Design of an Insulin Glargine Manufacturing Facility in Singapore to Target the Rise of Diabetes Cases in Asian-Pacific Countries
(Technical Paper)

The Insulin Price Discrepancy in the United States and United Kingdom: An Assessment of Government Regulations and Public Opinion
(STS Paper)

A Thesis Prospectus
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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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Prospectus

Introduction

The insulin market is expected to be worth $23.6 billion by 2030 ("Insulin Market Size to Worth Around USD 23.57 Billion by 2030," 2022). The large market exemplifies the vitality of the industry to health and society across the world. Insulin is a hormone produced by the pancreas to control glucose levels in the body and store this glucose for energy. People with diabetes have disfunctions with insulin release and use. Type 1 diabetes occurs when the body does not produce insulin, whereas type 2 diabetes occurs when the body does not respond to the insulin produced. In both cases, treatments such as insulin shots are needed to increase insulin in the bloodstream and help the body control and store glucose.

Often, diabetes patients take multiple insulin shots a day as part of their treatment, but a new therapeutic drug, insulin glargine, reduces the number of daily insulin shots needed. Insulin glargine is a long-acting insulin; thus, it remains in the bloodstream longer than other types of insulin. One shot of insulin glargine can last in the bloodstream up to 24 hours easing the treatment for diabetic patients (DrugBank, 2022). New insulin treatments are continuously developed to ease treatment and application of the drugs for patients, but the prices of these products remain high in the United States.

Insulin has been on the market for over 100 years, yet the price of insulin continues to rise in the United States. Further, the price of insulin is also much greater in the United States than in other countries. In 2018, the average price of insulin in the US was $98.70, whereas the price of insulin is $6.94, $7.52, and $12 in Australia, the United Kingdom, and Canada respectively (Mulcahy et al., 2020). The high insulin prices in the United States can be attributed to government regulations and cause a negative public opinion of the pharmaceutical industry. I

will explore this broader socio-technical issue in my STS research paper, as I investigate the relationship between insulin prices and government regulations in the US and UK. In a technical project, my capstone group will design an insulin glargine manufacturing facility in Singapore.

Technical Design Project

Insulin production is a vital process, as 72 million people in the world, about 1% of the population, require insulin to treat diabetes (Uildriks, 2021). A contemporary insulin technology is insulin glargine, a slow-releasing insulin product that is beneficial to those that have to take insulin every day. Insulin glargine remains in the bloodstream longer allowing patients to take insulin less often; thus, they need fewer injections every day. The motivation behind exploring this technology now is to study how the sustainability and efficiency of the process can be optimized as diabetes cases continue to rise.

