperate to construct this complex sociotechnical system.

For my research paper, I have decided to use document analysis as my primary research method. I will utilize academic journals, scholarly articles, and policy legislature to provide substantial evidence behind my claims. My sources will come from a variety of databases. Some of these will be directly related to STS while others will focus on the technical aspects of biosimilars. An example of this will be technical papers investigating the similarity and drug potential of similar biologic drugs or the accuracy and risk associated with clinical trial data extrapolation. Possible sources of bias involve underlying political or economic ideologies which I hope to address by consulting a variety of sources from multiple academic journals.

Data Analysis

For data analysis, a series of primary and secondary sources were referenced. Primary sources include consolidated data obtained from surveys and studies along with Food and Drug Administration (FDA) and European Medicines Agency (EMA) regulatory frameworks. Academic literature on the societal impact of biosimilars were used as secondary sources. All data collected from both types of sources were interpreted within scope of the chosen STS frameworks for this research paper.

As previously discussed, there are a multitude of stakeholders involved in this complex sociotechnical system that must work together to successfully introduce biosimilars into the market. The relevant social groups surrounding the development of biosimilars include pharmaceutical companies, governments, regulatory agencies, medical professionals, and patients. Each social group supports biosimilars in order to empower patients and improve patient healthcare. However, each has different motivations behind this shared goal. Some operate with self-interest in mind, while others are bound by the delicate interplay of government policy and implementation of new technology. Others may be selfless and entirely dedicated to promoting the

betterment of the average patient. While these reasons vary, they ultimately work together in a delicate balance to build this sociotechnical system. Thus, they are all equally responsible in facilitating the adoption of biosimilars in order to address drug affordability, accessibility, and quality of healthcare in the United States.

To understand the complexity of the system, it is necessary to analyze the individual niche of each social group. Pharmaceutical companies invest capital to develop, manufacture, and market biosimilars. Governments are responsible for passing biosimilar-related legislation on a federal and state level. Regulatory agencies focus on ensuring safety and efficacy of novel drugs. Medical professionals modulate consumer access to biosimilars via prescriptions. Patients are the end consumers of biosimilars and reap the benefits of their therapeutic properties.

Each of these groups has a different motivation behind its involvement in this social construction. Pharmaceutical companies are driven by revenue and profits. American government, as a representative democracy, is responsible for passing legislation to improve the quality of life for everyday Americans. Regulatory agencies put patient well-being first by demanding high quality products that are both efficacious and safe. Medical professionals have an obligation as caregivers to treat patient illness to the best of their ability. Patients are the ultimate beneficiaries of this technology, but unfortunately must also bear the financial burden attached. They are responsible for creating demand for these lower-cost biologic therapies in order to lower drug prices and raise healthcare affordability.

Individually, none of these groups are capable of causing meaningful changes to the biologics market. However, key interactions between many of these groups are able to construct a successful sociotechnical system. These interactions occur between several human actants and biosimilars, as a non-human actant. This non-human actant is at the center of this societal

construction. From a top-down approach, the flow of biosimilars through society can be traced from the inventors, or pharmaceutical companies, to the end consumers, or patients. Along the way, each of the other stakeholders has an important role to play in constructing this system. Due to the different roles the associated social groups play, an inherent social hierarchy exists driven by interdependence and balance of powers. This social hierarchy is reinforced by artefactual politics. Biosimilars are a very important non-human actant, as they have the potential to solve many problems plaguing the American healthcare system. In order for society to benefit, each of the social groups must work together and compromise. This allows biosimilars themselves to act as powerful political actants by dictating terms of each relationship in the system.

Governments and regulatory agencies are at the helm of biosimilar social construction since they serve as key intermediates between technological development and social implementation. They both share a common interest in improving conditions for the average patient via political and bureaucratic means. Both groups participate in the building of this sociotechnical system by working together as partners. Governments involve elected officials who are responsible for representing their constituents. Regulatory agencies are government entities and therefore share the same commitment to the public. As such, they have the best interest of the public in mind. Without both government and regulatory agencies, pharmaceutical invention and innovation would lead nowhere. Therefore, a balance of power exists between pharmaceutical companies, government administrations, and regulatory agencies. Pharmaceutical companies in the United States may utilize their lobbying power to influence politics. Influencing politics may then progress legislation in either direction: for or against biosimilars. The main disagreement between pharmaceutical companies and government administrations lies within the legality of biosimilars. Pharmaceutical companies may argue that biosimilars will disincentivize further drug

