Understanding the Need for Public Assistance to Overcome Obstacles in the Biosimilar Sociotechnical System

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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

Due to the financial burden imposed by expensive pharmaceutical products, as many as 20% of patients will neglect treatment with lifesaving medicines (Kantarjian et. al., 2014, p. 208). One of the primary reasons for the high prices is the patent system, which allows companies to patent the discovery of a new drug for up to 20 years (Raj et al., 2015, p. 404). These patents prevent any other company from selling a medicine that serves a similar purpose and allow the original company to sell their drug at an uncontested high price. However, when patents for medicines expire, other companies can produce generics, which are drugs designed to mimic an existing therapeutic. Generics have the potential to greatly reduce the costs of medicine by introducing competition. Improving the production of generic medicine is of particular interest for biologics as they "account for approximately 40% of total US pharmaceutical expenditures despite being used by less than 2% of Americans" (Sarpatwari et al., 2019, p. 92).

Biologics, or drugs that originate from cells, are newer and typically more complex than small molecule drugs, which are drugs produced by chemical processes as shown in Figure 1.

Biologics	Small molecules
Produced by living cell cultures	Produced by chemical processes
High molecular weight	Low molecular weight
Complex, heterogeneous structure	Well-defined structure
Strongly process-dependent	Mostly process-independent
Not entirely characterizable	Completely characterizable
Unstable	Stable
Immunogenic	Nonimmunogenic

Figure 1. Major Differences Between Biologics and Small Molecule Drugs. Biologics have properties that make them much more complex (Makurvet, 2021, p.2).

Since they are newer, many patents for biologics are just now expiring, allowing the opportunity for generic versions, termed biosimilars, to enter the market. Conversely, small molecule drugs have been on the market for much longer and have many generic versions already on the market. These generics have reduced the cost of name brand medicine by 80% or more; however, approval of biosimilars thus far has "rarely led to meaningful price reductions" (Sarpatwari et al., 2019, p.

93). For example, in the European Union, biosimilars have been found to cost only 30% less than the brand name drug (Blackstone et al., 2013, p. 471). Consequently, biosimilars have not been as effective in penetrating the market. As seen in Figure 2, historically, there has only been a 2-4% increase in the demand for a medicine after the introduction of a biosimilar. Conversely, prescriptions for small molecule generics grew significantly from only 19% in 1984 to 89% in 2019 (Sarpatwari et al., 2019, p. 93).

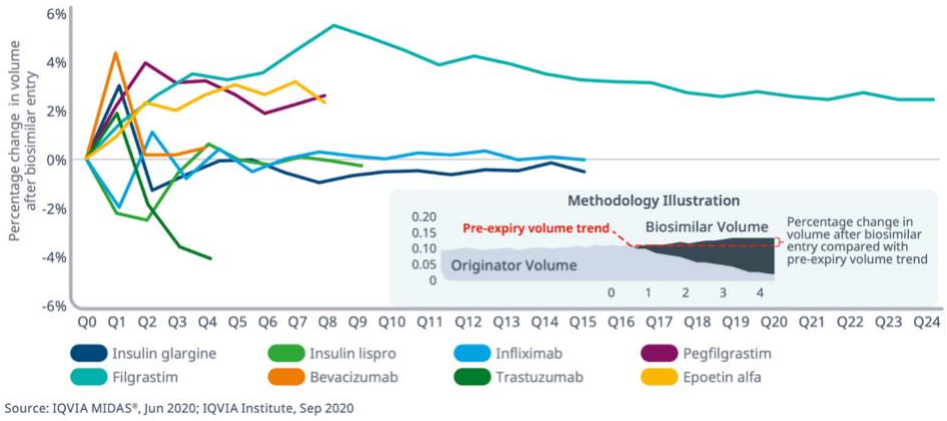

Figure 2. Market Increase After the Addition of Biosimilars. Historically, the demand for a medicine has only increased 2-4% with the addition of biosimilars (IQVIA Institute, 2020, p. 13).

