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

Analyzing Accessibility Issues to Monoclonal Antibody Treatments in the United States using Actor Network Theory
(STS Topic)

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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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Introduction

The American Cancer Society estimates that in 2020, nearly 276,480 women in the United States will be diagnosed with breast cancer and approximately 42,170 will die from breast cancer (American Cancer Society, 2020). Breast cancer has detrimental impacts on the patients, friends, and families affected. In addition to the emotional and physical hardships associated with breast cancer diagnoses, there are severe financial burdens that the patients face. Treatments for breast cancer generally incur out-of-pocket costs of tens of thousands of dollars each year (High Cost of Cancer Treatment, 2020). This generates immense financial pressure for patients who rely upon treatment in order to get through this devastating disease. Depending on a patient's social and economic background, treatment accessibility can be an overwhelming concern.

To address this issue, we will be designing a pharmaceutical manufacturing facility to produce Herceptin, a monoclonal antibody (mAb) treatment for HER2+ breast cancer chemotherapy, under continuous operation. Herceptin has been used to treat about 2.3 million patients since it's FDA approval in 1988 (About Herceptin, 2020). Therefore, we will design the complete upstream and downstream processes, from mammalian cell culturing through final filtration, to produce purified mAb product. By incorporating perfusion bioreactors into the upstream design, this portion of the process will become continuous and make the overall production more efficient and timelier.

Optimizing the drug manufacturing will help reduce production costs and increase revenue for the pharmaceutical company, but does not necessarily reduce costs to the patients. By saving money on mAb production, the pharmaceutical company can increase their funding for research and development, as well as clinical trials, and FDA approval. When a new treatment is brought to market, the pharmaceutical company will patent their product to prevent competition with other

large pharmaceutical companies. This is extremely beneficial to the discovering company as these biologics utility patents create a monopoly on the treatment for 20 years (Brewster & Singh, 2019). After the 20 years, other companies may begin producing biosimilars which helps demonopolize the economy surrounding the specific treatment. In turn, this increases competition between companies and ultimately reduces treatment costs for patients.

However, the long duration of these patents prevents economic competition and incurs devastating financial obligations to patients during the patented time period. Cancer impacts a variety of people independent of social and economic backgrounds. This creates an inequality between upper-class patients who can better afford treatment and lower-class patients who may struggle to pay for treatment. This socioeconomic barrier also plays a role in healthcare coverage as upper-class persons likely can afford better insurance policies compared to lower-class persons who may rely on Medicare or Medigap to assist with medical expenses. In addition, health insurance companies provide different plans ranging policies on cancer treatments. Because cancer can often be an unforeseen disease, people who do not anticipate or incorporate these sorts of life-threatening diseases pertaining to them. Therefore, this can leave patients without coverage for cancer treatments which makes it challenging for them to access adequate treatment.

In order to reduce HER2+ breast cancer treatment costs to patients, regardless of social and economic backgrounds, I will be investigating the technical and social aspects of the drug's pricing. In this prospectus, I will outline the technical process and motivation for designing a biopharmaceutical manufacturing facility to continuously produce Herceptin. I will also use STS frameworks, such as Actor-Network Theory and wicked problem solving to analyze biologics patent policy and political factors that contribute to the accessibility issues associated with mAb treatments.

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 growing and aging population. With this rise comes an increase in the need for pharmaceutical technology and therapeutics (*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

