Optimizing the Design of Insulin Glargine Manufacturing: A Sustainable Approach for Diabetes Management in Africa
(Technical Paper)

From Bench to Market: A Multifaceted Examination of Insulin Pricing, Profit Margins, and Patient Advocacy
(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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INTRODUCTION

Insulin is a therapeutic peptide produced by the pancreas to regulate blood sugar. Millions of individuals a year are affected by diabetes, Type 1 or Type 2, which affects their pancreas' ability to produce insulin and regulate blood sugar (Siew & Zhang, 2021). This is a critical biological process which regulates glucose and subsequently energy and other biological functions. The current solution for diabetes is the injection of insulin, which comes in a plethora of forms from a wide variety of manufacturers. The insulin market globally is massive – and is projected to continue increasing, with developing countries looking to take steps in addressing their diabetic populations that have largely been ignored (Beran et al., 2021).

My STS project will explore how pharmaceutical pricing strategies, profit margins, market dynamics, and political entities impact the affordability and accessibility of insulin for patients in developing countries. By tracing the interactions between various actors involved in the insulin supply chain, I aim to understand how decisions made by pharmaceutical companies, regulatory bodies, and advocacy groups shape the insulin market as well as the path from the manufacturing floor to the patient themselves not just in a modern context, but historically as well. My technical project aims to take this research and contextualize it by designing an insulin manufacturing process in the region of Sub-Saharan Africa. My research questions center around the challenges and opportunities of insulin production in this region; I ask how the design and operation of an insulin manufacturing facility can be optimized to ensure cost-effective production while maintaining sustainability.

TECHNICAL PROJECT

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). Half 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. Today, diabetes is a global epidemic that 420+ million people (6% of the world's population) are dealing with every day. 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). 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 understanding of the importance of insulin, it 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 vary from country to country due to supply chain and economic differences, so 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., 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. Therefore, my project will be geared toward insulin glargine production in Sub-Saharan Africa to meet the growing demand for diabetic treatment in that region.

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.

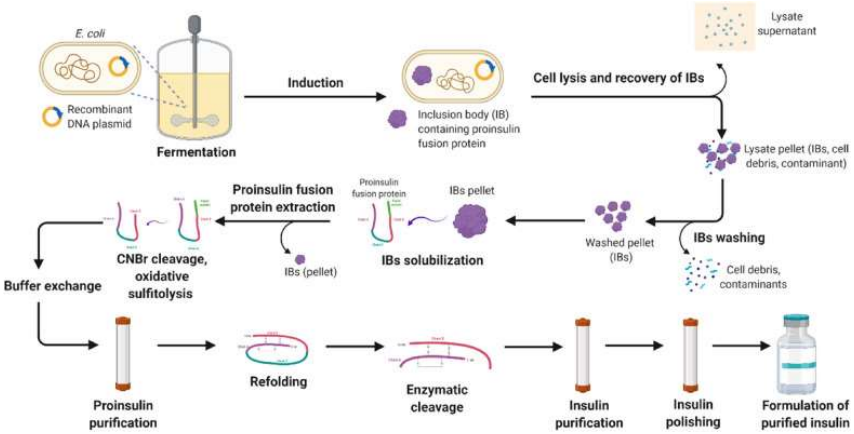

Figure 1. Process Flow Diagram of Insulin Production from E. Coli[2]

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

The primary research question is: How do pharmaceutical pricing strategies, profit margins, market dynamics, and political entities, both currently and historically, impact the affordability and accessibility of insulin for patients in developing countries? It's no secret that insulin is often prohibitively expensive, notoriously more so than a large swath of commonly used therapeutics on the market (Beran, 2019). A diabetic patient not receiving their insulin, however, can have deadly consequences. An easy answer would be to just point fingers at the pharmaceutical companies who produce them – and although they are not without a level of responsibility, it ignores the wider network of individuals and organizations that create the material conditions for this issue to arise. Understanding how each piece of the puzzle comes together to impact affordability and accessibility of insulin is critical in determining solutions for the future.

Subjects of this research will vary wildly, from the considerations involved in the technical manufacturing of insulin to the sociotechnical network that governs the production, distribution, and pricing of the medicine itself. On the technical side: downstream purification techniques are incredibly expensive, especially considering some of the criteria that government agencies require for the final product. Methods such as centrifugation, filtration, chromatography, pH adjustment, and various reactions throughout the process all need to be carefully fine-tuned so that they ensure the quality of medicine to an incredibly precise degree (Moks et al, 1987). Specific technologies in the process can also vary between country to country depending on regulation. On the sociotechnical side: a large amount of political and financial characters contribute to the ins and outs of pricing and distribution for therapeutics. Analyzing

the connections between these different organizations and determining their motivations will contribute to understanding how exactly the therapeutic pipeline is constructed and why.

