Designing a Facility for the Commercial Production of an Adalimumab Biosimilar
(Technical Paper)

The Attractions of Homeopathy
(STS Paper)

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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 disease be treated effectively?

Currently, 6 out of 10 Americans live with a chronic illness (CDC, 2021). Conventional medicine predominates in U.S. healthcare, in hospitals, in private medical practices, and in insurance standards. It is based substantially upon clinical research and quantitative reviews, and is administered largely through pharmaceutical treatments, surgical procedures, physical therapies, and dietary regimens. It includes, for example, the therapeutic use of monoclonal antibodies (mAbs), which have been beneficial in the treatment of many diseases since the 1990s. Yet conventional medicine is far from universally accepted. In the U.S. and worldwide, other forms of medical care are common. These alternatives include traditional systems of medicine, and medical systems, such as homeopathy, derived from original theoretical models of health and wellness. These forms of medicine may supplement or supplant conventional medical care.

Designing a Facility for the Commercial Production of an Adalimumab Biosimilar

How can a facility be designed for the continuous manufacturing of an Adalimumab biosimilar?

Adalimumab (Humira®) is a mAb therapeutic produced by AbbVie designed to target and block Tumor Necrosis Factor Alpha (TNF-α), a protein which leads to inflammation in the body. Patients with rheumatoid arthritis, psoriatic arthritis, Crohn's disease, and other autoimmune diseases may produce too much TNF-α and may take Humira® to treat the inflammation (Lee et al., 2019). Globally, the market for therapeutic mAbs has surpassed US$100 billion, with an expected revenue of $300 billion by the end of 2030 (Lu et al., 2020). Adalimumab is no exception to this, as it is the highest grossing therapeutic with $20.4 billion in

2020 sales and could cost patients $72,000 per year despite being only the 152nd most prescribed drug (ClinCalc, 2021; Mikulic, 2021; Rowland, 2020).

A select few companies control this market and maintain their dominance through a complex system of product patents. This prevents competition from developing drugs that serve the same function as the original. This allows companies to drive up the prices of their mAb therapeutics and forces patients to pay exorbitant amounts for medicines. When these patents expire, other companies can introduce biosimilar drugs that serve as an approximation to the structure of a reference compound while demonstrating no clinically significant differences in quality, safety, and efficacy (Jacobs et al., 2016). Biosimilars for mAbs add new, typically more affordable versions of successful drug products to a high-demand market. The U.S. patent for Humira® is expiring in 2023, allowing for opportunities in the development of an adalimumab biosimilar (Vaidya, 2021). The goal of this technical project is to design an adalimumab biosimilar process plant to produce adalimumab at a lower cost in order to compete with Humira®.

The current production process for mAbs provides the basis for our design with alterations for our specific product included. MAbs, including adalimumab, are often produced in Chinese Hamster Ovary (CHO) cells which have been genetically modified to contain the gene sequence for the target antibody (Azevedo et al., 2016). Viable CHO cell lines are grown to increase cell density in an upstream continuous fermentation process. As cells grow, they will produce and release the target antibody. Our process will make use of a perfusion bioreactor to continuously filter out product and recycle cells to the reactor, which will improve the yield. After that, centrifugation and various filtration techniques separate the antibodies from the CHO cells and larger debris before a series of downstream purification steps (H. Liu et al., 2010). In

the first downstream step, the mAb undergoes sterile filtration followed by Protein A chromatography in order to isolate the protein from any impurities (Azevedo et al., 2016). A viral inactivation step occurs in order to remove virus contamination, followed by three more chromatography steps for further polishing. Finally, ultrafiltration concentrates the mAb solution before it is put into vials (H. Liu et al., 2010). Formulation and filling will be the final step in our design.

There are large amounts of published data on mAbs of similar molecular weight that can provide the basis for our kinetic data. Monod kinetics are a model for cellular growth and will be useful for our bioreactor design in order to ensure we meet the oxygen and substrate requirements of the cells. In addition, bioseparation theory provides equations for the design of downstream unit operations. We will consult experts in upstream cell growth and downstream separations, such as Professors George Prpich and Giorgio Carta in the University of Virginia Department of Chemical Engineering respectively.

We will complete this project over two semesters as a part of CHE 4474/4476 in a team of five. Two team members will focus on the upstream process while two will focus on downstream purification. The final member will be the expert in quality control and waste disposal. We will evaluate our progress at weekly team meetings and at scheduled sessions with our capstone advisor, Professor Eric Anderson. Our final report will consist of material and energy balances, design of equipment, an economic evaluation, and a discussion of the safety and environmental concerns of the process.

The Attractions of Homeopathy

Why do some groups prefer homeopathy to conventional medicine?

In the United States, 6 million people use homeopathic medicine, and homeopathy is growing in popularity (Dossett et al, 2016). Homeopathy is founded upon a theoretical proposition: *similibus curentur*: like cures like cures like, or the law of similars. Homeopaths contend that medicines that tend to cause a symptom that is like a disease symptom will induce a counteracting physiological response that treats the disease. According to homeopaths, extremely small doses are sufficient to cause this therapeutic benefit. In homeopathic medicines, the therapeutic ingredient is diluted, sometimes several hundred-fold, until it may no longer be detectable in the solution.

Manufacturers of homeopathic medicine often sell their products for their safety. According to one manufacturer, Boiron, its products " are not known to interact with other medications or supplements, making them one of the safest choices for self-treatment" (Boiron, 2021). In the United States, homeopaths are represented by the American Institute of Homeopathy, the oldest national medical association in the United States. The U.S. Food and Drug Association, however, does not recognize homeopathy as a valid medical model, and cautions the public about homeopathic remedies. For example, FDA has warned the public "not to rely on asthma products labeled as homeopathic that are sold over-the-counter" (CDER, 2015).

Influential defenders of homeopathy include Charles, Prince of Wales, who uses veterinary homeopathic treatments on his livestock "as part of a programme to reduce the use of antibiotics" (Dearden, 2016). The reason suggests that homeopathy's popularity is due in part to some of the harmful excesses in the application of conventional medicine, including the overuse

of antibiotics, which has promoted the development of antibiotic-resistant bacterial strains. Another factor is cost. Homeopathic remedies may be far cheaper than conventional pharmaceuticals. The proliferation of misinformation about conventional medical therapies, such as FDA-approved vaccines, can deter people from seeking conventional care in favor of alternative therapies, including homeopathy. The misinformation propagated through online searches, YouTube recommendation algorithms, and social media posts includes medical misinformation. In 2019 U.S. Representative Adam Schiff, a California Democrat, wrote a public letter to Sundar Pichai, CEO of Google, and Mark Zuckerberg, CEO of Facebook, that accused their companies of undermining public trust in conventional medicine. Schiff warned: "if a concerned parent consistently sees information in their Newsfeed that casts doubt on the safety or efficacy of vaccines, it could cause them to disregard the advice of their children's physicians and public health experts and decline to follow the recommended vaccination schedule" (Schiff, 2019).

Researchers have studied distrust in conventional medicine. Armstrong (2006, 2008) found distrust "is higher among individuals who do not have health insurance and individuals between 31 and 60 years of age," and found differences by race in both the degree and the cause of medical distrust. Online misinformation, and especially in social media, has promoted distrust of conventional medicine. Robertson (2021) concludes that "the rise in vaccine hesitancy" is due largely to "misinformation about safety," and "coincides with the rise in social media."

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