Key Causes of Monoclonal Antibody Access Limitations

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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

Antibodies help the body fight against infections and diseases; monoclonal antibodies are single antibody clones that can be artificially replicated for large-scale production (Carter, 2021; Daintith, 2010). Monoclonal antibodies are used to treat many diseases including cancer, asthma, rheumatoid arthritis, and multiple sclerosis; this is done by their ability to target harmful cells to destroy them, block them from multiplying, or deliver treatments, such as chemotherapy (Cleveland Clinic, 2022). The first therapeutic monoclonal antibody product, muromonab-CD3 (Orthochlone OKT3), was produced in 1986 and was used to prevent kidney transplant rejection (Liu, 2014). In 2015, sales of monoclonal antibodies were estimated to increase by $20 billion per year with over 30 monoclonal antibodies approved by the FDA for human treatment (Liu, 2014). During this time, sources estimated at least 70 monoclonal antibody products to be developed by 2020 with worldwide sales exceeding $125 billion (Ecker et al., 2020). However, in 2019, sales of monoclonal antibodies were much greater than estimated, approximately $163 billion, making up 60 percent of the total $230 billion biopharmaceutical revenue. Also, over 139 monoclonal antibody products were produced by 2020, nearly doubling the estimated value (Ecker et al., 2020).

This data shows the rapid advancement in monoclonal antibody production over the past 30 years and its dominance in the pharmaceutical industry today. My STS research question is: "What are the leading issues that prevent access to monoclonal antibodies?" I analyze the social and technological factors in monoclonal antibody access and its relation to society using the actor-network theory. In the subsequent sections, I provide a brief description of my proposed research question with an overview of the relevant social groups, methods, and frameworks. I begin the results and analysis section with a brief description of the history of the development

process for monoclonal antibodies and alternative production methods, followed by an analysis of treatment conditions and various limitations. Finally, I summarize my argument and supporting claims in the discussion section.

Research Question

A study in Thailand found that lower respiratory infections were the leading cause of hospitalization with over 1.4 million children hospitalized between 2015 and 2019, most between the ages of 1 and 5; approximately 10% of these hospitalizations were the result of a respiratory syncytial virus (RSV) (Sitthikarnkha et al., 2021). RSV is a leading cause of acute lower respiratory tract infections in infants and inhabitants of low- and middle-income countries (LMICs) (Ananworanich & Heaton, 2021). Currently, there are no vaccines available for treatment of RSV in infants, but there are RSV monoclonal antibodies available. However, an approved RSV monoclonal antibody is expensive and requires monthly administration which prevents access to LMICs. As shown, low affordability is a leading cause of limited access to monoclonal antibodies. I explore cheaper alternative production methods to reduce the costs of monoclonal antibodies and make them more affordable.

Relevant Social Groups

The patients, those in need of monoclonal antibody treatment, are most important when analyzing issues with global access; all individuals globally should have access to the same treatments and medications. Monoclonal antibody access can be limited based on societal class, such as being inaccessible to low- and middle-class individuals, or countries. The manufacturers and process engineers play a critical role in designing monoclonal antibody production methods in a manner that is cost-effective for all patients. The government is also an important social group; governmental agencies can assist by sending manufactured drugs to low-income

countries, especially those in critical need of treatment. Government administration can implement equity policies and regulations regarding monoclonal antibody distribution to ensure all patients have a fair opportunity to obtain treatment. Also, large donors and organizations can assist LMICs to ensure that proper storage and treatment facilities are built all over the world.

Methods/Frameworks

The main framework that I use to answer my research question is actor-network theory. Actor-network theory involves evaluating the human and non-human influencers in network creation and their relation within the network. The actors, in this case, are factors of monoclonal antibody development including material and production costs, treatment conditions such as limitations in monoclonal antibody access for specific conditions, and technological limitations of shipping and storage such as high refrigeration costs. The network is global monoclonal antibody access. I use history and literature reviews as my STS methods of focus in which I explore the history of process development, treatment conditions, and shipping/storage limitations. I use case studies related to COVID-19, Henrietta Lacks, and government authorizations to describe various ethical limitations.

