Dear Insulin,

I’ve spent the last 4 years learning every technique needed to ensure that I can produce your lifesaving structure identically on massive scale. I’ve learned how to model the complexities involved in growing genetically modified E. coli which contains a plasmid for you. I’ve learned the theory behind your best reactor conditions to be produced, how to efficiently release you from E. coli’s cell wall, how to concentrate you down with tangential flow filtration, how to purify you from other proteins through liquid chromatography, and how to formulate and fill you into vials. I thought I had known everything there is to know about you.

I should have known that was only one small side of you. Your chemistry, your structure, your production is not how the world sees you. The world sees you as a sellout, someone with so much potential for good who is too expensive for the uninsured patient to afford. People are dying because of your price. They can’t see past your expensive price tag, they can’t see the true lifesaving potential you hold. The world believes that you are a pawn used by big pharma, they don’t realize how much better you’ve gotten each year and how expensive getting better was. But why should they care, you were a lifesaving drug years ago, why do you need to keep changing? Why do you reinvent yourself every few years and allow yourself to become more expensive. Is your improvement each time worth the price?

I don’t know. No one seems to have a good answer for that. It does help a majority of patients and it allows innovation to continue in the field. But it also seems like you’re only concerned about big pharma’s profits. I just wish I never realized this side of you. It was so easy when the focus was on chemistry and engineering and ensuring high quality medicine. I never thought I would have to be concerned with pricing, accessibility, and corporate profit when I began studying you. Now I don’t feel the same when I think of you. It seems like the rose tinted glasses have fallen off and I see a whole new side of you and its killing me.

Oh well. At least it was fun while it lasted.

Troy Rogerson

**Purpose and Significance of the Study**

An STS investigation is necessary to understand the current landscape surrounding insulin pricing. Insulin pricing remains one of the few pharmaceutical products that does not have strong competition in the form of biosimilar and generics to drive market prices down. The purpose of this study is to highlight factors that have prevented competition from entering the market. Additionally this study will focus on a benefit analysis on the incremental improvements being made to insulin and analyzing their value to patients. In order to address these themes the following research questions will be developed throughout the work:

1. Pricing
   1. Who are the relevant stakeholders involved in setting the price of insulin and how are they affected by this price? This will focus on patients, Eli Lilly and Company, regulators and competing companies.
   2. What market factors have maintained a unique environment for insulin sale as compared to the traditional business model for drug pricing?
   3. How has Eli Lilly historically balanced their guiding principles of meeting unmet needs for a patient with their responsibility to their shareholders to operate as profitable as possible?
2. Regulatory Issues
   1. What FDA regulation are responsible for the high cost of biologic drug development and testing? What additional restrictions are placed on therapeutic proteins that are not found in small molecule drugs?
   2. What regulatory factors have prevented generic insulin from replacing patented insulins? Who has been the driving force to maintain this environment?
3. Social Issues
   1. What level of responsibility do pharmaceutical companies have to overall public health by ensuring their products are accessible to patients?
   2. How do the relevant stakeholders define accessibility? How does accessibility impact each stakeholder?
4. Medical Issues
   1. How has the incremental improvement of insulin improved the quality of care available to diabetic patients?
5. Who benefits the most from the current insulin price point? How would each social group be affected by an increase and a decrease in insulin?

These questions are representative of current issues surrounding the pharmaceutical industry. The rapid increase in insulin price has caused the issue of accessibility to enter the national spotlight. However, an in depth analysis on the factors contributing to insulins price and the effects pricing has on patients has not been combined in a holistic analysis. In order to fully understand a cost benefit analysis of incremental improvements on insulin these two issues must be combined and analyzed together.

