DESIGN OF A SUSTAINABLE MANUFACTURING PROCESS TO PRODUCE AMOXICILLIN USING WASTEPAPER AS A GLUCOSE FEEDSTOCK

A LIFESAVING PILL: AN ANALYSIS OF THE GLOBAL PHARMACEUTICAL MARKET'S IMPACTS ON SUB-SAHARAN AFRICA

A Thesis Prospectus
In STS 4500
Presented to
The Faculty of the
School of Engineering and Applied Science
University of Virginia
In Partial Fulfillment of the Requirements for the Degree
Bachelor of Science in Chemical Engineering

By
Patrick Bruns

November 1, 2021

Technical Team Members:
Justin Harrington
Nathan Ruppert
Shining Wang
Kingsford Yeboah

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.

ADVISORS

Catherine D. Baritaud, Department of Engineering and Society

Eric Anderson, Department of Chemical Engineering

Pharmaceuticals are an ever-present item in American's lives. From over-the-counter headache medication to lifesaving cancer treatments, an estimated 48.6% of Americans have used at least one prescription drug in the past 30 days (Centers for Disease Control and Prevention, 2019). However, among the general public, relatively little thought is put into how the drug reached the pill bottle. The manufacturing process, the regulatory bodies in charge of pharmaceutical monitoring, and the individuals designing an researching new drugs are often forgotten. This can lead to a dangerous path where the companies formed to keep people healthy fail in their job in favor of increased profits. To this end, the technical thesis will present a manufacturing facility that takes in wastepaper and ultimately outputs amoxicillin, a vital antibiotic used to treat a number of life-threatening conditions. The STS portion of the thesis will address the antibiotic crisis in Sub-Saharan Africa using Actor-Network Theory as a framework of analysis. The technical portion will be conducted under the supervision of Eric Anderson, chair of the chemical engineering department along with a team comprised of Shining Wang, Justin Harrington, Kingsford Yeboah, and Nathan Ruppert. The work will be done over two semesters and completed by May of 2022. The technical process will be presented in full by April of 2022. The bulk of the STS research will be performed in the spring semester and the analysis will be completed by April.

DESIGN OF A SUSTAINABLE MANUFACTURING PROCESS TO PRODUCE AMOXICILLIN USING WASTEPAPER AS A GLUCOSE FEEDSTOCK

Antibiotics, or antimicrobials, are used to treat a variety of ailments including bacterial infections such as pneumonia, bronchitis, and gonorrhea as well as infections of the ears, nose, throat, urinary tract, and skin (Ahkavan *et al*, 2021). Considering cases of pneumonia, 2.56 million people died in 2017 alone. One proposed method for prevention is pneumococcal vaccines. However, they are amongst the most expensive vaccines in the world, costing an average of $3.05/dose in specific sponsored low-income countries. The relatively cheap treatment with antibiotics supersedes vaccine deployment as a method for proactive prevention of the spread of pneumonia. However, the core issue with this alternative is that the countries with the most deaths due to pneumonia (India, Nigeria, Pakistan, DRC, and Ethiopia) have limited access to antibiotics (Dadonaite, 2017). One of the most effective antibiotic treatments for pneumonia is amoxicillin (Grant et al, 2009). Therefore, patients in countries with high pneumonia burden and limited access to antibiotic treatment can benefit tremendously from an increase in domestic amoxicillin production or worldwide production through international pharmaceutical diplomacy.

Due to the complex molecular structure of amoxicillin, production typically requires expensive and materially intensive syntheses. Thus, designing efficient and cost-effective amoxicillin manufacturing routes is essential, which is the goal of this design project. The process of producing Amoxicillin can be done using chemical synthesis but is usually performed via fed-batch fermentation in *Penicillium Chrysogenum*. This method has several advantages over chemical synthesis in terms of cost of raw materials, environmental impact, product quality, and ease of processing. The fermentation process entails production of Penicillin G (PenG), a precursor, which is enzymatically hydrolyzed to form 6-aminopenicillanic acid (6-APA). This

compound is then enzymatically reacted with *p*-hydroxyphenyl methyl ester (PHPGME) to form amoxicillin, as shown in Figure 1.

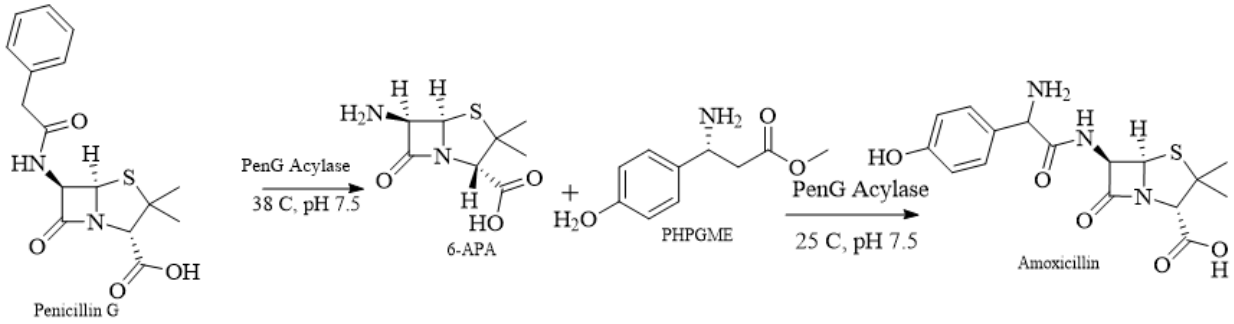

Figure 1: Amoxicillin Synthesis. This figure shows the reaction synthesis of amoxicillin from penicillin G. (Nunes *et al*, 2020).

