Design of an Insulin Glargine Manufacturing Plant to Increase Affordability and Accessibility of Diabetes Medication in the Sub-Saharan Region of Africa

Combatting the Disparities in Diabetes Healthcare Administration Among Minority Groups in America

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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Introduction

Before the discovery of insulin therapy, children with type 1 diabetes (T1D) resorted to counting calories, weighing food, and implementing starvation diets to stay alive (Beran et al., 2016). Half of type 1 diabetics died within two years of developing diabetes and more than 90% died within five years (LeWine, 2015). Over the past century, advances in insulin therapy have increased the life expectancies of type 1 diabetics. Today, diabetes is a global epidemic that 420+ million people (6% of the world's population) are dealing with everyday. This number is expected to increase to 700 million by 2045 (Siew & Zhang, 2021). With this projected rise comes the increased demand for insulin; however, affordability and accessibility of insulin remains as a challenge in many parts of the globe (Beran et al., 2021).

Specifically, limited access to insulin translates to a life expectancy as low as one year for a child with type 1 diabetes in Sub-Saharan Africa (Beran et al., 2016). The importance of human insulin is further highlighted by its inclusion on the World Health Organization's (WHO) Model of Essential Medicines. Despite the continuing understanding of the importance of insulin, insulin is widely unavailable in Sub-Saharan regions of Africa. In 2015 diabetes was one of the leading causes of non-communicable diseases (NCD) death, contributing 1.5 million deaths globally and 321,100 deaths in the African region. A staggering 79% of these deaths in Africa occurred among people below the age of 60 (Mutyambizi et al., 2018). The Sub-Saharan region faces numerous diabetic challenges including compounding infectious diseases, lack of diabetes education and awareness, and the government's inability to treat patients and distribute affordable insulin (Azevedo & Alla, 2008). Insulin costs vary from country to country, however many citizens are still unable to afford diabetes health care. Additionally, there are direct and

indirect costs to treating this disease. Drug cost often constitutes 50% of the total direct costs, which in some African countries equates to a whole month's pay (Mutyambizi et al., 2018). In contrast to developed countries where the majority of people with diabetes are over the age of 65 years, in sub-Saharan Africa by 2025 most people with diabetes will be in the economically productive age group of 30-45 years. This increases the potential for chronic complications and premature mortality, thus imposing additional financial and socio-economic costs (Mbanya & Mbanya, 2003). The credibility of these estimates vary due to the fact that a large portion of African diabetics are left undiagnosed, stressing the importance of awareness and having insulin widely available in these countries. Therefore, this project will be geared toward creating an insulin glargine manufacturing plant in order to make it affordable and accessible in Sub-Saharan Africa to meet the growing demand for diabetic treatment in that region.

Technical Project Proposal

Insulin glargine, a long-acting form of insulin, is a key player in diabetes management. It helps individuals with diabetes maintain stable blood sugar levels, reducing the risk of debilitating complications. As a long-acting form of insulin, insulin glargine helps manage the body's general needs and lasts typically for 24 hours as opposed to fast-acting forms of insulin which help reduce blood glucose levels at meal times and lasts for a shorter duration of time (Beran et al., 2016). The current standard process for insulin production relies on genetically engineered *Escherichia coli* (E. coli) bacteria. In our project, we leverage this well-established biotechnology to create a scalable and efficient manufacturing process for Insulin Glargine.

Our insulin glargine product will be synthesized using unit operations such as fermentation, cell harvesting, cell disruption, initial filtration, precipitation, chromatography -

ion exchange, chromatography - size exclusion, chromatography - reversed-phase, concentration, sterilization, buffer exchange, and purification. We plan on modeling our process based on the flow diagram below, gathered from the research done by Yin Yin Siew.