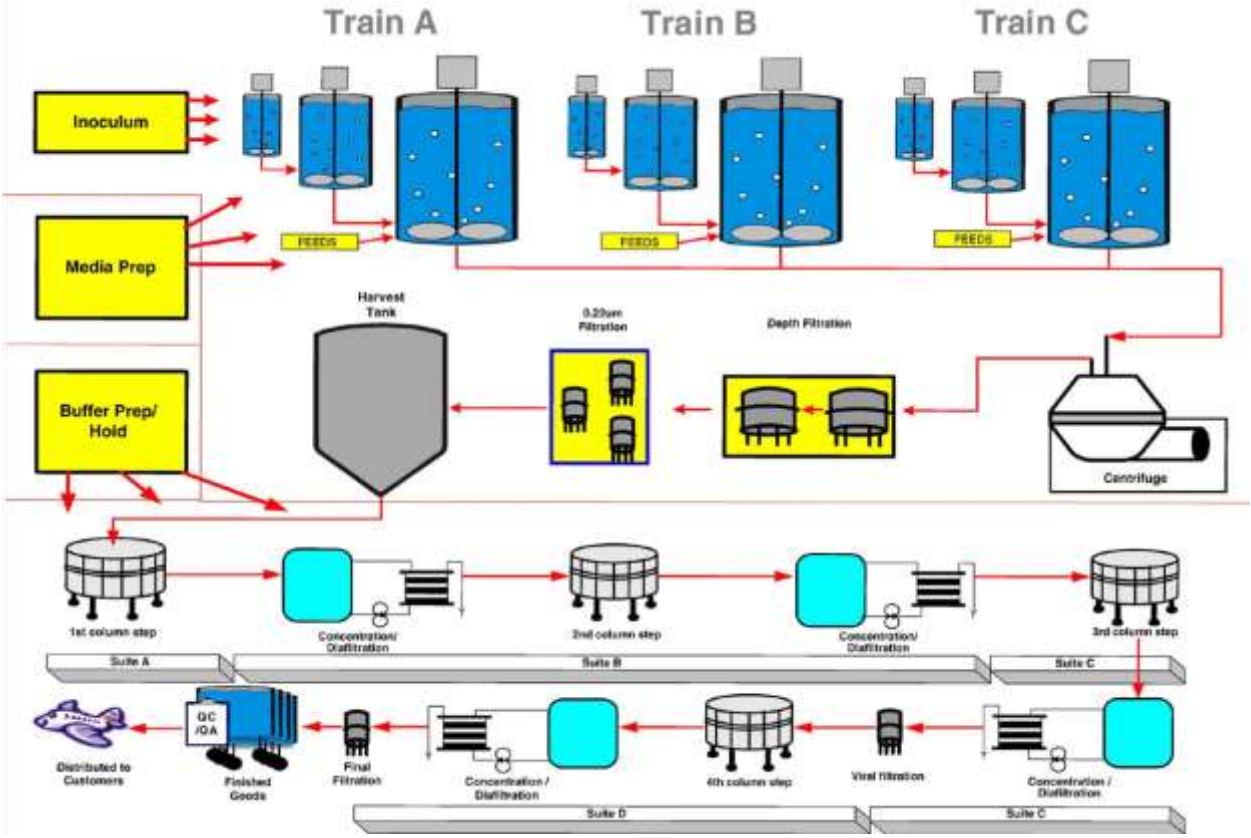
[1] This section was written collaboratively with Molly Caveney, David Lee, Joseph Letteri, and Morgan Pellegrin in order to comply with direct and specific requirements of my technical advisor, Eric Anderson

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 on the following page. 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



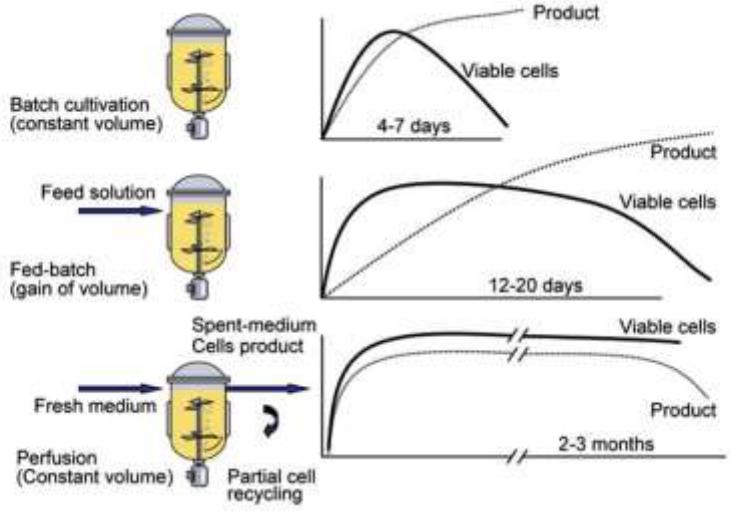
(Birch, J. R., & Racher, A. J. (2006). Antibody production. Advanced Drug Delivery Reviews. 58(5–6), 671–685. https://doi.org/10.1016/j.addr.2005.12.006)