Through comparison of biosimilars and small molecule generics, it is clear that biosimilars have the potential to be more effective in lowering costs and penetrating the market. If the biosimilar system does not improve, a select few companies will continue to dominate the industry, resulting in high costing drugs with little accessibility. Consequently, some patients will not receive the life improving medicine that they need. Therefore, this paper seeks to identify the unique characteristics of the biosimilar system that are preventing success and to evaluate how the public and private domains of the system can better interact to overcome these obstacles using Mesthene's framework on economic and political organizations. Through analyzing the challenges facing the biosimilar system, it is clear that the problems are political and economical in nature and that the private domains need public support.

Unique Characteristics of Biologics Create Manufacturing, Regulatory, and Marketing Obstacles for the Biosimilar Sociotechnical System

Although small molecule generics have been successful in penetrating the market, the main and most influential factors preventing biosimilar success are unknown. As mentioned previously, biosimilars do not reduce the cost of medicine as drastically as small molecule generics. The lack of price reduction could be due to the fact that manufacturing biological medicines is much more complex and thus expensive than small molecule drugs. For example, the average cost of medicine per pack is $5 for small molecules but $60 for biologics (Makurvet, 2021, p. 4). Therefore, it is much more expensive for companies to produce biosimilars than it is small molecule generics. One reason for this is simply due to the fact that biologics are larger and require much more material to produce, whereas some small molecule medicines can be made with as little as 5 ingredients (Makurvet, 2021, p. 4). More importantly, however, the use of living cells to produce biologics imposes additional constraints that are not of concern in the chemical synthesis of small molecule drugs.

Cells are extremely sensitive to the environment in which they are grown, resulting in biologics being highly path dependent. For example, Price and Rai explain that "selection of the host organism, the identification of a particular cell line, culture and media conditions, and purifications procedures all impact the characteristics and activity of the final product," so biosimilar manufacturers often require process specific information that is patented (2016, p. 1033). Conversely, the chemical synthesis of small molecule drugs is a highly predictable and repeatable process (Price & Rai, 2016; Heinrichs & Owens, 2008). The steps taken to produce the drug typically do not affect the quality and efficacy of the final product as long as the final product is chemically the same as the originator drug. Therefore, generic manufacturers do not

need any patented information or specialized knowledge to try to produce a generic. In fact, in 2009, Sarpatwari et al. estimated that it took "8-10 years and $100-$200 million to manufacture a biosimilar" while small molecule generics only took 3-5 years and $1-$5 million (2019, p. 95).

In addition to manufacturing being more complex, biologics have more rigorous regulatory requirements as their intricate structure can trigger an immune response, whereas small molecules cannot (Makurvet, 2021, p. 1; Weinberg et al., 2005). Therefore, biologics have added risks to patients, such as unintentionally infecting cells or causing a violent response from the immune system. Additionally, the impurities in small molecule drugs are often well known and predicted chemical byproducts. However, for biologics, impurities are hard to predict and can be introduced by the host cell (Price & Rai, 2016). Due to this, fewer biologics get approved than small molecules. For example, only 91 biologics were approved in the years 1982 to 2013 while 777 small molecule drugs were approved (Makurvet, 2021, p. 6). Consequently, less biosimilars get approved than small molecule generics, leading to less competition and less price reductions.

There is also a clear misconception around the quality of biosimilars, which could be contributing to the lack of market penetration. As shown in Figure 3, many patients do not trust biosimilars as much as brand name drugs as they view them as less safe and effective. Therefore, a majority of patients would not be comfortable switching to biosimilar medications (Jacobs et al., 2016). The lack of trust in biosimilars is specifically a problem in the United States, which has fewer approved biosimilars than the global market (Makurvet, 2021, p. 7). Alarmingly, this lack of education even extends to physicians. In one study, it was found that 2 to 25% of physicians did not know what biosimilars were and 65 to 67% had concerns with these medications (Sarnola et al., p. 1). Because many patients rely on the recommendations and

advice of their doctors, it is vital that doctors are well educated and advertise the safety of biosimilars. However, it is unknown how significantly these misconceptions would impact a doctor's decision to prescribe a biosimilar or a patient's decision to take a biosimilar.

