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

(Technical Paper)

The Orphan Drug Act as an Intervention Point to Pharmaceutical Innovation

(STS Paper)

A Thesis Prospectus Submitted to the

Faculty of the School of Engineering and Applied Science

University of Virginia • Charlottesville, Virginia

In Partial Fulfillment of the Requirements of the Degree

Bachelor of Science, School of Engineering

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Fall, 2020

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Introduction

Cancer is a life-threatening illness that effects billions of people each year along with the families, friends, and lives of those diagnosed. The American Cancer Society estimates the number of new cancer cases in 2020 in the United States will be 1.8 million (*CDC - Expected New Cancer Cases and Deaths in 2020*, 2019). Of these, 276,480 are estimated to be breast cancer diagnoses, and approximately 42,170 women will die from the disease (*Breast Cancer Facts & Figures | American Cancer Society*, n.d.). Even through treatment may exist for these women, the diagnosis comes with a heavy financial burden. The typical out-of-pocket expenses surmount to approximately $30,000 a year which is almost half of the average household income in the United States (Kantarjian et al., 2014). Because of these high drug prices, many patients decide not to undergo treatment or choose a significantly weakened treatment plan against doctors suggestions (Kantarjian et al., 2014).

To address this problem, my capstone team is designing a pharmaceutical manufacturing facility for production of the HER2+ breast cancer chemotherapy drug brand named Herceptin, or generically trastuzumab on a Genentech campus in Hillsboro, Oregon. This process involves defining multiple unit operations, from mammalian cell culture to purification of the product to the point at which it is ready for injection. As of 2016, over 2.3 million patients worldwide have been treated with Herceptin, and improving its process to implement continuous manufacturing will render the drug more accessible to thousands of patients by decreasing the production costs (Müller et al., 2018).

While designing a more efficient manufacturing process for Herceptin may benefit thousands of patients with HER2+ breast cancer, there are also 20-25 million patients who suffer from approximately 5000 rare diseases that have no drug treatment options (Commissioner,

2019). Due to the for-profit nature of the pharmaceutical industry, drugs for rare diseases often are never developed or reach a stagnant point in clinical testing because they are too costly to produce or the revenue margins are too small. These drugs are deemed "orphan" drugs. This leaves a large population living with a disease with no hope for medical intervention. I am critiquing the way in which the current patent system coupled with the political and economic structure in the pharmaceutical industry is an inadequate method for driving innovation. I will present the Orphan Drug Act (ODA) as an intervention point to innovation in the pharmaceutical industry. I will discuss the benefits that have resulted from the act along with the concerns on drug cost and accessibility that still exist.

Technical Topic

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

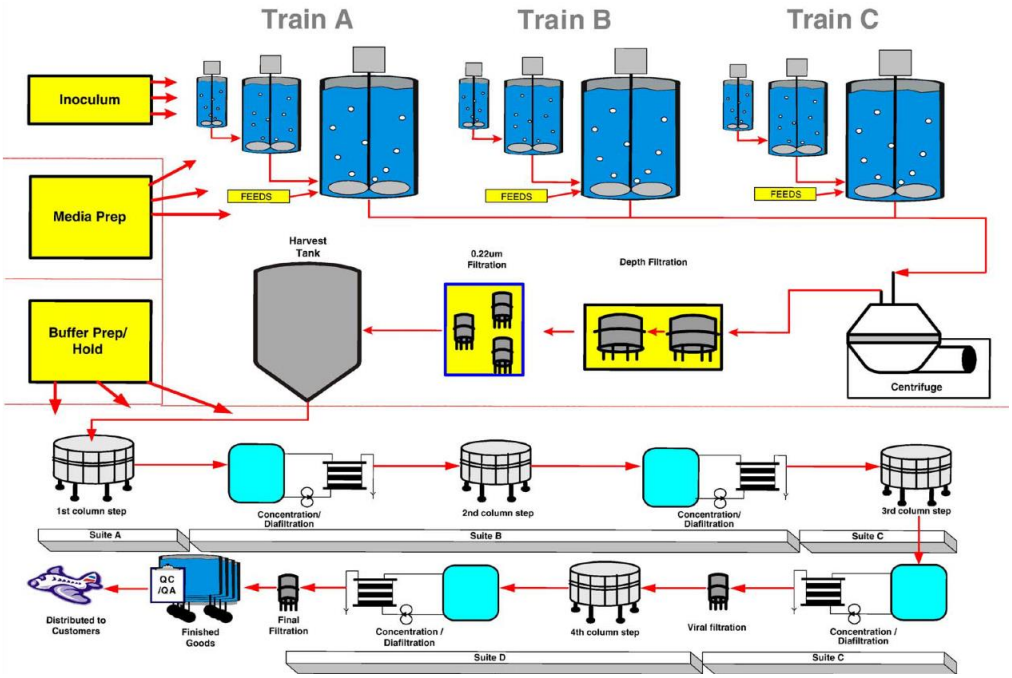
Genentech developed and manufactures Herceptin. It was originally approved to treat metastatic breast cancer in 1998, and it was then approved to treat early breast cancer in 2006 and stomach cancer in 2010 (*What Is Herceptin® (Trastuzumab) for HER2+ Cancer?*, n.d.). Potential future approvals for other 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



