Manufacturing an RNA Therapeutic for Duchenne Muscular Dystrophy
(Technical Paper)

Sociotechnical Construction of Biosimilars in the United States
(STS Paper)

A Thesis Prospectus Submitted to the

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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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Approved _____ Date _____
Sharon Ku, Department of Engineering and Society

Introduction

With the massive research effort into gene therapies, new pharmaceutical drugs are being developed to aid and potentially cure a wide new range of disorders. My technical capstone project involves the development of a novel therapeutic drug to treat Duchenne muscular dystrophy. The therapeutic of choice will be an antisense ribonucleic acid (RNA) oligonucleotide. This technical project addresses the need for an orphan drug therapeutic from a purely one-dimensional technological problem.

However, there is a larger societal problem that emerges from the implementation of novel biologic drugs. Due to the high research and development costs and long regulatory timelines associated with producing a novel therapeutic, the price of these "wonder drugs" has greatly outpaced any other commodity or service in the United States. These drugs were aimed at addressing many major diseases areas such as cancers, respiratory illnesses, and diabetes. However, there have been noticeable adverse effects on the American healthcare system. While some biologics are capable of greatly reducing patient mortality, their shrinking affordability has limited the availability and quality of healthcare. Biosimilars are biologic drugs with high similarity to patented, reference biologics. They have been touted as a potential solution to the rising drug prices, with many claiming that they could cause drastic drops in biologic drug prices similar to those seen with generic small molecule drugs. Biosimilars are an emerging technology with the intention of solving a societal problem and must therefore be studied from an interdisciplinary perspective focused on the interactions between science, technology, and society. This societal project addresses the function of biosimilars in aiding healthcare reform in the United States.

Technical Prospectus

Duchenne muscular dystrophy (DMD) is a genetic disorder characterized by progressive muscle degeneration and weakness that impacts roughly 1 in 3,500 males born worldwide each year. DMD is caused by mutations in a gene that encodes for dystrophin, a protein responsible for the structural integrity of muscles during contraction and relaxation. In the majority of those born with DMD, deletions of segments of this gene interrupt the production of dystrophin, leading to the formation of weak and damage-prone muscle cells. Typically, the symptoms of DMD onset early in childhood between the ages of two and three, occurring almost exclusively in males. DMD causes muscular atrophy, usually starting in the core muscular region before impacting the muscles in the limbs. By the age of twelve, those affected will experience multiple organ dysfunction, resulting in serious heart and lung conditions (Nguyen and Yokota, 2019). There is currently no cure for DMD and diagnosed individuals on average do not live past their twenties. This life expectancy varies greatly and has increased with improvements in cardiovascular and respiratory care, with some patients living into their thirties and forties (Malcolm, 2019).

Nearly all current treatments for DMD focus on treating the associated symptoms, but there have been breakthroughs in new oligonucleotide therapies with potential to prolong the lives of those afflicted by the disease in recent years. These new treatments target the DMD gene mutation itself, tackling the problem at its source. Vyondys 53, or golodirsen, is the first FDA-approved therapeutic aimed at mitigating DMD-related symptoms and serves as motivation for this project. This technology is centered around the *in vitro* synthesis of RNA, genetic material that provides instructions to the body on how to construct proteins. By creating an RNA molecule specific to the mutated DMD gene and introducing it to diseased muscle cells, DMD

symptoms can be alleviated, and life expectancy can be extended. Crucial materials in this therapeutic process are antisense oligonucleotides (AOs): short, synthetic, single-stranded DNA or RNA sequences that can either reduce, restore, or modify protein expression (Rinaldi and Wood, 2017). A study published in 2019 describes how an AO can be designed to modify the RNA sequence associated with the mutated dystrophin gene in such a way that it would produce a truncated and partially functional dystrophin protein rather than no dystrophin protein at all as can be seen in Figure 1 (Nguyen and Yokota, 2019). This increases the presence of dystrophin in muscle cells, reducing the symptoms of DMD.

