Analyzing Accessibility Issues to Monoclonal Antibody Treatments in the United States using Actor Network Theory

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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

Monoclonal antibodies (mAb's) are some of the most common and effective drug therapies in today's pharmaceutical market. Global pharmaceutical companies like 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. In 2017, mAb's captured nearly half of the top 20 US therapeutic technology sales (Scolnik, 2009). These include name-brand drugs such as Humira, Keytruda, Herceptin, and countless others. The efficacy and proven methodology for mAb technology has resulted in a continuously growing market for mAb treatments. However, despite the effectiveness of mAb treatments, they are very expensive in the U.S. and often unaffordable to lower- and middle-class persons. One study found that across all mAb therapies approved by the FDA between 1997-2016, the average annual price for treatment was $96,731 (Rodriguez et al., 2018). These high prices create a socioeconomic barrier between people that can afford treatment and those who can't. This thesis seeks to analyze the factors contributing to mAb treatment accessibility issues using actor-network theory to better understand the various actors and actants in this complex network that contribute to the high pricing of these treatments.

To adequately assess these factors, there are a few underlying research questions that I would like to consider. These questions will help guide my research and discussion throughout this thesis. For starters, I want to gain an in-depth understanding of how the interactions between consumers (patients), pharmaceutical companies, U.S. patent laws, FDA, and insurance companies (as well as other actors) contribute to the high cost of mAb's. This will be useful in setting the big picture, understanding the motivations of the various actors from a top-down perspective.

Secondly, I want to better understand what microeconomic and social factors influence a patient's decision making for mAb treatments. I expect these factors will vary among patients of different socioeconomic and cultural backgrounds. Lastly, I want to analyze how social, political, and economic factors, such as accessibility and financial disparities, can be incorporated into the pricing of mAb treatments to make them more affordable and equitable.

Literature Review

Existing literature has shown that other drug products, similar to mAb's, have generated similar accessibility issues in the past and in present-day. Whether it's the discrepancies in healthcare systems between developed and underdeveloped countries, or the lack of accessibility within the U.S. itself, the price of medicine has always been a limiting factor in drug accessibility. 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. 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. Not only does this impact patients, but this also impacts health insurance companies, healthcare workers, and government programs such as Medicare and Medigap that all base their decisions off of current medial technology. These actors are all impacted when a mAb treatment is patented, driving prices up and reducing accessibility.

Previous studies have shown that the absence of generic competition with the name-brand mAb treatment is a primary reason why mAb prices are so high. Biologics drug patents are used to protect pharmaceutical companies that are introducing new mAb treatments to market upon

Investigational New Drug (IND) application approval. Biologics can obtain patent protection for 20 years before generic competition is allowed to enter the market (Blackstone & Joseph, 2013). This provides the original pharmaceutical company with a complete monopoly over their mAb treatment for the duration of their patent. Unlike traditional patents, biologics patents (and patents for mAb's in particular) are far more complicated as the technology being patented has the power of improving and even saving peoples lives. Many politicians, scholars, and experts in the field have debated the details and duration of these biologics patents because of the ethics surrounding these decisions. On one end, allowing the original pharmaceutical company to maintain trade-secrets over their mAb is what fuels the company's profitability by allowing them to set high prices. This supports the company with funding for R&D innovation, manufacturing costs, and operation costs while maintaining a significant profit margin. On the other hand, by preventing other companies from making the mAb biosimilars, this reduces accessibility to mAb treatment by raising prices through simple supply and demand principles. Given the 20-year duration of these patents, this could be the difference between life and death for low-income patients who would only be able to afford the generic drug alternative. This patent controversy, unique to mAb treatments and other biologics, is one of the primary motivations for this thesis due to its complex social and ethical issues. Finding a better balance between pharmaceutical profitability and patient drug accessibility is a major area for investigation with this thesis.

In addition to the patent regulations, another 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. Previous studies have shown that communication surrounding the efficacy of biosimilars in comparison to the brand-name drug is a prominent aspect of today's pharmaceutical market (Manca, 2018). 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. Some experts believe 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). This begs the question, should initiatives be implemented to help regulate these promotion strategies from industry, government, and nongovernmental organizations? It seems that increasing transparency between actors in this network would improve network efficiency, but by what means should this be done? Another area this thesis intends to further investigate is the use of advertisement to make the general public more knowledgeable about the safety and efficacy of biosimilars.

