Design of an Insulin Glargine Manufacturing Facility in Singapore to Target the Rise of Diabetes Cases in Asian Countries

The Failure of The Affordable Insulin Now Act for the Uninsured

A Thesis Prospectus
In STS 4500
Presented to
The Faculty of the
School of Engineering and Applied Science
University of Virginia
In Partial Fulfillment of the Requirements for the Degree
Bachelor of Science in Chemical Engineering

By
Bethany Iudica

October 27, 2022

Technical Team Members:
Lauren Laughlin, Ben Ford, Yixuan Yuan

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.

ADVISORS

Benjamin Laugelli, Department of Engineering and Society
Eric Anderson, Chemical Engineering
Insulin Prices

Introduction

An estimated 2.2% of the U.S. population rely on insulin to survive, but the number of people that actually take insulin is strikingly less (Yunusa, 2021). This issue can be attributed to the rising insulin prices in the United States and across the world. Currently, three manufacturers control the insulin market in the United States: Eli Lilly, Novo Nordisk, and Sanofi (Cefalu et al., 2018). The monopoly on insulin by these three companies elevates consumer costs; the companies are aware that their consumers are vulnerable and not in place to negotiate the cost of this life-saving drug (Cefalu et al., 2018). To combat this socio-technical challenge, lawmakers and politicians in the United States have introduced laws and proposals, like the Affordable Insulin Now Act, with the goal of lowering insulin prices.

Diabetes is also prevalent outside of the United States; 60% of diabetes cases are in Asia with the majority in India and China (Ramachandran et al., 2012). Thus, it is suitable to produce insulin for the Asian market as insulin prices can be an obstacle in this region. It is crucial to target the developing nations of Asia, as more than 80% of the world's Type 2 Diabetes cases are in developing countries (Ramchandran et al., 2012). In order to reduce distribution difficulties in these regions, I will propose that an insulin manufacturing plant is built in Singapore to service the developing and developed nations in the surrounding areas of Asia. This insulin manufacturing plant will efficiently and sustainably produce a contemporary insulin technology: insulin glargine. Insulin glargine is a slow-releasing insulin product that is beneficial to those that have to take insulin every day by easing the application and use of the drug. This insulin technology remains in the bloodstream longer allowing patients to take insulin less often.

In addition to technical improvements, economic and political factors greatly carve the path towards preventing Eli Lilly, Novo Nordisk, and Sanofi from continuing to increase insulin

prices in the United States. These factors include insulin demand, insurance and affordability policies, and the insulin market. It is vital to analyze and understand these factors in order to work towards a world in which insulin is readily available and affordable for everyone across the world.

To improve the distribution and affordability of insulin, the technical and social aspects of the problem must both be addressed. I will create an efficient and sustainable insulin glargine manufacturing model and simulation using chemical engineering software. I will also use actor-network theory to analyze The Affordable Insulin Now Act, which caps cost-sharing for Medicare Part D enrollees and private insurance holders for a month's supply of insulin at $35, to determine how human and non-human factors prevent the success of affordable insulin technologies.

Technical Project Proposal

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

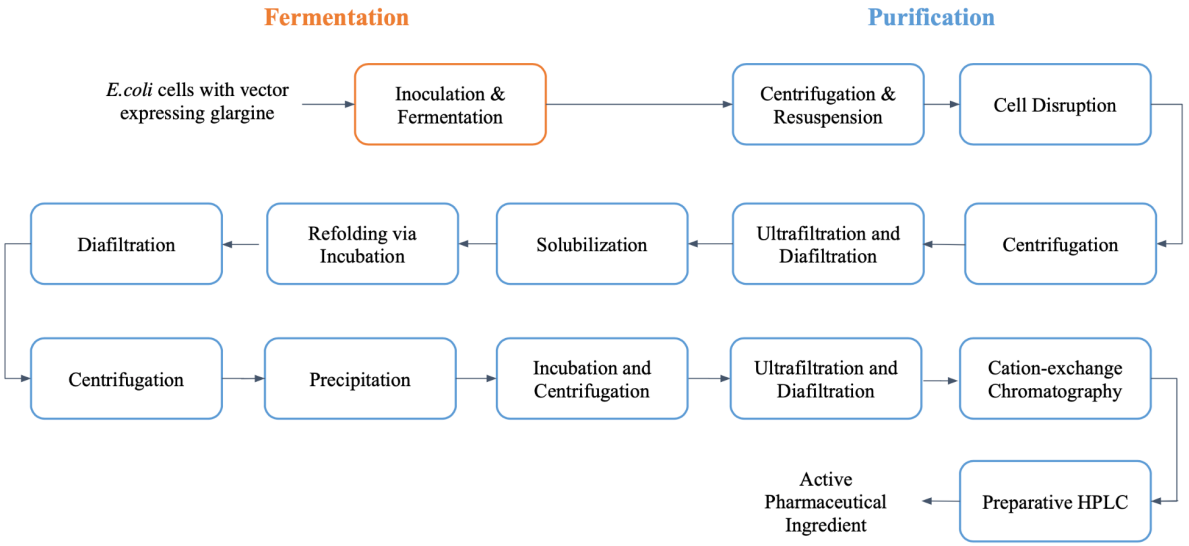
an obstacle in these regions. More than 80% of Type 2 diabetes cases occur in developing countries where it can be very difficult to manage the high out-of-pocket costs of insulin treatment (Ramchandran et al., 2012). Further, diabetics in lower economic groups spend 25-34% of their income on treatment (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* ("Insulin glargine", 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. (2016) as a reference 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 Project Proposal

Recently, addressing the problem associated with the cost of insulin has been at the forefront of many policy discussions. The Affordable Insulin Now Act, which, beginning in 2023, will cap cost-sharing for enrollees in the Medicare Part D plan for a month's supply of covered insulin products at $35, was signed into law in September of 2022 (H.R.6833, 2022).

