Production of Adalimumab: A Humira® Biosimilar

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

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By
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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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Accessibility of Monoclonal Antibody Therapeutics

Despite being used by less than 2% of Americans, biologics, drugs which originate from cells, account for approximately 40% of pharmaceutical expenditures in the United States (Sarpatwari et al., 2019, p. 92). One of the most commonly produced class of biologic therapeutics is monoclonal antibodies (mAbs), accounting for 10 of the 13 new biologics approved in 2020 (de la Torre & Albericio, 2021, p. 2). MAbs are naturally occurring proteins that specifically bind to harmful antigens as part of the immune system's response to destroy pathogens, viruses, and infections (Wootla et al., 2014). However, they can also be engineered and manufactured at an industrial scale to provide medicine for a plethora of diseases such as various cancers and autoimmune disorders. Engineered mAb therapeutics are designed to target and bind to one specific disease-causing antigen.

Due to this specificity, mAbs are becoming more favorable by doctors and scientist when researching new medicines. However, these therapeutics are often expensive and require many and routine doses. For example, Humira®, a mAb therapeutic currently under patent by AbbVie, requires patients to receive a dose every two weeks and can cost up to $5,000 each month even with insurance (Coghlan et al., 2021, p.1576; SingleCare Team, 2021). The expensive nature of these drugs causes limited and delayed access with as many as 20% of patients neglecting treatment due to the financial burden (Kantarjian et. al., 2014). Furthermore, pressure to increase access to these medicines can lead to less rigorous evaluation standards and thus implicit pressure to neglect patient safety (Ghinea et al., 2017).

Currently, a majority of mAb therapeutics are protected by patents. This allows for the company that discovers a new drug to prevent any other company for selling or manufacturing a similar medicine. However, as patents for these therapeutics start to expire, other companies can

produce biosimilars, which are drugs designed to mimic an existing biologic therapeutic. Biosimilars have the potential to greatly reduce the costs of mAbs such as Humira by introducing competition. However, thus far, they have not been as successful as nonbiologic generic medicines in penetrating the market (Sarpatwari et al., 2019). As some companies may begin producing a Humira biosimilar in 2023, my capstone team will design the manufacturing process to produce a Humira biosimilar (Vaidya, 2021). To complement this, I will analyze the current shortcomings of the sociotechnical system of biosimilar production and the lack of market penetration seen by biosimilar products thus far in hopes that future biosimilars can better increase accessibility to mAbs.

Production of Adalimumab: A Humira® Biosimilar

Adalimumab (Humira) is a mAb therapeutic produced by AbbVie designed to target and block Tumor Necrosis Factor Alpha (TNF-α), a protein which leads to inflammation in the body. Patients with rheumatoid arthritis, psoriatic arthritis, Crohn's disease, and other autoimmune diseases may produce too much TNF-α and may take Humira to treat the inflammation (Lee et al., 2019). Globally, the market for therapeutic mAbs has surpassed US$100 billion, with an expected revenue of $300 billion by the end of 2030 (Lu et al., 2020). Adalimumab is no exception to this, as it is the highest grossing therapeutic with $20.4 billion in 2020 sales and could cost patients $72,000 per year despite being only the 152nd most prescribed drug (ClinCalc, 2021; Mikulic, 2021; Rowland, 2020).

A select few companies control this market and maintain their dominance through a complex system of product patents. This prevents competition from developing drugs that serve the same function as the original. This allows companies to drive up the prices of their mAb therapeutics and forces patients to pay exorbitant amounts for medicines. When these patents

expire, other companies can introduce biosimilar drugs that serve as an approximation to the structure of a reference compound while demonstrating no clinically significant differences in quality, safety, and efficacy (Jacobs et al., 2016). Biosimilars for mAbs add new, typically more affordable versions of successful drug products to a high-demand market. The U.S. patent for Humira is expiring in 2023, allowing for opportunities in the development of an adalimumab biosimilar (Vaidya, 2021). The goal of this technical project is to design an adalimumab biosimilar process plant to produce adalimumab at a lower cost in order to compete with Humira.

The current production process for mAbs provides the basis for our design with alterations for our specific product included. MAbs, including adalimumab, are often produced in Chinese Hamster Ovary (CHO) cells which have been genetically modified to contain the gene sequence for the target antibody (Azevedo et al., 2016). Viable CHO cell lines are grown to increase cell density in an upstream continuous fermentation process. As cells grow, they will produce and release the target antibody. Our process will make use of a perfusion bioreactor to continuously filter out product and recycle cells back to the reactor, which will improve the yield. After that, centrifugation and various filtration techniques separate the antibodies from the CHO cells and larger debris before a series of downstream purification steps (H. Liu et al., 2010). In the first downstream step, the mAb undergoes sterile filtration followed by Protein A chromatography in order to isolate the protein from any impurities (Azevedo et al., 2016). A viral inactivation step occurs in order to remove virus contamination, followed by three more chromatography steps for further polishing. Finally, ultrafiltration concentrates the mAb solution before it is dispensed into vials (H. Liu et al., 2010). Formulation and filling will be the final step in our design.