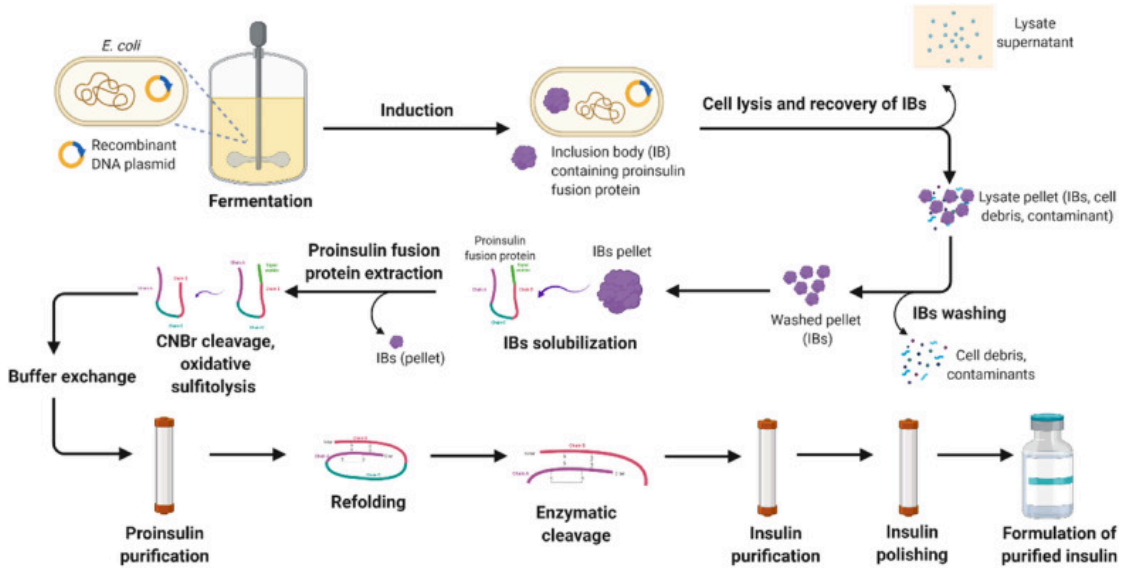

Figure 1. Process Flow Diagram of Insulin Production from E. Coli (Beashen et al., 2014)

We will use *E. Coli* as our host cells for creating insulin glargine. "Using *E. coli* as the expression system for large-scale recombinant insulin production possesses the advantages of high growth rate, simple media requirement, ease of handling, high yield, and cost effectiveness" (Siew & Zhang, 2021). To create the slow-release and long-acting effect of insulin glargine, modifications to the amino acid chain, including asparagine to glycine on the A chain at position 21 and adding two arginines to positions 31 and 32 on the B chain, need to be made during the production process. This change causes the insulin to act for up to 24 hours after injection and allows for the insulin to remain soluble at a pH of 4.0, which is the pH of the solution that the insulin resides (Cunningham & Freeman, 2022). We will consult the professors of chemical engineering at the University of Virginia to help refine this process and scale it to the available

laboratory specifications. Additionally, we will be referencing a previous capstone project from 2022, “Design of an Insulin Glargine Manufacturing Facility in Singapore to Target the Rise of Diabetes Cases in Asian Countries” (Iudica, 2022).

Our project will be a collaborative effort, consisting of 4 team members throughout the course of CHE4474 and CHE4476. We plan to meet as a group weekly about the current work we are completing, with a Google Drive and GroupMe used to coordinate file-sharing and further communication as needed. Design data will be sourced from various experimental trials and genetic engineering studies. Currently we have kinetic parameters, such as specific growth rate and production rate for a batch bioreactor (Baeshen et al., 2014). We also have the kinetic data for a chemostat (CSTR) based bioreactor (Senn et al., 1994). The project's tasks will be distributed equally based on interest and any relevant expertise, and each team member will be responsible for their specific contributions. Regular peer reviews and quality checks will ensure the highest standard of work.

STS Project Proposal

Although diabetes technology and insulin advancements have increased the level of treatment for diabetic patients in America, there are still disparities among the people who are able to afford and access the tools necessary to manage the disease. Low-income, uninsured, and underinsured populations of Americans, which are disproportionately represented by racial and ethnic minorities because of structural inequities, are more likely to face economic barriers to accessing insulin, and endure the subsequent health consequences (Peek, 2021). The aim of this proposal is to answer the question of why these disparities exist and how America's healthcare

system can close the gaps caused by the disproportionate care administered to its underrepresented citizens.

Specifically, minorities with diabetes experience barriers to initiating newer diabetes medications (Elhussein et al., 2021). One innovation, the insulin pump, has led to improvements in glycemic control, quality of life, satisfaction with treatment, and lower diabetes distress. However, during a study conducted by UCLA, insulin pump use was 67% among whites, 41% among Hispanics, 29% among Black, and 46% among other racial and ethnic groups (Everett, 2022). Another study found that Black patients with T1D are half as likely to receive insulin pump devices and continuous glucose monitors even though they have a threefold increased risk of hospitalization with diabetic ketoacidosis and hypoglycemia, 1.5% higher A1C, and a twofold increased risk of death compared with white patients (Kanbour et al., 2023). These inequalities might be due to healthcare providers not having as many discussions and prescribing these technologies. Another explanation could be insurance or clinical practice requirements related to diabetes self-management skills, fulfillment of subjective criteria regarding appropriate patient selection, factors influencing the process of shared decision making, and provider implicit racial bias (Kanbour et al., 2023).

