Prospectus

Design of a Monoclonal Antibody Manufacturing Genentech Facility in the United States to Continuously Produce Herceptin, a HER2+ Breast Cancer Treatment
(Technical Topic)

Actor Network Theory and the Risk of Evergreening to US Biosimilars
(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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Eric Anderson, Department of Chemical Engineering

Introduction

The American Cancer Society estimates that in 2020 alone, there will be approximately 276,480 new breast cancer diagnoses in women, and approximately 42,170 women will die from breast cancer (American Cancer Society, 2020). These women have families, friends, and lives that are turned upside down by the diagnoses. Although there are treatments that exist, these treatments come with a price tag of tens of thousands of dollars a year. These treatments are not the only costs associated with a cancer diagnosis, but they are often nonnegotiable because they can be the only hope of getting through the devastating disease. The economic burden of treatment adds stress to the patient and their family, and in some cases, it can block a treatment as an option at all (Cuellar, 2020). Currently, the most widely used biologic manufacturing fermenters are operated in fed-batch mode, despite processes using fermenters operated in continuous mode costing approximately 67% less (Yang et al., 2019).

To address this problem, I am designing a continuous biopharmaceutical manufacturing facility for the production of the HER2+ breast cancer chemotherapy drug brand named Herceptin, or generically trastuzumab. This will involve developing an entire process from mammalian cell culture to a completely purified product in accordance with Good Manufacturing Practice (GMP) guidelines. Herceptin has been used to treat 2.3 million patients worldwide, and improving its manufacturing process will make it more accessible to many thousands of patients in the future by decreasing its production costs (Genentech, n.d.).

However, redesigning the manufacturing process is not enough to make Herceptin affordable for patients. Biopharmaceutical research and development scientists and engineers work to design and manufacture a drug that is safe and effective for patients, but the high cost of biologics comes later in a drug's lifetime. After research, development, clinical trials, and FDA

approval, the drug company understandably and fairly patents its product. Patents have a limited life, and for biologics, only last for 20 years (Feldman, 2018). After 20 years, biosimilars are allowed to enter the market and compete for patients, which effectively ends a monopoly and begins competitive pricing. Biologics are complex and difficult to perfect, so companies want to maintain their monopoly for as long as possible. Evergreening is a technique that increases the patent life by making minor changes and effectively blocks any biosimilars from entering the market (Feldman, 2018). This involves hundreds of thousands of dollars in patent and litigation fees, and it prevents competitive pricing, keeping the cost of biologics high for patients. Failing to address the social causes of high drug pricing alongside the technical causes will allow biopharmaceutical companies to maintain monopolies and charge high prices, despite advances in technology lowering their manufacturing costs. High prices will continue to limit drug accessibility and prevent patients from receiving the medicines they need.

In order to make HER2+ breast cancer treatment accessible and save as many lives as possible, both the technical and social aspects of the drug's cost must be addressed. I will outline the technical process and motivation for designing the biopharmaceutical manufacturing plant from a cell to a finished product. I will also use Michel Callon's Actor-Network Theory (ANT) to analyze how evergreening is preventing both the original and biosimilars of trastuzumab from competitive pricing that would increase drug accessibility to patients.

Technical Problem[1]

Cancer is the second leading cause of death in the U.S., and the number of cases is only increasing due to a rising and aging population. With this rise comes an increase in the need for

[1] This section was written collaboratively with Geoffrey Burns, David Lee, Joseph Letteri, and Morgan Pellegrin in order to comply with direct and specific requirements of my technical advisor, Eric Anderson.

pharmaceutical technology such as monoclonal antibodies (*CDC - Expected New Cancer Cases and Deaths in 2020*, 2019). Monoclonal antibodies (mAbs) are important therapeutics that are among the best-selling drugs. They treat a wide array of deadly diseases from cancers to autoimmune disorders. Antibodies present an acute specificity for their target antigens, and they have the potential to recognize and bind to a small region of the antigen. Binding to the HER2 antigens causes cell growth arrest and allows rapid recognition by specialized components of the immune system. The global mAb market is projected to generate $300 million in revenue by 2025 (Lu et al., 2020).