Furthermore, this perception gap surrounding safety and efficacy worsens when individuals are unaware of biosimilars as shown in Figure 3. For example, Jacobs et al. showed that the percentage of patients that believe biosimilars are an effective treatment drops by 18% when patients were previously unaware of biosimilars (2016, p.942). Therefore, trust in biosimilars could be increased significantly just by informing individuals of biosimilar products. Jacobs et al. acknowledges that "there remains an unmet need for education about this class of drugs;" however, it remains unknown how to meet this need (2016, p. 943). In the case of small molecule generics, trust and education grew over time, so it may be possible to streamline this process for biosimilars. However, much more research remains to be done on the best way to market biosimilars in order to increase awareness and trust of these products.

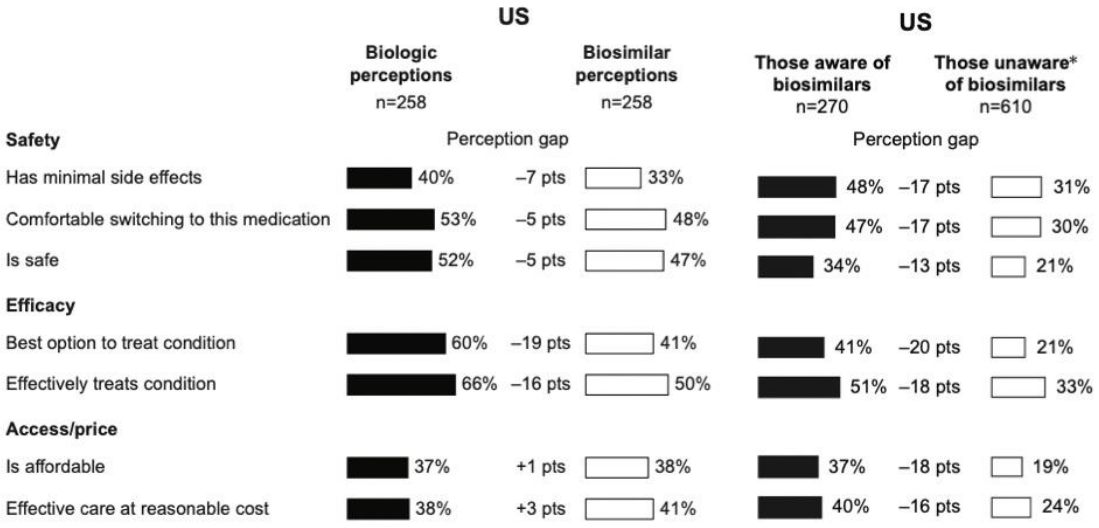

Figure 3. Gaps in Perception about Biosimilars. Patients perceive biosimilars as less effective and safe than biologics. This problem worsens for patients who are less aware (Jacobs et al., 2016, pp. 941-942).

As identified above, there are many unique characteristics of biologics that make biosimilars more complex to produce, regulate, and market than small molecule generics.

Despite these challenges, biosimilars have the potential to increase accessibility to lifesaving medicines as seen with the success of small molecule generics. However, until these obstacles are addressed and overcome, biosimilars will never achieve the same success. Some of the obstacles such as the manufacturing complexity of biologics are unavoidable and will not change through an analysis of the sociotechnical system. However, as technology and expertise continue to grow, manufacturing may become less costly. Conversely, the regulatory and marketing issues should be evaluated and improved now. To better understand the relationship between the various organizations involved in regulating and marketing pharmaceuticals, Mesthene's framework on economic and political organizations will be implemented in the subsequent section.