Note. From "Antibody Production," by J. R. Birch & A. J. Racher, 2006, *Advanced Drug Delivery Reviews, 58*(5–6), p.681. 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 time

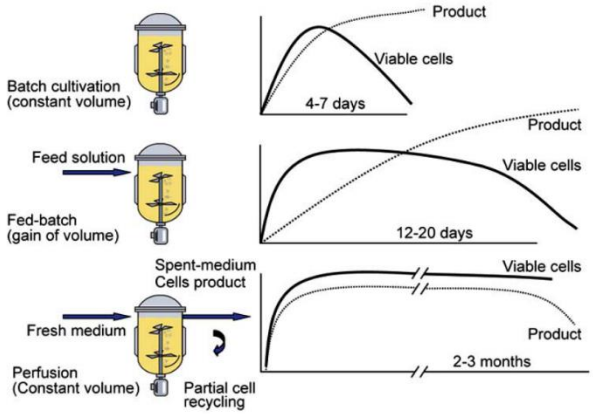


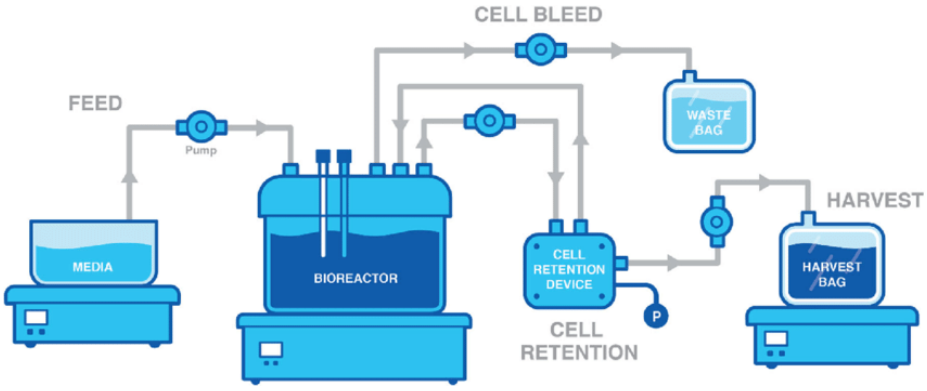
Fig. (4). mAb production processes.
Overview of operations and typical cell viability and product production over process time. The average maximum cell densities are ~1-2 10^6 cells/mL for batch cultivation, 8-12 10^6 cells/mL for fed-batch cultivation, and 10-30 10^6 cells/mL for perfusion cultivation.

Note. From "Development of Therapeutic Antibodies for the Treatment of Diseases," by R. Lu, Y. Hwang, I. Liu, C. Lee, H. Tsai, H. Li, & H. Wu, 2020, *Journal of Biomedical Science*, *27*(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



Note. From "Recommendations for Comparison of Productivity Between Fed-Batch and Perfusion Processes," by M. Bausch, C. Schultheiss, & J. Sieck, 2018, *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 critical review* (Bielser et al., 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 Topic

Because pharmaceutical companies are commercial enterprises, they tend to focus their resources on the highest potential markets in order to obtain the greatest financial returns (Crompton, 2007). If a disease affects a limited number of patients, then therapeutic products for that disease may never be fully developed as the cost of private investment cannot be recovered. It has been found that pharmaceutical companies have possessed therapeutic drugs with promising benefits to rare diseases, but because these drugs were not patentable or the costs to complete develop were too high relative to the commercial demand these potentially life-altering drugs were "orphaned" (Yin, 2008). In the 1980's, a grass roots coalition of patients and advocacy groups were formed to lobby government officials and Department of Health and Human Services organizations to join the fight for recognition of rare diseases within the realm of pharmaceutical innovation (Commissioner, 2019). Subsequently, in 1983, Congress passed The Orphan Drug Act (ODA) to provide incentives for pharmaceutical industry investments in treatments for these rare diseases (Field et al., 2010). Throughout my research, I will discuss the severely flawed patent and innovation network in the for-profit pharmaceutical industry. I will use Michael Callon's actor-network theory (ANT) to discuss both the successes and failures of a

specific actor, namely the Orphan Drug Act, within the innovation network along with the complex nature and punctualization of the ODA.

