

Undergraduate Thesis Prospectus

Cost Effective Plant Design for Producing Long-acting Insulin
(technical research project in Chemical Engineering)

The High Cost of Insulin in the US
(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

In the U.S., how can equitable access to insulin be improved?

“Throughout history, up to the early part of the 20th century, diabetes has been a devastating disorder, particularly when diagnosed in childhood when it was usually fatal” (Buse et al., 2021). After the discovery of insulin, diabetes was no longer a death sentence and a person could go on to live a long life as long as they took insulin as needed. Diagnoses for diabetes have increased in the past century and with insulin production being at its highest one might assume that diabetics have access to this life saving drug. However, this could be further from the truth due to the skyrocket of insulin prices in the last few decades. Diabetics are faced with such high prices for insulin that as stated by Human Rights Watch, “[a]lmost every insulin-dependent person interviewed said they had rationed analog insulin because it was so expensive, taking less medicine than recommended by their doctor to stretch out their supply” (Human Rights Watch, 2022). It is definitely a problem that U.S. citizens can’t access insulin and ways to make insulin more affordable must be sought out.

Cost Effective Plant Design for Producing Insulin Glargine

How can a process plant cost-effectively and safely produce insulin glargine using E. coli bacteria?

Myself, Jack Dunleavy, James Kim, and Gabriella Recce will be working as a team to reach our goal of designing a process to synthesize insulin glargine under the supervision of our advisor Eric Anderson for our capstone project. 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 (fig. 1), gathered from the research done by Yin Yin Siew.

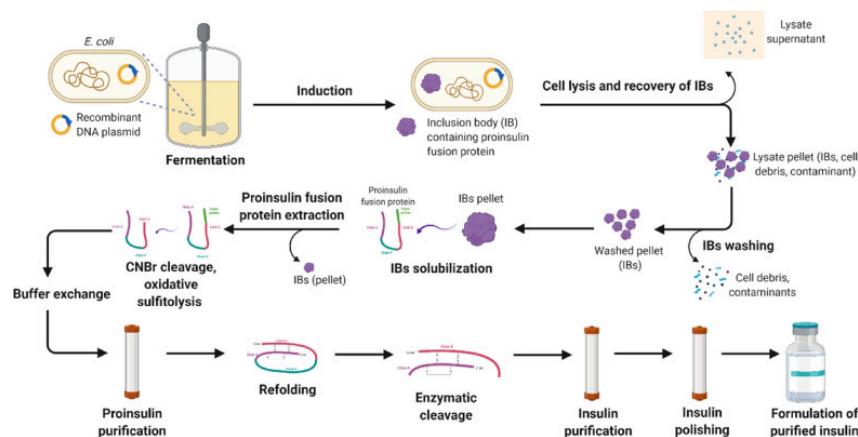


Figure 1. Process Flow Diagram of Insulin Production from *E. Coli* (Siew & Zhang, 2021)

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. At the end of our project we hope to have produced insulin at a cheaper price so it is more affordable for the average person.

The High Cost of Insulin in the US

In the US since 2000, how have pharmaceutical companies driven a steep rise in insulin prices?

Millions of Americans are afflicted with the chronic disease diabetes and require insulin at least once a week or as frequently as daily. Insulin's high demand has allowed pharmaceutical companies such as Eli Lilly, Novo Nordisk, and Sanofi to ramp up prices across the past few decades. "One vial of Humalog (insulin lispro), which used to cost \$21 in 1999, costs \$332 in 2019, reflecting a price increase of more than 1000% " (Rajkumar, 2020). Brand-name companies can keep high prices by extending current patents and delaying generic brand companies from selling similar products (Herman & Kuo, 2021).

Participants in the war for affordable insulin prices include the three aforementioned pharmaceutical companies who dominate the insulin manufacturing industry, small companies who wish to make alternatives, diabetics who require insulin, and advocates pushing to make insulin accessible to everyone. Major pharmaceutical companies push their agendas by deterring generic drug companies from putting out new patents for medication by paying them off so they release their drugs later. Major pharmaceutical manufacturers also make small changes to their

current patents so they seem like “new” patents to keep intellectual property over their medications and keep prices high (Herman & Kuo, 2021). In addition, it’s difficult for generic companies to produce biosimilar insulin because they have to invest a lot of funds into the process of creating insulin with a slightly different formula which still has the same efficacy and safety of name brand insulin (Rotenstein et al., 2012).

Advocates for diabetics, such as the American Diabetes Association, push their agenda by trying to get more affordable prices and making current resources known to diabetics such as coverage via Medicare and Medicaid (American Diabetes Association). Other groups such as, the NGO, Human Rights Watch believe that “[u]naffordable insulin undermines human rights under international law, including the right to the highest attainable standard of health, the right to equal and affordable access to essential medicines, the right to equal protection under the law and non-discrimination, and the right to an adequate standard of living.” They support these claims by describing how diabetics often have to pay expensive out of pocket costs instead of basic necessities just to sustain themselves (Human Rights Watch, 2022). For these reasons the Human Rights Watch is seeking to get rights for those who have diabetes. Diabetics themselves are affected directly because they can’t afford the prices by big companies. A college student stated, “There are no generics. We have to go through these big companies, and they charge so much” (Picchi, 2016). With few alternatives available to insulin consumers, they are often faced with the harsh reality of having to pay exorbitant prices to stay alive.

Research about the surge in insulin prices since 2000 has been conducted by many. For example, Tseng explains how Medicare Part D has steadily caused patients to pay more out of pocket costs (Tseng et al., 2020). This occurred because there was a gap in Medicare Part D that stated, “. . .beneficiaries [had to] pay a percentage of a drug’s price until reaching catastrophic

coverage.” Insulin providers took advantage of this by ramping up prices so they could get more money out of consumers (Tseng et al., 2020). Herman, also comments about how insulin prices have skyrocketed and says the transition to higher prices began when the switch from animal to human insulin occurred (Herman & Kuo, 2021). Lastly, research about where funds are actually going has shown that in more recent years manufacturers haven’t gotten most of the profit, but pharmacies and middlemen have been receiving the funds from consumers (Miller, 2022). Miller suggests that the solution to combating distributors and others from charging high prices is to get to legislative involvement via policies that make distributors more transparent about their pricing (Miller, 2022).

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