discovery, while government administrations may argue that additional competition is necessary to protect patient from further exploitation. By association, a similar balance of power exists between pharmaceutical companies and regulatory agencies who are responsible for enforcing drug regulation. Disagreements exist between pharmaceutical companies and regulatory agencies regarding the approval process for biosimilars. Pharmaceutical companies may argue that the approval process is still too long, while regulatory agencies may argue that necessary steps are being taken to ensure patient safety. Compromise between the two parties is necessary to establish a regulatory path for biosimilars that is attractive to investment from pharmaceutical companies without sacrificing quality and safety.

Another important relationship to consider is that between medical professionals and patients. Medical professionals hold power within their own right by being an unavoidable middleman to patients seeking biosimilar treatments. Without a medical prescription, biosimilars are inaccessible to patients. Their goal is to utilize their medical expertise to assist in caring for patients with no ulterior motives preventing access to quality care. It is important for medical professionals to be well-informed on the benefits of biosimilars in order to facilitate the flow of technology to patients. Pharmaceutical companies, regulatory agencies, and governments are each responsible for ensuring a clear flow of information down to medical professionals about novel biosimilars. Information may also flow up from well-informed patients advocating for cheaper alternatives. Poor relay of information to medical professionals enables medical professionals to have unbounded power over this system, as they may serve as dead-ends to the flow of technology.

The passing of the Biologics Price Competition and Innovation Act by the United States government is an important factor of the social construction of biosimilars. In the hopes of improving healthcare coverage for the average American, the government encouraged necessary

market competition by incentivizing pharmaceutical companies to invest in second-to-market drugs. Simultaneously, the bill also laid out frameworks for an abbreviated FDA licensure pathway so that regulatory agencies may continue to put patients first by enforcing high degrees of safety and efficacy (Lim, 2018). This interdependence of the social groups also extends down to doctors and patients. The legalization of biosimilar products enables doctors to continue to prioritize patient care through cheaper, yet equally effective therapies. Conversely, patients will experience the improved quality of healthcare that has trickled down from the governments, regulators, and pharmaceutical companies.

Interpretation of good technological design is another important factor of social construction of technology. Pharmaceutical companies primarily focus on the market potential of a biologic as a metric for good design. A successful biologic, in the eyes of a pharmaceutical company, is one that has high return on capital and time invested, while also being sufficiently safe and effective. Untreated disease areas have traditionally been prime targets for biologic development as they ensure limited competition and high profitability (Simoens & Vulto, 2020). However, the popular proprietary biologics with patents nearing expiry are key focus areas for biosimilar development. Governments focus on the affordability and quality of healthcare, with the goal of benefiting their constituents. Regulatory agencies are tasked with ensuring safety and efficacy. Governments may focus on cheap and affordable aspects of biologic design, while regulatory agencies will focus on their safety and efficacy metrics. Legislature and regulatory frameworks are tools that governments and regulatory agencies may employ to leverage control over the implementation of this technology in society. Doctors have the interests of the patient as their primary focus. A good design to a doctor is one that covers all previously defined parameters of this sociotechnical system. It must be safe, effective, and promote a high quality of healthcare,

yet remain affordable and accessible to the patient. As consumers of novel biosimilars, patients share this definition of good design. However, it may be argued that patients are particularly interested in the affordability and accessibility of these alternative biologics. As the end users of these technologies, they are reliant on these life-changing drugs and must bear the associated financial burden. Animosity towards pharmaceutical companies that have held monopolies over key proprietary biologics may be responsible for this focus on drug affordability and accessibility. Although each social group may define good design differently, the focus of each on ensuring good design aids in strengthening the underlying interdependence responsible for the success of biosimilars in the United States.