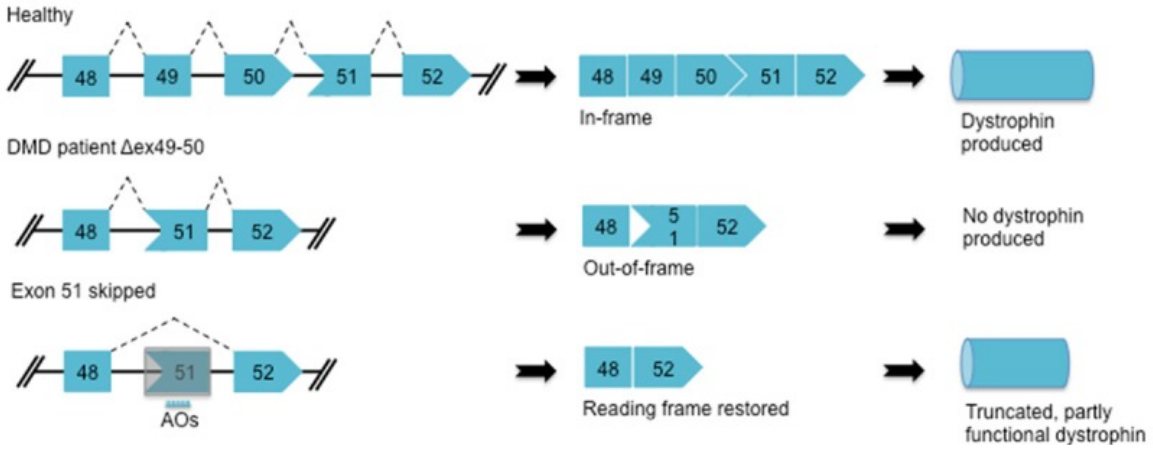

Figure 1. Normal, mutated, and treated dystrophin gene, showing the process through which the oligonucleotide functions (Nguyen and Yokota, 2019).

This capstone project will focus on developing a biochemical process to manufacture this RNA therapy and formulate it for delivery. Figure 2 shows an overview of the RNA production process (Bancel et al., 2019). The scope of our project will include the *in vitro* transcription process through the ultrafiltration/diafiltration and sterile filtration process. *In vitro* transcription will be carried out by an RNA polymerase and linearized DNA template in a fed-batch bioreactor. The bioreactor will also contain a transcription buffer, nucleoside triphosphates, magnesium chloride, and RNase inhibitors. Production of the linearized DNA from recombinant

E. coli will be outsourced to a contract manufacturing organization. The nucleotide triphosphates, magnesium chloride, and RNase inhibitors will be purchased from a supplier.

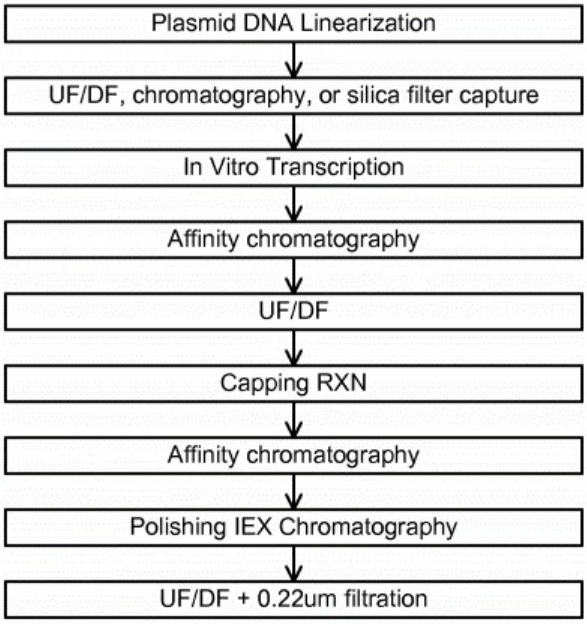

Figure 2. Overview of the generalized RNA production process (Bancel et al., 2019).

