Production of a Biosimilar for Humira®: Cutting the Price on the Highest Grossing Drug

The Use of the Word "Stealing" with Respect to Intellectual Property

A Thesis Prospectus
In STS 4500
Presented to
The Faculty of the
School of Engineering and Applied Science
University of Virginia
In Partial Fulfillment of the Requirements for the Degree
Bachelor of Science in Chemical Engineering

By
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November 1, 2021

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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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Overall Introduction

Monoclonal antibodies (mAbs) are therapeutics created by cloning antibodies, which are naturally formed in the body in response to diseases. Injected intravenously, mAbs bind to disease-causing cells or viruses, making them promising therapies for novel and complex health issues. Adalimumab (Humira®) is a monoclonal antibody designed to treat rheumatoid and psoriatic arthritis. Arthritis is an inflammatory disease that leads to joint pains and has been described in a range of feelings from "like licking a 9-volt battery" to "jumping off the top of a jungle gym and landing on concrete" (Andersen, 2019, para. 7, para. 12). Through a system of complex patents, Humira® is able to be sold as the highest grossing drug with $20.4 billion in 2020 sales as shown in Figure 1 (Mikulic, 2021, n.p.). It is also quoted to cost some patients $72,000 per year (Rowland, 2020, para. 7). These margins are disproportionate to the 4.2 million prescriptions Humira® had in 2019, making it the 152nd most prescribed drug (ClinCalc, 2021, n.p.). In America, 7% of households cannot afford at least one prescription drug, and 10% have skipped medication (Picchi, 2021, para. 4). AbbVie is the company that holds the patent on Humira® and has reached settlements with nine other companies to allow for the production of adalimumab in 2023. Based off of previous drops in prices of drugs after the release of generics in the European Union, it is expected that an adalimumab biosimilar will lower the cost of Humira® to a more affordable price (Blackstone & Joseph, 2013, p. 471). The goal of our capstone project will be to develop the manufacturing process design for the production of adalimumab in order to lower the current cost of treatment. The STS research will focus on how the word "steal" has been used with respect to intellectual property and how to better frame the drug patent application process.

