Prospectus

Design of a Pembrolizumab Manufacturing Plant in Ireland Using Continuous Bioprocess Technology and Single-Use Bioreactors
(Technical Topic)

Historical Analysis of Insulin Pricing and the Implications for Low-Access States such as Kentucky
(STS Topic)

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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Introduction

Protein therapeutics encompass a large portion of pharmaceutical drugs, and yet they are relatively new in healthcare. Protein medications include recombinant proteins, vaccines, and monoclonal antibodies, and they primarily treat diseases in oncology, hematology, endocrinology, and diabetes (Leader et al., 2008). These medications began with the introduction of human insulin—the first recombinant protein therapeutic—in 1982, and new therapeutics have since developed at a rapid rate (Leader et al., 2008). Protein therapeutics cannot be synthetically produced and are therefore grown in cell cultures (Lagassé et al., 2017).

In recent years, monoclonal antibodies (mAbs) have comprised approximately 48% of medications approved by the U.S. Food and Drug Administration (FDA) (Lagassé et al., 2017). mAbs elicit an immune response to counteract a disease by flagging cancer cells, promoting malignant cell lysis, and preventing blood-vessel angiogenesis (Mayo Clinic Staff, 2019). The technical portion of this study will develop a manufacturing facility of Keytruda® or pembrolizumab, which is a form of mAb used to treat skin cancer, lung cancer, Hodgkin's lymphoma, and other forms of cancer. Many cancer cells use the PD-1 pathway to avoid detection by immunogenic T-cells. The PD-1 protein downregulates the immune system to prevent autoimmune diseases, but this can also prevent attacks on cancer-cells. Keytruda functions by blocking the PD-1 pathway to promote cell detection (Merck & Co., 2019). Keytruda was the 9th best-selling drug in 2018, and it is expected to become the second best-selling therapeutic by 2024 with projected sales of $12.7 billion (Lindsley, 2019). Therefore, this project will develop an additional manufacturing facility to accommodate the increased demand for mAb therapeutics, while decreasing the overall manufacturing price by using continuous bioprocess techniques and single-use bioreactors.

Although insulin is a less contemporary protein therapeutic, it is still regarded as one of the most revolutionary. The discovery of insulin in 1921 transformed the prognosis of diabetes—a disease that prevents the body from naturally controlling blood-glucose levels (Vecchio et al., 2018). Even after the discovery of insulin, the prevalence of diabetes has increased from 12.05 million in 2000 to 30.3 million in 2019 (CDC, 2019). Diabetic cases in the U.S. are projected to increase by 54% between 2015 and 2030 (Rowley et al., 2017). Additionally, diabetes costs the U.S. approximately $327 billion per year (Cefalu et al., 2018). While this disease affects many people in the U.S., low-income states in the southeast U.S. exhibit significantly higher rates of diabetes (Barker et al., 2011). Therefore, I will analyze the historical changes in insulin pricing between 1980 to 2019 with the corresponding growth of different stakeholders. Furthermore, I will examine the implications of price increases for high-risk states such as Kentucky.

Technical Topic: Design of a Pembrolizumab Manufacturing Plant

Cancer is the second leading cause of death in the U.S., with the number of cancer cases expected to rise from 14.1 million in 2012 to 23.6 million in 2030 (National Cancer Institute, 2015). Associated with this increase in disease rates is a shift in focus towards the pharmaceutical industry in hopes of addressing these concerns. Antibody-based drugs, specifically, have risen as the fastest growing class of protein therapeutics due to their increased efficacy, decreased immunogenicity, improved deliverability, and decreased potential to adversely affect normal biological processes (Awwad & Angkawinitwong, 2018).

The focus of this technical solution is Keytruda or pembrolizumab, a checkpoint inhibitor monoclonal antibody (mAb) manufactured by Merck. Keytruda works by blocking the PD-1 pathway. By doing this, the immunogenic T-cells can locate cancer cells and induce a natural immune response (Merck & Co., 2019). This novel mechanism of action, coupled with low side

effects when compared to chemotherapy, makes Keytruda an extremely promising drug in the fight against cancer. Due to increasing global demand, Merck announced that it will build a $300 million Keytruda manufacturing facility in Dublin, Ireland. The facility will begin manufacturing operations in 2022 (The Irish Times, 2018).

