Production of Adalimumab: A Humira® Biosimilar

Inaccessibility and Unaffordability of Prescription Drugs in the United States: Assessment of Contributing Factors and Methods for Improvement

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
William Gawryłowicz

November 1, 2021

Technical Team Members: Taylor Bloom, Susan Furlough, Brandon Hudson, John Kilduff

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.

ADVISORS

Hannah Rogers, Department of Engineering and Society

Eric Anderson, Department of Chemical Engineering

Introduction

The adaptive immune system of an organism identifies and eliminates pathogens by inducing the production of antibodies that bind to antigens on their surfaces. Once bound, the antibodies may serve as tags for further attack or inhibit the pathogen directly. In the biopharmaceutical industry, researchers optimize, isolate, and replicate the production of antigen-specific antibodies through a single parent cell to produce monoclonal antibodies (mAbs). The primary application of mAbs is for therapeutic uses, where they can be injected intravenously and bind to specific antigens to inhibit the function of infectious agents in the body. These therapies treat a wide-variety of conditions, including but not limited to cancers, autoimmune diseases, inflammatory diseases, and viral infections.

Despite the improvement these products have in people's lives, they also happen to be very expensive treatments. In the United States, pharmaceutical industry giants often obtain market exclusivity such that they may maintain prescription drug prices—especially those for name-brand drugs—at more than 250% higher than other countries (Doheny, 2021). Both the market exclusivity and trend in high drug pricing present the broader socio-technical issue addressed in this work, which aims to explore different ways in which mAb therapies and other prescription drugs can be made more affordable and accessible to the general public in the United States. In the technical project, my team proposes a design for commercial-scale production of a mAb that competes with the highest-grossing drug on the market. In the STS research, I explore the underlying causes of high drug pricing in the United States and detail the avenues through which effective change in policy and practice can increase accessibility to life-saving drugs for those who need it most.

Technical Design Project

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). 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.

STS Research Project

Pharmaceutical products improve the quality of life for people all over the world, but many still experience significant barriers in accessibility for much needed drugs. This is especially true for mAbs, where a patient can expect to pay an annual average of $96,731 for their treatment plans (San-Juan-Rodriguez et. al, 2020). In the United States, this greatly exceeds the median household income of $67,521, demonstrating the general unaffordability of mAb therapies (U.S. Census Bureau, 2021). It has been estimated that as many as 10% to 20% of patients may neglect to use a treatment due to the associated financial burden (Kantarjian, 2014). 60% of prescriptions for medications that are over $500 go unfilled ("Medicine Spending," 2020). These metrics are few of many that must be improved upon, as medications are intended to improve quality of life, not to leave patients in financial ruin.

Before attempting to solve the presented issues, one must understand how they have come to be and how they exist today. The modern pharmaceutical industry began with the discovery and commercialization of substances like penicillin and insulin, two keystone products on which the entire world heavily relies (Malerba & Orsenigo, 2015). The industry is also responsible for the research and development of vaccines that have essentially eradicated once epidemic diseases. In the present, we have seen an increasing level of pharmaceuticalization, as defined by Abraham (2010). This concept involves the shaping of perspectives on human experiences in the context of pharmaceutical products, framing problems in specific ways that indicate the necessity for drug treatments. The industry accomplishes this through extensive marketing schemes and public

relations campaigns, further nurturing societal dependence on its products. This also creates a requirement for companies to maintain high drug prices, since as much as 45% of company spending may be allocated to marketing (Kantarjian, 2014). Ultimately, I will use the history and present status of the industry's public relations to discuss how the United States supports its problematic system of unaffordability and inaccessibility to prescription drugs.