The Pharmaceutical System Creates Problems that are Economical and Political in Nature

The main challenge when evaluating the pharmaceutical system is that "there is no explicit consensus on what constitutes a pharmaceutical system, and no clearly defined framework or agreed approach to measure progress toward stronger, more resilient pharmaceutical systems" (Hafner et al., 2016, p. 573). Therefore, many different frameworks have been proposed for effective evaluation of the pharmaceutical system. The World Health Organization (WHO) has assigned eight main functions to the pharmaceutical system: registration of medicines, licensing of pharmaceutical business, inspection of establishments, medicine promotion, clinical trials, selection of essential medicines, procurement of medicines, and distribution of medicines (WHO, 2009, p. 7). Each of these functions require a variety of different actors who may have different goals, resulting in the creation of a highly complex system. Throughout the remainder of this analysis, it will be assumed that the pharmaceutical subsystem "consists of all structures, people, resources, processes, and their interactions within

the broader health system that aim to ensure equitable and timely access to safe, effective, quality pharmaceutical products" (Hafner et al., 2016, p. 572).

Due to the high complexity of this system, Mesthene's framework on economic and political organizations will be used to evaluate the roles of the different organizations involved in regulating and marketing medicines. Mesthene's framework is advantageous for complex systems because the organizational actors can be grouped into domains instead of evaluating all actors individually. When evaluating a sociotechnical system, Mesthene argues that it is vital to focus on the organizational domains because they are often the least understood and have the most intricate relationships (1970). Additionally, his work is particularly relevant to the pharmaceutical system as the technology of medicine has created problems that are political and economical in nature. For example, Hafner et al. argues that "ensuring equitable access to essential medicines, vaccines and technologies, and their appropriate use is a core function of the health system" (2016, p. 573).

Another idea that makes Mesthene's work particularly insightful is the idea that technology is neither good or bad. Mesthene believed that technology creates problems that are "trade-offs between countervailing impacts" (Drucker, 1969, p. 522). Drucker explains that these different impacts of technology are "political choices of great complexity" (1969, p. 522). When applied to the biosimilar system, there is a clear tradeoff between increasing access to medicine and protecting intellectual property as the role of the patent system was to help originator companies fund all the research required to discover new drugs. However, as patents begin to expire, the focus needs to shift to increasing access. Therefore, now is the perfect time to reevaluate and change the interactions between domains in the biosimilar system using Mesthene's framework.

The first step in this framework is to identify the public and private domains of a system (Mesthene, 1970). The next step is to identify how these domains affect one another and how they can work together in a more effective way (Mesthene, 1970). Drucker explains that it is important to understand that no one organization or domain is guilty or responsible for the problems facing a system (1969, p. 523). Applying Mesthene's work, he believes that the goal should be to identify "at what point benefits, public or private, threaten to cost more than what they are worth" (Drucker, 1969, p. 523). In the case of biosimilars, the cost is preventing any significant benefit to many patients. Therefore, it is clear that changes need to be made to this system in order to achieve the full benefits of the technology of biosimilars. However, this change will require the different domains working together.

When evaluating the roles of the different domains, a key feature of this framework is the assumption that the private sector prioritizes profit and efficiency and often neglects public needs. On the other hand, the public domains often prioritize the good of the public but work less efficiently. Because of this, Lezaun and Montgomery have proposed a new approach to pharmaceuticals called product development partnerships, which are public-private partnerships (2015). These partnerships make use of philanthropic and state funds of the slow acting government to incentivize experienced and quick acting companies. A key characteristic of these partnerships is the sharing of ideas, but this will require a "rearticulation of the relationship between property and value" (Lezaun & Montgomery, 2015, p. 6). Lezaun and Montgomery argue that this could be achieved by "altering the way actors calculate the value of their assets" as traditional economic incentives will be insufficient (2015, p. 6).

Additionally, it is important to note that interactions between various actors will evolve over time as a system grows, and therefore they should be continually evaluated (Mesthene,

1970). For example, once trust in biosimilars is established, the role of marketing agencies can be decreased. However, establishing who decides this remains a challenge. Furthermore, it is vital to understand how the actions of these domains affect the individual as they are the final customer (Mesthene, 1970). Mesthene believes that the individual has the right to be educated on the issue at hand, which currently is a major obstacle of the biosimilar system as shown above in Figure 3. To apply this framework as summarized in Figure 4, previous research done on the history of biosimilars and small molecules generics by Sarpatwari et al. was analyzed with the goal of identifying ways in which the domains of the pharmaceutical system can change and better interact to meet the unique needs of biosimilars.