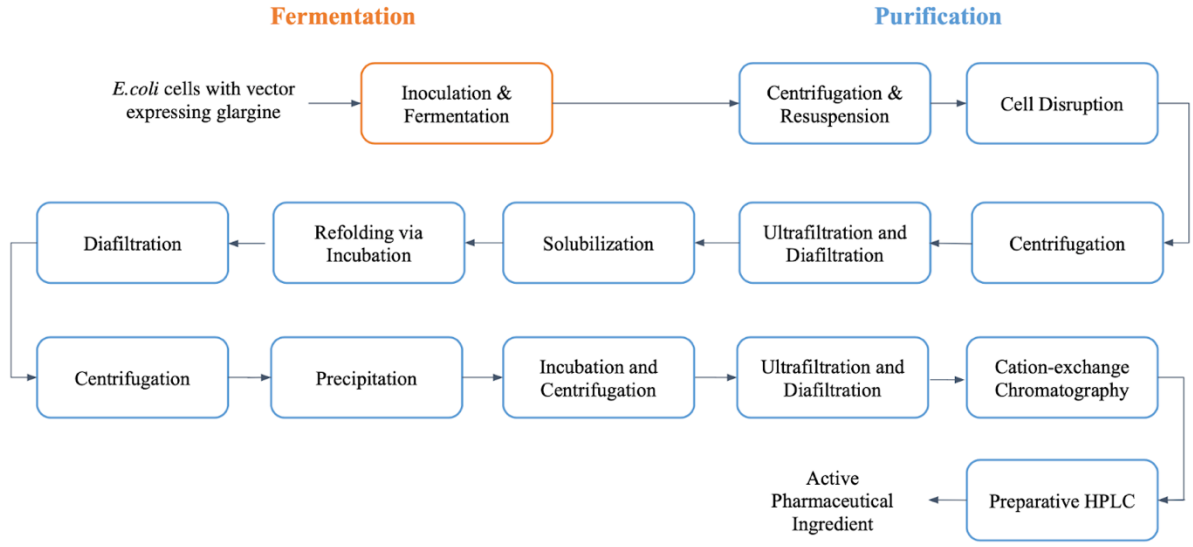
The prevalence of diabetes in Asia is rising; 60% of diabetes cases are in Asia with the majority of these cases in India and China (Ramachandran et al., 2012). It is, therefore, germane to produce insulin for the Asian market, specifically developing nations as insulin prices can be an obstacle in these regions. More than 80% of Type 2 diabetes cases occur in developing countries where it can be very difficult to manage the high out-of-pocket costs of insulin treatment (Ramchandran et al., 2012). Further, diabetics in lower economic groups spend 25-34% of their income on treatment (Ramachandran et al., 2012). According to a study conducted in China (Liu et al., 2017), 16 day's wages of the lowest paid unskilled government worker is required to purchase a month's treatment of a long-acting basal insulin analog. The study found that these high prices could be attributed primarily to the manufacturer's selling price (MSP). The high selling prices of insulin can be attributed to a variety of factors including the vulnerable population which is willing to pay thousands of dollars for a lifesaving drug, a virtual monopoly

in the insulin market, and patent abuse by evergreening (Rajkumar, 2020). Patent evergreening has been used in the insulin industry by the top manufacturers for almost a decade as new formulations continue to be made that provide more reliable control of diabetes. These patents allow for monopoly control of the insulin market hindering biosimilars from entering the market and targeting specific areas of manufacturing; thus, distribution of insulin to lesser developed countries remains difficult. To target lower economic groups and reduce distribution difficulties to developing countries, it is proposed that an insulin manufacturing process be designed in Singapore to serve the developing and developed nations in the surrounding area. Our goal will be to design a process to provide a more affordable and accessible insulin glargine product for all people suffering from type 2 diabetes in Asia.

Our insulin glargine product will be slow release; produced via recombinant DNA technology using a strain of *Escherichia coli* (DrugBank, 2022). Insulin can be rendered long acting by replacing asparagine with glycine in position 21 of the A-chain and by carboxy-terminal extension of B-chain by 2 arginine residues (Bolli, 1999). The arginine amino acids shift the isoelectric point from 5.4 to 6.7, making the molecule less soluble in physiological blood; this allows the product to crystallize prior to dissolving, rendering it “slow-release”. The unit operations that will be used to manufacture the drug include, but are not limited to: fermentor, centrifuge, incubator, ion-exchange chromatography column, cation-exchange chromatography column, and preparative high-performance liquid chromatography column (Preparative HPLC) (Hwang et al., 2016).

Figure 1

Block Flow Diagram



Note. This block flow diagram was adapted and created from the research performed by Hwang, H. et al, 2016.

The steps in our insulin glargine production process can be seen in Figure 1. In general, the whole process for insulin production includes fermentation, primary recovery, inclusion body solubilization, and chromatography. We will not be addressing formulation in our project. We will use *E. coli* as host cells for our insulin precursor production, purchased already containing the vector expressing glargine. An insulin precursor is produced as a soluble inclusion body which can be used in the solubilization and refolding steps shown in Figure 1 (Baeshen et al., 2014). *E. coli* is the most widely used host cell for recombinant proteins as it is widely studied and has less associated costs (Hwang et al., 2016). We will use the process and data described in "Recombinant Glargine Insulin Production Process Using *Escherichia coli*" by Hwang et al. as a reference (2016) as well as finding further sources of information and data. We will design a

process to produce insulin glargine which will include upstream and downstream processes. We will consult experts in these fields, Professor Michael King, Professor Giorgio Carta, and Professor George Prpich. We will also reference a University of Virginia capstone project from 2015, "Continuous Manufacturing Process for the Economically-Efficient Production of Biosynthetic Analog Insulin Glargine Active Pharmaceutical Ingredient" (Wilson 2015).