In addition to direct consumer relations, I will also describe how the pharmaceutical industry's manipulation of the legal system enables many companies to establish and maintain high drug prices. Many pharmaceutical companies protect their products by applying for patents on different aspects of the drug and its production processes that provide approximately 15 years of market exclusivity. In the case of Humira®, for example, AbbVie has obtained a complex series of secondary patents to nearly double to original duration (Moorkens et. al, 2021). This is the case for a wide variety of drug products on the market, and without competition from other pharmaceutical companies, healthcare providers have no other option than to pay high prices and subsequently charge patients high premiums. My discussion here will also include analysis of the ethicality legality of various litigation settlements with reference to antitrust law (Ponsoldt, & Ehrenclou, 2006). All of the aforementioned political and economic factors will provide a sufficient depiction of the pharmaceutical industry in the United States.

My STS research paper will first discuss the root causes behind the drug-pricing problems in the United States by exploring a variety of economic, political, and social factors, drawing especially on the work by Abraham on pharmaceuticalization (2010). I will then propose several routes through which society can achieve effective change and promote accessibility to mAbs therapeutics and prescription drugs in general. Much of my discussion will be formulated based on the concept of a "corporate duty to rescue" (Wolitz, 2019). This idea suggests that the

biopharmaceutical industry has a moral responsibility to address product accessibility on its own. Many possible courses of action that come from this will be in direct relation to principles discussed above as part of fiscal and legal analysis, but I will also propose ways in which the general public can take direct action to create effective change.

Conclusion

My research portfolio will address many ways in which the issue of unaffordability and inaccessibility to life-saving medications can be improved. As a specific example to a general task that can be done for many drug therapies, my team's technical project will propose a design for a commercial-scale production plant of a competitive biosimilar to Humira®, the most profitable drug on the market. In my STS research, I will propose steps that can be taken in regards to public policy and social activism that can, if not completely solve the issue through public policy mandates, apply pressure to the pharmaceutical industry to take it upon themselves to increase access to those who need it most.

References

1. Abraham, J. (2010). Pharmaceuticalization of Society in Context: Theoretical, Empirical and Health Dimensions. *Sociology*, *44*(4), 603–622. https://doi.org/10.1177/0038038510369368

2. Azevedo, V., Dela Coletta Troiano Araujo, L., Bassalobre Galli, N., Kleinfelder, A., Marostica Catolino, N., & Martins Urbano, P. C.. (2016). Adalimumab: a review of the reference product and biosimilars. *Biosimilars*, *Volume 6*, 29–44. https://doi.org/10.2147/bs.s98177

3. ClinCalc. (2021, August). *The Top 300 Drugs of 2019*. https://clincalc.com/DrugStats/Top300Drugs.aspx

4. Doheny, K. (n.d.). *U.S. Drug Prices Much Higher Than in Other Nations*. WebMD. Retrieved October 31, 2021, from https://www.webmd.com/health-insurance/news/20210129/us-drug-prices-much-higher-than-in-other-nations

5. Jacobs, I., Singh, E., Sewell, L., Al-Sabbagh, A., & Shane, L. G. (2016). Patient attitudes and understanding about biosimilars: An international cross-sectional survey. *Patient Preference and Adherence*, 937. https://doi.org/10.2147/PPA.S104891

6. Kantarjian, H., Steensma, D., Rius Sanjuan, J., Elshaug, A., & Light, D. (2014). High Cancer Drug Prices in the United States: Reasons and Proposed Solutions. *Journal of Oncology Practice*, *10*(4), e208–e211. https://doi.org/10.1200/JOP.2013.001351

7. Lee, J. J., Yang, J., Lee, C., Moon, Y., Ahn, S., & Yang, J. (2019). Demonstration of functional similarity of a biosimilar adalimumab SB5 to Humira®. *Biologicals*, *58*, 7–15. https://doi.org/10.1016/j.biologicals.2018.12.002

8. Liu, H. F., Ma, J., Winter, C., & Bayer, R.. (2010). Recovery and purification process development for monoclonal antibody production. *Mabs*, *2*(5), 480–499. https://doi.org/10.4161/mabs.2.5.12645

9. Lu, R.-M., Hwang, Y.-C., Liu, I.-J., Lee, C.-C., Tsai, H.-Z., Li, H.-J., & Wu, H.-C. (2020). Development of therapeutic antibodies for the treatment of diseases. *Journal of Biomedical Science*, *27*(1), 1. https://doi.org/10.1186/s12929-019-0592-z