In 2019, Herceptin, a mAb, was the 6th highest selling drug in the U.S. with approximately $7 billion in sales (*The Top Selling Prescription Drugs by Revenue*, 2019). Herceptin is the brand name for trastuzumab, which is a mAb used to treat HER2+ cancer. It targets the HER2+ receptor to fight tumor cell growth for breast and stomach cancer. Within the immune system, trastuzumab acts via interactions with effector cells which are relatively short-lived activated cells that defend the body in an immune response (Chartrain & Chu, 2008). The mAb forms a complex with a membrane protein, which prompts various mechanisms that may lead to the destruction of the targeted cell via cell lysis or triggering apoptosis, a pre-programmed self-destruction pathway.

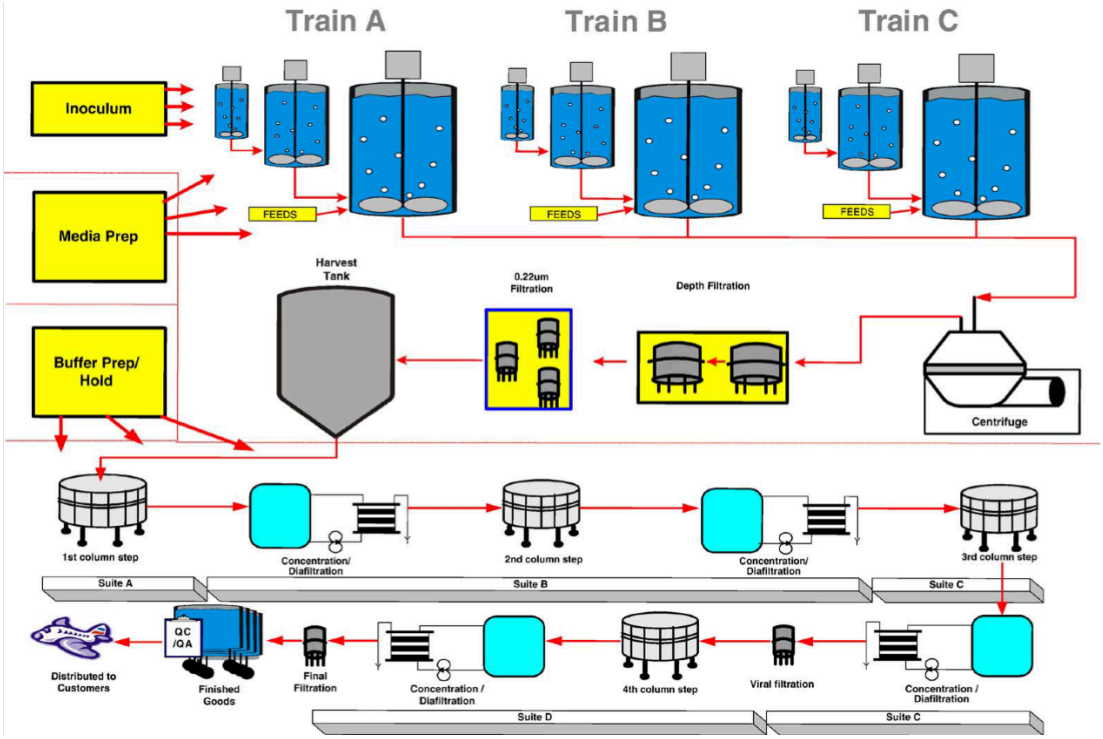
Genentech developed and manufactures Herceptin. It was originally approved to treat metastatic breast cancer in 1998, and it was then approved to treat early breast cancer in 2006 and stomach cancer in 2010 (*What Is Herceptin® (Trastuzumab) for HER2+ Cancer?*, n.d.). Potential future approvals for other diseases or patient segments will increase the demand for Herceptin and require Genentech to increase its manufacturing capabilities. Genentech's U.S. patent for Herceptin expired June 2019. This allows competing biopharmaceutical companies to

produce Herceptin biosimilars and compete for market share. Amgen, Pfizer, Merck and Samsung Bioepis, Celltrion and Teva, and Mylan and Biocon have approved trastuzumab drugs (*FDA Approves 20th Biosimilar, 5th for Roche's Herceptin*, n.d.). Genentech must improve its manufacturing process to effectively compete with the emerging biosimilars.