There are large amounts of published data on mAbs of similar molecular weight that can provide the basis for our kinetic data. Monod kinetics are a model for cellular growth and will be

useful for our bioreactor design in order to ensure we meet the oxygen and substrate requirements of the cells. In addition, bioseparation theory provides equations for the design of downstream unit operations. We will consult experts in upstream cell growth and downstream separations, such as Professors George Prpich and Giorgio Carta in the University of Virginia Department of Chemical Engineering respectively.

We will complete this project over two semesters as a part of CHE 4474/4476 in a team of five. Two team members will focus on the upstream process while two will focus on downstream purification. The final member will be the expert in quality control and waste disposal. We will evaluate our progress at weekly team meetings and at scheduled sessions with our capstone advisor, Professor Eric Anderson. Our final report will consist of material and energy balances, design of equipment, an economic evaluation, and a discussion of the safety and environmental concerns of the process.

Identifying and Understanding Biosimilar Perception Gaps

Biologics are relatively new to industry compared to nonbiologically derived, or small molecule, based drugs and "are the fastest-growing sector of the pharmaceutical market" (Sarpatwari et al., 2019, p. 92). Therefore, many are still under patent with only 11 mAb therapeutics having FDA approved biosimilar (Food and Drug Administration, 2021). However, there are over 100 approved mAb therapeutics, meaning that many generic brand biosimilars will soon be entering the market. Figure 1 highlights the importance of these patents beginning to

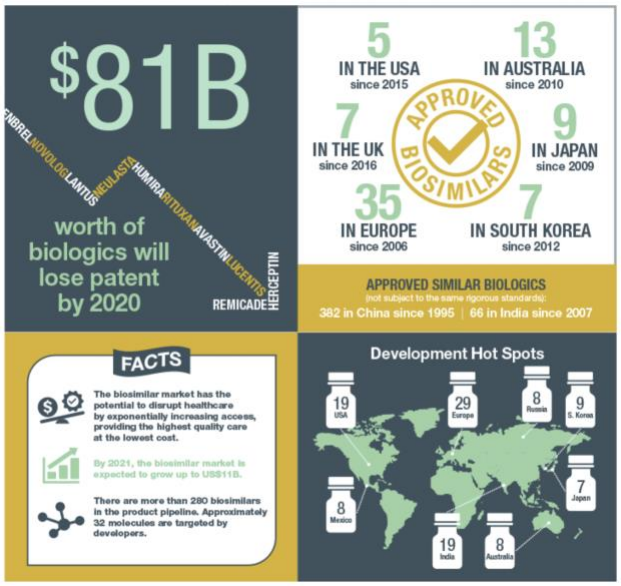

Figure 1. Future Implications of Biosimilars. $81B worth of biologics lost their patent in 2020 giving biosimilars the potential to penetrate and disrupt the market (Battaglia & Thomas, 2017).

expire and shows the current prevalence of biosimilars throughout the world. Due to this novel nature of biosimilars, small molecule generic brand medicines have been on the market for much longer and thus are more prevalent than biosimilars. Therefore, comparing the success of biosimilars thus far to the established system of small molecule generics can help highlight the current shortcomings of the biosimilars system. By better understanding the shortcomings, the system can be improved in the future so that biosimilar products better increase accessibility to expensive therapeutics.

Production of small molecule generic medicines was streamlined in 1984 through a series of new laws, successfully reducing their cost by 80% or more (Sarpatwari et al., 2019, p. 93). In addition to greatly reducing costs, prescriptions for small molecule generic brand drugs grew significantly from only 19% in 1984 to 89% in 2019 (Sarpatwari et al., 2019, p. 93). Therefore, overall, it appears that the law changes enacted in 1984 and subsequent changes were successful in lowering costs and increasing accessibility of small molecule drugs. As stated in the introduction, despite the success of small molecule generics, biosimilars have not been as successful in penetrating the market since their introduction in the US in 2015 (Sarpatwari et al., 2019). For example, as of 2018, approved biosimilars reduced costs only by 17% to 57%, which is significantly less than the 80% reduction achieved by small molecule generics (Sarpatwari et al., 2019, p. 93). This highlights the need for the biosimilar system to be improved in order to achieve higher cost reductions.