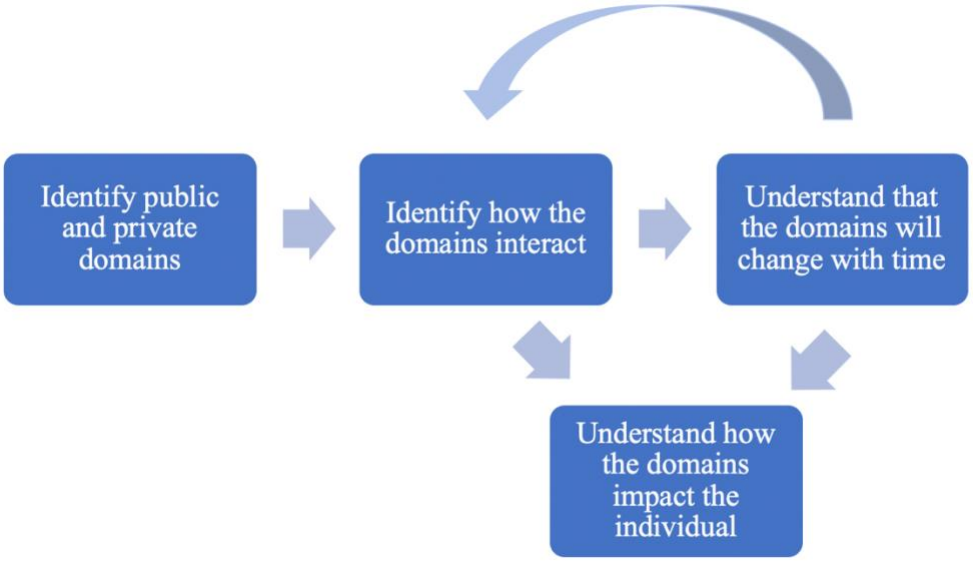

Figure 4. Mesthene's Economic and Political Organizations Framework. This framework aims to understand how public and private domains interact to impact the individual (created by author).

Private Domains Need More Public Support in the Biosimilar System

As previously mentioned, the first step of this framework is to identify the public and private domains of the system. Figure 5 shows a list of a variety of actors involved in the pharmaceutical system although it is by no means comprehensive. In general, actors that fall into

the private domains are aiming to discover and produce medicines. However, they are heavily regulated and influenced by actors that tend to fall into the public domains. Due to the vastness of this system, it is impossible to identify one actor or domain responsible for the regulatory and marketing problems preventing the success of biosimilars. As such, there will be no one solution to these problems. However, through evaluating the success of small molecule generics, it is clear that the public domains need to adjust the regulatory standards to help the private domains achieve success.

- Ministry of Health (e.g. health service department, pharmaceutical units, national programmes for disease controls, medical stores, procurement division, etc.);
- Medicine Regulatory Authority (registration, inspection, control of promotion, licensing and clinic trial units/departments, etc.);
- Procurement agencies, importers and distributors both from the private and the public sector (including tertiary care hospitals, primary-care facilities, pharmaceutical brokers and consolidators, hospital pharmacists, etc.);
- Members of committees, such as tender committees, therapeutics committees, selection of essential medicines committees at national and local level;
- Ministries of finance, industry and commerce, customs and importation;
- National quality control laboratories;
- Audit departments (internal, external, and state auditors);
- Pharmaceutical industry (multinationals and national) and associations;
- Nongovernmental organizations, such as those engaged in health service activities, patient advocacy groups, "watch-dog" organizations;
- International donor organizations, such as WHO, UNICEF and the World Bank;
- Academic institutions (national colleges, state universities and research institutes);
- Professional associations (medical association, pharmacy association, biochemist associations, etc.);
- Media (if knowledgeable about the pharmaceutical sector);
- Ethics committees, institutional review boards;
- Health insurance funds.