For this project, the aim is to design a plant to produce amoxicillin using wastepaper as a source of glucose feedstock. Paper can be converted to glucose using enzymatic hydrolysis from cellulose, a homopolysaccharide made up from β-D-glucose. Figure 2 shows a generic process flow diagram for production of molecular glucose from wastepaper (Vynios *et al*, 2009). The general schema presented in this figure will be used, however, the facility for this project is anticipated to be much larger, so some adjustments to reactors and filters may be required.

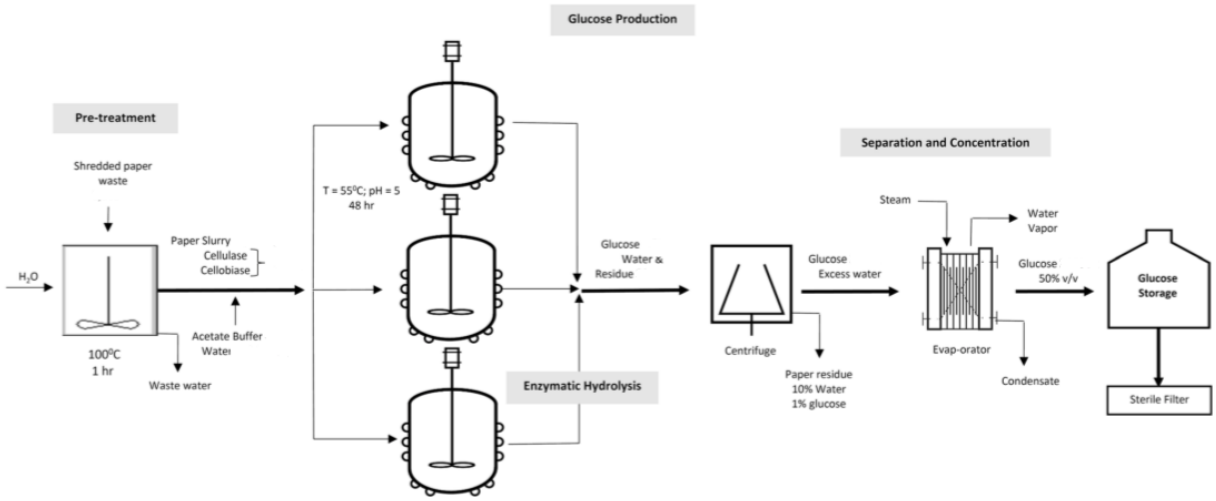

Figure 2: Process Flow Diagram, Part 1. Process flow diagram for production of glucose from wastepaper. (Nunes *et al*, 2020).

The glucose can then be used as the carbon-source feedstock for the fermentation step for penicillin G production. Following fermentation, multiple downstream purification and chemical synthesis steps are required to complete the manufacturing process. These steps include centrifugation, filtration, extraction, and crystallization. Figure 3 shows a generic model for industry-scale manufacturing of amoxicillin, which will be used as a model for this design project.

