Prospectus

Design of a Pembrolizumab Manufacturing Plant Using Continuous Bioprocess Technology and Single-Use Bioreactors

(Technical Topic)

Actor Network Theory of Humalog Pricing in the United States

(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

Insulin prices have skyrocketed over the last decade in the United States, leaving insulin-dependent patients hopeless, helpless, and desperate. A vial of insulin cost just $21 dollars when it first came on the market in 1996. A vial now costs $275 dollars (Werner, 2019). As a result, diabetic patients have resorted to using expired insulin, relying on untrustworthy sellers to sell them insulin at cheaper prices, or rationing insulin. Rationing insulin is quite deadly, in fact, one study finds the underuse of insulin could affect nearly 40 million people with diabetes by 2030 (Werner, 2019). One quarter of people with diabetes in the U.S. are rationing their insulin, and while 70% of these people report having some coverage for their costs, two-thirds report that they have no financial support for remaining costs (Silverman, 2019). Before the 1920's, Type I diabetes was a death sentence for patients (Sable-Smith, 2018). Despite the revolutionary discovery of insulin, in 2019 four people have died from rationing insulin so far, meaning diabetes can still be a death sentence (rightcarealliance.org, 2019).

Clearly, many social, political, and economic factors play a role in making insulin unaffordable for the common person, which has contributed to insulin rationing. Currently, some critics claim that pharmaceutical companies raise prices to fund incremental changes to insulin, which are necessary to adhere to requirements that demand changes to the drug for patent extension, ensuring market exclusivity for the drug and keeping competitors out of the market (Sullivan, 2018). If pharmaceutical companies do not at least attempt to then tweak and manufacture drugs like insulin in a more cost-effective manner, in an effort to reduce prices, they run the risk of further debilitating patients who rely on their medicine. Therefore, a technical solution must be implemented to develop and manufacture insulin in a more economical manner.

What is complicated is that these social factors render a simple technical fix an incomplete solution to this problem. Currently, some critics blame PBMs (Pharmacy Benefit Managers) for demanding huge rebates from pharmaceutical companies and pocketing discounts. Some critics blame the government, or insurance companies.

Below I outline a technical solution to design a manufacturing facility that produces Keytruda, a drug similar to insulin. This design will utilize innovative and cost-effective manufacturing and engineering strategies such as single-use technology and perfusion reactors, in an effort to decrease production costs. However, to remedy this crisis, a technical solution alone is insufficient to resolve this socio-technical problem fully as it does not address the social aspects, such as faults in the American healthcare system and the many actors that affect drug pricing, which are consequently affected by the development of this advanced technology. I also use the STS framework of actor-network theory to analyze how four main actors play a role in dictating drug prices, specifically with the insulin product Humalog. Both technical and social aspects of this socio-technical problem must be addressed, otherwise drug prices will continue to rise, and more tragedies will result from insulin rationing.

Technical Problem[1]

The cancer immunotherapy drug Keytruda, also known as pembrolizumab, is a checkpoint inhibitor monoclonal antibody (mAb) manufactured by Merck. 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 technology within the pharmaceutical industry in hopes of

[1] Collaborated with Brian Abt, Clayton Burruss, Noah Rushin, Summer Xu, advised by Eric Anderson

addressing these rates of disease. 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 compared to standard chemotherapy treatments (Awwad & Angkawinitwong, 2018).

Keytruda works by blocking the PD-1 pathway. By doing so, 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 many types of cancer. Although Keytruda was initially used to treat lung cancer, it has, and is continuing to receive increased market approvals for oncology indications. 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 mammalian cells that produce 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 (Gillepsie, et al., 2014). 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 (W. Runstadler, 1992). A lack of the aforementioned changes to process design can contribute to high production costs, 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.

We plan to design 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 ensure product purity between batches (Jacquemart, et al., 2016). 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 (W. Runstadler, 1992).

Therefore, we propose 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. The mAbs produced by the cells will continuously be 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.

