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

Issues of an Insular Insulin Industry

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 resorted to counting calories, weighing food, and implementing starvation diets to stay alive (Beran et al., 2016). About 50% of type 1 diabetics died within two years of developing diabetes and more than 90% died within five years. A study conducted by Harvard reports that due to insulin therapy advances over the past years, people with type 1 diabetes have life expectancies of over 50 years. Although far less deadly, type 2 diabetes also affects millions of people and can lead to serious health problems. Today, diabetes is a global epidemic that affects over 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 a challenge in many parts of the globe (Beran et al., 2021). Using Sub-Saharan Africa as a case study, limited access to insulin translates to a life expectancy as low as one year for a child with type 1 diabetes (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.

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 are varied from country to country, however most 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., 2017). 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. This project will be geared toward insulin glargine production in Sub-Saharan Africa to meet the growing demand for diabetic treatment in that region and explore the evolutionary technical state of the insulin industry.

Designing an Insulin Glargine Manufacturing Facility

Insulin glargine, a long-acting form of insulin, is key to 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, one dose of insulin glargine helps manage the body's general needs and typically lasts 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 standard process for insulin production relies on genetically engineered *Escherichia coli* (E. coli) bacteria. This project will use well-established biotechnology to create a scalable and efficient manufacturing process for insulin glargine with hopes of increased accessibility .

The proposed 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. The proposed process will be modeled off of the flow diagram below, gathered from the research done by Yin Yin Siew (2021).

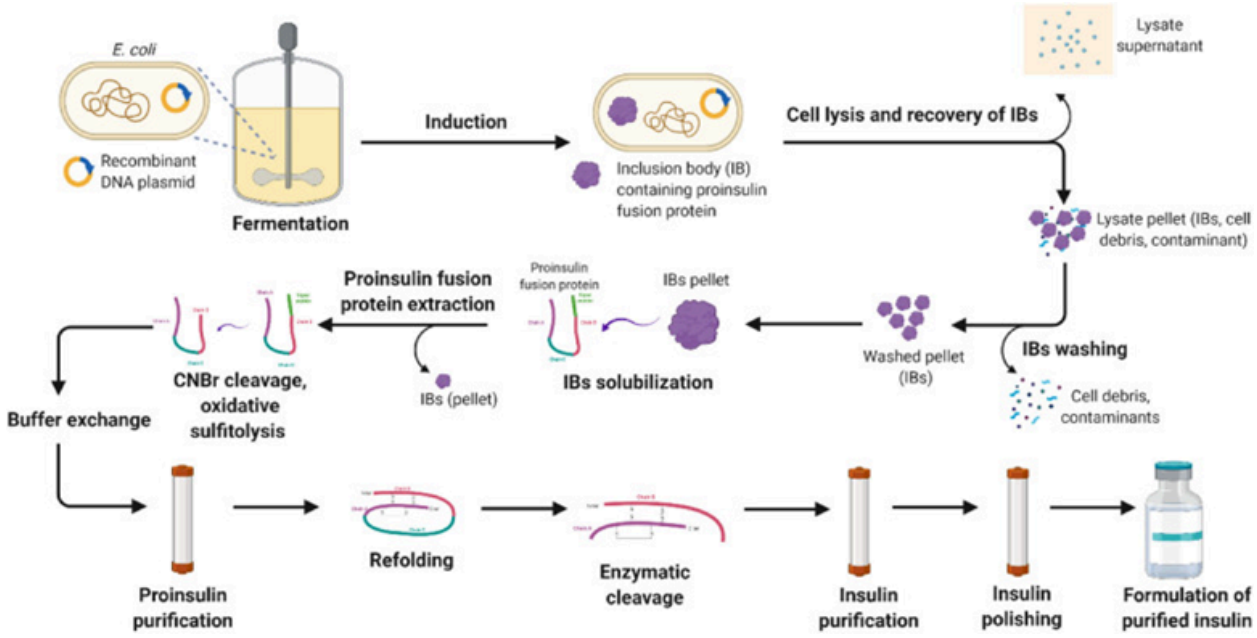

Figure 1. Process Flow Diagram of Insulin Production from E. Coli (Siew, 2021)

E. Coli has been chosen as host cells for creating insulin glargine since, utilizing *E. coli* as the expression system for large-scale recombinant insulin production is advantageous by providing high growth rates, simple media requirements, 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).