STS Framework and Research Method

To better understand mAb accessibility in the United States, I will be employing actor-network theory to characterize and analyze some relationships between different actors and actants in this technical system. Actor-network theory is a methodological approach to describing a technical system in which the relationships between different actors and actants help to explain the overall success of the system. In this case, the actors include the patients that can afford treatment, pharmaceutical companies holding original drug patents, FDA, U.S. patent system, 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 as the central technology in this system. These actors and actants behave in symbiotic, dynamic relationships with one another, in which each actor and actant are inter-dependent and are constantly changing to accommodate

one another. Through this, the actors and actants make the technical system a success, benefiting all groups within the network.

While these actors and actants contribute to the success of this system, certain social groups are left out of this network and are harmed. These groups, such as the patients who cannot afford treatment and pharmaceutical companies who cannot produce biosimilars due to patent restrictions, are negatively impacted by being excluded from the system. This paper seeks to understand the motives and interactions among the actors and actants contained within the network as well as better understanding the methods for including these neglected social groups.

In terms of data collection for my thesis, I will be gathering large amounts of secondary data from health journals, pharmaceutical company sites, medical databases, FDA regulations, drug patent policies, etc. I will also be gathering financial and socioeconomic data for cancer patients from advocacy groups like "Living Beyond Breast Cancer" and "CancerCare," as well as from the American Cancer Society. 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 the unique patent regulations and FDA processes for mAb treatments. With these different data sources and using actor-network theory, I will deconstruct this wicked problem and provide further insight into the mAb accessibility issues in the U.S. which I will then use to make policy recommendations.

Data Analysis

Many of the cancer treatments on market today utilize mAb technology. They are highly effective but are very expensive to cancer patients. For the average cancer patient, monthly out-of-pocket costs are $2,500 for a $10,000 treatment each month (High Cost of Cancer Treatment, 2020). This is equal to 70% of the average American's monthly income. For most people, this is

an incredible financial burden that can be devastating to low- and middle-class patients and their families. For people that cannot afford treatment, they are forced into an unbearable situation in which they must decide whether or not it's financially worth it for them to get treatment. This is a moral predicament that no person should ever have to face.

While this may be the extreme case, the reality is that many cancer patients are faced with difficult decisions when it comes to finding ways to pay for cancer treatment and medications. Studies have shown that cancer death rates are 20% higher in poor U.S. counties in comparison to wealthier counties (High Cost of Cancer Treatment, 2020). In addition, U.S. states with higher poverty rates tend to have some of the highest cancer death rates. By allowing large pharmaceutical companies to set high prices for their drugs and biologics products, this creates a socioeconomic injustice that benefits wealthier patients that can afford treatment. Cancer is a disease that can affect the lives on anyone, regardless of wealth, social status, race, or ethnicity. Therefore, it is irresponsible to assume that every cancer patient will be able willing to pay the same amount for treatment. As a result, there is an inequity in the accessibility to mAb treatments that is the root of an STS problem that needs to be addressed. In order to increase accessibility, changes need to be made to incorporate the low- and middle-class patients into the actor-actant network instead of disregarding them.

It's important to recognize that the financial burden of mAb treatments is not just an ethical problem that affects cancer patients solely. The high costs associated with mAb treatments also applies to non-cancer diseases and conditions that require treatment. These conditions and diseases impact a wide range of persons with varying socioeconomic backgrounds. That being said, as of 2018, 23% of U.S. adults ages 19-64 were classified as "underinsured," meaning that their out-of-pocket costs for health care (excluding premiums) equal 10% or more of their yearly income. This

accounts for over 75 million people in the U.S. alone that would consider prescription drugs and medications a significant expense, hindering accessibility. It's important to emphasize that a person's financial capabilities are what creates the divide between the patient actors that can afford treatment who are in the network and the social group of patients that can't afford treatment who are left out of the network. Therefore, this system is unfair in providing healthcare to all U.S. citizens because it isolates a significant portion of society outside of the mAb treatment network.