The current process of mAb production includes culturing the recombinant mAb protein in a large steel batch reactor. This is followed by several unit operations to separate the desired product from the fermentation media. These batch steel reactors are large, expensive to operate and have low product yields. They also require extensive cleaning protocols involving potent and abrasive chemicals, which are necessary to appropriately sterilize the reactor. A lack of further manipulation of process design can contribute to high production costs. This can decrease the ability of a single facility to produce different drug products and cause additional conflicts with environmental regulations due to the potency of the reactor cleaning chemicals.

This study will serve as a design for the new Merck Keytruda production facility with perfusion reactors and single-use bags. Incorporating single-use reactor bags will decrease the need for extensive cleaning protocols, save time, reduce employment costs, improve compliance with environmental regulations, improve the modularity of the manufacturing facility, and help ensure product purity between batches. Using a perfusion reactor will allow continuous production of Keytruda, rather than the production of the drug in batches. Perfusion bioreactors culture cells over longer periods by continuously feeding and removing media while keeping cells in culture (Bielser, Wolf, Souquet, Broly, & Morbidelli, 2018). This continuous production will increase product yields and subsequently decrease production costs. Perfusion reactors also traditionally require fewer operators, further decreasing production costs.

Therefore, this study proposes the design of a Keytruda manufacturing plant that uses the aforementioned manufacturing strategies. This process will start with the fermentation of Chinese hamster ovary (CHO) cells with incorporated recombinant DNA for Keytruda. These cells will be grown in serum-free CHO media in a stirred 10,000-liter perfusion reactor. These cells will be continuously fed into downstream purification unit operations of protein A chromatography, anion exchange chromatography, cation exchange chromatography, and diafiltration (see *Figure 1*). A water-for-injection purification system will also be designed for the facility in order to provide sterile water for each production step.

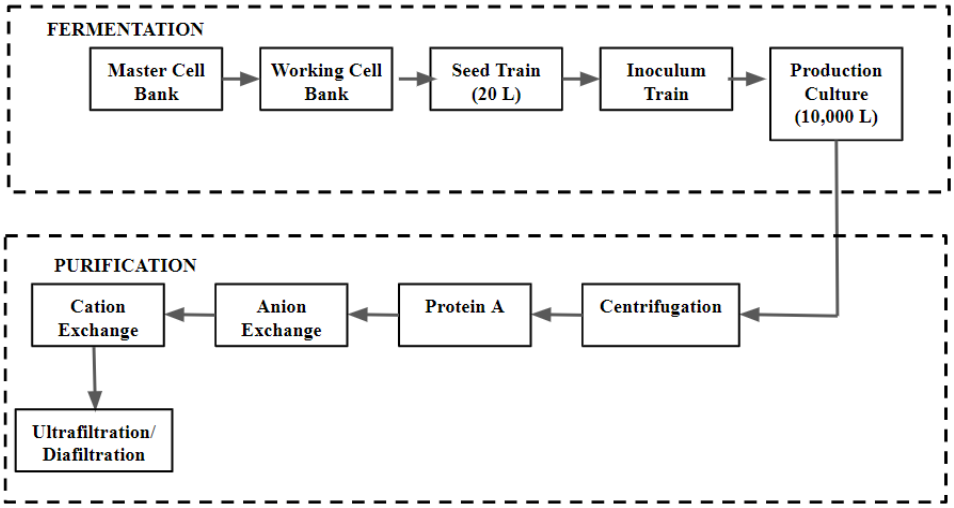

Figure 1. Generalized process flow diagram for the production of monoclonal antibody. Adapted from Petrides, Siletti, Carmichael, & Koulouris, 2014.

Aspen Plus V11 and MATLAB will be used to model the several unit operations involved in Keytruda production while implementing theories of bioseparations, kinetics, transport phenomena, and thermodynamics. The team will need to estimate projected Keytruda demands in order to calculate how much drug should be produced to appropriately size equipment. The team will produce a Design Basis Memorandum in Fall 2019 and implement the technical design in Spring 2020.

Socio-Technical Connections

The price of a pharmaceutical primarily depends on the estimated demand and cost-effectiveness of the product. However, the final cost can be reduced through an optimized manufacturing design process. Both mAb treatments such as Keytruda and diabetic therapeutics such as insulin fall under the classification of a protein therapeutic, and the two medications are manufactured using similar techniques. Therefore, an optimization of a Keytruda manufacturing facility can theoretically reduce the manufacturing cost of diabetes treatment and, thus alleviate the financial burdens of patients in the future.