10. López-Meza, J., Araíz-Hernández, D., Carrillo-Cocom, L. M., López-Pacheco, F., Rocha-Pizaña, M. del R., & Alvarez, M. M. (2016). Using simple models to describe the kinetics of growth, glucose consumption, and monoclonal antibody formation in naive and infliximab producer CHO cells. *Cytotechnology*, *68*(4), 1287–1300. https://doi.org/10.1007/s10616-015-9889-2

11. Malerba, F., & Orsenigo, L. (2015). The evolution of the pharmaceutical industry. *Business History*, *57*(5), 664–687. https://doi.org/10.1080/00076791.2014.975119

12. *Medicine Spending and Affordability in the U.S.* (2020). Retrieved December 5, 2021, from https://www.iqvia.com/insights/the-iqvia-institute/reports/medicine-spending-and-affordability-in-the-us

13. Mikulic, M. (2021, March 26). *Top pharma products by global sales*. Statista. https://www.statista.com/statistics/258022/top-10-pharmaceutical-products-by-global-sales-2011/

14. Moorkens, E., Godman, B., Huys, I., Hoxha, I., Malaj, A., Keuerleber, S., Stockinger, S., Mörtenhuber, S., Dimitrova, M., Tachkov, K., Vončina, L., Palčevski, V. V., Achniotou, G., Slabý, J., Popelková, L., Kohoutová, K., Bartels, D., Laius, O., Martikainen, J. E., … Vulto, A. G. (2021). The Expiry of Humira® Market Exclusivity and the Entry of Adalimumab

Biosimilars in Europe: An Overview of Pricing and National Policy Measures. *Frontiers in Pharmacology*, *11*, 1993. https://doi.org/10.3389/fphar.2020.591134

15. Norman, P. (2017). Humira®: Recent developments. *Pharmaceutical Patent Analyst*, *6*(3), 89–90. https://doi.org/10.4155/ppa-2017-0012

16. Ponsoldt, J. F., & Ehrenclou, W. H. (2006). The Antitrust Legality of Pharmaceutical Patent Litigation Settlements. *University of Illinois Journal of Law, Technology & Policy*, *2006*(1), 37–62.

17. Rowland, C. (2020, January 8). Why price of Humira keeps rising despite FDA approval of generic competition. *Washington Post*. https://www.washingtonpost.com/business/economy/why-humiras-price-keeps-rising-despite-fda-approval-of-generic-competition/2020/01/07/549ed0ce-2e3a-11ea-bcb3-ac6482c4a92f_story.html

18. San-Juan-Rodriguez, A., Parekh, N., Newman, T. V., & Hernandez, I. (2020). Pricing of Monoclonal Antibodies in the United States. *Global Journal on Quality and Safety in Healthcare*, *1*(1), 4–5. https://doi.org/10.4103/JQSH.JQSH_1_18

19. U.S. Census Bureau. (2021, September 14). *Income and Poverty in the United States: 2020* (Report No. P60-273). Retrieved October 31, 2021, from https://www.census.gov/library/publications/2021/demo/p60-273.html

20. Vaidya, M. (2021, February 19). *AbbVie's successful hard-ball with Humira legal strategy unlikely to spawn similar efforts; potential appeals outcome unclear*. Pharmaceutical Technology. https://www.pharmaceutical-technology.com/comment/abbvies-successful-hard-ball-with-humira/

21. Wolitz, R. E. (2019). A Corporate Duty to Rescue: Biopharmaceutical Companies and Access to Medications. *Indiana Law Journal*, *94*(3), 1162–1221.

22. Wouters, O. J. (2020). Lobbying Expenditures and Campaign Contributions by the Pharmaceutical and Health Product Industry in the United States, 1999-2018. *JAMA Internal Medicine*, *180*(5), 1–10. https://doi.org/10.1001/jamainternmed.2020.0146