Figure 5. List of Actors in Pharmaceutical System. There are many actors that make up the pharmaceutical system making up both private and public domains (WHO, 2009, p. 10).

Federal regulation of biological products started in 1902 with the Biologics Control Act; however, overall biologics have been neglected in new legislation until recently as little existed (Sarpatwari et al., 2019, p. 92). As production of biologics has become more prevalent in the private domain, it is vital that government regulations also become more prevalent, which are now controlled by Food and Drug Administration (FDA) in the US. For example, the success of

small molecule generics can be largely traced to the 1984 Hatch-Waxman Act, which created abbreviated application pathways for versions of approved drugs by eliminating costly clinical trials. In fact, it is estimated that the US healthcare system has saved over a trillion dollars due to generics entering the market via this pathway (Sarpatwari et al., 2019, p. 93). However, originally, this only applied to small molecules and not biologics.

Biologics have since been able to use another abbreviated pathway created by this act by allowing manufacturers to prove similarity but not bioequivalence (Sarpatwari et al., 2019). However, these drugs were classified as new drugs, not generics, and therefore did not lead to significant cost reductions. In attempts to solve this problem, the 2010 Biologics Price Competition and Innovation Act was passed. This act was modeled after the Hatch-Waxman Act that allows the FDA to approve biological products that can prove high similarity. However, as biological products are more complex, this act still requires more testing for biosimilars than small molecule generics. As of 2018, 13 biosimilars were approved under this pathway leaving patients, physicians, payors, and policymakers to be "frustrated by the small number of biosimilars approved by the FDA" (Sarpatwari et al., 2019, p. 95).

The success of the Hatch-Waxman Act shows that regulations can be effective in increasing approval and access to generic based medicine. However, thus far, the private domains have been failing to meet the public domains' requirements to prove biosimilarity. A major barrier to success is the patent system as manufacturers do not have the technical knowledge needed to pass the FDA standards (Sarpatwari et al., 2019). Additionally, in order to enter the market, manufacturers have to either participate in lengthy proceedings surrounding the originator's patent, or open themselves to lawsuits from the original manufacturer (Sarpatwari et al., 2019). Therefore, new companies may not have the ability to overcome this hurdle. Since

small molecules are much simpler to produce, the abbreviated approval pathway was enough for manufacturers to effectively produce generics. However, it is clear through this analysis that additional regulations may be required for the success of biosimilars.

Additional regulations should be focused towards intellectual property rights as the patent system and lack of published data seems to be one of the major obstacles for private manufacturers to produce biosimilars. One reason for this is that biosimilar manufacturers are required to give the original manufacturer a 180-day notice that they plan to enter the market, allowing the originator to try to delay the patent proceedings (Sarpatwari et al., 2019, p. 95). The public domains could improve the system by creating new regulations to prevent originator companies from dragging out the lives of their patents and from postponing patent settlements for new manufacturers. Additionally, as mentioned above, manufacturers often lack the technical expertise to produce biosimilars (Sarpatwari et al., 2019). By creating new regulations that require or promote data sharing, other manufactures may have access to the data that they need to succeed. As mentioned previously, Lezaun and Montgomery argue that new regulations could achieve this goal by creating incentives and changing the way manufactures value their assets (2015). Additionally, data sharing could be mandated at the end of a patent to promote competition.

In addition to more regulations, it is clear that private domains need more public support in order to meet FDA approval. One way this could be achieved is through product development partnerships. As mentioned previously, these partnerships use public funds to support private companies (Lezaun & Montgomery, 2015). Small molecules have shown that generic medicine can save the government trillions. Therefore, the government should invest in biosimilar manufacturers in order to increase the probability that they make it through the patent

proceedings and to ensure they have enough funds for the abbreviated clinical trials. Sarpatwari et al. give an example of this being done in South Korea where there are now 7 different biosimilar manufacturers (2019, p. 97). Additionally, if data from biosimilars in other countries is shared with the FDA, the government could more effectively choose companies and products to invest in.

