Design of a Pembrolizumab Manufacturing Plant Utilizing a Perfusion Bioreactor and Precipitation Chromatography

Analysis of the Eventual Failure of Aflibercept in Australia

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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

The human immune system treats foreign invaders by identifying and eliminating pathogens by producing molecules called antibodies which bond to the surface of antigens and act to directly inhibit the antigen, or as a flag to trigger a greater immune response. These antibodies can be produced in the pharmaceutical industry and delivered intravenously to aid patients in fighting a variety of maladies including cancer and viral infections. However, there are several inhibitions for the delivery of these life-saving medications since they come with a high cost. These antibodies are often expensive due to the extensive research behind their development, as well as the production costs required to safely produce a product that is injected into a patient. Furthermore, there is an extensive reviewing process of a drug by a country's regulatory agency, such as the Food and Drug Administration in the United States, or the Therapeutic Goods Agency in Australia, which is a new drug's final test before reaching a market.

Due to the long process of bringing a new therapeutic from the laboratory bench into the market, there are several factors, such as production costs and gaining regulatory approval, that limit a company's success. In my technical project, my team proposes a new method to produce pembrolizumab, a monoclonal antibody, through the use of perfusion reactor and precipitation chromatography in order to reduce production costs of this multi-use life-saving drug. In my STS project, I will explore the failure of Zaltrap to succeed in Australia despite global use, employing Actor Network Theory to examine how Sanofi failed to build a successful network to gain lasting regulatory approval. Together, these projects will work to address the complicated sociotechnical process of bringing a drug to market, by optimizing the production scheme and examining the regulation requirements involved, for a better understanding of the overall sociotechnical problem of pharmaceutical drug pricing.

Technical Project

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 & Martin, 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 (*Monoclonal Antibody Therapy For Cancer*, 2022). As of 2021, cancer is one of the leading causes of death in the United States (Murphy et al., 2021). Pembrolizumab (Keytruda), is a monoclonal antibody manufactured by Merck & Co as a treatment for advanced melanoma, lung, bladder, stomach and colon cancers (*How KEYTRUDA® (Pembrolizumab) Works | Patients*, n.d.). 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 & Co., Inc., 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 (*Expanding Access to Monoclonal Antibodies*, 2020; Reck et al., 2016). The high cost of mAbs leads to these barriers in both LMICs and underprivileged regions of high-income countries (*Expanding Access to Monoclonal Antibodies*, 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).

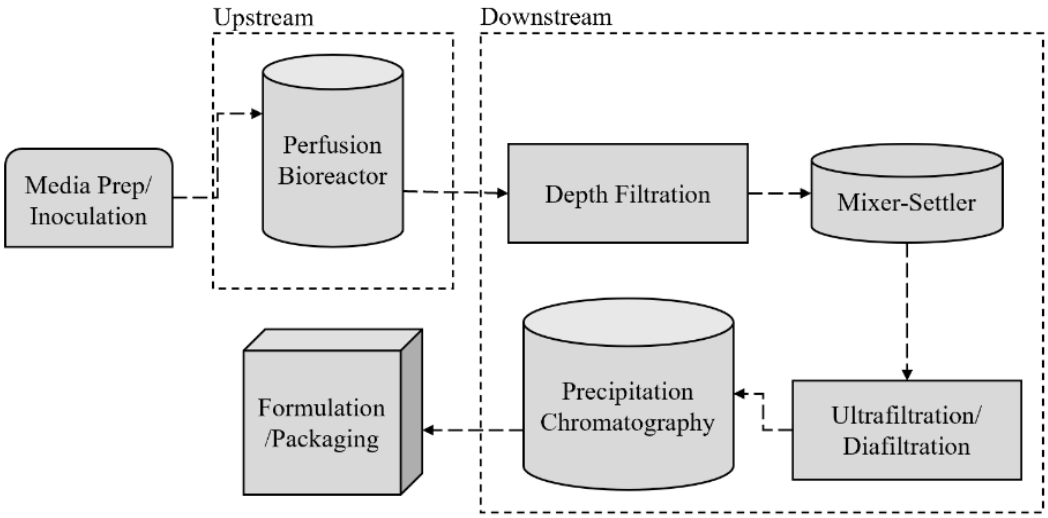

Figure 1. General Process Flow Diagram for Continuous mAb production (Kornecki et al., 2019).