In order to conduct the research multiple professors of chemical engineering at the University of Virginia have been requested to help refine this process to scale it to the available

laboratory specifications. Additionally, a previous capstone project from 2022, authored by Bethany Iudica, will be referenced throughout the project (Iudica, 2022). Design data will be sourced from various experimental trials and genetic engineering studies. Kinetic parameters, such as specific growth rate and production rate for a batch bioreactor have been established (Baeshen et al., 2014). The kinetic data for a chemostat (CSTR) based bioreactor have also been determined (Senn et al., 1994). Regular peer reviews and quality checks will ensure the highest standard of work.

Patterns of Technical Evolution Within the Insulin Industry

Insulin prices are largely regulated by insulin companies themselves. Insulin companies patent their products and own exclusive rights, discouraging generic drugs from being produced. Insulin companies make small incremental improvements to their insulin and renew their patents, extending their control over the insulin market. In order to make the drug more accessible to the public, the US government has attempted to put a cap on the price of insulin with the Affordable Insulin Now Act which caps cost-sharing for enrollees in the Medicare Part D plan for a month's supply of covered insulin products at $35. The price of insulin remains high for the uninsured, but recently, Eli Lilly's has demonstrated willingness to provide more accessible products by lowering its prices directly on its insulin products and as a result, more insulin companies may follow suit. As government regulations on insulin price caps continue to tighten, insulin companies are likely to be eager to become the first to market an affordable product to the public to entice brand loyalty from their customers. This is an indication of technical momentum within the insulin industry. Historian Thomas Hughes argues that technical evolution can be determined through observing a pattern of evolution consisting of invention, development, innovation,

technology transfer and style, technological style, growth, competition, and consolidation (Hughes, 1987).

Invention is described as a radical or conservative creation of a new system, or the improvement of a previously failed system (Hughes, 1987). Insulin glargine is the product and invention in this project. There is a high demand for insulin considering the fatal and debilitating effects due to diabetes. Insulin was discovered after researching the pancreas of dogs, and researchers extracted and purified insulin to inject into a diabetic patient which resulted in his blood glucose reduction (Quianzon et al., 2012). This led to the development of insulin which is described as "the phase in which the social construction of technology becomes clear" (Hughes, 1987). As further studies were conducted into insulin, different types of insulin were synthesized. Hughes identifies this process as innovation where an innovation is renovated to be adapted to an environment. Different insulin types were synthesized in order to respond and provide different effects. As insulin entered the public market, some governments began regulating prices and standards, which can be described as a technological transfer/style described by Hughes as when an artifact or system is recreated and adapted to fit into a different structure (Hughes, 1987). Different insulin manufacturing companies formed which led to the growth, competition, and consolidation of the insulin industry. As the need for insulin continues, it is essential for the insulin industry to continue to evolve and adapt in order to meet the demands of those who require insulin, however, there may be some indications that the insulin industry is no longer evolving but stagnating. Hughes claims that decline typically follows stasis, which would be devastating for an industry that lives are dependent upon.

Research Question and Methods

In the US, accessibility to insulin has been limited by its expensive costs, and despite the progression of time, insulin prices remain high. This leads to the question of whether the insulin industry has stagnated or is potentially backsliding. To address this question, this project will explore and review the challenges of increasing insulin accessibility, industrial property rights, patent expiry, government and global roles, monopolies, incentives, and economics using multiple resources. Many of the resources reference other papers or panel sessions and perform statistical tests that this paper will reference. This project will analyze these resources for connections to the patterns of technical evolution defined by Hughes. By investigating these resources, the paper will compare the growth and changes within the insulin industry and to other pharmaceutical industries, particularly those with generic drugs. The goal of the research is to determine a pattern of technical evolution or stagnation in the insulin industry.

Conclusion

As the lives and well-being of many people depend upon the insulin industry, it is essential for insulin industries to continue to demonstrate technical evolution as they make their products more accessible and affordable. The deliverable for the technical project detailed in the paper will be the concept for a design of an efficient and sustainable insulin glargine manufacturing plant to provide insulin to the Sub-Saharan regions of Africa. The STS research paper will analyze and explore the technical evolution or stagnation of the insulin industry. The patterns of technical evolution described in this paper will be used to characterize the evolution, stagnation, or decline of the insulin industry. In conjunction, the results of these deliverables will address the issue of the inaccessibility of insulin products and the evolutionary technical state of the insulin industry in order to increase accessibility and affordability of insulin products.

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