Results and Analysis

Tracing Monoclonal Antibody Development

History of Process Development

The general monoclonal antibody production process consists of three steps: fermentation, purification, and formulation which includes filling product into vials for distribution. The upstream process of manufacturing refers to obtaining and growing a cell culture to produce the desired monoclonal antibody; the downstream process refers to the steps

involved in capturing, purifying, and packaging the protein product (Biotech-Careers, 2023). A cell culture refers to the combined cell and nutrient mixture. Nutrients aid in cell growth and can include sugars, yeast, and vitamins. Fermentation is a key part of the upstream process and refers to growing cells under necessary conditions to efficiently extract the desired protein, or monoclonal antibody. Chinese Hamster Ovary (CHO) cells are the most common type of mammalian cells used for protein expression. Reactors are used to ensure even mixing of the cell culture and to maintain parameters such as temperature, pH, and oxygen level automatically, based on specified values to achieve optimal cell growth. CHO cells are typically grown in batch reactors. Batch reactors are non-continuous in which the cell feed must be manually added and removed. The reactors must then be cleaned and maintained before the next batch can be made.

Alternative Production Methods- Continuous Process Operations

Today, alternative methods are being studied and explored to reduce the production costs of monoclonal antibodies. Ou Yang and coauthors describe the benefits of operating with continuous process conditions instead of traditional batch conditions:

> "The publication showed integrated continuous [bio]process operations reduced operation cost by 21 % and capital cost by 47 % in monoclonal antibody production and 80 % and 72 % cost for non-monoclonal antibody production, respectively. The breakdown cost analysis showed the ICB process has higher upstream filters and media cost but less upstream labors and downstream resins cost. In every unit operation, the capital cost is lower compared to conventional process[es]. This is mainly due to the reduced facility footprint, less frequent process turnaround, and single-use system used… Arnold et al. [67] compared integrated continuous antibody production with batch processing using experimental and computational results. By keeping the same

annual production rate, the continuous processing has 15 % lower operating cost in COG/g and the capital cost in continuous processing reduces 50 % comparing to that in batch" (Yang et al., 2019).

As shown, the overall operating and capital costs in bioprocessing are significantly reduced by utilizing continuous process operations. Additionally, David Lin confirmed that continuous bioprocesses reduce costs but also have other benefits such as the need for smaller-scale equipment, increased productivity, improved quality, and increased flexibility (Lin, 2022). However, processes today continue to operate in batch mode. In BioPlan's 18th Annual Report on Biopharmaceutical manufacturing released in 2021, BioPlan surveyed to determine the concerns and perceptions related to perfusion, or continuous bioprocessing compared to the traditional batch-fed processes (Lin, 2022). These concerns were the need for more process control, general developmental challenges, and operational complexity. However, BioPlan conducted another survey in which 75% of respondents agreed that the pharmaceutical industry would adopt completely continuous commercial-scale manufacturing facilities by 2026 (Lin, 2022). BioPlan also reported that upstream continuous processing, followed by downstream continuous purification methods were among the top two systems to be evaluated within the next year by biomanufacturers. Based on the report, biomanufacturers plan to test continuous processes themselves before hiring contract manufacturing organizations (CMOs) to implement continuous technologies. Increased popularity and hiring of CMOs are expected once companies become more familiar and comfortable with the process.

I conclude that continuous technologies have not been widely adopted due to a lack of familiarity by manufacturers and the great investment required to convert from the traditional batch process. Manufacturers would need to purchase completely new technologies and

equipment which makes implementation a costly investment. As a result, it may take some companies months, and others, years to regain investment costs and begin earning a profit. One may initially believe that investing in continuous processes would be easier for larger companies with greater revenue. However, larger companies tend to produce multiple drug products with a vast production scale of over one thousand kg per year; it would cost over 40 million dollars to fully implement continuous operations, taking up to 10 years for commercial savings (Taylor, 2021). This can be put into perspective of a homeowner considering an investment in solar panels. In Virginia, the average cost of solar panels is $11,650 with the average light bill being $200 (Brill, 2022; U.S. Department of Energy, 2023). It would take the average homeowner five years to develop a return on investment. However, in 30 years, they can expect to save over $100,000. Therefore, the initial investment of integrating continuous practices can save facilities millions or even billions over a 15-to-30-year life span.