In addition to patients, health insurance companies are affected by the high prices because it impacts their decision making for whether they cover certain treatments in their health insurance plans. Higher prices for mAb treatments mean not only higher costs to patients, but also higher costs to insurance companies that cover some of the expenses for insured patients. The regulations enforced by the FDA and U.S. patent office ultimately drive the structure of private and public health insurance companies. These fluctuations in healthcare plans then circle back to the patients by changing annual costs for coverage. This goes to show that these different actors are interdependent and no one actor is able to succeed in this system without the others. With such a large number of people impacted by the high costs of medications, it only seems logical that the solution to drug accessibility would be to lower prices.

On the other hand, the large pharmaceutical companies that develop and manufacture these drugs argue that the high costs cover the expenses associated with research and development. From these actors' perspective, they believe they should be able to capitalize on their investment in R&D by charging the highest price for their products that consumers will pay for. However, despite R&D and production expenses, global pharmaceutical revenues in 2019 totaled $1.25 trillion (Mikulic, 2020). Of this global market, the United States captures roughly 45% which means that pharmaceutical companies in the U.S. are taking tremendous profits from the drugs they produce.

If better regulated through legislation and increased market competition, pharmaceutical companies would still be able to capitalize on significant profit margins, but their lost excess in profits would be returned to the consumers. By lowering prices, this reallocates power from the large pharmaceutical companies and gives it to the patients that now have more control over their financial decisions surrounding healthcare and medications.

There are a handful of different means by which the prices for mAb treatments can be lowered. From a simple economics perspective, a low supply drives a high demand which means that consumers are forced to spend more for a given product. In today's pharmaceutical market, drugs are patented by the producing company which protects it from competition for a given amount of time. Compared to small molecules, biologics are more difficult to patent as the process for producing the mAb and the mAb itself are far more complex. This makes the patenting process for mAb's unique in that there is no consistent method for patenting their technology. Some pharmaceutical companies may opt to patent their unique mAb production process while some may only gain patent protection over the final mAb product itself.

As previously mentioned, these biologics patents are normally awarded for 20 years, though the first 8 or so are typically spent in development and clinical trials (Aitken, 2016). During this period, the pharmaceutical company can price their drug without any competition from other companies. Because of this protection, the prices for drugs and mAb treatments are significantly higher than they would be without the patent. One way to reduce the costs of mAb treatments is to increase competition by reducing the patent timeframe which allows drug generics to be introduced quicker. The lack of generic competition within the pharmaceutical industry maintains large profit margins for pharmaceutical companies while forcing people to pay more out-of-pocket. In addition to harming individuals, this lack of competition is also problematic for the U.S. healthcare system

which is already under significant financial strain (Scolnik, 2009). Therefore, changes need to be made such that the U.S. healthcare system can adapt to this technology without suffering financially. Action needs to be taken in order to incorporate the group of pharmaceutical companies producing generics into the actor-actant network. By changing patent regulations, this may allow competitor pharmaceutical companies to enter this network and establish a relationship with the other actors sooner than they would otherwise.

Studies have shown that the cost for cancer treatment is increasing faster than the rate of inflation (Cornes, 2012). To combat this rise in price, the introduction of biosimilars and generics appears to be the primary tool for lower costs of cancer treatments. When a drug patent expires and other companies are able to manufacture biosimilars, the price of the original drug drops significantly. On average, the price of the drug drops by 50% within the first year and 80% within 8 years (Aitken, 2016). This is the direct result of increased competition within the given pharmaceutical market sector. Lowering the price of the mAb treatments has the positive impact of lowering patient expenses as well as government healthcare expenses. By reducing the 20-year lifespan of drug patents and introducing biosimilars sooner, this would drive drug prices down which in turn makes mAb treatments more accessible. Implementing a program that promotes generic substation with biosimilars will not only return the financial power to patients, but will also ensure sustainable healthcare costs (Cornes, 2012).

In addition to the stricter patent regulations, the promotion of biosimilars is a very important aspect to implementing this type of system. Often times, cancer patients and patients of other rare diseases want the very best medication for their treatment. Even when the patent on a mAb treatment expires and less expensive biosimilars are introduced to the market, patients often feel more comfortable buying the original drug as opposed to the biosimilar. Many Americans are

unaware that biosimilars are essentially identical to the original drug. This is a byproduct of direct-to-consumer advertising of prescription drugs which inadvertently suppress biosimilar sales (van de Pol & de Bakker, 2010). Large pharmaceutical companies are incentivized to claim their own product as the very best treatment because this helps generate their revenue. In doing so, the average person is placed under the impression that the name-brand drug is better than the generic alternative. This misunderstanding ultimately places patients at a disadvantage and encourages them to spend more than they need to for the same treatment which ultimately negatively impacts the patient, health insurance companies, health care providers, and other actors in the network.