My research delves into the dynamics of various social groups that directly or indirectly impact insulin accessibility, as well as a minor focus on those directly impacted by lack of said accessibility. These groups encompass pharmaceutical companies, regulatory bodies, health insurances, patients with diabetes, and policymakers. The pharmaceutical companies, acting as key economic players, wield immense influence through their pricing strategies and profit margins (RAND, 2021). My focus will specifically be on Eli Lilly, Novo Nordisk, and Sanofi who are responsible for most of the global insulin production. Regulatory bodies, both at the national and international levels, establish pricing standards and quality controls. Health insurance providers ultimately determine the final cost of medicine to those who have it, and how much the pharmaceutical company is paid. Patients, of course, are the ultimate end-users whose lives are directly impacted by insulin accessibility. Policymakers shape the broader healthcare landscape and drive policy changes, as well as influence the specifics of production and how the medicine is eventually distributed.

These social groups I have just mentioned are going to be categorized based on their critical roles and influence in shaping insulin accessibility. While my research aims for comprehensive coverage of the major stakeholders in the insulin accessibility landscape, there may be indirect influencers and interest groups that impact insulin pricing and accessibility. These could include patient advocacy groups, economic entities indirectly tied to the pharmaceutical industry, and public health organizations. Though I do not plan to explicitly delve into these groups, they remain relevant in the broader healthcare ecosystem.

For this research, my analytical framework is Actor-Network Theory (ANT), providing a robust perspective for understanding the intricate relationships and power dynamics among these actors. ANT's focus on actor interactions and the interplay of technologies, both human and non-human, provides a nuanced lens through which to analyze the complex sociotechnical network that governs insulin accessibility. ANT is particularly well-suited for this research because while many individual parts of the therapeutic pipeline receive the spotlight for their role, ANT enables us to unveil the intricate relationships and the interplay of both human and non-human factors that influence insulin accessibility, as parts rather than a whole. My research will be generally qualitative research methods, to provide context-specific data and allow my findings to illustrate the nuances of the problem. Together, these methodologies and the ANT framework provide a holistic view of the insulin accessibility landscape.

My research will occur over the next semester and a half. Research will include data collection through document analysis, tracing networks of relationships, analysis of how figures in the network are portrayed, followed by data analysis/synthesis and the subsequent compilation of findings. Over the next few months, my focus will be on literature review and initial data collection. This will include the technical side of insulin manufacturing, as well as the major regulatory considerations that concern its production globally. I will also include a rudimentary economic analysis of the cashflow throughout the insulin pipeline. The beginning of next semester will be the start of my work on data analysis and framework application – taking all the information gathered and synthesizing it into the framework of the research question and actor network theory. The semester will conclude with a final compilation of findings and writing of the final report. This timeline ensures thorough exploration of insulin accessibility and pricing

dynamics, allowing for sufficient data collection, in-depth analysis, and the comprehensive representation of findings.

KEY TEXTS

Moks, T., Abrahmsén, L., Österlöf, B., Josephson, S., Östling, M., Enfors, S.-O., … Uhlén, M. (1987). *Large–Scale Affinity Purification of Human Insulin–Like Growth Factor I from Culture Medium of Escherichia Coli*. Nature Biotechnology*, 5(4), 379–382.* doi:10.1038/nbt0487-379

- This research article goes in depth about the manufacturing process of insulin. It describes the exact materials, techniques, and processes associated with large-scale production and will help inform design and economic analysis.

The astronomical price of insulin hurts American families. (2021). *RAND*. https://www.rand.org/blog/rand-review/2021/01/the-astronomical-price-of-insulin-hurts-american-families.html

- Overview on the cost of insulin globally, and how that price point is reached. References other comprehensive resources that indicate prices and how they're formulated.

Kawaldip Sehmi and Janet L. Wale. (2022). *Where National Medicines Policies Have Taken Us With Patient Involvement and Health Technology Assessment in Africa.* Frontier Medicine Technology. 4: 810456.

- Advancements in public health and therapeutic technology in Africa, one of the focus regions of this research

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- Overview of the global distribution of insulin and the economic considerations

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