Discussion

Biologics such as recombinant proteins and monoclonal antibodies, were introduced as novel medicines that could address disease with high specificity and minimal side effects. For instance, monoclonal antibody treatments were instrumental in improving the lives of those living suffering from autoimmune diseases or cancers. Biologics were rapidly adopted and replaced several small molecules as standards of care. The biologics market is projected to grow at an annual rate of 13.8% until 2030 (Mulcahy et al., 2017). While intended to improve quality of healthcare, biologics have had an adverse effect on those dependent on them. Approximately only 2% of the U.S. population is treated by biologics annually (Stiff et al., 2019). However, biologic therapies account for almost 40% of all annual prescription drug spending due to their incredibly high cost per dose (Mulcahy et al., 2017). This negative effect has also been seen across the world. In a multinational survey in Europe and Canada, it was found that 23% of psoriasis cases could not receive proper biologic therapies due to cost (Simoens & Vulto, 2020). In Europe, the average annual cost of biologics exceeded the gross domestic product per capita in 57% of countries

(Simoens & Vulto, 2020). As a means of tackling the exorbitant drug prices, biosimilar legislation has been passed across North America, Europe, and Asia.

Until the early 1980s, complex small molecule drugs were on the forefront of healthcare. Patented small molecules did not have the same effect as biologics on drug prices due to the existence of generics. Due to the molecular simplicity of traditional small molecule pharmaceuticals, achieving the exact pharmacological effects of patented medicines was as simple as replicating the exact same chemical structure. Prior to the biotech revolution of the 20th century, these generic small molecules were able to reduce prices up to 80% relative to their reference counterparts (Pfizer, 2020). Widespread adoption of biosimilars is aimed at eventually achieving similar reductions in drug prices for patients in need. In the European Union, the expansion of biosimilars has introduced competition into the biologics market and resulted in discounted biologic prices between 10% and 30% (Stiff et al., 2017). Similar effects on biologic drug prices have been seen in the United States. According to the RAND Corporation, approximately $54 billion in biologics spending will be reduced in the United States alone between 2017 and 2026 (Mulcahy et al., 2017).

To further understand the potential long-term effects of biosimilars on the American healthcare system, it is necessary to compare biosimilar rollout between the United States and the European Union. The European Union was the first to pass biosimilar legislation, with the United States quickly following suit. Both the United States and the European Union have established expedited regulatory pathways to minimize capital risk for pharmaceutical companies and encourage investment into biosimilar development. As per the FDA definition, a biosimilar is any biological product that has demonstrated similarity to an FDA-licensed biological product (Lim, 2018). Furthermore, a biosimilar must have no clinically meaningful differences from the

reference product in terms of safety, purity, and potency (Lim, 2018). Given the necessary similarity between biosimilars and reference products, regulatory processes for biosimilars follow a different approach to ensuring patient safety and efficacy. Under the Biologics Price Competition and Innovation Act, an expedited FDA approval process for biosimilars was established in order to incentivize investment into biosimilar development. Standard reference drug approval focuses on determining the clinical effect and safety of new biologics. Biosimilar drug approval instead relies on molecular similarity to determine safety and efficacy (Lim, 2018). While reference drugs must go through extensive clinical trials, biosimilars must go through extensive analytical testing to prove similarity (Lim, 2018). Due to the molecular similarity to reference drugs, biosimilars are not required to go through extensive multi-phase clinical trials. Instead, they may extrapolate drug safety and efficacy from their reference product after demonstrating high degree of similarity to the reference drug via extensive analytical testing (Lim, 2018). An abbreviated clinical trial focused on pharmacodynamics, pharmacokinetics, and immunogenicity then follows to confirm its therapeutic properties before the biosimilar is ready for market (Pfizer, 2020). The European Medicines Agency has a nearly identical regulatory process.

One example of the potential long-term success of biosimilars in the United States is filgrastim. Filgrastim is a recombinant form of granulocyte colony-stimulating factor that stimulates neutrophil production in the bone marrow. It is manufactured and distributed by Amgen as Neupogen. Biosimilar versions of filgrastim were first introduced in 2012. These filgrastim biosimilars were priced between 30% and 45% below the originator biologic (Mulcahy et al., 2017). By late 2016, the combined filgrastim biosimilar market share had reached approximately 30% by sales and 40% by volume (Simoens & Vulto, 2020). As a result, the average cost of filgrastim decreased by about 24% during the same period (Simoens & Vulto, 2020). The increase

in market share by volume is indicative that the reduction of drug prices by simple supply and demand in the market are capable of eliminating price barriers and increasing accessibility to biologic therapies.