The output of the bioreactor will primarily contain the desired RNA sequence, premature sequences, linearized DNA, and polymerases. The RNA produced in the *in vitro* transcription reaction will need to be capped to prevent degradation. The purification process must be designed such that the target RNA is not destroyed or harmed, while effectively removing contaminants. High level separations will occur to achieve the proper purity and potency requirements of the final product. Chromatographic systems are biochemical separations processes that allows for the separation of compounds based on physical and chemical interactions between mobile and stationary phases. This project will predominantly involve the design of the bioreactor and the chromatographic separation systems, as well as intermediate filtration units. Chromatographic methods used in this manufacturing process include anion exchange, biospecific affinity, and ion exchange. Ultrafiltration and diafiltration will be used to

both concentrate our RNA and to formulate it into water for injection. The final sterile 0.22-micron filtration will be designed to fill our final product into vials. The output of the process as a whole will be a high purity, high potency RNA therapeutic formulated for delivery to the patient.

This design project will be completed with a four-person team consisting of Catherine Barton, Emma Laudermilch, Will McDevitt, and I over the course of two semesters as part of CHE 4438 and 4476 with Professor Eric Anderson as our technical advisor. In the Fall semester, we will formulate a preliminary design plan that will outline the process and provide details pertaining to the final product being manufactured, the intended starting materials, production scale, brief economic appraisal, and process overview. The process overview will include high-level schematics depicting the flow of material through the process and required equipment for the synthesis, purification, and formulation of our final product. In the Spring of 2021, we will complete our process design, which will include specifications for each unit operation such as the type, scale, energy requirements, and operating conditions of all equipment used, product purity standards, environmental and safety considerations, and an economic analysis of the process.

To complete this work, responsibilities will be split evenly amongst the four group members with weekly meetings for progress checks and working meetings as needed. In addition, we will meet with Professor Anderson as needed to share progress and obtain project recommendations. Other resources for this project are members of the UVA Chemical Engineering faculty with a background in bioengineering, pharmaceuticals, bioseparations, and process safety. The primary tools we plan to use for this project are MATLAB for complex calculations and plotting, Aspen Plus for design simulations, and Lucidchart for process flow

diagrams. Design data will be retrieved from literature and patents available on RNA therapeutics and oligonucleotide manufacturing. We aim to apply elements of previous designs to this project to create a safe and cost-effective process to manufacture RNA based therapeutics that can remedy DMD at its genetic source and alleviate symptoms of the disease, extending the life expectancy of the millions impacted.

STS Prospectus

Research Question

Biosimilars have been proposed by many as a possible solution to drug accessibility and affordability. This stems from the expectation that they will have a similar groundbreaking impact on the overall American health care system as generic small molecules. This is an ongoing conversation in the United States with the Food and Drug Administration redefining insulin as a biologic rather than a small molecule in March. This would allow for future biosimilar insulins and interchangeable insulins to enter the market and therefore reduce the financial burden on patients. However, this problem is not simply a one-dimensional technical problem. Proponents of biosimilars advocate for their ability to improve both quality and affordability of healthcare. However, ethical concerns exist regarding their expedited regulatory processes which may introduce safety and efficacy risks to the patient. The effects of biosimilars on society is a wicked problem that has been extensively studied by others within the realm of science, technology, and society. Much research into drug affordability and availability has been centered on the origin of this sociotechnical problem, the development of biosimilars, and future improvements to the integration of biosimilars onto the market. This sociotechnical analysis of the impact of biosimilars in the United States will aim to answer the following research questions via social construction of technology, actant-network theory, and artefactual politics:

- How can the expansion of biosimilars address drug affordability and availability?
- Can expedited regulatory approval processes and drug interchangeability be morally justified, given potential for increased risks to patient?
- Could biosimilar expansion in the United States mirror similar successes seen in Europe and other major countries around the world?