Alternative Purification Techniques

Purification, a step in downstream processing, is the most expensive part of the monoclonal antibody production process and involves removing impurities, or unwanted substances, from the grown CHO cells. The product leaving the batch reactors following fermentation is a mixture of cells, a large volume of growth media, or solution, containing the necessary nutrients for cell growth, and the desired protein, or monoclonal antibody product. Therefore, the downstream process begins with purification methods that are used to remove impurities such as the growth media, cells, and other nonessential components to obtain a purified monoclonal antibody product. This process normally begins with a sequence of chromatography steps. Chromatography is a separation technique used to separate the desired monoclonal antibody protein from other present proteins. There are many different types of

chromatography methods that can be used depending on the desired separation. Instead of completely transitioning from batch to continuous operations, other researchers have explored new chromatography methods instead of those commonly used in monoclonal antibody production. A study found that utilizing two more efficient chromatography units in sequence resulted in maintaining similar capital costs to batch operations, but a 20% reduction in operating costs (Yang et al., 2019). Researchers used a simulation design software to design an upstream continuous process using the chromatography methods described in the study; with a production goal of 2000 kg per year, this design simulation displayed a higher net present value (NPV), higher internal rate of return (IRR), and shorter payback time (Yang et al., 2019).

Utilizing Single-use Equipment

Studies show that the stainless-steel equipment used in batch processes result in higher costs due to greater cleaning requirements (Yang et al., 2019). Ou Yang and coauthors argue that multi-use systems with stainless-steel technologies are no longer feasible approaches to drug manufacturing as competition and release of biosimilars have increased in the monoclonal antibody market. Therefore, manufacturers have explored more cost-efficient single-use systems integrated with continuous processes. However, manufacturers have concerns related to cost and scaling up these processes utilizing this more efficient production method. Renaud Jacquemart and coauthors describe a strategy in which facilities can overcome "scale limitations and enable cost-efficient manufacturing to support the growing demand for affordable biologics" (Jacquemart et al., 2016). Single-use systems result in a decreased risk of cross-contamination and reduced start-up time. A particular single-use facility had 22% lower operating costs than a stainless-steel facility due to reduced labor, utilities, maintenance, and minimal waste. Investing in a new single-use manufacturing facility rather than redesigning a current facility is less costly

due to the need for smaller equipment and building space, with an initial total capital investment of approximately $150,000,000 less than building a stainless-steel facility. Other benefits include a space reduction of 87%, a decrease in capital costs of 67%, and an overall decrease in the cost per gram of the monoclonal antibody product. Single-use monitoring systems for measuring temperature, pH, dissolved oxygen level, and biomass decrease sterilization and contamination requirements (Jacquemart et al., 2016).

However, single-use technologies are often made from plastic materials which raises the concern of extraction of certain contaminants (Jacquemart et al., 2016). Compounds toxic to living cells can leach from single-use bags, negatively affecting the growth of the cell culture. Environmental effects such as the safe disposal of large amounts of plastic waste are also concerning. Manufacturers would need to utilize landfills to properly dispose of the plastic material. However, environmental benefits such as reducing the use of cleaning products, energy and water consumption, and carbon emissions outweigh the proposed disadvantages (Jacquemart et al., 2016).

Treatment Conditions and Limitations

Treatment of Infectious Diseases

There are currently a limited number of monoclonal antibodies available to treat infectious diseases. However, there are some in development to treat Ebola, influenza, hepatitis B, HIV, and COVID-19 (Kelley et al., 2021). For example, the World Health Organization (WHO) has recommended two monoclonal antibodies for Ebola virus treatment; clear benefits were observed based on clinical trials done in the Democratic Republic of the Congo during an Ebola outbreak (United Nations, 2022). However, the UN also emphasizes that access to those in critical need, which includes poorer, underserved communities, is continually challenging. One

of these key challenges is regulatory issues; resource-constrained countries such as Africa lack defined pathways to register biologics, or treatments such as monoclonal antibodies. As a result, the process to launch the use of treatment drugs can be heavily delayed. A more defined and collaborative regulatory process will aid in the faster launching of drugs. The US Health Affairs encourages technical agencies and donors to assist LMICs in this process (Sanders et al., 2021).