As of December 2020, there are 29 biosimilars approved in the United States and over 45 approved in the European Union (Harson, 2021). The discrepancy in approval between the approval of biosimilars in each is largely due to regulatory leniency and interchangeability. While both the FDA and EMA require the same regulatory steps, the FDA has taken a more conservative stance on biosimilar approval. On average, most clinical trials for biosimilars took longer, required more participants, and cost more in the United States than the European Union (Harson, 2021). In 2018, the FDA released its Biosimilar Action Plan focused on facilitating approval for many more biosimilars. This plan improved efficiency of filing biosimilar and created application templates formatted for biosimilars. This also clarified many gray areas surrounding the specifics of what is required for each regulatory study. Furthermore, the FDA took a harsher stance towards companies engaging in anti-competitive practices such as patent abuse or exclusivity contracts with vendors (Harson, 2021). The FDA has also moved towards encouraging interchangeability clauses for all approved biosimilars. The lack of interchangeability blocks pharmacies and hospitals from lowering drug costs by substituting prescriptions with biosimilar alternatives. In the European Union, interchangeability was handled on a country-by-country basis. The majority of the European Union has since passed legislation expanding interchangeability clauses for biosimilars. The FDA previously took a similar stance by allowing individual states to pass legislation in favor of biosimilar interchangeability. This was met with heavy resistance by both states and companies alike. In the spirit of protecting American free enterprise, legislators and lobbyists alike have

increased difficulty for biosimilars to be considered interchangeable, even though studies have shown little to no difference in efficacy and safety.

The FDA has also taken steps to expand biosimilar legislation to previously approved drugs. In 2020, language was included to classify any drug that is a peptide as a biologic. Insulin is a protein that regulates the amount of glucose in the blood. The first human insulin, Humulin, was approved in 1982. Since there was no proper legislation or regulatory process for biologics at the time, Humulin was approved as a small molecule. To extend their patent protection, pharmaceutical companies were known to release new forms of insulin that contained added amino substitutions and post-translational modifications. One such example is Humalog, or insulin lispro. This drug has a lysine replaced with a proline in order to make it longer lasting in the blood. With insulin classified as a small molecule, these products could be marketed as novel products as they are not chemically identical to prior FDA approved products. By reclassifying insulin as a biologic, it will now be subject to biosimilar legislation. Humalog is the 8th most prescribed drug in the United States (Harston, 2021). This will incentivize a lot of pharmaceutical companies to enter the insulin market by developing biosimilars. This will potentially cause significant decreases in insulin prices, improve insulin availability, and quality of life for millions of Americans suffering from diabetes.

While biosimilars in the United States have been partially able to meaningfully benefit the American healthcare system, there are still several barriers limiting their systemic benefit to patients long-term. Many of these barriers are propagated by the inherent power structure in healthcare. Medical professionals, such as physicians, are required to write prescriptions to allow consumers to access necessary medicines. As such, they are responsible for directly impacting the depth of market penetration for many newly approved biosimilars. Lack of information and

skepticism are two factors currently acting against the widespread adoption of biosimilars. Due to the relative novelty of biosimilars, there is a healthy amount of skepticism surrounding their efficacy compared to their reference counterparts. As medical professionals tasked with treating patients under their care, doctors are responsible for using their best judgment in order to make decisions that will improve the wellbeing of their patients. Biosimilars have only been legal in the United States for little over a decade, during which there has been a gradual increase in the market penetration of biosimilars as medical professionals become more well-informed and educated on these new biologics. Improving transparency and communication of clinical data to medical professionals will likely greatly increase the adoption of biosimilars within the next several decades and may result in drug price reductions mirroring that of small molecule generics. These inhibitors to the societal benefits of biosimilars should be the future focus of biosimilar development in order to secure the long-term benefits on the average American.

Conclusion

Drug affordability and accessibility is a complex problem with no clear-cut, simple solution. It is inherently wicked and requires a complex sociotechnical solution. Biosimilars are just another example of how technological innovation requires cooperation with the relevant social groups to better society. However, biosimilars are still a relatively new technology in the United States, having only been around for the last decade. As shown through this sociotechnical analysis, they are capable of causing meaningful change with regards to affordability, accessibility, and quality of healthcare for the average American. By 2025, an additional 1.2 million people will have access to biologic therapies in the form of biosimilars (Pfizer, 2020). This effect can only be expected to increase exponentially as market penetration of biosimilars accelerates in the near future. However, this will only be manageable if all of the relevant social groups can successfully

work together to improve society. Continued coordination and cooperation between each interconnected social group over the next several years and potentially decades have the potential to uplift millions of people barred from quality healthcare and promote equity in healthcare for all.

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