Direct-to-consumer advertising of prescription drugs needs to be viewed from a corporate responsibility perspective (van de Pol & de Bakker, 2010). Pharmaceutical companies should be responsible for providing the pertinent details of their medication in comparison to generic drugs. Advertisements for name-brand drugs should be required to acknowledge the legitimacy of generic alternatives, because not doing so creates the illusion that their treatment is objectively superior when in reality it isn't. Furthermore, initiatives should be implemented by the U.S. government to regulate the promotion of these drugs and provide better platforms for biosimilars to be promoted. I believe the U.S. government should budget for paid advertising to better educate the general public on generic drug alternatives. The U.S. government as an actor has the power to make the final decisions surrounding drug patents and healthcare policies, making it a very important actor. If they choose to do so, implementing this type of initiative would increase transparency between all actors in this technical system. Incorporating scientific data into advertisements that validate biosimilars would be a strong tool to help communicate the fundamental similarities between original drug and biosimilars. This should help increase sales and production of biosimilars which will create more options for patients and give them more power over their health care decisions.

Discussion

Monoclonal antibody technology as a nonhuman actant and the various significant actors in this holistic network have direct impacts on one another. They have intricate relationships that shape the actions and motivations of the others. Ultimately the network and the actors and actants involved work together to achieve the common goal of providing mAb treatment to particular diseases and conditions. The underlying process of identifying the health problem to actors uniting around the issue through production and distribution to consumers is consistent throughout various mAb technologies. These technologies are constructed and integrated into society through a heterogeneous actant network, though this intricate network is being strained by the imbalance of power between actors. The actors, including patients who can afford mAb treatments, pharmaceutical companies, healthcare workers, etc., are unified by the common goal of identifying diseases and treating them. However, when particular actors are given a greater freedom over decision-making, this leads to exploitation and gives rise to the accessibility issues surrounding mAb treatments. Pharmaceutical companies are driven by nonhuman components like various cancers and autoimmune diseases. Their goal is to make mAb treatments that will cure these diseases while profiting off of their products. However, the patients are in a position of less power, as they are often unable to choose between different treatments in a monopolized market when a particular treatment is patent-protected. This creates an opportunity for the pharmaceutical companies to take advantage of this freedom of price-setting which creates financial strain on patients, health insurance companies, and healthcare organizations. Furthermore, these actors have relationships that are deeply interconnected with one another and contingent on the decisions made by the patent regulatory agency actor. Upon analyzing the research gathered in this thesis, it seems that the U.S. regulatory agencies have the greatest capability for implementing change that will

help incorporate the neglected social groups (i.e., the patients that cannot afford treatment and the pharmaceutical companies that are unable to produce biosimilars until the original biologics drug patent expires).

Based on the ANT analysis, legislation should be implemented to created a more equitable distribution of power among actors within this network. This legislation should work to reduce drug patent lifespans while creating opportunities for biosimilars to reduce drug prices and patient costs. By allowing generics to enter the market sooner, this benefits all patients (regardless of socioeconomic status) and health insurance companies who pay for the mAb treatments as well as the pharmaceutical company selling generics. This would also relieve some of the strain placed upon the U.S. healthcare system by slowly reducing the financial obligations faced by Medicare and Medigap programs. Implementing this type of policy would certainly be unfavorable in the short term to the original pharmaceutical company that produces the name-brand mAb treatment. However, the company would still maintain high profit margins and may actually benefit in the long term as they would be able to introduce their own biosimilars to market sooner when their competitors patent a novel mAb treatment in the future.

By implement this type of policy revision, the actors and actants in the network, as well as the neglected social groups which would now be introduced into the network, would all benefit in the long term. Along with this policy revision, increased public knowledge about biosimilars and their safety and efficacy is essential. I would also recommend that government action be taken to improve communication between scientists and the greater public, whether this be through the form of government-paid advertisements or other means. Between the reduced patent duration and increased communication to the public, these policy changes would have an overall positive impact on the entire network and make the mAb healthcare system more sustainable moving forward.