Patient Side Effects

As described previously, monoclonal antibodies can be used to treat conditions such as cancer and to detect diseases such as HIV and AIDS. Scientists initially believed that monoclonal antibodies would be widely used to identify and treat many conditions. However, the bodily side effects of monoclonal antibodies have made them not as widely used as initially expected. In 2006, a human drug trial for a monoclonal antibody treating arthritis and leukemia resulted in organ failure in the participants even after successful testing in animals (BBC, 2022). Other side effects are specific to the monoclonal antibody which can include bleeding, skin toxicity, and a negative reaction at the infusion site (Manis, 2023).

Technological Limitations of Shipping and Storage

Many monoclonal antibodies are required to be transported under refrigerated conditions to maintain the quality of the drug product. This makes it more complex to safely ship drugs from US and European manufacturing companies to LMICs. Storage temperatures are relatively low, typically ranging from 35°F to 47°F (Intelligent Audit, 2023). Prolonged storage at higher temperatures are not recommended. Shipping companies offer various methods to safely regulate the temperature of pharmaceuticals during transport. Pharmaceutical products can be packed into portable refrigeration units which requires a power source, or stored in insulated containers with coolants such as gel packs (Flat World Global Solutions, 2022). Refrigeration units allow for

unexpected shipment delays while insulated containers are only safe for a predetermined amount of time, typically 4 to 5 days. The destination country must also have appropriate storage warehouses and administration facilities to hold the monoclonal antibodies at required temperatures. Shipping and storing monoclonal antibodies can be costly for both the manufacturer and the destination country. It is imperative for manufactures to consider all shipment methods and ensure that other countries, especially LMICs in critical need, have appropriate storage facilities.

It is also critical for countries to have administration locations to treat adverse reactions and to accommodate the extensive infusion time. Data to determine the efficacy of certain monoclonal antibodies have not been collected in LMICs such as on African populations. Therefore, LMICs must have the appropriate technology to collect and transmit data to manufacturers to monitor patient efficacy. Providers including doctors, nurses, and pharmacists in LMICs must also be well-trained in monoclonal antibody administration and the treatment of side effects. Manufacturing companies can also send doses to countries in need; in 2021, Eli Lilly planned to deploy doses to treat COVID-19 to LMICs (Sanders et al., 2021).

Social and Cultural Factors on Susceptibility to Monoclonal Antibody Treatment

Social and cultural factors play a role in the decision of high-risk patients to consent to monoclonal antibody treatment for mild-moderate COVID-19. A variety of covid-19 monoclonal antibodies were offered to 2,820 adults in the Midwest over a 1-month study in 2020. 59.1% accepted monoclonal antibody treatment; most of these patients were non-Hispanic white with English as their primary language. Other common characteristics were having a life partner, or spouse, being religious, and having more than one medical diagnosis. In summary, race,

language, ethnicity, and support system were determined to play a role in the susceptibility to monoclonal antibody treatment (Bierle et al., 2021).

Ethical Limitations: Case Studies

Covid-19 Case Study

Healthcare company, ASPR TRACIE, conducted an interview with COVID-19 healthcare experts regarding ethical issues related to COVID-19 treatments (Debruin et al., 2022). Debra DeBruin describes an ethically troubling "level of inconsistency" in vaccine access worldwide. JP Leider infers a difference between the Trump and Biden administrations and previous administrations on equity considerations for vaccines. Those who were white and more privileged had an advantage in access over colored communities. Also, younger groups were given priority for vaccines over the dying 80+ age COVID-19 patients. The government had a goal to get as many people vaccinated as possible. Consequently, privileged individuals were able to get vaccinated more easily due to reasons such as the ability to pay, take time away from work, access information, and trust in the healthcare system. Therefore, the government's focus on speed, rather than equity, allowed greater inequities to arise in vaccine distribution. The MNRAP was a Minnesota-founded web-based questionnaire to determine patient eligibility for the new COVID-19 monoclonal antibody treatment. Higher scores on this questionnaire corresponded to a greater priority and need for treatment. However, the MNRAP was only available online and in English, excluding input from a large percent of the population (Debruin et al., 2022).