Historical Analysis of Insulin Pricing and Implications for Low-Access States

Diabetes mellitus is a disease that causes hyperglycemia or high blood glucose levels. This disease is classified as type 1 or type 2. Type 1 indicates that an individual's pancreas produces insufficient insulin, and type 2 is characterized by a bodily resistance to insulin. Insulin is a hormone that regulates blood glucose levels. The National Institute of Health indicates that one in five people died within 20 years after a diagnosis with type 1 diabetes in 1950, and today, this mortality rate has decreased to approximately 3.5 percent within 20 years of diagnosis (2010). This is primarily due to the commercialization of recombinant human insulin which was first manufactured by Genentech and Eli Lilly and Co. in 1982 (Vecchio et al., 2018). Since then, insulin therapeutics have continued to develop with prices reaching as high as $594 for a month's worth of Eli Lilly's Humalog® (Lovelace Jr, 2019). The Center for Disease Control (CDC) estimates that 30.3 million people in the U.S. have diabetes (2019). Drug price inflations, therefore, poses a unique risk for this expansive community.

Currently, the price of insulin is not the only source of debate among pharmaceuticals. The debate surrounding drug pricing has, in fact, existed for many years. Insulin, however, poses a unique case due to its duration as a high-cost medication. Typically, new molecular entities (NME)

or new pharmaceuticals are sold by a company under patent, and no generic formularies are produced until the patent expires (Keyhani et al., 2010). Additionally, the U.S. does not employ drug price regulation due to concern that a decrease in profits may reduce the influx of NMEs (Keyhani et al., 2010). Consequently, companies often sell products at high prices, and they will stop manufacturing after patent expiration. For example, Weintraub notes that while Cialis®, an erectile dysfunction medication, accounted for 10% of Eli Lilly's (Lilly) revenue in 2017, the company no longer manufactures the product due to generic developments after patent expiration in 2018 (2018). On the other hand, the patent of Lilly's Humulin®—a form of short-acting insulin—expired in 2000, and yet the product accumulated a revenue of $1.3 billion in 2012 (Al-Samarrie, 2012). The three major producers of insulin—Lilly, Nova Nordisk, and Sanofi—exhibit a hegemony within the market for diabetes therapeutics, and while these companies clearly affect insulin pricing, it is necessary to understand the impact of insurance companies, pharmacy benefit managers (PBM), and government policy on the price that patients inevitably pay. Therefore, this study will primarily serve as a historical analysis of insulin prices within the U.S. in conjunction with an analysis of the active networks involved in this pricing.

While diabetes is clearly an issue throughout the U.S., Barker et al. (2011) implemented health surveys to characterize counties with noticeably high diabetic incidence rates. The 644 counties identified were localized to 15 southern states with Kentucky being one of the most prevalent (see Figure *2*). Therefore, this study will focus on the implications of insulin pricing for individuals in low-income states, specifically investigating the Commonwealth of Kentucky.

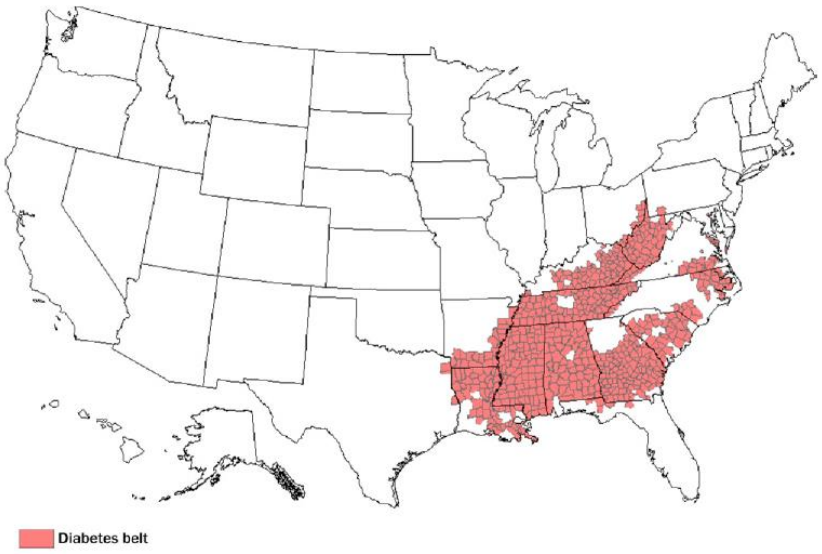

Figure 2. Depiction of the "diabetes belt". Adapted from 'Geographic Distribution of Diagnosed Diabetes in the U.S. (Barker et al., 2011).