However, even if changes are made that are able to increase the amount of biosimilars being approved, there remains the problem of biosimilars being used. Small molecule generics have been successful because the ones that are approved can automatically replace the original in pharmacies, but this does not often apply to biologics as biosimilars are typically only classified as similar and not as identical to the original (Sarpatwari et al., 2019). However, in Australia, interchangeability of biosimilars is being recommended based off the same data that has been submitted to the FDA (Sarpatwari et al., 2019, p. 97). Therefore, the public domains in the US need to develop a new and better way to establish and grant interchangeability. Interchangeability could be granted by the FDA changing their methods or by having states change their laws.

One obstacle to interchangeability is concerns that switching between different versions of biologic medicines can increase adverse immune responses (Sarpatwari et al., 2019, p. 96). However, there has been little evidence to support this including in Europe where use of biosimilars is more widespread. To increase trust and promote FDA changes, formal post approval studies should be done to show that interchanging biologics is safe, which could easily be done by better record keeping and surveillance of patients who have switched to a biosimilar product. Additionally, it has been found that the FDA naming requirements contribute to this skepticism (Sarpatwari et al., 2019, p. 97). In fact, in the European Union where biosimilars see

more success, the FDA naming convention is not used, there is no centralized regulation regarding interchangeability as imposed by the FDA, and there is greater control over choosing which medicines patients use (Sarpatwari et al., 2019, p. 97). All this is also true for small molecule generics, indicating that these changes could drastically improve the current system.

However, patients and physicians need to trust the biosimilars being approved and interchanged for current medicine. Therefore, education on the safety and efficacy of biosimilars need to be greatly improved as there is currently a large perception gap as presented earlier. The FDA and manufacturers do not directly interact with patients often. However, the FDA and government could have a course for doctors and healthcare providers about the biosimilar approval process and how it is safe and effective. Additionally, if biosimilars are not automatically exchanged for the original biologic, doctors could be notified of when new biosimilars are released, so they can educate their patients. Since many small molecule drugs are in pharmacy, patients can see and choose a cheaper option. However, this is often not true for biosimilars, and therefore the doctor will be responsible for presenting options to their patients.

It is vital that more biosimilars start to gain approval in order to induce competition and lower the costs of biological medicine. Because small molecule medicines are simpler, abbreviated application pathways were sufficient for efficient approval of generic medicines. However, it is clear that the private manufacturers of biosimilars need public help and support in addition to the abbreviated pathways. With more assistance from the public domains, biosimilar manufacturers may be more successful in getting products approved. These approved products will then be used with more frequency if there is some way to ensure they are interchanged with the original medicine at hospitals and pharmacies. If this exchange is not automatic as it often is with small molecules, it is vital that doctors are aware of the biosimilar options so that they can

offer and advertise the medicine to their patients. These results are summarized below in Figure 6.