This project will be completed by a group of four chemical engineering students over the course of two semesters in CHE 4474 and CHE 4476. We will have weekly group meetings to evaluate our progress and discuss further work to be completed in the following week. The work will then be divided evenly between all group members. We will meet with Professor Eric Anderson, our advisor, every week to discuss our progress. Our project will consist of a design of the system and all equipment in the facility, an economic analysis of the viability of our project, and a discussion of risk, safety, and sustainability in our plant.

STS Research Project

Insulin has been on the market for over 100 years now, and yet people continue to struggle to pay for diabetes treatment in the United States. The cost of insulin is disproportionate in the US compared to other countries. Further, the cost of the most commonly used insulin is 10 times more in the US than other developed countries (Rajkumar, 2020). This price discrepancy is evident in the United Kingdom where insulin costs more than 13 times that of the United States (Mulcahy et al., 2020). Not only is the price of insulin remaining high in the US, but it is increasing exponentially. The price of one insulin analog has increased from $21 in 1999 to $332 in 2019, an increase much greater than that of inflation (Rajkumar, 2020). The price of insulin puts pressure on many patients so much so that many diabetics are forced to choose whether to pay for insulin treatment or housing and food (Hirsch, 2016). The high insulin prices in the US

are becoming life-threatening for many patients; thus, the causes of the increasing prices need to be investigated.

The three most prevalent reasons cited by pharmaceutical companies for the high cost of prescription drugs, the high cost of development, the product of a free-market economy, and the costs of innovation, do not apply to insulin (Rajkumar, 2020). The exorbitant prices of insulin in the United States can be attributed to politics and government regulations such as patent laws, lack of a market cap, monopoly of the product due to a lack of biosimilars, and pharmaceutical lobbying. I will investigate these regulations in comparison to regulations in the United Kingdom where insulin prices are not as high.

The high insulin prices and drug prices in general in the United States cause the public opinion of the pharmaceutical industry to decline. Further, the pharmaceutical industry is increasingly distrusted by the public in the US today. According to a Harvard news article, "A Gallup Poll conducted in August [2019] found that 58% of Americans held negative views of the pharmaceutical industry while only 27% held positive views of it. It's the lowest the industry has ever been ranked in the poll, which began in 2001" (Harvard, 2019). Further in the article, the author attributes the rapid spike in public disapproval to "high drug prices…and Big Pharma's lobbying efforts" (Harvard, 2019). According to David Mitchell, founder of Patients for Affordable Drugs, the decline in trust in the pharmaceutical industry is related to drug pricing. Further, he argues that countries with more concern for drug pricing, such as the United States and Germany, have more distrust for the pharmaceutical industry as compared to the United Kingdom where drug pricing is not as prevalent in news and media (Lo, 2018).

The sociotechnical issue of insulin price discrepancy in the US and the UK is a complex network of many entities. Bruno Latour, a French sociologist and philosopher, theorized the

Actor Network Theory (ANT) in which actors create an inter-woven network made up of the changing relationships between the actors (Cressman, 2009). In this sociotechnical project, actors include but are not limited to the general public, diabetics, physicians, pharmaceutical companies, government regulations, capitalism, etc. ANT will be used to explore the relationships between these actors and the insulin price discrepancy in the US and UK. Actor network theory has been criticized for the assumption that human and non-human actors are both equally present in the network, as non-human actors are not able to make intentional choices (Winner, 1993). While human actors are inherently different than non-human actors, focus will be on the relationships between actors not the intent of the actors.

To conduct the research for this project, I will use network analysis to investigate the relationships between actors in the sociotechnical issue of insulin prices in the US and UK. Legal documents and federal policies will illuminate the differences in acceptable regulation of the pharmaceutical industry in the United States and the United Kingdom. Meanwhile, I will use literary research about the public opinion of insulin prices to investigate the relationship between diabetics, the general public, and pharmaceutical industry.

