Prospectus

Production of Golodirsen for the Treatment of Duchenne Muscular Dystrophy
(Technical Topic)

An Analysis of the Prescription Drug Pricing System in the United States
(STS Topic)

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

At just three years old, doctors diagnosed Jack Hogan with Duchenne Muscular Dystrophy (DMD), a genetic disorder characterized by progressive muscle degeneration and weakness. By age 7, Jack was wheelchair bound and struggled to hold his head up on his own. By 12, Jack's respiratory and cardiac systems were severely comprised. With the help of corticosteroids and anti-angiotensin enzyme inhibitors to prevent muscle degradation and heart damage, his condition began to stabilize. In late 2018, his doctors predicted that he could live into his mid-20s, around the average life expectancy for DMD patients (Diseases- DMD 2020). Around this time, doctors informed Jack's parents of a newly approved gene therapy for DMD that could address the mutation in Jack's dystrophin gene that caused the disease. The dystrophin gene codes for the production of the dystrophin protein, which is responsible for the structural integrity of muscles during contraction and relaxion cycles. This new gene therapy could trigger the production of a partially functional dystrophin protein in Jack's body, addressing the cause of his medical issues rather than the symptoms. However, with an annual price tag of $300,000, and Jack's condition relatively stable, his parents decided to delay the use of the therapy until the need was more dire. Unfortunately, on March 31, 2019, Jack's lungs suddenly failed in his sleep. Without any prior indication that his health was worsening again, Jack passed away at just 14 years old.

DMD impacts roughly 1 in 3,500 males born worldwide each year, with an estimated 250,000 active cases in the United States today (Sarepta Therapeutics 2020). In the majority of those born with DMD, deletions of segments of the dystrophin gene interrupt the production of dystrophin protein which leads to the formation of weak, damage-prone muscle cells. DMD causes muscular atrophy, usually starting in the core muscular region, and then impacting the muscles in the limbs. By the age of 12, those affected will experience multiple organ dysfunction, resulting in serious heart and lung conditions (Nguyen & Yokota 2019). Currently, there is no cure for

DMD, and nearly all treatments for DMD focus on treating the associated symptoms (Malcolm 2019). In recent years, however, there have been breakthroughs in mutation-targeting oligonucleotide and RNA therapies like the one Jack's doctors mentioned to his parents. These new therapies offer an exciting possibility to prolong the lives and improve the standard of living of those afflicted by the disease. Vyondys 53, or golodirsen, is an FDA-approved therapeutic aimed at mitigating DMD-related symptoms and serves as motivation for this project (Sarepta Pharmaceuticals 2020). The technical aspect of this capstone will center on the design of a process to produce golodirsen, including an *in vitro* bioreactor followed by several separation and purification steps. As exciting as these new therapies are, so many Americans are unable to access them as prices of both new and existing prescription drugs continue to rise. The STS aspect of this project will analyze the factors which have contributed to this continual rise of prescription drug prices in the United States.

Design of a Manufacturing Process to Produce Golodirsen

Currently, Duchenne Muscular Dystrophy patients undergo treatment that manages their symptoms rather than targets on the genetic mutation that causes the disorder. Glucocorticoids are often used to maintain muscle strength and function in children. (Strehle & Straub 2015) Corticosteroids, ACE inhibitors, and other medications typically used to help improve heart function are often prescribed. These medications can greatly improve the standard of living of patients and have been proven to significantly delay the onset of serious heart and lung conditions (Nguyen & Yakota 2019). However, there are significant complications associated with the long-term use of these medications, including weight gain and bone fractures (Strehle & Straub 2015). Furthermore, none of the common practices trigger the production of the dystrophin protein, so symptoms can at best be mitigated, never eliminated. As gene therapies continue to develop, more

clinical trials show promising evidence that manufactured mRNA can be used to trigger the production of dystrophin in certain DMD patients. The following will describe the function of golodirsen, a conditionally FDA-approved mRNA therapy, in the production of dystrophin as well as describe the necessary steps to design a process to manufacture the drug.

Crucial materials in this therapeutic process are Antisense Oligonucleotides (AOs), short, synthetic, single-stranded DNA or RNA molecules that can alter RNA molecules in such a way that they can either reduce, restore, or modify protein expression (Rinaldi & 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 & Yokota 2019). This enables fully-functional dystrophin to exist in some muscle cells, weakening the symptoms of DMD (The Science and Fundamentals of mRNA Technology 2020).