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, O2, CO2, 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



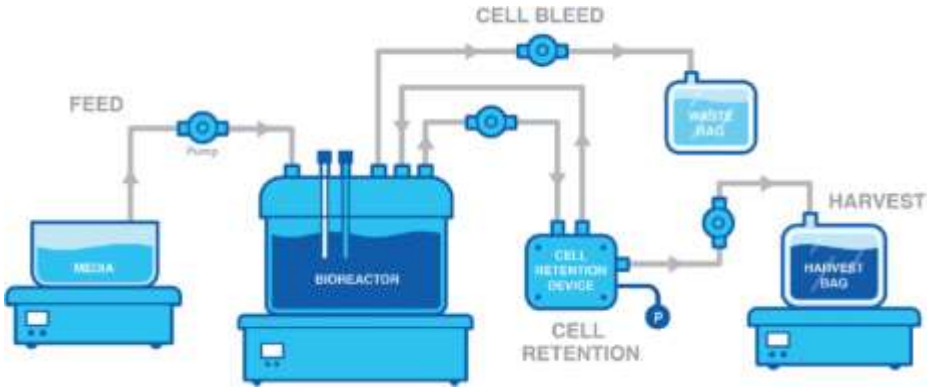
(Lu, R.-M., Hwang, Y.-C., Liu, I.-J., Lee, C.-C., Tsai, H.-Z., Li, H.-J., & Wu, H.-C. (2020). Development of therapeutic antibodies for the treatment of diseases. Journal of Biomedical Science, 27(1), 1. https://doi.org/10.1186/s12929-019-0592-z)

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 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 Prospectus

Introduction

Monoclonal antibodies are some of the most common and effective drug therapies in today's pharmaceutical market. Companies such as Genentech, Eli Lilly, Amgen, and many more are using antibody technology to develop therapies for numerous autoimmune diseases and cancers. Over the past 10 years, mAb's have gained increasing FDA approval rates making them a popular and widespread option for drug therapies. As a result, these global pharmaceutical companies have recently been pursuing monoclonal antibodies as a platform for developing a safe and effective COVID-19 vaccine. Despite the effectiveness of mAb treatments, they are very expensive in the U.S. and often unaffordable to lower- and middle-class persons. This creates a socioeconomic barrier between people that can afford treatment and those who can't. The proposed project seeks to research the factors contributing to mAb treatment accessibility issues through STS frameworks to better understand the social and economic impacts of these treatments.

Research Question

To adequately assess the factors that contribute to accessibility issues of mAb treatments, there are a few underlying research questions that I would like to consider. These complex questions will be the basis for my research. The research questions are as follows,

1. What interactions between consumers, pharmaceutical companies, U.S. patent laws, FDA, and insurance companies (as well as other actors) contribute to the high cost of mAb's?

I hypothesize that the patent laws will have the largest impacts on the high pricing of mAb treatments because they are what contribute to the monopolization of these treatments. However, there are other actors within this network that play a key role in setting the prices to patients which need to be investigated.

2. What microeconomic and social factors influence a patient's decision making for MAB treatments? How do these factors vary among patients of different socioeconomic and cultural backgrounds?

In addition to the macroeconomic factors from Question 1, I would like to investigate the microeconomic factors and that directly impact a patient's day-to-day decisions. Furthermore, I want to get a sense for how many options are available for specific mAb treatments, like Herceptin and its biosimilars, and how different factors influence a patient's decision for a treatment plan.

3. How can social, political, and economic factors, such as accessibility and financial disparities, be incorporated into the pricing of mAb treatments to make them more affordable and equitable?

