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

Key Causes of Monoclonal Antibody Access Limitations

A Thesis Prospectus
In STS 4500
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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

Monoclonal antibodies are used to treat many diseases including cancer, asthma, rheumatoid arthritis, and multiple sclerosis. The first therapeutic monoclonal antibody product, muromonab-CD3 (Orthochlone OKT3), was produced in 1986 and was used to prevent kidney transplant rejection (Liu, 2014). In 2015, sales of monoclonal antibodies were estimated to increase by $20 billion per year with over 30 monoclonal antibodies approved by the FDA for human treatment (Liu, 2014). During this time, sources estimated at least 70 monoclonal antibody products to be developed by 2020 with world-wide sales exceeding $125 billion (Ecker et al., 2020). However, in 2019, sales of monoclonal antibodies were much greater than estimated, approximately $163 billion, making up 60 percent of the total $230 billion biopharmaceutical revenue; over 139 monoclonal antibody products were produced by 2020 (Ecker et al., 2020).

This data shows the rapid advancement in monoclonal antibody production over the past 30 years and its dominance in the pharmaceutical industry today. My technical project will focus on designing a manufacturing plant for a particular monoclonal antibody, pembrolizumab, also known as Keytruda, to assist with its growing demand. My team and I will utilize process intensification methods to reduce the cost and energy required for pembrolizumab production. My STS research question is: “What are the leading issues that prevent access to monoclonal antibodies?” In relation to my STS project, my technical project offers a solution to improve access to monoclonal antibodies; a more efficient production method of pembrolizumab will increase the affordability of the product for patient treatment, increasing global access. I will analyze the social and technological factors in monoclonal antibody access and its relation to society using the actor-network theory.

Technical Project[1]

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

[1] This section was co-written by all technical team members in order to satisfy the requirements of our technical advisor.

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).

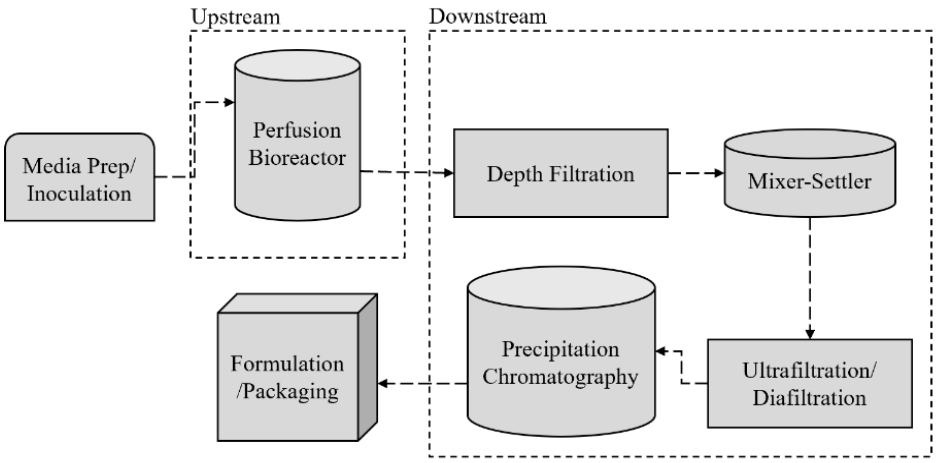

Figure 1. General Process Flow Diagram for Continuous mAb production (Kornecki et al., 2019).

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

Reseach Question

A study in Thailand found that lower respiratory infections were the leading cause of hospitalization with over 1,423,509 children hospitalized between 2015 and 2019, most between the ages of 1 and 5; approximately 10% of these hospitalizations were the result of a respiratory

syncytial virus (RSV) (Sitthikarnkha et al., 2021). RSV is a leading cause of acute lower respiratory tract infections in infants and inhabitants of low- and middle-income countries (LMICs) (Ananworanich & Heaton, 2021). There are currently no RSV vaccines for infants, but there are monoclonal antibodies available that can aid in RSV treatment (Ananworanich & Heaton, 2021). However, an approved RSV monoclonal antibody, palivizumab, is expensive and requires monthly administration which prevents access to LMICs. (Ananworanich & Heaton, 2021). In my STS project, I will answer the following question, "What are the leading issues that prevent access to monoclonal antibodies?" As described, one of these issues is affordability. I will answer this question by tracing monoclonal antibody development, the conditions they help treat, and the technological limitations of shipping and storage.

Relevant Social Groups

The patients, those in need of monoclonal antibody treatment, are most important when analyzing issues with global access; all individuals globally should have access to the same treatments and medications. Monoclonal antibody access can also be limited based on societal class, such as being inaccessible to low- and middle-class individuals, or countries. The manufacturers and process engineers play a critical role in designing monoclonal antibody production methods in a manner that is cost effective for all patients. The government is also an important social group; some people may believe that no matter the cost of production, US manufactured drugs should be sent to low-income countries for free if we have access to them, especially if that particular country is in critical need of treatment. Government administration can implement equity policies and regulations regarding monoclonal antibody distribution to ensure all patients have a fair opportunity to obtain treatment. Transportation companies also

play a role in determining both reasonable and profitable prices for product shipment and storage costs.