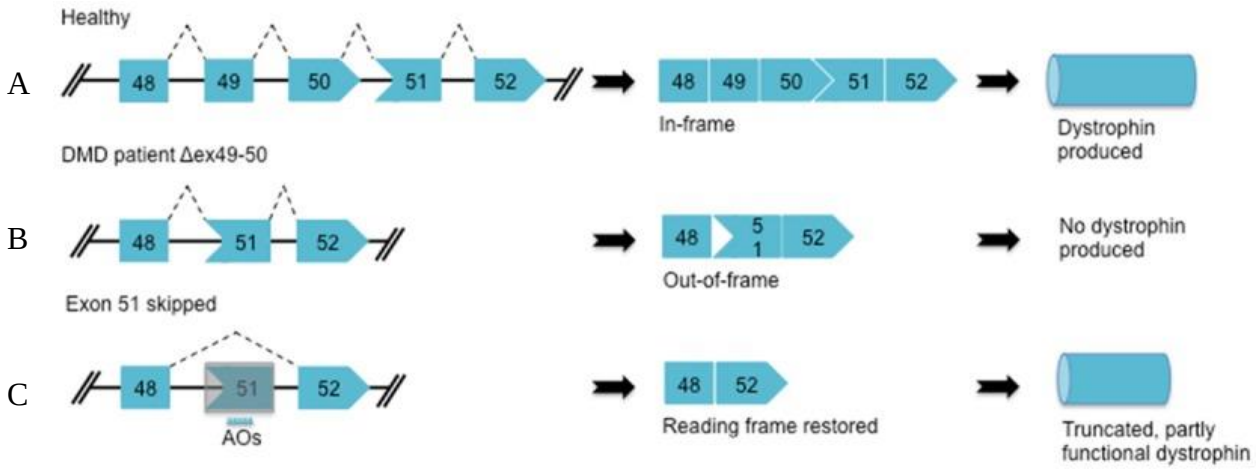

Figure 1. Retreived from Nguyen and Yakota, 2019. Description of exon skipping in DMD patients. A shows a healthy person's exons joining in frame to produce dystrophin. B shows a DMD patient's exons. Because exons 49 and 50 are missing, exons 48 and 51 cannot join in frame, resulting in an early termination of the amino acid sequence and a complete lack of dystrophin protein. C shows the function of the AO. The AO will bind to exon 51, causing it to fall out of the sequence. Exons 48 and 52 can then join in frame and a partially functional dystrophin protein will be produced

Our capstone project will focus on developing a biochemical process to manufacture this RNA therapy and formulate it for delivery. The general production process described in the patent filed by Bancel, Issa, Ins & Chakraborty will be followed (2014). *In vitro* transcription will be carried out by an RNA polymerase and linearized DNA in a batch bioreactor. Production of the linearized DNA from recombinant *E. coli* will be outsourced to a contract manufacturing organization. The bioreactor will also contain a transcription buffer, nucleoside triphosphates, and RNase inhibitors. We will assume that the nucleotide triphosphates and RNase polymerases are purchased from a supplier. The output of the bioreactor will contain the desired RNA sequence other short nucleotides, linearized DNA, and polymerases. All mRNA sequences must be capped to prevent degradation. Co-transcriptional capping will be employed in this process, so the mRNA will be produced and capped in the same bioreactor. This combination of synthesis and capping will allow for much higher protein yield from the bioreactor (Funkner et. Al 2020).

All contaminants must be removed, and the purification process must be designed such that the target RNA is not destroyed or harmed. Affinity chromatography will be employed immediately after the bioreactor as it separates completed, capped mRNA sequences from all other contaminants. Following affinity chromatography, ion exchange chromatography and size exclusion chromatography will be employed to isolate the desired mRNA sequence from the undesired sequences. Ion exchange chromatography allows for separation based off differences in charge in the proteins, so any sequences with a different number of charged nucleotides will be removed (Issa, Barberio, Aunins & Afeyan 2014). Size exclusion chromatography separates proteins on the basis of molecular weight, so much shorter and much longer proteins will be removed from solution. Finally, tangential flow filtration is used to remove any unwanted buffer

or salt, ensure the solution is fit for injection into the human body, and concentrate it to the desired formulation.

The capstone project will include the design of each unit operation: the bioreactor, the affinity chromatograph, the ion exchange chromatograph, the size exclusion chromatograph, and the tangential flow filter. All design specifications will be determined, including, but not limited to, the temperature of the unit operations, flow rates, concentrations, residence times, and heat and power requirements. Cost efficiency will be considered at each stage of the design process to ensure the drug can be sold to families at the most reasonable price obtainable.

