Design of a Pembrolizumab Manufacturing Plant Utilizing a Perfusion Bioreactor and Precipitation Chromatography
Technological Momentum of NovoLog Insulin Pricing in the United States

A Technical Prospectus submitted to the Department of Chemical Engineering

Presented to the Faculty of the School of Engineering and Applied Science
University of Virginia • Charlottesville, Virginia

In Partial Fulfillment of the Requirements for the Degree
Bachelor of Science, School of Engineering

By
Ethan Kutner

October 27, 2022

Technical Project Team Members
Rebecca Bailey
Christina Harris
Emma Ritchie
Chloe Seng

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.

Signature _____ Date_____

Approved_____ Date_____
Eric W. Anderson, Department of Chemical Engineering

Introduction

In recent years the inaccessibility of pharmaceuticals due to price and demand have resulted in users forgoing treatment or attempting to extend doses to reduce cost (Beran, 2018; Kantarjian, 2014). Pharmaceuticals treat a variety of illnesses and conditions that are otherwise immediately life threatening such as cancers and diabetes. The cause of these pricing issues is frequently under debate as to whether manufacturers, insurance companies, high demand, monopolies, or intellectual property preventing generics are the cause of these pricing deficiencies in the United States.

To address the growing demand of pharmaceuticals and increase supply to decrease price and increase accessibility, this project seeks to design a more efficient Keytruda manufacturing facility. The facility will function as a contracting facility for Merck & Co. to meet the rising demand for this drug which has expected user growth from 1 million to 2 million users by 2024 (Liu, 2022). The technical improvements to this facility include the use of process intensification steps: semi-continuous perfusion bioreactor and precipitation chromatography. The purpose of these improvements is to reduce the use of expensive Chinese Hamster Ovary (CHO) cells from the master cell bank and to increase the efficiency of purification steps to increase yields.

While technical factors are the primary avenue to decrease costs, understanding the non-technical factors that contribute to the pricing issues with pharmaceuticals is also important to increasing accessibility and affordability. Specifically, the evolution of insulin production systems as their shaping by society over the past century into mature systems by governing bodies, lobbying, research and development, intellectual property, and innovations in the industry have contributed to the high costs associated with many pharmaceutical products.

To effectively reduce the cost of pharmaceuticals, both the technical and social aspects of the problem must be addressed. If only one aspect of the project is attended to, pricing may be reduced in the short-term, but over time significant changes to the system or environment that controls Keytruda pricing could cause significant price changes negating the gains achieved by the improved manufacturing facility. Using chemical processes and modelling my team will address this issue by developing the design of a Keytruda manufacturing facility that will meet growing demand. I will apply the theory of Technological Momentum to the pricing issues related to NovoLog analog insulin produced by Novo Nordisk to analyze the development of pricing issues and the societal influences that have resulted in the unaffordability of NovoLog insulin in the United States.

Technical Project Proposal

Antibodies help the body fight against infections and diseases; monoclonal antibodies are single antibody clones that can be artificially replicated for large scale production and treatment for specific diseases (Carter, 2021; Daintith, 2010). They can be used for cancer treatment by specifically targeting cancer cells to destroy them, block cells from multiplying, or to deliver other treatments, such as chemotherapy (Cleveland Clinic, 2022). As of 2021, cancer is one of the leading causes of death in the United States (CDC, 2021). Pembrolizumab (Keytruda), is a monoclonal antibody manufactured by Merck & Co as a treatment for advanced melanoma, lung, bladder, stomach and colon cancers (Merck & Co., 2019). It averaged a 38% reduction in risk of death due to cancer versus chemotherapy, and it drew 17.2 billion dollars in sales in 2021 alone, the fourth highest sales of all pharmaceuticals on the market (Dunleavy, 2022; Merck, 2020).