Methods/Frameworks

A framework used will be the actor-network theory. The actor-network theory involves evaluating the human and non-human influencers in network creation and their relation within the network. The actors in this case are factors of monoclonal antibody development including material and production costs, treatment conditions such as limitations in mAb access for specific conditions, and technological limitations of shipping and storage such as the inaccessibility to certain parts of the world. The network will be global monoclonal antibody access. History will be the STS method of focus in which the history of process development, treatment conditions, and shipping/storage limitations will be explored.

Timeline

This research question will be solved in two semesters between STS 4500 in the fall and STS 4600 in the spring. This fall will be focused on creating a detailed bibliography containing possible sources and resources that will be useful in answering the proposed research question. The bibliography will contain a detailed explanation of each entry and its relevance to my proposed research questions for easy reference when preparing the thesis project in the spring. I plan to study the science, technological, and societal relations of each actor involved in the network individually. I will then provide a section to analyze interrelation between actors and their involvement in the network, offering final conclusions to my proposed question.

Key Texts

Bierle, D. M., Ganesh, R., Wilker, C. G., Hanson, S. N., Moehnke, D. E., Jackson, T. A., Ramar, P., Rosedahl, J. K., Philpot, L. M., & Razonable, R. R. (2021). Influence of Social and Cultural Factors on the Decision to Consent for Monoclonal Antibody Treatment among High-Risk Patients with Mild-Moderate COVID-19. *Journal of Primary Care & Community Health*, *12*. https://doi.org/10.1177/21501327211019282

This journal articles relates the social and cultural factors involved in the decision for high-risk patients to consent for monoclonal antibody treatment for mild-moderate COVID-19. A variety of covid-19 monoclonal antibodies were offered to 2,820 adults in the Midwest over a 1-month study in 2020. 59.1% accepted mAb treatment; most of these patients were non-Hispanic white, primarily speaking English. Other common characteristics were having a life partner, or spouse, being religious, and having more than one medical diagnosis. Therefore, race, language, ethnicity, and support system were determined to play a role in the susceptibility to mAb treatment. This article will aid in determining access issues related to social and cultural factors involved in the perception of mAbs.

Glassy, M. C., & Gupta, R. (2014). Technical and ethical limitations in making human monoclonal antibodies (an overview). *Methods in Molecular Biology (Clifton, N.J.)*, *1060*, 9–36. https://doi.org/10.1007/978-1-62703-586-6_2

This article argues that the technical problems related to monoclonal antibody production have been solved and therefore, there are no current technical limitations. This article also explores the ethical limitations in monoclonal antibody production which are important to consider in the STS analysis portion of the product development section of

the thesis. Ethical considerations include the source of B-cells; should patients who donate cells for research be compensated if useful results are found using the patient's cells? The article also mentions that Henrietta Lacks, whom we've learned about in STS 4500, was never compensated for her donation to cancer research. Another consideration is the ability to trace patient information.

Governor DeSantis Staff. (2022, January 24). *Governor DeSantis Condemns Biden Administration's Haphazard Decision to Revoke Authorization of Lifesaving Monoclonal Antibody Treatments*. Ron DeSantis. https://www.flgov.com/2022/01/24/governor-desantis-condemns-biden-administrations-haphazard-decision-to-revoke-authorization-of-lifesaving-monoclonal-antibody-treatments/

Governor DeSantis bashes Biden for revoking the emergency use authorization for Regeneron and Eli Lilly monoclonal antibodies, preventing those in need to obtain treatment. DeSantis argues that this action was done by the FDA with no specific technical reasoning based on health care providers and clinical studies. There were over 2000 appointments to receive treatment using the mAbs that were canceled on January 25, 2022. This article describes an example of politics and the government playing a role in mAb access.

Sitlani, A., Malhotra, S., Aggarwal, P., Casas, C. P., & Keir, L. (2021). Monoclonal Antibodies For COVID-19 Are A Potentially Life-Saving Therapy: How Can We Make Them More Accessible? *Forefront Group*. https://doi.org/10.1377/forefront.20210901.667955

This article describes how monoclonal antibodies, specifically those to treat COVID-19 can be made more accessible. Covid 19 mAbs require high dosages which increase production costs. Also, obtaining government authorizations can be a lengthy process. A

proposed solution to increasing global access is to manufacture mAbs that are effective in treatment, but require lower dosages and can be administered in multiple ways. Global manufacturing for a particular antibody cannot be increased without disrupting the production of vaccines and therapeutic monoclonal antibodies for other conditions.

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