An Analysis of the Factors Influencing Prescription Drug Prices

Like Jack's family, so many Americans must factor cost into the decision to use a potentially live saving drug. New medications, such as golodirsen, rely on millions of dollars in general research, development, and technological advancement, and enter markets without any reasonable competition. Furthermore, evidence suggests that companies are listing new, introductory drugs at prices much higher than would be required to make profit (Waxman 2020). As such, these drugs tend to be listed at unreasonably high prices that could deter any American from filling the prescription. Sarepta Therapeutics, who obtained FDA approval to manufacture and sell golodirsen in 2019, estimated the average annual cost of the therapy to be about $300,000 (Figueiredo 2019). Because the medication is a therapy and not a cure, this is an annual cost for the lifetime of the patient. According to the 2019 Census, the cost of Vyondys 53 is approximately 336% higher than the median household income in the United States (U.S. Census Bureau 2019). Even with private health insurance, price tags this high can place an undue financial burden on individuals and families with the misfortune of health complications.

The issue of high drug prices is not limited to new high-cost specialty drugs such as Vyonyds 53. Americans face rising prescription drug prices for commonplace drugs already on the market, as "the median net cost of the 49 highest-volume brand drugs increased 76 percent between January 2012 and December 2017" (Waxman 2020). Net price growth has been significantly above inflation for all brand name drugs in recent years (Aitken 2015). As prices for prescription drugs continue to rise, under- or uninsured patients are faced with higher and higher copays that are often too high to afford. The drug supply chain is facing growing pressure from citizens and the federal government to change the structure of the chain, but any change could result in higher drug prices or higher insurance premiums (Entis 2019). Due to these unreasonably high prices, Americans are more likely to leave a prescription unfilled than a citizen of 9 other high-income countries (Glied & Zhu 2020). In a 2017 issue brief, the Commonwealth Fund reported findings that the United States pays significantly more for the same prescription drug than any other country studied. The political and economic systems of the United States foster environments where profit supersedes patient health, more so than any other developed country.

The Social Construction of Technology (SCOT) will be used to analyze the impact of these systems. I will study the key social groups of residents of the United States, private health insurance companies, the federal government, and large pharmaceutical manufacturers and how the interaction between these groups has led to the current drug pricing system. I will also examine proposed solutions to the issue and how these solutions impact different social groups, offering an explanation of why potential solutions have not yet been employed. I will use a multidirectional model, as proposed by Pinch and Bijiker (2008) to understand how different stakeholders view different issues surrounding the pricing of drugs. I can then analyze the potential solutions to different issues to understand how the current system addresses or fails to address these issues and

determine why certain social group's interests prevailed over others. Furthermore, the potential solutions and stakeholder interests of the two cases can be compared to understand why the pricing structure and government intervention has been different.

Research Question and Methods

This paper seeks to determine which political and economic factors have fostered an environment that allows for the continuous rapid growth of prescription drug prices in the United States. The analysis will focus on the impact of the government, major pharmaceutical manufacturers, and private health insurance companies on the determination of drug prices. Two case studies will be examined and compared to answer the question.

The first case study will examine the price of human insulin over time and determine how government intervention has or has not been successful in regulating the price of a prescription drug used by 7.4 million Americans (Cefalu et al 2018). The pricing model of insulin will be examined in depth, providing evidence of how private insurance can leave many Americans without means to afford basic life-saving medication (Glied & Zhu 2020). In contrast, the second case study will focus on orphan drugs, or specially designated drug products that treat or cure rare diseases. Because the diseases these drugs treat are so rare, their development would not typically be profitable as the market for the drugs is too small. Therefore, the United States governments provide tax breaks and other special incentives to produce these drugs to ensure these treatments are developed. However, pharmaceutical companies have taken advantage of the financial incentives (The Rise of Orphan Drugs 2019), and I will examine how and why intervention by the United States government failed in this case.

The design project will be completed with a four-person team consisting of Catherine Barton, Emma Laudermilch, Will McDevitt, and Daniel Torrico over the course of two semesters

as part of CHE 4438/4476 with Professor Eric Anderson who will serve as our technical advisor. In the Fall of 2020, 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 the development of 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.

Conclusion

Golodirsen, a newly approved mRNA therapeutic drug, shows promise in greatly lengthening the life span and improving the quality of life of patients with Duchenne Muscular Dystrophy. However, the current list price of the drug makes the therapy all but inaccessible to a significant portion of the population. Thus, a process will be designed to manufacture golodirsen in a way that can significantly reduce the annual cost of the drug. Four unit operations will be designed, and the final product of the process will be a drug product formulated for injection. Furthermore, the role of the economic and political systems in the determination of drug prices will be analyzed to determine why the United States is faced with unreasonably high drug prices. The influence of pharmaceutical companies, the federal government, and private insurance companies on drug prices will be analyzed using the Social Construction of Technology to determine how these different social groups frame the issue. Lastly, alternative drug pricing systems will be discussed to determine viable methods of reducing drug prices for Americans while appeasing other key stakeholders.