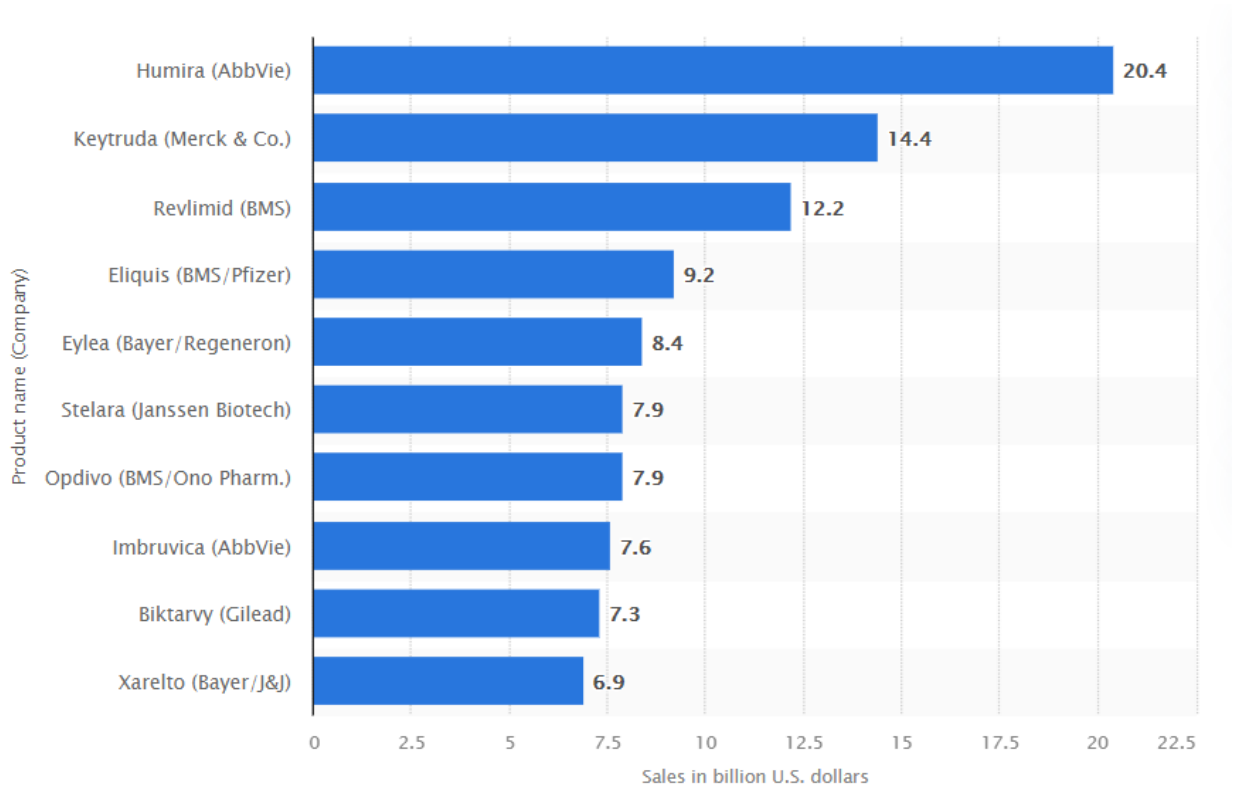

Figure 1: Sales of the highest grossing drugs in 2020. Humira® has the most sales of any drug by a large margin, with over 33% more sales than the next highest selling drug (Mikulic, 2021, n.p.).

Technical Prospectus - Production of an Adalimumab Biosimilar

Adalimumab (Humira®) is a monoclonal antibody (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, p. 7). 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, p. 1). 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, n.p.; Mikulic, 2021, n.p.; Rowland, 2020, para. 7).

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, p. 938). 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, para. 5). 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, p. 29-30). 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, p. 481-484). 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, p. 36). 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, p. 490-492). 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.

STS Topic: The Context of "Stealing" Intellectual Property

Beyond developing the technical design plans for a new drug, filing for patents is a crucial part of the drug development process. A patent is a license given out by the government that protects the intellectual property of the inventor, whether that be a product or process. The "protection" offered is the exclusive rights to processing and production for a limited time. In return for obtaining a patent, the inventor must publicly disclose and document all information on the intellectual

property. In order to obtain a patent, the inventor must demonstrate that: the technology achieves its designed purpose, it separates itself from currently available technology, and it is not an obvious addition to another patent. Patents can be bought, and they can also be rented in the form of royalties (Pistilli, 2021, para. 1-4).

In the drug and pharmaceutical industry, patents typically have 20 years of protection before expiration. However, if a new distinct function is added to a previously patented drug, a secondary patent may be granted, which also offers up to 20 years of protection. Complex drugs such as monoclonal antibodies may have more than 100 secondary patents placed on them. Monoclonal antibodies will typically have both the process and product protected under the patent because their complicated structure makes it difficult to analyze whether products are identical (Pistilli, 2021, para. 5).

There are some ethical concerns that have risen over the topic of patenting drugs. The "protection" offered in the form of exclusive rights creates a monopoly which can raise the price to be 200% or 300% more than what they would be with competition, limiting the availability of drugs to people with less income and developing nations. Acquiring patents also induce many legal fees, which patients are forced to cover when they purchase the needed drug. Much of the funding for research and development is also provided in the form of grants, so is it fair that pharmaceutical companies may reap the profits when not all of their money is at stake. Finally, the profitability from patents encourages development of drugs that are more profitable, yet not necessarily drugs that are providing a lifesaving impact (Sterckx, 2005, p. 82-92).

There are many legitimate reasons the patent system exists, but one of the most common arguments is that the research and development phase of creating a drug is so high cost and high risk that it would not be fair for a company who did not contribute to this research should be able

to reap the rewards from production. Sources will claim that this is “stealing” intellectual property (Stephen, 2021, para. 1; Sterckx, 2005, p. 85). Traditionally, “stealing” refers to a physical item that was in the possession of the owner and is now in the possession of the thief. In this scenario, both the owner and the thief cannot be in possession of the physical item at the same time. The idea of “stealing” intellectual property is more complex as it cannot be physically exchanged, and both the owner and the thief have the opportunity to be in possession of the intellectual property at the same time. The deliverable of the STS research will be a paper examining the history of this term “stealing” with regards to patents and intellectual property and research ways to frame the “stealing” of intellectual property.

Overall Conclusion

Our technical deliverable will be a design for a process to produce an Adalimumab biosimilar, including materials, equipment, energy requirements, process conditions, safety, and quality analysis. The STS deliverable will be a paper investigating the use of the word “stealing” with regards to intellectual property, the history of its usage as a defense for more stringent patents, and how it can be better framed with respect to intellectual property. If the design for an Adalimumab biosimilar is successfully executed, the design process could be sold to another pharmaceutical company which would introduce more biosimilars to the market, break the monopoly on adalimumab, and lower the price patients currently pay to get treated for autoinflammatory diseases. Americans and citizens of the world should not be forced to pay an unreasonable price for life-improving medicine, especially when the technology to produce it cheaply is readily available.

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