This bill extends the model introduced by the Centers for Medicare & Medicaid Services in 2020, under which Medicare part D enrollees have a capped copayment for a month's supply of insulin at $35 (Cubanski et al. 2020). The passing of the Affordable Insulin Now Act in the United States of America lays the foundation towards lower insulin prices worldwide, but it fails to address gouging insulin prices for the broader population that relies on insulin.

The failure in the creation of this policy yields many consequences: enrollees of Medicare Part D will have a $2,000 out-of-pocket cost for prescription drugs beginning in 2025, uninsured diabetics see no change in insulin prices, and there is no limit to the price that insulin manufacturers can charge ("The Inflation Reduction Act Lowers Health Care Costs for Millions of Americans", 2022). Insulin manufactures will continue to earn enormous profit margins in insulin vials that take $5 to produce while Americans will pay upwards of $300 per vial of insulin (Marston, 2022). 31 million Americans remain uninsured, and the 2 million uninsured Americans with diabetes must continue to ration other priorities in order to afford this life saving drug (Hirsch, 2022). While the lack of inclusivity of The Affordable Insulin Now Act has been attributed to the gross negligence of Congress incumbents, this fails to address the power of insulin manufacturers. If we continue to solely blame incumbent politicians, we will fail to understand how other actors can influence the course of action in policy creation. I will explore the pressures that insulin manufacturers put on those in the insulin network as well as the power that they hold over the market.

I argue that pressure from large manufacturers as well as negligence with respect to rising insulin prices and out-of-pocket costs for many Americans led to the failure of The Affordable Insulin Now Act to be inclusive, which I will analyze using actor-network theory. Actor-network theory attempts to identify a network builder who recruits both non-human and human actors

into their network to accomplish a specific goal. The process of recruiting said actors to form and maintain an actor network is known as translation. Using actor-network theory, I will describe the creation of the Centers for Medicare & Medicaid Services and how the network failed to gain an understanding of the human and non-human actors that must be accounted for to successfully accomplish affordable insulin for all Amerians. To support this argument, I will analyze evidence from reports and interviews with insulin manufacturers and the politicians that created The Affordable Insulin Now Act, reports from the Centers for Medicare & Medicaid Services, and accounts from individuals that suffer from diabetes.

Conclusion

The deliverable for the technical problem discussed in the paper will be the concept for a design of an efficient and sustainable insulin glargine manufacturing plant in Singapore to provide insulin to China, India, and the developing nations of southeast Asia. The STS research paper will analyze and understand the contributors to the failures of The Affordable Insulin Now Act. Actor-network theory will be used to characterize how human and non-human actors play a role in shaping the development of insulin products and prices. In conjunction, the results of these deliverables will address the issue of the monopoly that insulin manufactures have over the insulin market and the power that they hold in the determination of insulin prices.

Word Count: 1974

References

Baeshen, N. (2014, October 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., & Koivisto, V. (1999, September). Diabetologia. *Insulin analogues and their potential in the management of diabetes mellitus*. doi: 10.1007/s001250051286

Cefalu, W. T., Dawes, D. E., Gavlak, G., Goldman, D., Herman, W. H., Van Nuys, K., ... & Yatvin, A. L. (2018). Insulin access and affordability working group: conclusions and recommendations. *Diabetes care,* 41(6), 1299-1311.

Cubanski, J., Neuman, T., True, S., & Damico, A. (2020, June 4). *Insulin costs and coverage in medicare part D*. KFF. Retrieved October 24, 2022, from https://www.kff.org/medicare/issue-brief/insulin-costs-and-coverage-in-medicare-part-d/

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

Hirsch, I. B. (2022). Insulin pricing in the USA: the saga continues. *The Lancet Diabetes & Endocrinology,* 10(10), 695.

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

H.R.6833 - 117th Congress (2021-2022): Making continuing appropriations for fiscal year 2023, and for other purposes. (2022, September 30). http://www.congress.gov/

The Inflation Reduction Act lowers health care costs for millions of americans. CMS. (2022, October 5). Retrieved October 24, 2022, from https://www.cms.gov

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

Marston, L. (2022). The failed promise of the US's Inflation Reduction Act for patients with diabetes. bmj, 378.

Rajkumar, S. (2020, January 01). The High Cost of Insulin in the United States: An Urgent Call to Action. *Mayo Clinin Proceedings.* doi: 10.1016/j.mayocp.2019.11.013.

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

Uildriks, L. (2021, November 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, April 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.

Yunusa, I. (2018, November 18). *Fewer diabetes patients are picking up their insulin prescriptions – another way the pandemic has delayed health care for many*. University of South Carolina. Retrieved October 27, 2022, from https://www.sc.edu/uofsc/posts/2021/11/11_conversation_insulin.php#.Y1qsb3ZKi5c