Undergraduate Thesis Prospectus

An Insulin Glargine Production Plant in Singapore

(technical research project in Chemical Engineering)

Improving Access to Care Among Marginalized Diabetics in the United States

(sociotechnical research project)

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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General research problem

How can we provide accessible care for Type 2 diabetes?

Type 2 diabetes results from when cells in one's body does not respond normally to insulin, which is a hormone made by pancreas that lets blood sugar, glucose, into the cells for energy. In this case, the pancreas cannot make enough insulin for the body and high blood sugar arises, damaging the body and causing serious health problems. According to the U.S. Centers for Disease Control and Prevention (CDC), "37 million Americans have diabetes (about 1 in 10), and approximately 90-95% of them have Type 2" (2021). The major concern in the nation and world over the past decade is the expensive and ill-accessible supply of insulin to treat diabetes. A critical care doctor at Harvard Medical School said that "16.5% of people who use insulin report rationing" (Thomas, 2022). People are being forced to ration their insulin because prices are unaffordable and difficult to purchase, especially for citizens in developing countries and marginalized groups in the United States.

Insulin glargine production plant in Singapore

How can the project team design an insulin manufacturing plant in Singapore that can distribute the product to Asian Pacific countries?

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.

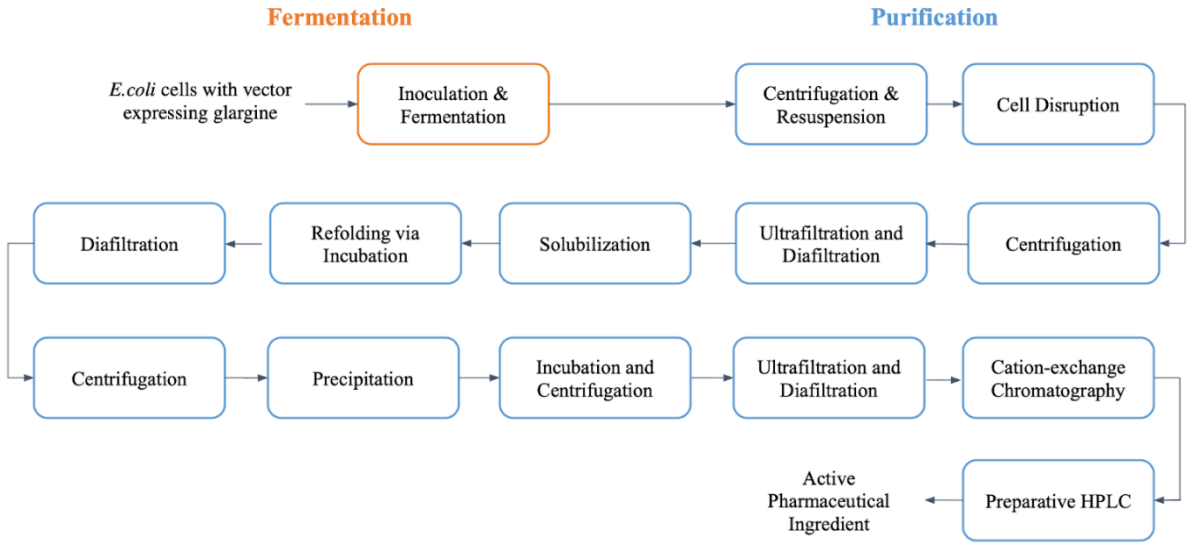
The prevalence of diabetes in Asia is rising; 60% of diabetes cases are in Asia with the majority of these cases in India and China (Ramachandran et al., 2012). It is, therefore, germane to produce insulin for the Asian market, specifically developing nations as insulin prices can be an obstacle in these 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 (Ramachandran 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.