While pembrolizumab offers oncological benefits over chemotherapy, such as increased efficacy and reduced negative side effects, mAbs including pembrolizumab are insufficiently accessible in low to middle income countries (LMICs) due to differences in global regulations, a lack of government and manufacturer awareness towards registering mAbs, and a lack of healthcare infrastructure required for mAb production (Reck et al., 2016; Wellcome, 2020). The high cost of mAbs leads to these barriers in both LMICs and underprivileged regions of high-income countries (Wellcome, 2020).

In June 2020, the FDA approved pembrolizumab as the first-line treatment for people with two different types of colorectal cancer. This is the first immunotherapy approved as a first-line treatment in the US, which would be administered to people without chemotherapy. With the pembrolizumab patent due to expire in 2028, it is an opportune time to develop a cheaper alternative process to the current one (Hagen, 2021).

We plan to design a more efficient pembrolizumab manufacturing plant. Operating with perfusion or continuous bioreactors instead of batch bioreactors allows for increased product quality and productivity (Yang et al., 2019). Currently, the most expensive part of the process is the chromatography used to separate and purify the final protein product; many chromatography methods have been explored to optimize chromatography cost, including continuous antibody precipitation (Burgstaller et al., 2019). We will utilize Chinese Hamster Ovary (CHO) cells to express pembrolizumab in a perfusion reactor and precipitation chromatography supplemented by other continuous filtration methods for product purification.

The general mAb production process can be described by several stages of processing: fermentation, purification, formulation, and fill/finish. Fermentation uses bioreactors to grow

CHO cells to produce the active ingredient. Purification processes use filtration methods such as chromatography columns and membrane-based separations to isolate the active ingredient from impurities after fermentation. Formulation adds excipients to aid in transport, patient delivery, and stability of the drug substance. Following filtration, to ensure patient safety and drug purity, the drug product is filled into a vial or syringe and packaged as a final product. We will design these elements and the utilities and disposal systems needed for a pharmaceutical manufacturing site (Kelley, 2009).

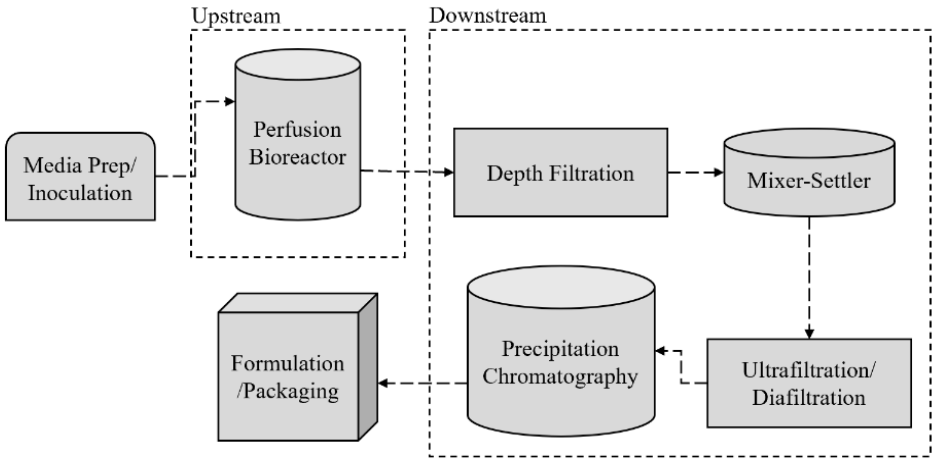

Figure 1. General Process Flow Diagram for Continuous mAb production (Kornecki et al., 2019).

We will design the facility to produce 1400 kg of pembrolizumab annually to provide approximately 7 million doses, accounting for 20% of the 2024 projected demand, as users of pembrolizumab are projected to double (Liu, 2022). This growth in demand is driven by pembrolizumab's continued market lead in treating lung, gastric, and kidney cancers with the potential for use in early-stage treatment around surgery (Dunleavy, 2022).

Matlab and Aspen Plus V11 will be used as a process simulation tool to design our equipment and to obtain appropriate material and energy balances. This design process will take place over two semesters in a team of five people as a part of CHE 4474 and CHE 4476. We plan

to work fluidly as a team on all parts: upstream, downstream, formulation, WFI production, and packaging. We will meet weekly to analyze progress.