The proposed project seeks to design a manufacturing facility in the United States to continuously produce Herceptin. The framing of the project will be from the perspective of Genentech to improve their manufacturing process internally. Genentech has an established main cell bank engineered to successfully express trastuzumab and an optimized culture media recipe. The scope of the project will include process design of the large scale upstream and downstream bioprocessing of Herceptin. The upstream process consists of CHO cell culture and synthesis of the target protein, and the downstream process consists of multiple methods of purification and formulation of the protein into a drug substance or product. Unlike previous production designs that have utilized batch or fed-batch bioreactors, the proposed project will adopt perfusion as a technique for continuous upstream cell culturing. The downstream bioprocess design will use various continuous centrifugation, homogenization, and chromatography technologies. A schematic overview of the upstream and downstream processes for mAb production is shown in Figure 1. Our proposed design will not use fed-batch reactors like Figure 1, but the depicted flowchart is a useful schematic overview for the production process.

Figure 1

General Flowchart for mAb production



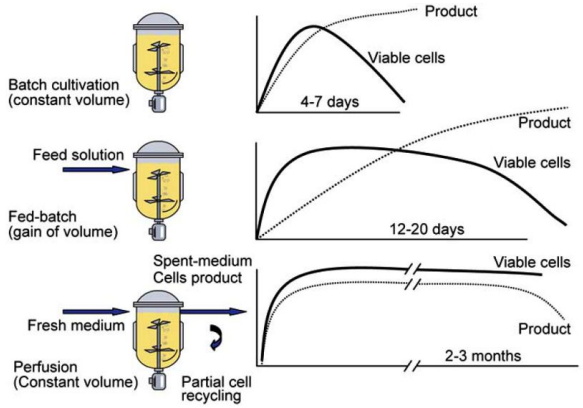
(Birch, J. R., & Racher, A. J. (2006). Antibody production. *Advanced Drug Delivery Reviews*. *58* (5–6), 671–685. https://doi.org/10.1016/j.addr.2005.12.006)

Bioreactor design will be studied extensively because bioreactor controls are one of the most important and well-defined areas of mammalian cell culture, encompassing pH, temperature, O_2, CO_2, and agitation controls (Chartrain & Chu, 2008). Although a batch process is simple and easy to implement, it is commonly difficult to provide sufficient nutrients in the medium without generating disproportional levels of waste product or obtaining toxic levels of some components. The purpose of incorporating perfusion bioreactors into the upstream process design is to maintain cell growth and minimize the time required to shut down and start up the bioreactor for cleaning and maintenance. As opposed to batch or semi-batch fermentation,

perfusion bioreactors maintain high concentrations of viable cells. This is done by continuously introducing fresh media and nutrients while continuously removing spent media, dead cells, and product. Birch and Racher (2006) showed that perfusion bioreactors can create a throughput of antibody approximately 10 times higher than that of a batch or fed-batch system. Perfusion bioreactors lead to relatively large and consistent product generation, as shown in Figure 2. Figure 2 shows that the viable cell concentration stays high in the perfusion reactor while it drops in the batch and fed-batch reactors. The time scale is 2-3 months of product generation for perfusion compared to 4-7 days for batch and 12-30 days for fed-batch. This is a significant difference in the amount of product being produced, which has serious economic implications. Other factors that contribute heavily to the pricing of therapeutic mAbs are costs associated with development time, cultivation medium, purification resins, and general facilities. Our designed plant will consider these factors.

Figure 2

MAB production processes: Overview of operations and typical cell viability and product production over process time