Henrietta Lacks Case Study

Monoclonal antibody design can either be done synthetically, through artificial cells or naturally, using human cells (B cells) (Glassy et al., 2014). Where and how these cells are

obtained becomes an ethical dilemma. There are certain instances when human cells are necessary to design an effective monoclonal antibody. These cells can be obtained from human blood donations. This causes ethical questions to arise such as, “If scientists make a substantial scientific breakthrough using the donated blood, should the donors be compensated?" Henrietta Lacks was an African American whose cells, also known as HeLa cells, were collected and are still used today to aid in scientific discovery. There is no record of Johns Hopkins hospital obtaining proper consent from Lacks and she was never aware of the impact that her cells had on the world. Her family was also never compensated for the contribution and great profit made on behalf of her cells. There was no medical rule or regulated law which required compensation either. However, concepts such as human respect, ethicality, and morality make this an important discussion. Other explored options to obtain B cells include inmates or military volunteers. Can the large amounts of leftover patient blood post-operations and procedures be used for research? Should patient consent be required or is the patient’s blood now the property of the facility? This article argues that introducing a consent system does require extra costs that could instead be used on research and scientific advancements. Therefore, the balance between ethics and improving human health is a challenge (Glassy et al., 2014).

Government Authorization Case Study

On January 25, 2022, there were over 2000 appointments in Florida for COVID-19 treatment (Governor DeSantis Staff, 2022). Biden’s Food and Drug Administration (FDA) revoked the emergency use authorization for Regeneron and Eli Lilly monoclonal antibodies, preventing those in need to obtain treatment. Governor Ron DeSantis argues that this abrupt action would prevent lifesaving treatments from being accessible to both Floridians and Americans. DeSantis argues that the FDA was a leading actor in this decision and did not have

adequate technical reasoning from proper sources such as healthcare providers or clinical studies. As shown, politics and governmental policies can influence access to monoclonal antibodies (Governor DeSantis Staff, 2022).

Discussion

As shown, the main cause of the inaccessibility of monoclonal antibodies to LMICs is that they are expensive products. However, the costs of production can be reduced by utilizing alternative methods. One of these solutions is utilizing continuous equipment and technologies rather than traditional stainless-steel batch reactors. Stainless-steel reactors are harder to clean and maintain, making them less feasible for use in production processes. The capital and production costs are also lower for continuous versus batch processes. Also, the environmental benefits outweigh the concerns that some may have regarding continuous production. Another cause of limited monoclonal antibody access is the lack of effective governmental regulation in LMICs. This causes a delay in the launch time for effective drugs and monoclonal antibodies. Therefore, more established countries should make aiding LMICs and poorer areas in developing collaborative policies a top priority to assist in faster launching and treatment of those in need. It is also important that the government issues equity policies to ensure that treatment is prioritized based on level of need rather than wealth, or social status.

There are also a limited number of monoclonal antibodies available for various infectious diseases. However, there are some available such as treatments for the Ebola virus. Therefore, it is imperative that the World Health Organization, major companies, and donors aid countries in obtaining the necessary storage facilities and treatment locations to safely store and administer drugs. Knowledgeable physicians, doctors, and other healthcare personnel should consider traveling internationally to these LMICs to offer assistance in the scope of their study to ensure

that the maximum number of people are treated. Local health organizations and medical programs should prioritize informing all patients and demographics of the benefits of treatment to reduce uniform resistance to treatment. Based on my analysis of both the human and non-human actors on limited global access to monoclonal antibodies, I conclude that global access can be improved at all levels: manufacturing companies, governmental regulation, patients, and providers. I believe that all social groups must work collectively for society to observe effective changes promoting an increase in global access.

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