**Literature** **Review**

Rapid urbanization and global increase in obesity has created an environment where diabetes is expected to significantly rise. Literature is available to characterize the genetic and behavioral traits that increase the likely hood of developing type II diabetes as well as global factors contributing to the observed increase in the patients (Wilcox, 2005). This will be used within the paper to develop the identity of the modern diabetes patient specifically developing the idea that some patients have made deliberate decisions that place them at high risk for diabetes. After developing the modern diabetes patient and highlighting the projected increase in the disease, analysis of the market will be used to give insight into the current economic situation surrounding diabetes. Specifically, literature is available on the projected growth, projected price increase and the environment that has prevented biosimilars from significantly impacting the price of insulin (Z.M., 2017). The research used will then transition into looking more closely at the environment contributing to Lilly being the only U.S. Company to produce insulin and some of the factors preventing generic insulin from coming to market. A brief review will be used to go through the medical development of the first insulin products highlight the advancements that Eli Lilly and Company made to use genetically modified E. coli to grow insulin (Quianzon, 2012). This will be further developed by a review article stepping through modern advancements in insulin production. A series of drug improvements have continually increased the quality of care available to patients however, this has also created issues wherein the highest quality drug continually remains under patent protection. Additionally the article explains the current situation that prevents identical generic therapeutics, instead producing biosimilar drugs after patent expiration. The final aspect of the pricing landscape that will be analyzed is the entry of biosimilars onto the market at a price point similar to the name brand insulins (Robins, 2016).

In order to help justify the price of the therapeutics the research will shift into focusing on the value that the therapeutics add to patients’ lives. Ishii (2013) examines the change in quality of life in a sample of 500 patients beginning insulin, additionally giving significant background into the different regiments used to fully tailor glycemic control within Japanese patients. The increase in quality of life is also examined by Elrayah-Elidarous (2009) which look into the impact of diabetes on family life in low income families through a survey of 375 families with and without diabetes. The article calculates the out of pocket medical expenses that each family must cover through matching families of similar starting economic. Sable-Smith (2018) reports a more extreme case of patient inaccessibility looking into the rise of insulin rationing amongst uninsured patients and the “Insulin as A Human Right” organization. This research points out that the price of insulins is not merely an economic issue, but could result in sever ethical impacts that further justify the urgent demand of cheaper insulin. Finally the piece will look into some of the production technology that will allow the affordable scale up of insulin production as demand increases (Baeshen et. al, 2014). This will be used to highlight that innovation in production is expected to benefit shareholders though, not to lower patients.

While significant work has been done in this area current research has not adequately developed the relationship between patients, pharmaceutical companies, shareholders and insurance companies and how these stakeholders influence the price point of insulin. Given the rise in diabetes patients and rapid increase in insulin price this merits further investigation through application of STS framework.

**STS framework & Methodology**

Social Construction of Technology (SCOT) will be the main STS framework applied to investigate the research questions of interest. SCOT will be used to develop who the relevant stakeholders are and how their personal interests influence their position on insulin pricing. This will be done by defining what the price of insulin means to each relevant stakeholder to create an understanding of their interest and their relationship to this price point. Additionally, this will give a framework and lens to view the findings of the literature review and the policy review to further understand factors affecting insulin price point.

For low income patients and for uninsured patient an increase in the price of insulin significantly affects their ability to access the lifesaving care they require. The literature review has shown that pharmaceutical companies are facing significant pushback for price increases with the formation of political action committees such as “Insulin as a Human Right” with the agenda of driving insulin accessibility. This is an opposite agenda of Eli Lilly and Company stakeholders. Insulin is one of the company’s most profitable and highest revenue products, it is in their best interest to insure its price point is as high as the market can support. In addition to these more apparent stakeholders, the position of the FDA, competing biosimilar insulin producers and health insurance providers must be developed to holistically understand the price point.

The complexity surrounding a definitive issue, the different stakeholders and the lack of clear influence each possesses makes this a worthwhile topic for an STS investigation. Specifically, the interpretational flexibility surrounding insulin’s price point, accessibility and quality of care makes the application of SCOT to this system practical and useful.

**Findings and Discussion**

In order to more holistically understand the controversy surrounding Insulin accessibility as well as Eli Lilly and Company’s recent release of a generic form of Humalog insulin it is useful to approach the topic using a SCOT’s framework analysis. The motivation to cut the price of insulin and release the first generic Humalog insulin is the culminating result of recent changes with insulin’s regulation, aligning with Lilly’s driving principles and the public pressure following patient dissatisfaction.