STS Project Proposal

In the United States, the costs of rapid-acting analog insulins such as NovoLog, produced by Novo Nordisk, have long been compared to that of other countries due to the financial burden it often presents thus reducing access and affordability (Beran, 2018). In 2018 the price for such a product averaged $111.39 in the United States vs. $8.19 outside of the United States (McGrail, 2020). The need for life saving insulin is a life and death matter with some financially stressed users rationing doses to cut costs which poses great risk to ketoacidosis, the condition insulin is used to prevent.

Many factors are considered to contribute to the pricing issues related to NovoLog such as monopolies by the three manufacturing companies that produce insulin including Novo Nordisk, the maker of NovoLog. Other factors include Novo Nordisk's development of analog insulins such as NovoLog differing from the original human and animal insulins, research and development costs, lack of price controls, and the role of intellectual property (Beran, 2018). The specific actors such as the government agencies, manufacturing and insurance companies, and other groups have previously been analyzed for their contributions to these pricing issues (Rajkumar, 2020). The past analyses of this issue do not account for the maturity of these complex insulin manufacturing systems that have been developing since the early 20th century following the discovery of insulin in 1921 and founding of Novo Nordisk in 1923 (*Novo Nordisk History*, n.d.). Novo Nordisk has gone through significant changes from solely producing animal insulins from the pancreases of dogs and cattle, to the first human insulin produced from E. Coli, to long lasting insulins, and analog insulins such as NovoLog (Quianzon, 2012). Not only has

insulin itself changed, but new delivery systems such as auto injector pens have been implemented, complex regulatory systems have developed, the number and diversity of users has vastly changed, and the global nature of business have all shaped the insulin manufacturing industry. If only the modern factors are taken into account to explain the issues of NovoLog's pricing, then the societal influences and early roles that insulin initially played during its evolution into a mature system will be ignored.

I will specifically research the pricing issues related to NovoLog, an analog insulin produced by Novo Nordisk, and how the development from solely animal insulin production in the 1920s to the modern system has resulted in these pricing challenges. Industrial insulin manufacturing has developed for nearly a century and the modern system is not reflective of the original systems. Novo Nordisk in 2021 had 140,800 million kroner in net sales, with marketed products in 168 countries and 48,478 employees worldwide (Novo Nordisk, 2021). The original patent for insulin from the University of Toronto sold for $1 and in 1982 a vial of insulin sold for $14 per vial, today one vial of NovoLog could be sold in excess of $300 in the United States (Hirsch, 2016).

The invention of insulin came from noble pursuits, however developments in technology, delivery systems, research and development, users, and lobbying have vastly changed the system that determines pricing. Novo Nordisk and the socio-technical system that determine the pricing of its products have gained momentum; this has resulted in a system that is far more rigid resulting in lofty prices resistant to change. Technological momentum seeks to describe a technology as a socio-technical system that has momentum. This momentum is characterized by a system acquiring increased diversity, complexity, scale, bureaucracy, social integration, skills and knowledge to maintain, special-purpose machines, and processes, and

large physical infrastructure. As a technology gains momentum people and groups become more invested in the system's maintenance and perpetuation. Also, the system begins to exert increasing influence on the society that developed it. These characteristics give the system durability, inertia, rigidity, and a resistance to change that can only be overcome by major events in the system's environment. I will use Hughes' "Networks of power: electrification in Western society, 1880-1930" as a model for technological momentum, the Novo Nordisk History, and "High-growth firms in changing competitive environments: the US pharmaceutical industry" (1963 to 2002) to examine how the insulin manufacturing system has gained momentum (Hughes, 2005; *Novo Nordisk History*, n.d.; Mazzucato, 2015).