Lastly, after understanding the large-scale and patient-level factors that contribute to mAb treatment accessibility, I want to propose definitive suggestions that will improve mAb accessibility for all persons. I hypothesize that my suggestions will be mainly through biologics patent law and health insurance policy recommendations because actors such as pharmaceutical companies and patients are much more independent and make decisions out of their best interest.

Literature Review

Nearly 2 billion people worldwide are unable to access or afford basic medicines provided by pharmaceutical companies (Cornes, 2012). This inaccessibility is the result of an inability to balance the pricing of medicines so that patients can afford treatment and companies can afford to manufacture the products and provide future funding to R&D. This imbalance is currently benefitting large pharmaceutical companies while hurting patients. To understand the scope of the mAb industry, mAb's captured nearly half of the top 20 US therapeutic technology sales in 2017, and the market for mAb treatments is only increasing (Scolnik, 2009). With the growing market, there is still conflict between the high costs of these drugs and lack of generic competition which financially strains the U.S healthcare system. Scolnik suggests that reducing patient costs is done by smaller companies developing new mAb treatments. By competing with the top-tier pharmaceutical companies, these smaller companies will generate a more challenging commercial environment which lower prices for the medicines.

Rising medicine prices also generates anxiety in patients, payers, providers, and policymakers worldwide and especially in the U.S. (Rodriguez et al., 2018). In this article, the average annual cost to patients between 1997-2016 for a mAb therapy was determined to be $96,731. The unsustainability in prices for monoclonal antibody products is frightening as these

prices only continue to increase. The authors recommend that policies be revised so that there is more transparency and sustainability of pharmaceutical coverage by public payers. One way this can be done is with stricter regulation of drug patents. The use of drug patents to consolidate a medical technology under one company to isolate a portion of the market increases prices for drug treatments, reduces supply, and creates greater accessibility issues to patients (Sterckx, 2005). Sterckx recognizes the benefits of drug patents, but argues that their use in the medical industry has a negative impact on healthcare system efficacy. Sterckx suggests a restructured patent system in which the mission in benefiting society is at the forefront. This restructuring is supported by the numerous challenges the U.S. patent system has faced with biotechnology (Plant, 1983). Plant investigates the balance between providing innovator patent protection and publicizing discoveries to further research and innovation. By providing a historical context on patent policy, this article can be used to address modern accessibility issues in the pharmaceutical industry.

An alternative approach to reduce costs is through the implementation of non-profit drug development corporations (Juliano, 2013). In doing so, these non-profit corporations will "bring key aspects of early-stage drug development into the pre-competitive public arena." This will increase patient accessibility to a wider range of medicines at lower prices. While I like this idea in theory, I believe that revising patent regulations for companies in today's capitalist market is a more realistic approach.

One important aspect of the mAb accessibility issues is the lack of communication between patients and health care providers about treatment options and the associated prices. Communication surrounding vaccine risks is a prominent aspect of today's vaccine market (Manca, 2018). This article is written prior to the COVID-19 pandemic, but provides key insight into the emotional and non-technical aspects of vaccine promotion that are highly applicable today.

Furthermore, advertisement has in many ways altered the perception of medical treatments. There are a variety of ways that promotion of pharmaceuticals affects the sale and prescription of other medicines (Alves et al., 2019). Pharmaceutical companies leverage direct-to-consumer advertising, and while effective, this can also be misleading and can have a variety of impacts on consumer decisions and health. It is the social responsibility of pharmaceutical companies to understand the consumer autonomy and safety effects this type of advertising has on patients (van de Pol & de Bakker, 2010). Therefore, initiatives should be implemented to help regulate these promotion strategies from industry, government, and nongovernmental organizations.

Biotechnology is incredibly powerful in combating harmful diseases, but also poses legitimate concerns surrounding its socioeconomical impacts and the inequalities it brings with it (Hornosty, 2011). Therefore, global regulation is needed to uphold human rights and prevent these inequalities from manifesting. Hornosty argues that regulation must be implemented to establish a consensus on biotechnology issues and their risks and benefits. Like Hornosty, I believe that further regulation must be installed to increase the production of biosimilars, increase competition, and reduce costs to patients so mAb treatments are more accessible.