- How do legislative and political differences between the European Union and the United States affect the potential of biosimilars?

Literature Review

The origin of drug availability and affordability can essentially be studied by analyzing the ethical and moral issues surrounding patenting of medicine. Sterckx (2005) studies the ethical question of drug patents, particularly whether or not they are morally justifiable. The author presents their analysis by investigating natural rights, distributive justice, and utilitarian arguments. The overall analysis is framed with the perspective that drug patents are evolving away from their initial humanitarian nature. An argument for reevaluating drug patenting is made in order to return to the ultimate goal of benefitting society and expanding accessibility to medicine. Crespi (2005) analyzes the ethical and legal dilemmas surrounding patenting of biologic materials and processes. The author presents the rationale and justification of both pro- and anti-patent arguments from the perspective of a patent professional. Each argument is framed with regards to the key stakeholders which include research scientists, governmental bodies, and health care organizations. A comparison study is also made between the United States and Europe regarding the role of patent law in the development of biomedicine.

The impact of biosimilars emerging onto the pharmaceutical market is the primary focus of this research study and has thus been evaluated extensively. Boccia et al. (2017) investigate the potential for biosimilars to address health care reform in the United States. The authors evaluate the current impact of biosimilar expansion on accessibility, affordability, and quality of health care. This evaluation is framed with regards to the goals of the Affordable Care Act, which sought to expand health care coverage, lower costs, and improve quality of care. Morton, Stern, and Stern (2018) investigate the effects of the entry of biosimilars onto the pharmaceutical

market, with a focus on prices and market shares. The authors stage their analysis to predict the impact and success of biosimilars in the United States over next several years. This analysis was carried out by investigating how market features and public policies influence product penetration and competition. Zhai, Sapatwari, and Kesselheim (2019) investigate the slow rollout of biosimilars onto the market since the Biologics Price Competition and Innovation Act of 2009 was passed. The authors focus on the lack of the lack of success biosimilars have seen in the United States by examining the current landscape of the pharmaceutical market, anti-competitive tactics employed by patent-holders, and ethical barriers to wide-spread adoption of biosimilars.

Biosimilars have had varying levels of success across the world and therefore it is necessary to study these differences to determine areas of improvement for the United States. Rathore and Bhargava (2020) provide an overview of the current status of biosimilar development in developed economies across the world. The innate complexity of biotherapeutics and their dominance over drug pipelines of pharmaceutical companies across the world have created unsustainable healthcare costs in many of these developed nations. The authors investigate the rise of biosimilars as a potential solution to address drug affordability. The regulatory processes for approval of biosimilars is of particular focus in this analysis. Furthermore, the authors provide comparisons between the current state of biosimilars in each development economy studied, including the United States, Europe, South Korea, Canada, and Japan. Moorkens et al. (2017) provide an overview of current biosimilar policies across Europe. The authors focus on drug availability, affordability, quality, and policies to promote their growth. The overview is framed with regards to the European Medicines Agency and its goal in establishing a sustainable yet competitive biologics market.

There are many current pitfalls and downsides to current biosimilar development that may be addressed to improve their societal impact. Diependaele, Cockbain, and Sterckx (2018) present an argument against the adoption of biosimilars. They argue that biosimilars are not the solution to improving costs and accessibility of health care. The authors present their argument via an analysis of the current regulatory pathway for biosimilars in the United States and the European Union. Potential solutions to the shortcomings of current biosimilar development are also presented. Hemphill (2020) reviews the current pitfalls of the regulatory processes in the United States. The author particularly focuses on areas of improvement regarding the interchangeability of biosimilars and incentives for second-to-market drugs. The arguments for these improvements are investigated with the aim of facilitating price competition for the benefit of the patient. Jones (2005) presents an argument against the overregulation of pharmaceutical drug development. The argument particularly focuses on the unnecessary and superfluous nature of phase III clinical trials. The author argues that including pharmaceutical companies in the development of regulatory clinical trials will establish a more efficient drug development process to minimize cost to the consumer.