Conclusion

This research portfolio will address the issue of unaffordable insulin prices both in the US and abroad. To address the high insulin prices in less-developed Asian countries, my group will design an insulin glargine production process in Singapore to reduce the cost of insulin manufacturing and distribution. My STS research aims to investigate the government regulations that allow for the high prices of insulin in the US as opposed to the UK. Both of these projects will aid the reduction of insulin prices in the world making the life-saving drug available to a greater percentage of the population.

References

Baeshen, N. (2014, Oct 02). Cell factories for insulin production. *National Library of Medicine.* doi: 10.1186/s12934-014-0141-0.

Bolli, G., Di Marchi, R., Park, G., Pramming, S., and Koivisto, V. (1999, Sep). *Insulin analogues and their potential in the management of diabetes mellitus*. Diabetologia. doi: 10.1007/s001250051286

Cressman, D. (2009). *A brief overview of actor-network theory: Punctualization, heterogeneous engineering & translation.*

DrugBank. (2022, Oct 16). *Insulin glargine.* https://go.drugbank.com/drugs/DB00047

Harvard. (2019, September 5). *Poll shows Americans are fed up with pharmaceutical industry*. Harvard T.H. Chan School of Public Health. https://www.hsph.harvard.edu/news/hsph-in-the-news/poll-shows-americans-are-fed-up-with-pharmaceutical-industry/

Hirsch, I. B. (2016). Insulin in America: A Right or a Privilege? Diabetes Spectrum, 29(3), 130–132. https://doi.org/10.2337/diaspect.29.3.130

Hwang, H. et al. (2016, Jun 30). *Recombinant Glargine Insulin Production Process Using Escherichia coli.* The Korean Society f/r Microbiology and Biotechnology. doi: 10.4014/jmb.1602.02053

Insulin Market Size to Worth Around USD 23.57 Billion by 2030. (2022, July 19). BioSpace. https://www.biospace.com/article/insulin-market-size-to-worth-around-usd-23-57-billion-by-2030/

Lo, C. (2018, August 20). *The People vs Big Pharma: tackling the industry's trust issues*. Pharmaceutical Technology. https://www.pharmaceutical-technology.com/analysis/people-vs-big-pharma-tackling-industrys-trust-issues/

Liu, C., Zhang, X., Liu, C., Ewen, M., Zhang, Z., & Liu, G. (2017). Insulin prices, availability and affordability: a cross-sectional survey of pharmacies in Hubei Province, China. BMC health services research, 17(1), 1-9

Mulcahy, A., Schwam, D., and Edenfield, N. (2020). *Comparing Insulin Prices in the United States to Other Countries: Results from a Price Index Analysis*. RAND Corporation. https://doi.org/10.7249/RRA788-1

Rajkumar, S. V. (2020). The High Cost of Insulin in the United States: An Urgent Call to Action. *Mayo Clinic Proceedings*, *95*(1), 22–28. https://doi.org/10.1016/j.mayocp.2019.11.013

Ramachandran, A., Snehalatha, C., Shetty AS., and Nanditha, A. (2012, Jun 15). *Trends in prevalence of diabetes in Asian countries.* World Journal of Diabetes. doi: 10.4239/wjd.v3.i6.110

Uildriks, L. (2021, Nov 17). *WHO report: A call to action to promote affordable insulin access.* Medical News Today. https://www.medicalnewstoday.com/articles/who-report-a-call-to-action-to-promote-affordable-insulin-access

Wilson, A. (2015, Apr 27). Continuous Manufacturing Process for the Economically-Efficient Production of Biosynthetic Analog Insulin Glargine Active Pharmaceutical Ingredient. University of Virginia: School of Engineering and Applied Science. Retrieved from Ivy Stacks Library.

Winner, L. (1993). Upon opening the black box and finding it empty: Social constructivism and the philosophy of technology. Science, technology, & human values, 18(3), 362-378.