

Undergraduate Thesis Prospectus

Design of a Pembrolizumab Manufacturing Facility Using Continuous Bioprocessing

(technical research project in Chemical Engineering)

Redesigning the Office Space: the Impact of Remote Work on Mental Health

(sociotechnical research project)

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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General Research Problem

How can the importance of public health in the United States be emphasized?

In recent years, societal perception of public health is rapidly evolving; the definition of public health is changing, and questions over the relationship between individual liberties and public health are increasing, largely due to the coronavirus pandemic. Physical health has been prioritized in the US for a long period of time, but the mental health is becoming less stigmatized, with millennials being more likely to talk about mental health than previous generations (Marie, 2019). Woolley (2005) found that Americans favor public health research as a national priority, and support more private and government funding of it. However, many Americans also protested public health policies during the coronavirus pandemic as imposing on their freedom, especially the coronavirus vaccine. Routine child immunization rates are rapidly decreasing due to the antivaccination movement, with experts predicting a new outbreak of measles among unvaccinated children (Hotez, 2020). Defining public health and examining its relationship with mental health, individual liberty, and more traditional ideas of health is necessary for the post-pandemic future of America.

Design of a Pembrolizumab Manufacturing Facility Using Continuous Bioprocessing

Technology

How can the production of pembrolizumab be optimized using continuous bioprocessing technology?

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 (fig. 1). We will design these elements and the utilities and disposal systems needed for a pharmaceutical manufacturing site (Kelley, 2009).

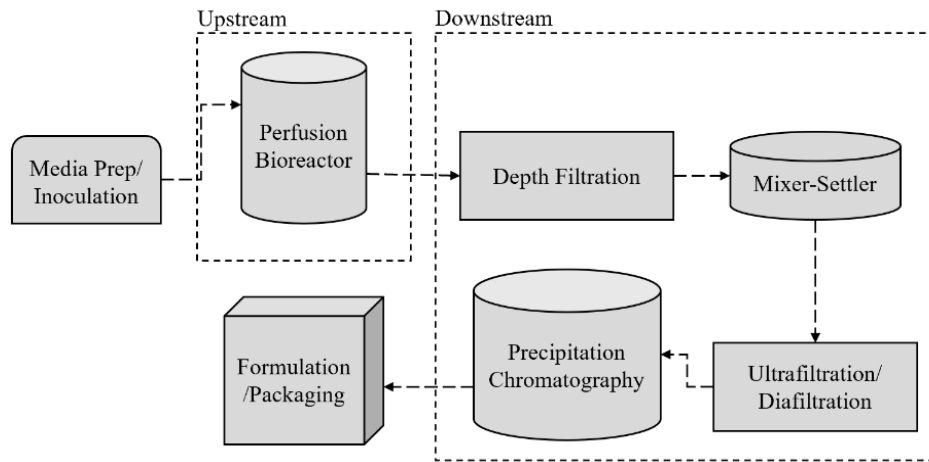


Figure 1. General Process Flow Diagram for Continuous mAb production (Kornecki et al., 2019).

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.

Redefining the Office Space: The Impact of Remote Work on Mental Health

What have employees who work from home in the United States said about the effect of their working conditions on their mental health?

Due to the coronavirus pandemic, remote work is becoming an option for many U.S. employees. However, the effects of remote work on mental health remain largely unknown; both increased depression and improved quality of life have been reported (Oakman et al., 2020). The increased depression is largely due to burnout, studies show 33% of remote workers during the pandemic felt they put in more hours than they did at the office (Gelles, 2021). Only 56% of employees feeling comfortable discussing their mental health with employers; studying the effects of remote work on mental health will be important for both the general population and individual employers moving forward (APA, 2021; Ho, 2018).

Important participants include GitLab's software developers; GitLab is an all-remote software company that provides conferences for its employees to discuss their experiences working from home. Even before the pandemic, many GitLab employees struggled with setting

boundaries between their work and personal lives, often feeling burnout (Ho, 2018). The American Psychiatric Association reported data on mental health during the pandemic, polling individuals working remotely to determine if they view their company's mental health resources as satisfactory. Of the individuals polled, 67% of people said they had a hard time getting away from their work at the end of the day, and 65% felt more isolated; 54% said their employer had become more accommodating to their mental health needs during the pandemic (APA, 2021).

The Mom Project helps mothers advance their careers, and includes many resources on teaching them how to advocate for more flexible work options, as well as forums for members. Some mothers prefer to work on-site as a break from the demands of family life, while others prefer remote or hybrid work options, partially to avoid the optics of regularly arriving late or leaving early to care for their children (Ziegler, 2021). Employers across industries have varying approaches to remote work, with some advocating for the office space and others preferring remote work, which often leads to increased productivity. Employers advocating for on-site work have aired concerns that younger employees will miss valuable learning opportunities from their older colleagues or will be less likely to be promoted if they choose to stay remote while their peers come into the office (Gelles, 2021).

Teachers were drastically affected by remote work during the pandemic, leading many to question if children learn effectively remotely. Many teachers found that the success of remote learning was dependent on the resources their schools already had; low-income schools or children with specialized learning plans fell behind more than school districts that received more funding. Cecily Corcoran, a middle school teacher, supports in person education, noting, "Teachers are often blindsided when they realize a student is in a shelter, neglected, [or] in any form of need. This realization is from personal contact and within a community of teachers,

counselors, administrators and the like, and then we help that individual student” (Alvarez, 2020).

Also noteworthy in the remote work debate are the groups who cannot participate in it; Unite Here, a North American hospitality and food services labor union had 98% of its members laid off during the pandemic. Many of them relied on union aid to feed their families, and economic and racial disparities put them at greater risk for catching the virus. I would like to examine the mental health of those unable to work from home to better understand the economic stress of the pandemic on marginalized groups, and to determine post-pandemic affects of remote work on their livelihood; many Unite Here hotel housekeepers had their hours reduced as fewer business trips occurred once virtual meetings were normalized (Unite Here, 2022).

During the pandemic, the impact of remote work on mental health by gender was researched; Oakman et al. (2020), notes women experienced fewer positive impacts of working remotely than men did; men experienced higher feelings of autonomy working from home than women did. With heightened strain on mental health resources during the pandemic, McDonald (2022) observed higher rates of worker burnout among mental health practitioners working from home, which could further negatively impact the well-being of their patients; McDonald notes, “Practitioners with high levels of burnout are more likely to make medical errors, have poor patient outcomes, and contribute to organizational turnover” (2022).

Researchers also examined nontraditional forms of remote work; Chappelle et al. (2013) found that non-deployed Air Force drone operators report similar PTSD symptoms to deployed officers, often due to the moral implications of ending a human life and then going home to one’s family at the end of the day. I intend to explore traditional definitions of on-site work as well; for Air Force drone operators, the US may be seen as “home,” while deployment overseas would be

their expected “on-site” work. Similarly, women, especially mothers, who have been given a more stereotypical role in the home may view the home as a place of “on-site” work, leading to fewer feelings of autonomy while working remotely.

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