STS Framework and Method

I will be adopting a variety of STS frameworks to gain an in-depth understanding of this accessibility issue. I will use Actor Network Theory to analyze how the different actors and actants in this technical system interact with one another. These actors include the patients, pharmaceutical companies, FDA, U.S. Patent and Trademark Office, health insurance companies, health care providers, and more. The mAb as a nonhuman actant also has significant influences over the different actors and plays a crucial role in this system. Not only do the humans and the other actors work to tame the mammalian cell cultures to produce the desired mAb products, but humans are

also tamed by the mAb itself by responding to its impact on the pharmaceutical market. By understanding the motives and interactions among the various actors and actants in this network, I will be able to provide better information and analysis on the mAb treatment accessibility issues in the United States. Furthermore, I will analyze this system from an additional perspective, as a sociotechnical system. From this point of view, the technology is viewed as a social construct by relevant social groups. I think this will be an excellent perspective to understand the social motivations for how these actors behave and interact. By gaining a complete understanding of this portion of the medical industry through multiple STS lenses, I will be able to deconstruct this wicked problem and provide further insight into this issue which I will use to make policy recommendations.

For my project, I will be gathering primary and secondary data. I plan to interview a patient who was diagnosed with and overcame cancer a few years ago. I'd like to understand her process for finding and receiving treatment, the options she was presented with, and the accessibility issues she faced when selecting treatment. I also plan to interview a patient who has type 1 diabetes. Though not a mAb treatment, insulin is very similar in terms of accessibility issues and high costs to patients. This will be helpful in comparing the individual experiences of a patients receiving mAb and non-mAb treatments. Furthermore, I'd like to send out a survey to multiple cancer patient and advocacy groups to better understand the background of the patients and the costs/difficulties the patients incur. Some of the groups I want to contact and survey include the "Breast Cancer Support" Facebook page, advocacy groups like "Living Beyond Breast Cancer" and "CancerCare," and the American Cancer Society. Lastly, I will be gathering large amounts of secondary data from health journals, pharmaceutical companies' sales reports, medical databases, FDA regulations, drug patent policies, etc. These will give me large-scale statistics on the number

of patients, patient demographics, and available mAb treatments and costs. I will also be looking at reports that analyze similar drug accessibility issues in recent history.

Timeline

By the end of the fall semester in late November, I will have submitted a finalized Prospectus that outlines my objectives and preliminary data for the Thesis in the spring semester. In the spring semester, I will continue to further investigate my research questions and gather primary and secondary data for the Thesis. By the end of February, I intend to have an outline of my Thesis and significant progress made with data collection. I intend to complete data collection for the STS portion of my Thesis by the end of March, along with a first draft of my Thesis. I plan to complete second and third drafts by the end of April, after meeting with advisors and completing peer review. My finalized Thesis will be submitted by the end of the semester in May, 2021.

Conclusion

Monoclonal antibodies are among the most popular and widespread technologies being used in the medical industry today. However, because of current patent laws, private pharmaceutical companies are allowed to set their own prices for new mAb treatments without competition. This has detrimental effects on patients who rely on these treatments of overcome serious autoimmune diseases and cancers. Because of this monopolization of a specific therapy, patients are forced to incur extreme financial burdens in addition to the emotional and social troubles associated with long term diseases. These patients come from a variety of social and economic backgrounds, so treatments may or may not be affordable to all people depending on external factors. Therefore, I believe that disparities in mAb treatment accessibility is an ethical issue that needs to be addressed. By gathering primary and secondary data surrounding this actor

network and analyzing this accessibility issue through Actor Network Theory and wicked problem solving, I will be able to provide direct and reasonable suggestions for policy modifications. I believe that analyzing this medical market sector, I will be able to provide contributions to current policies that may result in increased accessibility to mAb therapies in the United States.

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