Conclusion

In order to increase accessibility to mAb treatments in the United States, I believe that legislative action should be taken to decrease the lifespan of drug patents that prevent generics from competing with monopolized mAb treatments. By allowing competitors to manufacture and distribute biosimilars sooner, this would drive treatment prices lower, benefiting the patients, insurance companies, and the various other actors that react to treatment prices. The lower mAb treatment prices make them more accessible to a greater number of U.S. citizens, while still allowing the large pharmaceutical companies to profit off of their product. The extent to which drug patent lifespans should be reduced needs to be further researched in order to optimize mAb accessibility while maintaining sufficient profit margins for pharmaceutical companies. By increasing the capabilities of biosimilars and promoting the safety and efficacy of these biosimilars to the general public, monoclonal antibody treatments may become more widely accessible in the United States.

Bibliography

About Herceptin. (2020). *Genentech USA.* https://www.herceptin.com/patient/about-herceptin.html

Aitken M. (2016). Price Declines after Branded Medicines Lose Exclusivity in the U.S. *IMS Institute for Healthcare Informatics.* https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/price-declines-after-branded-medicines-lose-exclusivity-in-the-us.pdf

Alves, T. L., Lexchin, J., & Mintzes, B. (2019). Medicines information and the regulation of the promotion of pharmaceuticals. *Science and Engineering Ethics*, 25(4), 1167-1192. https://link-springer-com.proxy01.its.virginia.edu/article/10.1007/s11948-018-0041-5

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

Blackstone, E. & Joseph, P. (2013). The Economics of Biosimilars. *American Health & Drug Benefits.* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4031732/#:~:text=Biologics%20can%20obtain%20patent%20protection,the%20patent%20application%20is%20filed.

Brewster, M. & Singh, P. (2019). Intellectual Property Protection for Biologics. *Academic Entrepreneurship for Medical and Health Scientists:* Vol. 1 : Iss. 3 , Article 11. https://repository.upenn.edu/ace/vol1/iss3/11

CDC - Expected New Cancer Cases and Deaths in 2020. (2019, January 31). https://www.cdc.gov/cancer/dcpc/research/articles/cancer_2020.htm

Chartrain, M., & Chu, L. (2008). Development and production of commercial therapeutic monoclonal antibodies in Mammalian cell expression systems: An overview of the current upstream technologies. *Current Pharmaceutical Biotechnology*, *9*(6), 447–467. https://doi.org/10.2174/138920108786786367

Chusainow, J., Yang, Y. S., Yeo, J. H. M., Toh, P. C., Asvadi, P., Wong, N. S. C., & Yap, M. G. S. (2009). A study of monoclonal antibody-producing CHO cell lines: What makes a stable high producer? *Biotechnology and Bioengineering*, *102*(4), 1182–1196. https://doi.org/10.1002/bit.22158

Cornes P. (2012). The economic pressures for biosimilar drug use in cancer medicine. Target Oncology, 7.S: 57–67. *National Library of Medicine*. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3291824/

FDA Approves 20th Biosimilar, 5th for Roche's Herceptin. (n.d.). Retrieved October 6, 2020, from https://www.raps.org/news-and-articles/news-articles/2019/6/fda-approves-20th-biosimilar-5th-for-roches-herc

First mAb Produced via Fully Continuous Biomanufacturing. (2019, September 24). *GEN - Genetic Engineering and Biotechnology News*. https://www.genengnews.com/news/first-mab-produced-via-fully-continuous-biomanufacturing/

High Cost of Cancer Treatment. (2020). *The Mesothelioma Center*. https://www.asbestos.com/featured-stories/high-cost-of-cancer-treatment/

Hornosty, J. (2011). Regulation in a brave new world: Safeguarding against subversive threats. *Bulletin of Science, Technology & Society*, 31(1), 43-54. https://journals-sagepub-com.proxy01.its.virginia.edu/doi/pdf/10.1177/0270467610391292

Juliano, R.L. (2013). Pharmaceutical innovation and public policy: The case for a new strategy for drug discovery and development. *Science and Public Policy*, 40.3: 393–405. https://academic.oup.com/spp/article-abstract/40/3/393/1634274?redirectedFrom=fulltext