Conclusion

The deliverable for the technical problem discussed in this paper will be the complete design of a Keytruda manufacturing facility containing upstream, downstream, formulation, fill/finish capabilities and the necessary utilities, disposal systems, and WFI production necessary to produce 1400 kilograms of mAb product annually. This facility will provide Keytruda in quantities to capture 20% of the expected demand by 2024. The STS research paper will seek to analyze the pricing issues related to NovoLog, an analog insulin product produced by Novo Nordisk, in the United States. This will be completed by using Technological Momentum concepts to explain the evolution of the insulin manufacturing and pricing systems and how society and influences shaped early production, but the momentum acquired by the insulin manufacturing system has made pricing rigid. The results of the STS research paper will inform the technical project through determination of how to prevent manufacturing systems from developing momentum that results in inaffordability to the intended users. This will alter

design considerations for the Keytruda manufacturing facility to ensure the prices are reduced in the near future and after the maturity of the system. The combined results of this report will serve to address the inaccessibility and unaffordability of pharmaceuticals in the United States by designing a facility to meet growing demand and explain how the development of the manufacturing systems has led to stiff and unaffordable pricing.

References

Beran, D., Hirsch, I. B., & Yudkin, J. S. (2018). Why Are We Failing to Address the Issue of Access to Insulin? A National and Global Perspective. *Diabetes Care*, *41*(6), 1125–1131. https://doi.org/10.2337/dc17-2123

Burgstaller, D., Jungbauer, A., & Satzer, P. (2018). Continuous integrated antibody precipitation with two-stage tangential flow microfiltration enables constant mass flow. *Biotechnology and Bioengineering*, *116*(5), 1053-1065. https://doi.org/10.1002/bit.26922

Carter, D. (2021, November 10). T cells, B cells and the immune system. MD Anderson Cancer Center. https://www.mdanderson.org/cancerwise/t-cells--b-cells-and-the-immun e-system.h00-159465579.html#:~:text=B%20lymphocytes%2C%20also%20called%20B

CDC. (2021, December 21). Products - Data Briefs - Number 427 - December 2021. www.cdc.gov. https://www.cdc.gov/nchs/products/databriefs/db427.html

Cleveland Clinic. (2022, April 18). Monoclonal Antibody Therapy For Cancer: What It Is, Uses & Treatment. Cleveland Clinic. https://my.clevelandclinic.org/health/treatments/22774-monoclonal-antibody-therapy

Daintith, E. & Martin, J.. (2010). *Dictionary of Science (6th Edition) - monoclonal antibody*. Oxford University Press. https://app.knovel.com/hotlink/pdf/id:kt007X8B04/ dictionary-science-6th/monoclonal-antibody

Dunleavy, K. (2022, May 31). *The top 20 drugs by worldwide sales in 2021*. Fierce Pharma. https://www.fiercepharma.com/special-reports/top-20-drugs-worldwide-sales-2021

Hagen, T. (2021, April 7). PlantForm will challenge Merck's dominance for pembrolizumab.

AJMC, The Center for Biosimilars. https://www.centerforbiosimilars.com/view/plantform-will-challenge-merck-s-dominance-for-pembrolizumab

Hirsch, I. B. (2016). Insulin in America: A Right or a Privilege? *Diabetes Spectrum, 29*(3), 130–132. https://doi.org/10.2337/diaspect.29.3.130

Hughes, T. P. (2005). *Networks of Power: Electrification in Western Society, 1880-1930*. ACLS History E-Book Project.

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

Kelley, B. (2009). Industrialization of mAb production technology The bioprocessing industry at a crossroads. *MAbs, 1*(5), 443-452. https://doi.org/10.4161%2Fmabs.1.5.9448

Kornecki M., Schmidt A., Lohmann L., Huter M., Mestmäcker F., Klepzig L., Mouellef M., Zobel-Roos S., & Strube J. (2019). Accelerating biomanufacturing by modeling of continuous bioprocessing—piloting case study of monoclonal antibody manufacturing. *Processes, 7*(8), 495. https://doi.org/10.3390/pr7080495