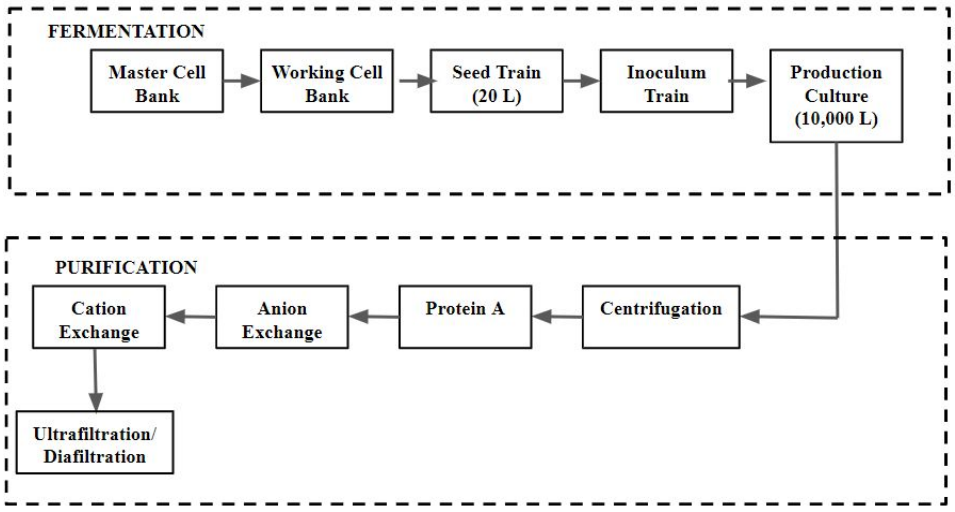

Figure 1: Generalized process flow diagram for the production of monoclonal antibody. Adapted from Petrides, Siletti, Carmichael, & Koulouris, (2014).

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. Our team will need to estimate projected Keytruda demands in order to calculate how much drug should be produced to appropriately size equipment. We will produce a Design Basis Memorandum in Fall 2019 and complete the technical design in Spring 2020.

STS Problem

Many insulin-relying patients are unaware of who to blame for rising insulin prices. I will specifically analyze the pricing challenges associated with Humalog, an insulin product manufactured by Eli Lilly & Company, and groups involved with its pricing.

Currently, most critics blame rising insulin prices on insulin manufacturers such as Eli Lilly. Eli Lilly argues that it must keep prices high in order to fund R&D, to further develop existing products like Humalog. However, insulin has been on the market since the 1920s, and

the most recent innovative breakthrough was made 20 years ago (Johnson, 2019). Lilly reported in 2018 that it made $24,555.7 million in revenue, while spending 21.6% on R&D (Eli Lilly & Company, 2018). Lilly can use this money to perform expensive minor tweaks on Humalog, essentially recycling the drug for the sake of patent extension to keep other competitors out of the market.

While it is true that Eli Lilly plays a major role in Humalog pricing, there are three other actors to consider. One is the government, which became involved through the implementation of Medicare Part D, an optional United States federal government program to help Medicare beneficiaries pay for self-administered prescription drugs through prescription drug insurance premiums. Under Medicare, drug manufacturers in the United States are allowed to set their own prices, and Pharmacy Benefit Managers (PBMs) are used to negotiate drug prices with the patient's insurance carrier's network of pharmacies (boomerbenefits.com, 2019). Therefore, another group involved is the insurance company. Health insurers work with PBMs to negotiate drug discounts, or rebates, from pharmaceutical companies. Those discounts often do not wind up in consumers' wallets, though insurance companies and PBMs claim they always pass rebates along to patients in the form of lower premiums (Livingston, 2018). Thus, the third group involved is the PBM, which serves as the middleman between Eli Lilly and insurance companies (Feldman, 2018). Lilly pays rebates to PBMs in exchange for priority placement of their drug on drug "formularies", the list of drugs the health insurer covers (Turner, 2019). Lilly also argues that it must raise drug prices to account for these rebates (LillyPad, 2019).

Eli Lilly often receives a lot of the backlash in this argument. However, in this case, I argue that it is not the sole cause of rising insulin prices; there are three other actors entangled in this crisis, and overall, the relationship among these four units is the underlying cause.

Without adequate understanding of the problem, the public will continue to be unaware of who is truly to blame. Therefore, by understanding the roles these four units play, one may better be able to understand the causes of the insulin pricing crisis.

My analysis of this insulin pricing problem draws on the Science, Technology, and Society (STS) framework of actor-network theory, an approach to understanding the technology-society relationship that examines power dynamics in heterogeneous networks, composed of different actors, both human and non-human (Cressman, 2009). I will use actor-network theory to analyze the patterns of insulin pricing, through the relationships of four main actors: PBMs, the government, insurance companies, and Eli Lilly. Actors become involved in networks through the process of translation, in which a network builder forms an actor-network to solve a problem or accomplish a goal (Callon, 1986). In this case, the PBM functions as the network builder. The PBM claims that it exists to help patients negotiate costs, but in reality its goal may actually be to recruit organizations into its network for its own benefit_to collect rebates from Lilly.

Conclusion

In this paper, the technical and social solutions are combined to analyze the root cause of insulin rationing. The technical report will deliver an innovative design for Merck's Keytruda manufacturing site located in Ireland. The results of the technical report will help address the broad socio-technical issue of insulin rationing as a result of high prices by exploring the effect

of the implementation of more economical manufacturing strategies on the list price of drugs similar to insulin. The STS research paper will seek to provide further insight into the causes of high insulin costs by using actor-network theory to analyze how the four aforementioned actors involved in this healthcare network contribute to rising Humalog prices. By understanding the technical details of drug production along with understanding how these four actors function within their network, insulin-relying patients can develop a better understanding of who or what is to blame for their pain.

Word Count:1885

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