STS Frameworks and Methodology

The main frameworks used to study this wicked problem will be social construction of technology, with artefactual politics and actant-network theory as supporting frameworks. Social construction of technology will aid in defining the various stakeholders present in this complex sociotechnical system. Artefactual politics will aid in analyzing the power and authority biosimilars hold in society. The interplay between each of these stakeholders will then be investigated through actant-network theory.

Due to the high quantity of stakeholders in this sociotechnical system, it is important to study the associated social construction. Social construction of technology analyzes the interdependence of social and technical elements by considering technologies as social constructs. There is much interpretational flexibility in the differing social groups involved in this system. Pharmaceutical companies and government legislators may have entirely different rationale behind pursuing biosimilars, leading to differing interpretations of the technology. The variability in interpretation is important to analyze to not only analyze the effectiveness of biosimilars in improving drug affordability and availability, but to determine key limitations that must be overcome in the United States to achieve their full potential in improving the American healthcare system.

The implementation of biosimilars onto the pharmaceutical market may be seen as an infringement on intellectual property rights and the free market. Therefore, it incorporates politics into this sociotechnical system that may greatly differ when switching perspective. These artefactual politics heavily influence the social order, decision making, and deployment of biosimilars. Pharmaceutical companies, regulatory agencies, and medical professionals together make up the social order of healthcare in the United States. As owners of intellectual capital, pharmaceutical companies are typically the sole decision makers. Finally, deployment of novel biosimilars is entirely dependent on cooperation between each of these stakeholders.

As part of the social construction of this system, key important actant-network interactions are worth investigating. In particular, it is especially important to analyze the interplay between human and nonhuman actants. Actant-network theory analyzes the role of different social or technical groups within the sociotechnical network. Besides biosimilars themselves, other important nonhuman actants include legislation and medical prescriptions.

Legislation holds significant power as it determines the legality and specifications of what constitutes a biosimilar. Furthermore, medical prescriptions are the final barrier to biosimilar treatments for patients and directly elevate the position of power for medical professionals within the established social order. Each of the stakeholders listed previously are important relevant social groups that together cooperate to construct this complex sociotechnical system.

For my research paper, I have decided to use document analysis as my primary research method. I will utilize academic journals, scholarly articles, and policy legislature to provide substantial evidence behind my claims. My sources will come from a variety of databases. Some of these will be directly related to STS while others will focus on the technical aspects of biosimilars. An example of this will be technical papers investigating the similarity and drug potential of similar biologic drugs or the accuracy and risk associated with clinical trial data extrapolation. Possible sources of bias involve underlying political or economic ideologies which I hope to address by consulting a variety of sources from multiple academic journals.

Timeline

To complete this work, I will space out the work over the course of the next semester by setting goals and milestones. Some of these milestones include an outline, first draft, second draft, and final draft. Each milestone will be evenly spaced over the course of the semester with ample time to make final adjustments prior to submission. I plan to set some time to work on this social paper every week. Furthermore, I will weekly self-evaluate the progress made towards the next milestone and decide if a meeting with Professor Ku would be beneficial.

Conclusion

The purpose of this research paper is to analyze the adverse societal effects of biologic therapeutic treatments on the quality of healthcare in America and to investigate a potential solution to a rather wicked problem. Biologic therapeutics have inadvertently reduced the quality of healthcare by reducing the affordability and availability of life-saving treatments. Biosimilars have emerged as a prospective solution, with the ability to greatly improve quality of patient care for the average American. However, biosimilars are still a new technology that requires sociotechnical analysis to determine its role in contemporary society. By including all relevant stakeholders in the implementation of biosimilars, they may result in profound improvements in American healthcare.

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