Liu, A. (2022, June 8). *With Keytruda leading the way, Merck tallies 80-plus potential oncology approvals by 2028*. Fierce Pharma. https://www.fiercepharma.com/pharma/keytruda-leading-way-merck-counts-over-80-possible-oncology-drug-approvals-2028

Mazzucato, M., & Parris, S. (2015). High-growth firms in changing competitive environments: The US pharmaceutical industry (1963 to 2002). *Small Business Economics*, *44*(1), 145–170. https://doi.org/10.1007/s11187-014-9583-3

Samantha McGrail. (2020, October 12). *Insulin Prices 8x Higher in the US Compared to Similar Nations*. PharmaNewsIntelligence. https://pharmanewsintel.com/news/insulin-prices-8x-higher-in-the-us-compared-to-similar-nations

Merck & Co. (2019). KEYTRUDA®. Keytruda. https://www.keytruda.com/how-does-keytruda-work/

Merck & Co. (2020, September 21). First-line treatment with Merck's Keytruda® (pembrolizumab) doubled five-year survival rate (31.9%) versus chemotherapy (16.3%) in certain patients with metastatic non-small cell lung cancer whose tumors express pd-l1 (tps ≥50%). https://www.merck.com/news/first-line-treatment-with-mercks-keytruda-pembrolizumab-doubled-five-year-survival-rate-31-9-versus-chemotherapy-16-3-in-certain-patients-with-metastatic-non-small-cell-lung-cance/

Merck & Co. (2022, September 11). Five-Year Data for Merck's KEYTRUDA® (pembrolizumab) Plus Chemotherapy Showed Sustained Survival Benefit Versus Chemotherapy Alone in Two Studies for Metastatic Non-Small Cell Lung Cancer (NSCLC). Merck. https://www.merck.com/news/five-year-data-for-mercks-keytruda-pembrolizumab-plus-chemotherapy-showed-sustained-survival-benefit-versus-chemotherapy-alone-in-two-studies-for-metastatic-non-small-cell-lung-cancer-nsclc/

Nadar, S., Shooter, G., Somasundaram, B., Shave, E., Baker, K., & Lua, L.H. L. (2021). Intensified downstream processing of monoclonal antibodies using membrane technology. Biotechnology Journal, 16(3), 1-11. https://doi.org/10.1002/biot.202000309

Novo Nordisk Corporation. (2021). Annual report 2021. https://www.novonordisk.com/content/dam/nncorp/global/en/investors/irmaterial/agm/2022/novo-nordisk-annual-report-2021.pdf

Novo Nordisk History. https://www.novonordisk.co.in/content/dam/Denmark/HQ/aboutus/documents/HistoryBook_UK.pdf.

Quianzon, C. C., & Cheikh, I. (2012). History of insulin. *Journal of Community Hospital Internal Medicine Perspectives*, *2*(2), 18701. https://doi.org/10.3402/jchimp.v2i2.18701

Rajkumar, S. V. (2020). The High Cost of Insulin in the United States: An Urgent Call to Action. *Mayo Clinic Proceedings*, *95*(1), 22–28. https://doi.org/10.1016/j.mayocp.2019.11.013

Reck, M., Rodríguez-Abreu, D., Robinson, A. G., Hui, R., Csőszi, T., Fülöp, A., Gottfried, M., Peled, N., Tafreshi, A., Cuffe, S., O'Brien, M., Rao, S., et al. (2016). Pembrolizumab versus chemotherapy for pd-l1–positive non–small-cell lung cancer. *The New England Journal of Medicine, 375,* 1823-1833. doi: 10.1056/NEJMoa1606774

Wellcome & Iavi. (2020, August 10). *Expanding access to monoclonal antibody-based products*. Wellcome.ac.uk & iavi.org. https://wellcome.org/reports/expanding-access-monoclonal-antibodies

Yang, O., Prabhu, S., & Ierapetritou, M. (2019). Comparison between Batch and Continuous Monoclonal Antibody Production and Economic Analysis. Industrial & Engineering Chemistry Research, 58(15), 5851–5863. https://doi.org/10.1021/acs.iecr.8b04717