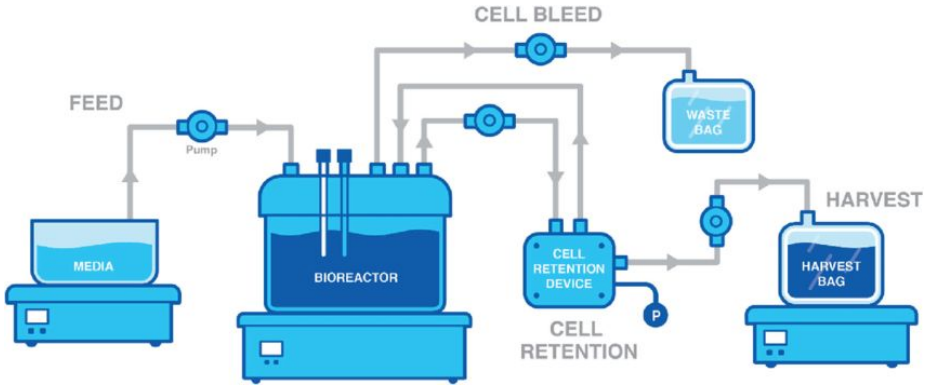


(Lu, R.-M., Hwang, Y.-C., Liu, I.-J., Lee, C.-C., Tsai, H.-Z., Li, H.-J., & Wu, H.-C. (2020). Development of therapeutic antibodies for the treatment of diseases. *Journal of Biomedical Science*, *27*(1), 1. https://doi.org/10.1186/s12929-019-0592-z)

A typical perfusion bioreactor design is shown in Figure 3. It's important to note that not shown in the figure, cell bleed is often from the concentrated stream being returned to the bioreactor. This design is more complex than the current batch or fed-batch bioreactors, but the payoff in production is significant. The feed, cell bleed, and cell recycle lines must be run in balance to keep the bioreactor running with viable cells. The cell retention device must be designed to avoid any product degradation.

Figure 3

Typical perfusion bioreactor setup for steady-state operation



(Bausch, M., Schultheiss, C., & Sieck, J. (2018). Recommendations for Comparison of Productivity Between Fed-Batch and Perfusion Processes. *Biotechnology Journal*, *14*, 1700721. https://doi.org/10.1002/biot.201700721.)

By optimizing the individual unit operations involved in the upstream and downstream bioprocesses and incorporating continuous technologies into the process design, this project will increase manufacturing efficiency by reducing maintenance costs and time between production runs.

A continuous manufacturing process is relatively new to the mAbs space. The first mAb to be produced by a fully continuous process received approval for clinical trials in February 2019 ("First MAb Produced via Fully Continuous Biomanufacturing," 2019). Continuous

manufacturing benefits include higher productivity, higher cost effectiveness, greater consistency, and a smaller environmental footprint. (Yang et al., 2020). These benefits will allow the mAbs to be produced at lower costs, which can lead to lower pricing and increased accessibility for patients who depend on them (Yang et al., 2019). Biosimilars have shorter FDA approval timelines and less investment in research because the original drug exists as a foundation, so they can typically be priced lower than the original drug. For Genentech's Herceptin to be competitively priced with biosimilars, Herceptin must be manufactured at a lower cost. This shift from fed batch to continuous represents a major change that should be of interest to all pharmaceutical companies, especially those with drugs in a newly competitive space.

Matlab and Excel will be our main forms of technical analysis, as we can create and model our hypothetical process scenario. Aspen will also be used in conjunction with Excel to perform an energy and cost analysis. The design data for cell growth will be obtained from a 2009 study of *Perfusion mammalian cell culture for recombinant protein manufacturing – A criticalreview* (Bielseretal.,2018) and data for mAb production rates can be obtained from *A Study of Monoclonal Antibody-Producing CHO Cell Lines: What Makes a Stable High Producer?* (Chusainow et al., 2009)**.** An important part of the downstream manufacturing process is chromatography. We will use the patent *A Highly Efficient Process Of Purification And Production Of Recombinant Trastuzumab,* which provides example affinity chromatography runs with exact measurements and results, to guide our chromatography analysis (Patell et al., 2011). The physical property data for trastuzumab will be obtained from Drug Bank (*Trastuzumab*, n.d.). Material balances will be performed around each unit operation – specifically, the group will hone in on the perfusion bioreactor. Professor Carta, Professor

Prpich, and Professor King will be consulted for design input due to their industry and research experience. We will have a weekly meeting on Wednesdays at 3:30 p.m. as a "check-in" to discuss what work has been done and what work needs to be completed. Here, we will treat it as an in-depth presentation so all group members can thoroughly understand the work that has been done. This will also be the main form of "check-ins" to ensure all group members are working efficiently and on the tasks that they set out to complete. We will assign weekly tasks to individuals. For the larger tasks, we will split up into groups of 2 or 3 to assure a manageable workload and provide multiple perspectives and sources of information. We will be sure to hold each other accountable for late or sub-par work, but we will always be understanding if a conflict comes up or a group member needs more help. Our main form of communication will be through text messaging. We will utilize the resources and time provided in CHE4438 and CHE4476 and meet with Professor Anderson for advice throughout the school year.