The lack of success of biosimilars thus far can be attributed to many factors including technical, cultural, and organizational concerns summarized in Figure 2. Technically, biosimilar products have complex structures and are therefore more difficult to produce than small molecule drugs. Therefore, biosimilar products have stricter regulations and tighter quality controls, which

raises cost (Weinberg et al., 2005). Culturally, there is a misunderstanding of the safety and efficacy of these products (Jacobs et al., 2016). For example, a majority of patients would not be comfortable switching to biosimilar medications as they view them as less safe and effective as seen in Figure 2. Organizations thus far have failed to address the education gap about the safety and efficacy of biosimilars. Furthermore, companies have found ways to prolong their product patent life, thus postponing the introduction of competition and giving rise to many ethical questions regarding the current patent system (Raj et al., 2015).

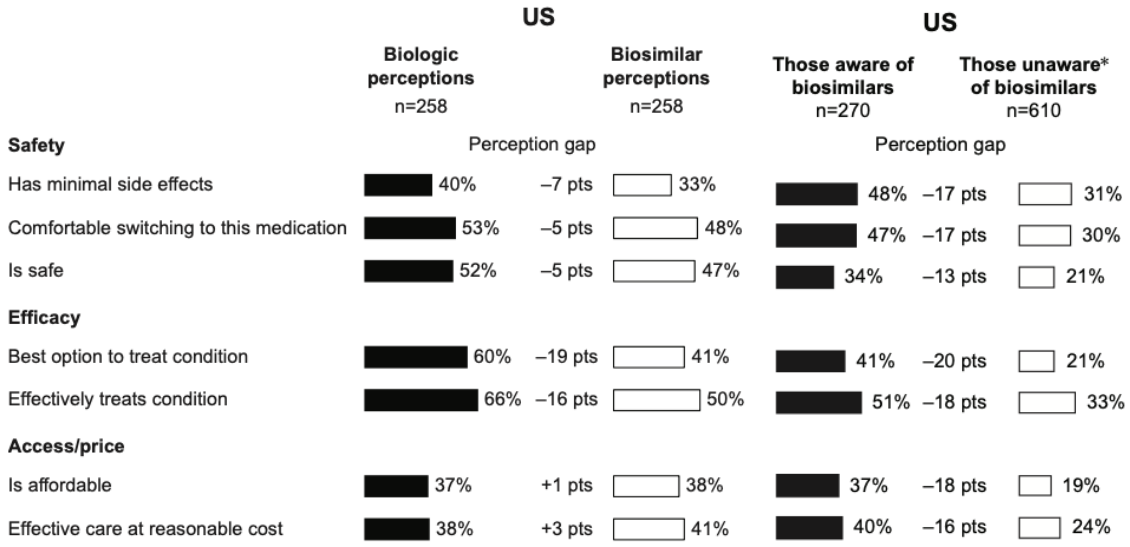

Figure 2. Gaps in Perception about Biosimilars. Patients perceive biosimilars as less effective and safe than biologics. This problem worsens for patients who are less aware (Jacobs et al., 2016, pp. 941-942).

If awareness and education of biosimilars do not improve, a few large companies will continue to dominate the industry, resulting in expensive drugs with low accessibility (Jacobs et al., 2016). Not only will this limit access to lifesaving medicine, but it will further contribute to the wealth gap in the US and can lead to patient dissatisfaction as it has been found that patients want to be fully informed and aware of their healthcare options (Kaser et al., 2010). Therefore, the STS research portion of this project will focus on analyzing the current sociotechnical system of mAb and biosimilar production using small molecule generics as a model. As stated earlier, by

studying small molecule generics, the many shortcomings of the biosimilar system can be better identified. To do this, actor-network theory will be utilized in order to identify the actors that are in tension and preventing the success of biosimilar products. Understanding the shortcomings of this system will help identify the most important factors preventing the success of biosimilars so that they can be addressed.

Conclusion

My capstone team will create a design including both process steps and equipment for the production of a Humira biosimilar. We are aiming to design our process to be able to support 40% of the current Humira market and hope sell our product for 40% of the current price. On the other hand, the STS research will provide an improved understanding of the shortcomings of the current sociotechnical system of biosimilar production. The goal of this research is to generate ways to improve the current perception gap by using the success of small molecule generic drugs as a model. If successful and appropriately implemented, this project could have the potential to provide a framework for designing biosimilar plants in the future as patents continue to expire. Additionally, it could increase awareness and trust of biosimilars and thus increase access to mAb therapeutics.

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