The first key stakeholder defined within the SCOT’s analysis was the Food and Drug Administration (FDA), the FDA is one of the main drivers responsible for the recent price reduction and release of generic insulin. In order to fully understand the action that the FDA has taken it is necessary to understand the relationship the FDA has with patients, biologic medicines such as insulin, and insulin manufacturers. First it is necessary to understand the traditional pharmaceutical pricing model and the FDA’s distinction between small and large molecule medicine in releasing generic medicine. In the current regulatory environment pharmaceutical companies have 7 years after patent application to exclusively sell their therapeutic (1). This creates an environment that rewards pharmaceutical companies for innovative medicines where they have xxx years of exclusive patent rights to recover their investment from research and profit from their therapeutic (1). After this 7 year window the company loses exclusive patent rights opening the door for other pharmaceutical companies to produce an identical version of the medicine. This creates competition and gradually drives the price of the therapeutics down (Cite Julia’s thing and maybe extend it). In order to qualify as a generic drug the emerging manufactory must demonstrate an identical chemical characterization (cite King). In the past, this has worked well for small molecule medicines, it is possibly to use analytical chemistry to demonstrate equivalence(1). This is not the case for large molecule therapeutics, complex biologics are orders of magnitude larger than small-molecule drugs making it impossible to know on an atom-by-atom if one large molecule drug is the same as another (1). Subtle differences in the overall process can lead to differences in the final product’s structure impacting the safety or efficacy of the product. There is a regulatory avenue that pharmaceutical companies may take in order to produce and sell biosimilar large-molecule products that mimic the overall clinical effect of the original drug. However, to ensure product safety and efficacy required for large-molecule biosimilar a full production scheme must be assembled, validated and may require clinical bridging studies to gain FDA biosimilar approval (Cite King).

Bob Meyer M.D., the former Director of the Office of Drug Evaluation who focused on insulin regulation during his 25 years of experience with the FDA outlined some of the subtle policy that have previously prevented generic insulin from entering the market. Dr. Meyer emphasized that in terms of policy the largest barrier from generic insulin was explained through its classification as a small molecule drug. Currently, insulin is regulated under the Federal Food, Drug and Cosmetics Act as a small molecule therapy. This is the result of how long insulin has been an approved drug as well as how well characterized insulin is. Under this classification companies cannot pursue the well-established biosimilar pathway to produce insulin, instead a company must go through an approval pathway under 505(b)(2) of the FDC Act. Dr. Meyer emphasized that this is not a well-established pathway for drug approval and is unattractive to potential biosimilar producers. The current pathway would involve 5 years to construct a full scale plant to demonstrate the biosimilar can be made and clinically demonstrate equivalence. After this period of time the insulin would be outdated and difficult to capture a significant portion of the insulin market. However, effective in 2020 insulin will be classified as a biologic product under the FDC act. He believed that this is the main driving force that has forced Eli Lilly and Company to release their generic version of insulin in anticipation of other insulin biosimilar products entering the market. This reclassification is the result of Scott Gottlieb, the FDA commissioner, overall to help lower the prices of insulin within the market scape (3).

However, currently and in 2020 after this new reclassification, it is necessary to understand how Eli Lilly and Company approach the idea of biosimilarity patient health and patient accessibility. Lilly is the largest insulin producer within the United States and has very clearly established public opinion towards the use of biosimilars in place of their name brand drugs. Unsurprisingly, Lilly does not have a positive stance on the use of biosimilarites. This is seen in Lilly’s defense that biosimilars should not be interchangeable with the name brand product in the same general manor that generic small molecule drugs are interchanged (site lilly policy). The company cites concern from subtle differences between the name brand drug and the biosimilar, in order to change to a biosimilar Lilly says this decision must be evaluated by a physician and then a new prescription must be written. The company believes that this ensures that patients will receive the highest quality medicine and allows a physician to evaluate the safety between their name brand drug and the biosimilar in question (cite lilly).