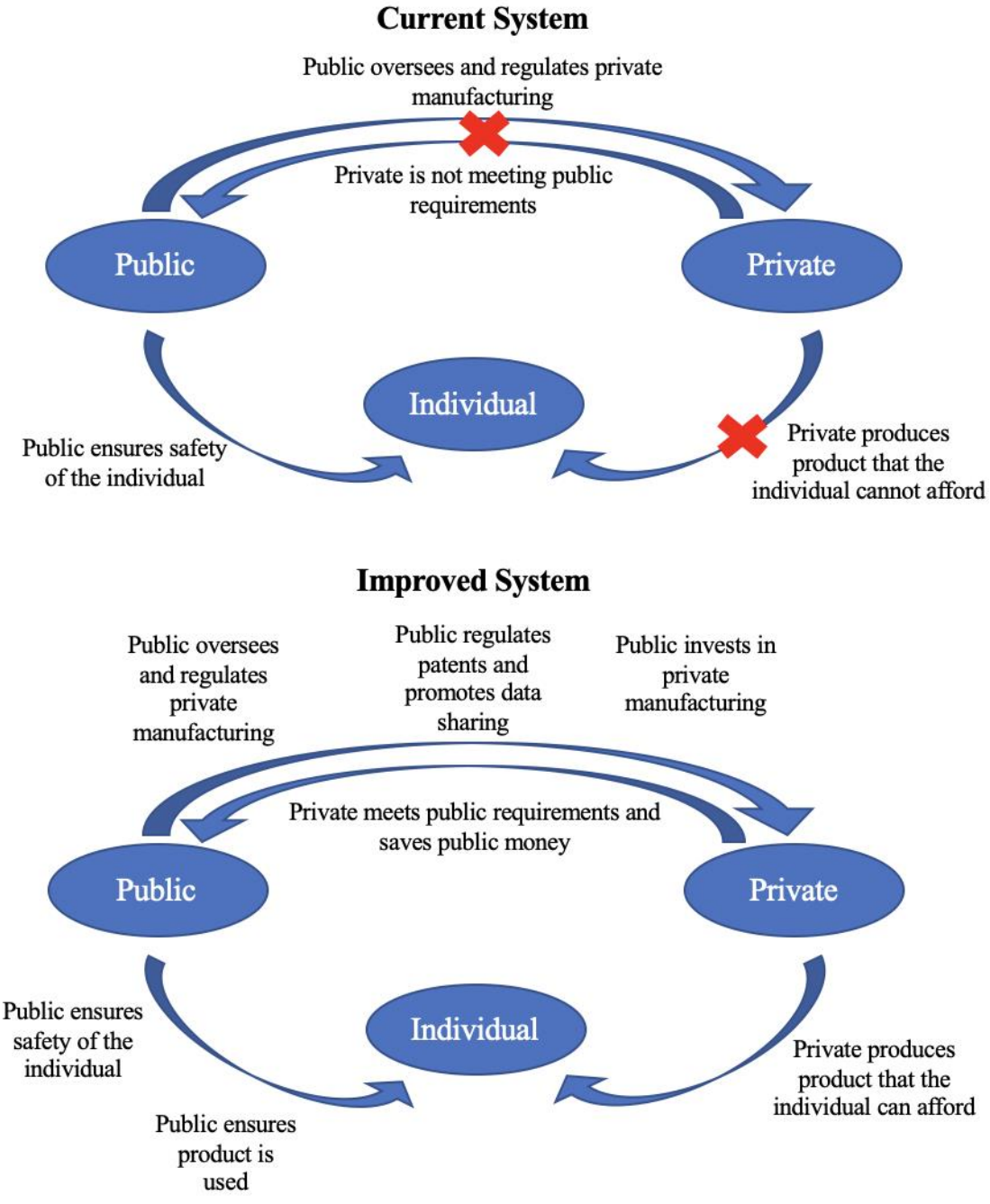

Figure 6. Summary of Interactions Between Domains. Currently, the private domain is not meeting the requirements of the public domain and failing to produce affordable medicine, so the public domain needs to provide more support and regulations (created by author).

Conclusion

Due to the added complexity of biological medicine, biosimilars have not been as successful as small molecule generics in increasing accessibility to medicine. The main obstacles preventing success are current regulations and a lack of marketing. Therefore, the organizations responsible for these activities need to be updated to meet the needs of the newer biosimilar system. Due to the complexity of this system, Mesthene's framework on economic and political organizations is useful for evaluating the relationships and interactions between the various domains. Through this analysis, it is clear that private domains need more public support and that no one organization should be held responsible for solving these problems. However, this method was limited in evaluating how the individual can have more of an impact on the system and how the individual should best be educated.

The results of this research could be useful in providing a future direction of focus when updating regulations. Currently, the technology of biosimilars is useless, as "the actual success in drug discovery and development… should be measured not only by the magnitude of scientific breakthroughs but also by the level to which [the drugs] are affordable to patients" (Makurvet, 2021, p. 1). If this system is not improved, biosimilars will continue to be unable to significantly lower costs of medicine, preventing many patients from receiving needed treatments. As patents for many biologics are beginning to expire, there is great opportunity for the system to be improved in order to ensure the next round of lifesaving biosimilars are as successful as small molecule generics in increasing access to patients.

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