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

Aflibercept (Zaltrap) is a recombinant fusion protein manufactured by Sanofi used for patients with metastatic colorectal cancer who have proven to be resistant to oxaliplatin (Karen

Linehan, n.d.). Developed through a partnership beginning in 2003 with another pharmaceutical company, Regeneron, the drug found an improved survival rate for metastatic colorectal cancer when combined with chemotherapy (Writer, 2011). Zaltrap was therefore approved for medicinal use in the United States in 2012 and the European Union in 2013, collected a reported 53 million euros in sales in 2013 alone (Karen Linehan, n.d.). However, despite being registered with Australia's Therapeutic Goods Administration (TGA) in May 2013, it was rejected by the Pharmaceutical Benefits Advisory Committee (PBAC) in August 2013, and is not currently available for use in Australia as of October 2022 according to the Australian Register of Therapeutic Goods (ARTG), which is the register for medicinal goods that can be lawfully supplied in Australia (Australia, 2022; Michael Wonder, 2014). Despite its' rejection by the PBAC, Zaltrap was registered in Australia and allowed for use, even topping the list of most costly drugs to the government in 2020 (Olivia Willis, 2020). Since registration in Australia does not expire, Zaltrap no longer met the strict criterion set by the TGA in order to be sold in Australia (McEwen, 2004). Some writers would argue that Zaltrap no longer met the quality, safety, and efficacy requirements set by the TGA for registration in Australia due to data about increased side effects for cancer patients (Vaughan, 1995; *ZALTRAP® (Ziv-Aflibercept) Injection, for Intravenous Use Prescribing Information*, n.d.). However, this overlooks the role played by other factors in the Australian drug approval process. If we attribute Zaltrap's failure to lack of balance between safety and efficacy, then we will not have a more comprehensive account of the range of factors that contributed to the drug's removal from Australian market.

After a 1987 amendment to the 1953 National Health Act, the PBAC is required to not only consider the quality, safety, and efficacy of a drug, but also the cost-effectiveness of the drug in the selection for public subsidy (Drummond, 1992; Smith & McGettigan, 2000). This 'fourth

hurdle' has granted the government negotiation power, and the power to remove an 'inconsequential' drug from the market, and has allowed Australia to act as a 'price taker,' setting prices far below the world average (Drummond, 1992). However, Zaltrap is still available in the United States and the European Union, collecting millions in sales globally in 2020, despite lack of approval in other countries (Regeneron Pharmaceuticals Inc, 2022).

There is question to the clarity of the Australian drug approval process, since the TGA is completely financed by fees from pharmaceutical companies, and is ranked among most secret of national drug regulatory agencies since reports for new medicines and lists of cancelled marketing authorizations and reports submitted by drug companies not publicly available (Vitry, 2008). While Australia is the first country to propose mandatory guidelines for economic analysis prior to reimbursement, there are more groups involved than just the regulatory board when it comes to approving a drug (Drummond, 1992). The restructuring of the drug pricing policy in Australia to incorporate cost-effectiveness before a therapeutic is approved have led to many Australian clinical pharmacologists involved in helping shape or implement medicinal drug policy, building unexpected partnerships between them and epidemiologists and economist (Smith & McGettigan, 2000).

In order to consider the failure of Sanofi's Zaltrap to stay on the Australian market, I will employ actor network theory (ANT) to consider the various actors involved in the network for Australian drug regulation, and how Sanofi failed the mobilisation, or the employment of human and non-human actors, in building its own network for Zaltrap's continued approval in Australia (Callon, 1984). Engineers shape society as network builders and ANT studies the activity of a network where the social and natural worlds exist together in a successful heterogenous network to solve a problem or accomplish a goal. Actor network theory considers the roles of many

different actors in the formation of a network to advance a technology and focuses on technology in the making, such as the approval of a new medicine (Cressman, 2009). The successful Australian network for drug approval consists of human actors such as pharmacologists, epidemiologists, economists, health professionals and the TGA, in addition to non-human actors such as the drug itself, Zaltrap, and the malady it aims to treat. To analyze Sanofi's failure of mobilisation, I plan to study the drug approval process in Australia through the legislation introduced for economic considerations and the available reports of the TGA and PBAC meetings which considered the drug for approval, but ultimately rejected it.

Conclusion

The technical project will deliver a comprehensive design of a new manufacturing plant from inoculation to packaging, aiming to control approximately 20% of the market share by 2028, when the Keytruda patent expires. The STS research will offer a better understanding of the roles many different actors play in bringing a drug to market, and the challenges and allies a pharmaceutical company needs to address in order to successfully market a new product to regulatory agencies. Additionally, the STS research will also gain insight into the safety requirements of drug regulation, which will work to inform design decisions of the technical project. Combined, these two projects will contribute to addressing the sociotechnical challenge of drug pricing and marketing, with the technical project exploring methods to reduce production costs, and the STS project investigating the post-development actions a company must take for their drug to succeed.

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