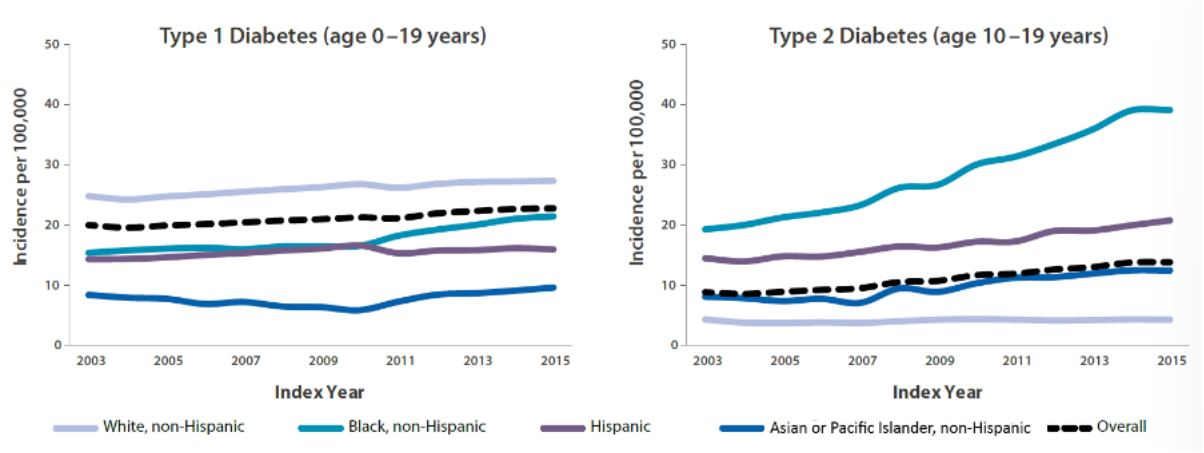
Improving access to care among marginalized diabetics in the United States

In the U.S., how have advocacies strived to improve access to care among indigent or marginalized diabetics?

According to the U.S. Food and Drug Administration (FDA), in the United States, the incidence of diabetes, poor diabetes control, and related complications is higher than in the general population (2020). Such disparities are particularly marked for Type 2 diabetes (fig. 2). Deficient access to healthcare, inconsistent diabetes management, poor diet, and endemic obesity contribute to the problem (FDA, 2020). Advocacies strive to reduce such healthcare inequities.

Figure 2

Incidence of Type 1 and 2 diabetes in U.S. children and adolescents by race and ethnicity, 2003-15 (CDC, 2022)



The incidence of diagnosed diabetes is higher among Hispanic populations than among the general U.S. population (fig. 2). Aguayo-Mazzucato et al. (2019) found that among U.S. Hispanics with annual incomes under $20,000, the incidence of diabetes exceeded that among Hispanics earning more $75,000. Among U.S. Hispanics generally, they report below average median household income, greater poverty rates, and the highest frequency of uninsured persons (Aguayo-Mazzucato et al., 2019). Education correlated inversely with diabetes incidence; adults with only a high school diploma were at greater risk of Type 2 diabetes than adults with a bachelor's degree or more (Aguayo-Mazzucato et al., 2019). DiabetesSisters is a "nonprofit organization whose mission is to improve the health and quality of life of women with diabetes, and to advocate on their behalf" (DiabetesSisters, 2012).

Some organizations object to some public policy efforts to improve access to care for diabetics. The Federalist Society opposes legislation in Minnesota to give insulin to patients who cannot afford it, contending that such policies are "positively immoral" because they inflict "an injustice" on pharmaceutical companies (Sandefur, 2020). Pharmaceutical companies that

manufacture insulin have a material interest in such policies. Eli Lilly for example, is developing an insulin injection that can "help adults living with type 2 diabetes manage key aspects of their disease" (Pfeiffer, 2022).

The CDC's Office of Minority Health and Health Equity (OMHHE) promotes inclusion of marginalized populations in clinical trials of drugs, biologics, vaccines, and medical devices for diabetes treatment (FDA, 2020). OMHHE is developing programs to improve health equity (CDC, 2020). The Black Women's Health Imperative (BWHI) is the only U.S. nonprofit striving to improve care access and equity among Black women. BWHI claims to "lead the effort to solve the most pressing health issues that affect Black women and girls" through "bold new programs and advocating health-promoting policies" (2022). BWHI has partnered with Aveeno, a skin and hair company, to "raise awareness around chronic disease and Black skin health" (Ligon, 2022). This partnership may join Change Your Lifestyle, Change Your Life (CYL2), a one-year program intended to prevent Type 2 diabetes and other chronic conditions and to improve diabetics' self-management (Ligon, 2022).

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