Research and development in the United States is typically dependent on both government funding and private investments. Government funding finances the exploratory science behind drug development and private investments finances the manufacturing processes and clinical research (Field et al., 2010). In the pharmaceutical firm's drive to maximize profits, the industry largely focuses on drugs to treat chronic conditions that affect many people, making minor, yet patentable, variation to existing drugs with no realized added value to the drug (Gøtzsche, 2018). The current system consequently promotes innovation in more profitable market sectors rather than incentivizing the study and development of therapeutic drugs for diseases which a marketed drug may not exist, despite the ODA. These pharmaceuticals that are commercially undeveloped due to the limited potential for profitability are known as orphan drugs (*What Is an Orphan Drug?*, n.d.). Orphan drugs typically treat rare diseases which are classified as a disease that affects less than 200,000 Americans (Yin, 2008). However, with the prevalence of over 5,000 rare disease, over 20-25 million patients are struggling to get the medical intervention they need (Commissioner, 2019).

Historically, the patent system and current market strategies used for drug innovation and usage has failed public health, especially for those with rare diseases. Although the passage of the ODA spurred some novel innovations immediately after, the ODA has since phased out and has been the center of criticism for promoting commercial abuses. In my STS paper I will use actor-network theory (ANT) to discuss the effect the ODA had on the conversation of orphan drugs and novel innovation. ANT attempts to explain the relation between human and non-human actors and how their interactions shape a complex network. (Sismondo, 2010). Within

many sociological, philosophical, and historical approaches the term “black box” is used to describe the erasure of complex sociotechnical relationships that constitute a technical artifact (Cressman, 2009). In ANT, the concept of punctualization is used to refer to the “black boxing” of complex actor-networks that are linked with other networks to create a large, intertwined actor-network (Cressman, 2009). This punctualization converts a network into a node in a different network. In the case of my STS research, the ODA is a complex node in the overarching network of innovation for orphan drugs. In ANT, it is recognized that black boxes are often “leaky” in which there are competing ideas and initiatives within the punctualized components of a larger actor-network. I will discuss the punctualization of this network as a way to study the failure of the ODA and the effects on the different stakeholders associated with the act.

To support my analysis, I will study empirical research of the impact that the ODA had in research and development for rare diseases. I will also discuss those who are fighting for extensions of the Orphan Drug Act, what is driving them, and what they are attempting to do to achieve an intervention point for the flawed system of innovation in the pharmaceutical industry.

Next Steps

Completion of both the technical capstone and STS research project will be done by the beginning of May 2020. A detailed schedule of deadlines for both projects is presented below:

Date	Capstone	STS Thesis
November 2020	• Design Basis Memorandum due	• Prospectus due to STS Professor and Capstone Advisor
December 2020	• Revise and resubmit Design Basis Memorandum	• Perform research on Orphan Drug Act (ODA) and proponents for an extension of the ODA • Perform Actor Network Theory analysis on the patent and innovation network of the pharmaceutical industry
January 2021	• Proposal Presentation • Progress Report (1)	• Begin writing thesis
February 2021	• Progress Report (2)	• First draft of thesis due
March 2021	• Progress Report (3) • Final Report draft due	• Second draft of thesis due
April 2021	• Final Report due	• Third draft of thesis due
May 2021	• Oral Presentation of Final Report	• Final thesis portfolio due

The technical and social solutions will come together to create a nuanced view of protein therapeutics. My capstone team is determined to deliver an in-depth model and analysis of a Genentech manufacturing facility to continuously produce Herceptin. The team will need to follow the timeline detailed above in order to perform the highest quality final paper and presentation. We hope to conclude that the design plant should be developed based on an economic analysis of the final design. Through my STS research, I plan to develop a thesis that discusses the struggle of innovation in biopharmaceuticals and provide an in-depth understanding of intervention strategies such as the Orphan Drug Act (ODA).

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