Moreover, it was found that racial and ethnic minorities often receive care at lower quality institutions, and interventions designed to improve care within healthcare systems may be an effective tool to reduce diabetes health disparities (Wilkes et al., 2011). Increased quality of care can lower the risk for diabetes complications and mortality. Researchers from the Commonwealth Fund gave health system performance scores by state and race/ethnicity. Figure 2 shows the staggering differences between races/ethnicities and how they received care in each state.

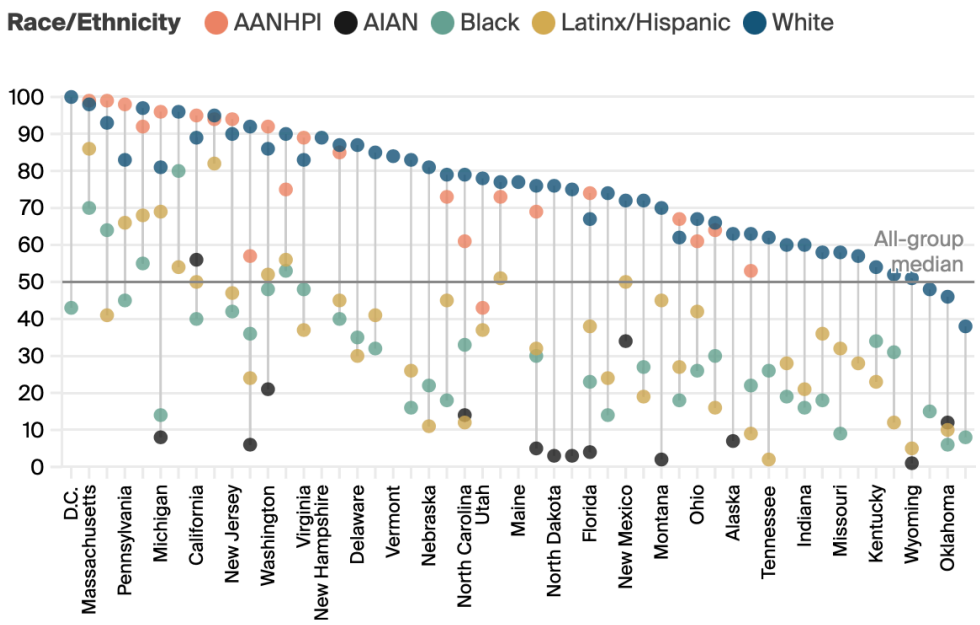

Figure 2. Health System Performance Scores (Radley et al., 2021)

To combat this imbalance, one study suggested that pharmacists, as one of the most accessible healthcare providers, are well poised to expand awareness about the risk factors for diabetes and can act as a patient identifier, educator, and advocate (Terrie, 2023). Interestingly, past survey evidence demonstrated that providers tend to consider patient factors (such as patient preferences and behaviors) as more important contributors to racial differences in care than provider factors (such as bias or poor communication) (Gollust et al., 2018). However, it is important to consider all factors in the multifaceted problem of diabetes care, including healthcare providers, patients, insurance companies, medication manufacturers, and policy makers. Unfortunately, there still remains research gaps to determine the exact reasons behind the disparities in diabetes care; however, the current research is shining light on these inequalities and raising awareness and hope that there can be solutions to these issues.

This proposal will analyze how disparities arose in the treatment and care of underrepresented groups in America and how the American healthcare system can strive toward administering equal and unbiased care to all of its citizens. Evidence will be collected through an analysis of previous research, current studies, and the personal experiences of healthcare professionals. The combined results from these sources will be used to provide suggestions of how the healthcare system can improve and what steps can be taken for this progress.

Conclusion

The deliverable for the technical problem discussed in the paper will be the design of a sustainable and efficient glargine insulin plant in South Africa to increase affordability and accessibility of insulin in the sub-Saharan region of Africa. The STS research paper will analyze and highlight the disparities of diabetes care among various ethnic and racial groups in America, and answer the question of how these disparities arose and what steps the American healthcare system can take to improve its care for all of its citizens. Actor-network theory will be used to characterize how human and non-human actors influence the development, marketing, and administration of insulin. The compiled results of these deliverables will address the issue that diabetes care is disproportionately administered based on socioeconomic factors such as income, ethnicity, and type of care facility.

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