Li, F., Vijayasankaran, N., Shen, A. Y., Kiss, R., & Amanullah, A. (2010). Cell culture processes for monoclonal antibody production. *MAbs*, *2*(5), 466–479. https://doi.org/10.4161/mabs.2.5.12720

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

Manca, T. (2018). Fear, rationality, and risky others: A qualitative analysis of physicians' and nurses' accounts of popular vaccine narratives. *Technology in Society*, 55, 119-125. https://www-sciencedirect-com.proxy01.its.virginia.edu/science/article/pii/S0160791X17301720#sec5

Mikulic, M. (2020). Global pharmaceutical industry – statistics & facts. *Statista*. https://www.statista.com/topics/1764/global-pharmaceutical-industry/#:~:text=The%20pharmaceutical%20industry%20is%20responsible,trillion%20U.S.%20dollars%20in%202019.

Monoclonal Antibodies. (2020). *National Cancer Institute, National Institute of Health*. https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/monoclonal-antibodies

Patell, V. M., Guzder, S. N., Maity, S., & Shekar, S. (2011). *A highly efficient process of purification and production of recombinant trastuzumab* (World Intellectual Property Organization Patent No. WO2011015920A2). https://patents.google.com/patent/WO2011015920A2/en

Plant, D. (1983). The impact of biotechnology on patent law. *Technology in Society*, 5.2, 95-106. https://www-sciencedirect-com.proxy01.its.virginia.edu/science/article/pii/0160791X83900039

Rapid Development and Scale-Up of Biosimilar Trastuzumab. (2015, April 14). *BioProcess International*. https://bioprocessintl.com/manufacturing/biosimilars/rapid-development-and-scale-up-of-biosimilar-trastuzumab-a-case-study-of-integrated-cell-line-and-process-development/

Rodriguez, A., Parekh, N., Newman, T., Hernandez, I. (2018). Pricing of Monoclonal Antibodies in the United States. *Global Journal on Quality and Safety in Healthcare*, 1 (1): 4–5. https://meridian.allenpress.com/innovationsjournals-JQSH/article/1/1/4/434796/Pricing-of-Monoclonal-Antibodies-in-the-United

Scolnik P.A. (2009). mAbs: A business perspective. *Europe PMC*, 1(2):179-184. Mabs. Landes Bioscience. https://europepmc.org/article/pmc/2725420

Shukla, A. A., & Thömmes, J. (2010). Recent advances in large-scale production of monoclonal antibodies and related proteins. *Trends in Biotechnology*, *28*(5), 253–261. https://doi.org/10.1016/j.tibtech.2010.02.001

Sterckx, S. (2005). Can drug patents be morally justified?. *Science and Engineering Ethics*, 11(1), 81-92. https://link-springer-com.proxy01.its.virginia.edu/article/10.1007/s11948-005-0059-3#citeas

Top-selling prescription drugs by revenue: Ranking the top ten. (2019, May 21). Pharmaceutical Technology. https://www.pharmaceutical-technology.com/features/top-selling-prescription-drugs/

Trastuzumab. (n.d.). Drug Bank. Retrieved October 8, 2020, from https://go.drugbank.com/drugs/DB00072

van de Pol, P.K.C., de Bakker, F.G.A. (2010). Direct-to-Consumer Advertising of Pharmaceuticals as a Matter of Corporate Social Responsibility?. *Journal of Business Ethics*, 94.2, 211–224. https://econpapers.repec.org/article/kapjbuset/v_3a94_3ay_3a2010_3ai_3a2_3ap_3a211-224.htm

What is Herceptin® (trastuzumab) for HER2+ Cancer? (n.d.). Herceptin. Retrieved October 6, 2020, from https://www.herceptin.com/patient/about-herceptin.html

Yang, O., Prabhu, S., & Ierapetritou, M. (2019). Comparison between Batch and Continuous Monoclonal Antibody Production and Economic Analysis. *Industrial & Engineering Chemistry Research*, *58*(15), 5851–5863. https://doi.org/10.1021/acs.iecr.8b04717

Yang, O., Qadan, M., & Ierapetritou, M. (2020). Economic Analysis of Batch and Continuous Biopharmaceutical Antibody Production: A Review. *Journal of Pharmaceutical Innovation*, *15*(1), 182–200. https://doi.org/10.1007/s12247-018-09370-4