STS Problem

Through the Biologics Price Competition and Innovation Act of 2009, Congress opened the US market to biosimilars (Fidelity Investments, 2020). According to the FDA, a biosimilar is a biological product that is "highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product." Biosimilars follow abbreviated approval pathways compared to the reference, or original, drug product. This accelerated timeline and reduction in requirements provides biopharmaceutical companies with an opportunity to create their own version of a successful biologic. The purpose of allowing biosimilars in the US was to provide additional treatment options, increase access to medications, and lower health care costs by allowing direct competition (Fidelity Investments, 2020). Since 2009, there have been 28 total biosimilar FDA approvals and 18 launches to the US biopharmaceutical market (FDA, n.d.).

Five of these approvals went to biosimilars for Herceptin, the last of which launched April 2020 after being approved January 2019.

The list price per 150 mg vial of Herceptin is $1,558, which results in a price of $4,675 per month (Chase, 2020). Each biosimilar option is priced for approximately 10-30% savings. Herceptin biosimilars clearly result in substantial savings for patients, and they have high potential to increase accessibility for patients. In Europe, three biosimilars were able to capture 38% of the trastuzumab market within 10 months of their introduction (Cuellar, 2020). The Herceptin biosimilars were able to overcome the typical barriers to acceptance, such as complex and expensive manufacturing processes, difficulty to differentiate from the brand drug, and establishing relations with hospitals and physicians (Moorkens et al., 2016).

Although Herceptin biosimilars were able to successfully claim a portion of the European market, the newer biosimilar network in the US may not find the same success. While it is true that four out of the five biosimilars successfully settled extensive patent litigation with Genentech to reach the US market, the patent trouble may not be over (Fish & Richardson, 2020). The US biosimilar network is being threatened by evergreening. The evergreening strategy employed by biopharmaceutical companies extends market exclusivity after their patent's expiration. A company will make a slight change to its drug or its drug's application and receive a new 20-year patent to effectively block competition. If successful in the US, Genentech can remove the other biosimilars or render them uncompetitive by the slight superiority of their brand name drug (Eddy, 2020).

In my STS research paper, I will use Actor-Network Theory (ANT) to show that evergreening is a threat to the US biosimilar network. By recognizing evergreening as a rogue actor in the network, we will see the fragility of biosimilar pricing in the US and form a better

understanding of how US patients rely on more than biopharmaceutical companies to provide them with cancer treatment. ANT examines complex relationships between both human and nonhuman actors that come together to create a dynamic network (Callon, 1987). ANT relies on network builders to create a socio-technical network in which actors have evolving power dynamics. A rogue actor can make a network unstable by disturbing existing connections and actors. Drawing on ANT, my paper will explore the US biosimilar network, specifically for trastazumab. This network involves biopharmaceutical companies, FDA approval processes, and US patent laws and court cases. My paper will show that the benefit of biosimilars to patients within the network is threatened by evergreening. To support my analysis, I will use public litigation records between Genentech and companies proposing biosimilars in both the US and Europe, records of proposed patents that show Genentech's intention to employ evergreening in South Africa, and current US patent office and FDA rules and regulations.

Conclusion

To effectively increase the accessibility of Herceptin to patients, both the social and technical aspects of the problem must be addressed. The results of the technical report will help to resolve the socio-technical issue of limited patient accessibility to Herceptin by decreasing the costs associated with manufacturing the drug. The STS research paper will help provide insight into how biosimilars' attempt at making biologic pricing competitive is being thwarted by evergreening. This analysis will focus on how Genentech has delayed other companies from competing with Herceptin after the patent expired, and how the actors in this biosimilar network are preventing patients from accessing the treatments they need at a fair price.

The technical report and STS research paper will come together to address the sociotechnical issue of providing cancer patients with the treatment they need by providing a

more affordable and accessible treatment. By creating effective drugs with efficient manufacturing processes and continuously improving their company's portfolio to stay competitive once a patent expires, biopharmaceutical researchers and engineers can provide life-saving treatments to more patients and help ease the financial burden of this disease.

Word Count: 2864

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