This study will utilize the actor-network theory (ANT) to analyze insulin as a socio-technical system. Latour introduces ANT by arguing that technology is built by and adapts through the interactions of various networks. These networks are comprised of people, organizations and technologies which are collectively referred to as actors. ANT argues that society must consider nonhumans or technologies when analyzing the structure of society (Latour, 1992). From this perspective, society should be understood as a system of relationships that link humans to nonhumans. By considering these diverse connections, Latour demonstrates how certain technologies can be discriminatory and exclude or discount certain stakeholders (Latour, 1992). ANT serves as a lens to view technology in society because it requires the viewer to analyze societal implications of a technology in its many contexts.

When insulin is viewed through this framework, an understanding of involved networks—namely PBMs, insurance companies, and the government—can first be analyzed, and the role that insulin plays in its own pricing through the pushback of a complex manufacturing process can be accounted for when considering the improvements in manufacturing techniques. Additionally,

environmental factors and networks may surround insulin pricing without affecting the final market price. These nonhuman factors must also be considered.

The historical component of ANT allows for the contextualization of social actors (Bilodeau & Potvin, 2018). This makes it possible to reconstruct the connections between relevant networks and technologies, and therefore document the events that lead to an observed price increase. The use of ANT will, therefore, provide a context-dependent analysis of insulin prices, both temporally and geographically. Finally, the ANT claim that a technology can be discriminatory can apply to insulin when understanding the lack of generic insulins seen today.

Research Question and Methods

The proposed research question for this research paper is: How has insulin pricing changed from 1980 to 2019, and how is this related to the growth of different stakeholders? Additionally, what do future price increases of insulin imply for high-risk states such as Kentucky?

I will approach these two sub-questions by using the actor-network theory as a form of descriptive analysis. In order to understand the trends behind insulin pricing, I will conduct a historical analysis of insulin prices within the United States beginning with the first marketed recombinant human insulin and ending with contemporary therapeutics in 2019. Historical accounts of insulin therapeutics will allow me to organize this analysis within the proper timeframe (Vecchio, 2018). I will additionally use patents and corresponding product timelines from the three main insulin manufacturers as previously mentioned. These sources will be obtained from the United States Patent and Trademark Office's online database and shareholder reports issued by the corporations. Additionally, I will analyze the growth of corresponding private healthcare corporations such as Humana and Anthem as well as government policy regarding Medicare and

Medicaid in recent years. Case studies such as Luo, Avorn, and Kesselheim's analysis of Medicaid reimbursements will aid in this analysis of healthcare involvement (2015).

I will then work to study the implications of these price inflations for low-access states such as Kentucky by implementing a geographically isolated historical analysis of governmental policies surrounding healthcare, patents surrounding insulin therapeutics, and statistics surrounding the physical health and socioeconomic status of Kentuckians. This analysis will work in conjunction with a justice-based evaluative analysis to illuminate the effect of various social determinants of health on diabetes prevalence. Geographical case studies of southern states such as those provided by Barker et al. will help provide compiled data sets describing the health of the Kentucky population (2011).

Conclusion

The STS research paper will analyze historical increases in insulin pricing while simultaneously assessing the implications that further price increases could have for high-risk states such as Kentucky. Using preliminary research from the Fall of 2019 and subsequent research from December 2019 to January 2020, I will produce a preliminary draft of my STS research paper by February 2020. I will then revise this draft and complete the thesis in March.

After completing this thesis, I will understand the finances required to manufacture a pharmaceutical product. Additionally, I will understand the implications of high drug prices for underserved populations. I expect the results of my STS paper to demonstrate connections between involved networks over time while also illuminating the societal factors that promote localized regions of diabetes prevalence. This assessment of the science and societal implications behind protein therapeutics will help maximize pharmaceutical process efficiency and provide insights to aid in drug-price reduction.

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