This brings into question the companies approach towards drug accessibility since the company’s position appears very negative towards cheaper alternatives available to patients. Lilly has maintained a position that they strive to make medicines accessible to those who require the medication (cite lilly). Lilly has said this position is seen in the current use of the Lilly Cares prescription program which provides free medication to low income and uninsured patients. The program covers all of Lilly’s insulin products and was established to ensure that low income patients may receive the current standard of care medication. From the interview with Dr. Meyer’s he did highlight that each new generation of insulin released by insulin manufacturers does have significant improvement over the previous generation that positively impacts patients’ lives. These improvements can range from improving some of the chemical characteristic of the active pharmaceutical ingredients to improve the delivery system of the applicator. This program ensures that patients all patients receive the improvements from each successive generation, however he also highlighted that this may not be concerned with patient quality of care but instead be a way to continually extend patent protection on their product while still ensuring the product is somewhat accessible to all income levels.

In order to understand the impact that these improvements have on patients it is necessary to develop the perspective of diabetic patients towards insulin. Both Lilly and FDA claim to operate in the way that is most beneficial to the patient. However there is a clear power struggle seen, there isn’t really an avenue that diabetic patients and their doctors can influence the price of insulin. It is well documented the hardship placed on low income diabetic patients. In a New York Times Opinion article endocrinologist Dr. Lipska described the hardship that the high price of insulin placed on some of her patients. She focused on the prevalence of insulin rationing among her low income patients. This involves patients taking less than their prescribed insulin amount in order to make each vial of insulin last longer. Specifically, Dr. Lipska talked about one anonymous patient that she prescribed human insulin, an older cheaper technology that requires more applications. She said that this outdated technology was more effective at managing her patient’s diabetes because she could afford the product and did not have to insulin ration.

**Ethical section on mediating theory**

In a purely biologic sense insulin is a hormone that mediates a response and allows a patient to regulate their own blood sugar. This life or death reliance on the technology also creates a dynamic relationship between the patient, the research and development team and the product itself. The patient requires an accessible therapeutic that can administered daily over the course of multiple years with minimal side effects. The research and development team continuously improves the technology of the medicine in an attempt to reduce the side effects of the therapeutics, however this results in an increased price from creating a system where the highest quality of care is continuously under patent protection such that it cannot be sold as a generic brand. This brings into the question whether the continuously improved product is an ethical design. To answer this the intention of the research team must be evaluated. If the motivation to continuously improve the quality of medicine is to address the side effects that patients are experiencing this is a more ethical system than if their primary motivation is simply to keep the therapeutic on patent protection. The development of this question and how insulin fits into mediation theory is one of the key focuses of this study.

**Conclusion**

Throughout the STS analysis the underlying question continues to come back to who benefits most from the incremental improvements to insulin. When the patient can afford their medicine there is genuine benefit between each successive generation of insulin, however, in the case of low income the medical benefits cannot be realized due to the inaccessible price. Currently the lack of competition and alternative options has created a landscape where patients do not have an effective voice in the balance between accessibility and medical technology. The recent reclassification of insulin within the FDA will create a more favorable pathway for biosimilar technology, by having multiple options on the market the patient will be more empowered to decide between the newest and most expensive technology as compared to an older but less expensive alternative. This will help include the patient in the conversation of what is the correct balance is.

This is investigation has focused on insulin and more specifically Lilly’s Humalog insulin, however the issue of rising health care cost and the associated patient inacessiblity is not exclusive to insulin. This is an issue facing the entire healthcare system within the U.S. and looking into the factors and key stakeholders that have allowed a generic insulin to enter the market is a useful case study. One key aspect surrounding the insulin case study is the lack of voice and power seen by the indivudlas most sensitive to insulin’s price, low income diabetic patients. In order to continue to make medical advancements accessible pharmaceutical companies and regulatory agency’s must always check their actions against this group to ensure their work is truly benefiting the patient. In the case of insulin very few options were available to patients and the FDA contributed to this landscape as the result of an outdated policy. As medicine becomes more inaccessible pharmaceutical companies, the FDA and patients will be responsible in balancing the direction that the technology moves and to prevent the technology from excluding vulnerable groups.

Bibliography:

* This is the last real content to be done for the thesis, I have all of my sources but need to ask a few questions about citations before turning in