References:

Aitken, M. (2015). *Branded Medicine Price Increases and the Impact of Off-Invoice Discounts and Rebates* (Issue brief). Retrieved November 1, 2020, from https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/branded-medicine-price-increases-and-the-impact-of-off-invoice-discounts-and-rebates.pdf?la=en&hash=0E3088077952BA9CA081595445D3B1A0

Bancel, S., Issa, W. J., Ins, J. G., & T. C. (2014). *U.S. Patent No. WO 2014/152027*. Washington, DC: U.S. Patent and Trademark Office.

Cefalu, W. T., Dawes, D. E., Gavlak, G., Goldman, D., Herman, W. H., Nuys, K. V., . . . Yatvin, A. L. (2018). Insulin Access and Affordability Working Group: Conclusions and Recommendations. *Diabetes Care, 41*(6), 1299-1311. doi:10.2337/dci18-0019

Diseases - DMD - Top Level. (2020, October 02). Retrieved October 04, 2020, from https://www.mda.org/disease/duchenne-muscular-dystrophy

Entis, L. (2019, April 9). Why Does Medicine Cost So Much? Here's How Drug Prices Are Set. *Time*. Retrieved November 1, 2020, from https://time.com/5564547/drug-prices-medicine/

Figueiredo, M. (2019, December 13). FDA, in Reversal, Approves Vyondys 53 to Treat Duchenne Patients... Retrieved November 01, 2020, from https://musculardystrophynews.com/2019/12/13/vyondys-53-for-duchenne-md-with-exon-53-mutations-fda-approval/

Funkner, A., Dorner, S., Sewing, S., Kamm, J., Broghammer, N., Ketterer, T., & Mutzke, T. (2020). *U.S. Patent No. US 10,760,070*. Washington, DC: U.S. Patent and Trademark Office.

Glied, S. A., & Zhu, B. (2020, September 25). *The Commonwealth Fund* (Issue brief). doi:https://doi.org/10.26099/xbne-tj76

Issa, William Jospeh., Barberio, Joseph Louis., Aunins, John Grant., Afeyan, Noubar B., . (2014). *U.S. Patent No. WO 2014/144767*. Washington, DC: U.S. Patent and Trademark Office.

Malcolm, Emily P. (2019, June 24). Life Expectancy. Retrieved October 04, 2020, from https://musculardystrophynews.com/life-expectancy/

Nguyen, Q., & Yokota, T. (2019). Antisense Oligonucleotides for the Treatment of Cardiomyopathy in Duchenne Muscular Dystrophy. *American Journal of Translational Research, 11*(3), 1202-1218. Retrieved October 4, 2020, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6456507/

Pinch, T. J., & Bijker, W. E. (1984). The Social Construction of Facts and Artifacts: Or How How the Sociology of Science and the Sociology of Technology Might Benefit Each Other. *Social Studies of Science*, *14*(3), 399-441. Retrieved October 18, 2020, from https://www.jstor.org/stable/285355?seq=1.

Rinaldi, C., Wood, M. (2018). Antisense oligonucleotides: the next frontier for treatment of neurological disorders. *Nat Rev Neurol* 14, 9–2 from https://www.nature.com/articles/nrneurol.2017.148

Sarepta Pharmaceuticals. Vyondys 53 [package insert]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211970s000lbl.pdf. Revised2019. Accessed October 17, 2020.

Sarnak, D., Squires, D., & Bishop, S. (2017, October 05). Prescription Drug Spending Why Is the U.S. an Outlier? Retrieved October 18, 2020, from https://www.commonwealthfund.org/publications/issue-briefs/2017/oct/paying-prescription-drugs-around-world-why-us-outlier

Strehle, E., & Straub, V. (2015). Recent Advances in the Management of Duchenne Muscular Dystrophy. *Archives of Disease in Childhood*, *100*(12), 1173-1177. http://dx.doi.org/10.1136/archdischild-2014-307962

The Rise of Orphan Drugs (Issue brief). (2019, September 10). Retrieved October 18, 2020, from AHIP website: https://www.ahip.org/the-rise-of-orphan-drugs/

The Science and Fundamentals of mRNA Technology. (2020). Retrieved October 04, 2020, from https://www.modernatx.com/mrna-technology/science-and-fundamentals-mrna-technology

U.S. Census Bureau (2019) *Households by Total Money Income, Race, and Hispanic Origin of Household.* Retrieved from https://www.census.gov/data/tables/2020/demo/income-poverty/p60-270.html

Waxman, H., Corr, B., Sharp, J., McDonald, R., & Kenyatta, K. (2020). *Getting to Lower Prescription Drug Prices: The Key Drivers of Costs and What Policymakers Can Do to Address Them* (pp. 1-45, Rep.). New York, New York: The Commonwealth Fund.