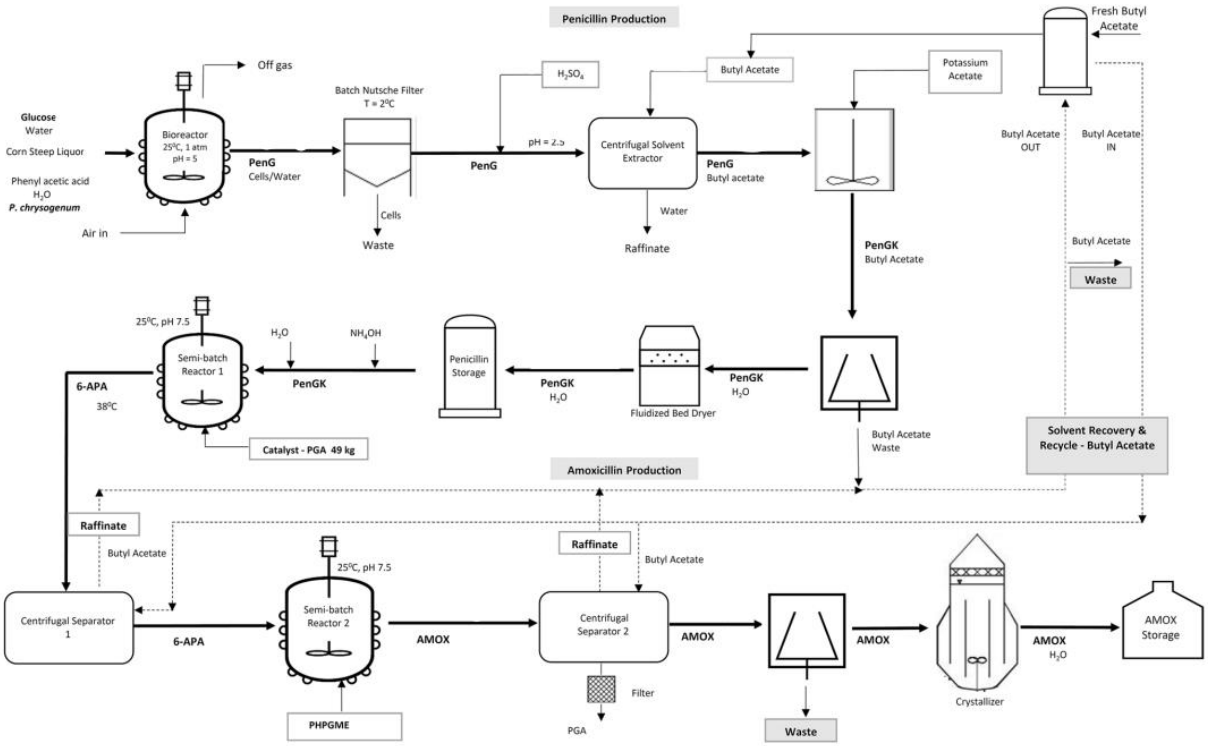

Figure 3: Process Flow Diagram, Part 2. Process flow diagram for production of amoxicillin via fermentation. (Nunes *et al*, 2020).

The team will meet weekly to assign individual tasks for the upcoming weeks and check each other's work from the previous week. Individual tasks will be split equally based on the level of difficulty and time required to complete the task, so everyone on the team can contribute equally to the project. Additionally, we plan to all work on one unit operation at a time to ensure that all members understand each stage of the process clearly.

We plan on gathering data from prior research done on the growth of *P. chrysogenum* for the design of bioreactors as well as from available literature studying similar antibiotic production processes (Kasche, 1986). Additionally, we will seek professional advice on fermentation and downstream processing design from industry and academia experts such as Professor Michael King and Professor Giorgio Carta at the Chemical Engineering department. The primary computational tools used for this project will be Aspen Plus, MATLAB, and Excel. Aspen Plus will be used to simulate unit operations, specifically post-fermentation chromatography and liquid-liquid extraction steps; MATLAB will be used to assist complex calculation of enzymatic reactions involved in the process; Excel will be used to perform an economic analysis of the overall operation.

A LIFESAVING PILL: AN ANALYSIS OF THE GLOBAL PHARMACEUTICAL MARKET'S IMPACTS ON SUB-SAHARAN AFRICA

Over the past few decades, more pharmaceuticals have been discovered, manufactured, and sold than ever before. Since 2001, the global pharmaceutical market has grown over 200%, from an estimated worth of $390.2 billion to $1265.2 billion today (Mikulic, 2020). Concurrently, drug waste is at all time high, with data from a 2007 drug collection program in California estimating about half of all drugs, both prescription and over the counter, are thrown away (Harvard Health Publishing, 2011). It would be easy to assume that waste is a product of overproduction, but this is a falsity. In the world today, millions die every year battling illnesses that could easily be treated by antibiotics if only they had access. As shown in figure 4, the World Health Organization estimated in 2019 that the fourth global leading cause of death was

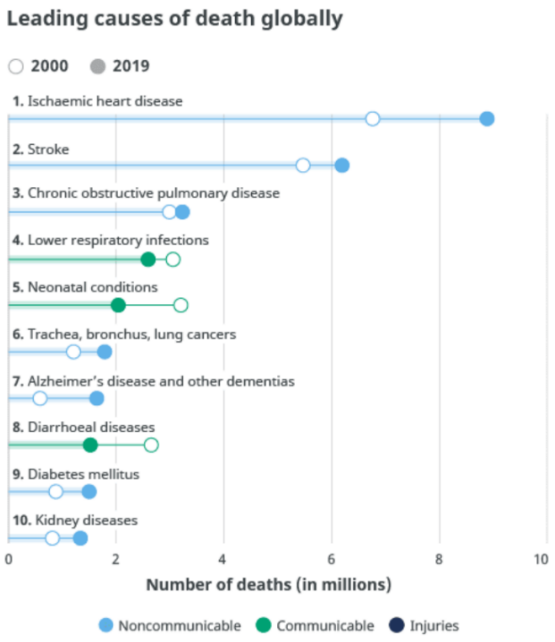

Figure 4: Leading Global Causes of Death. This figure shows the top ten global leading causes of death from 2000 and 2019 (World Health Organization, 2020a).

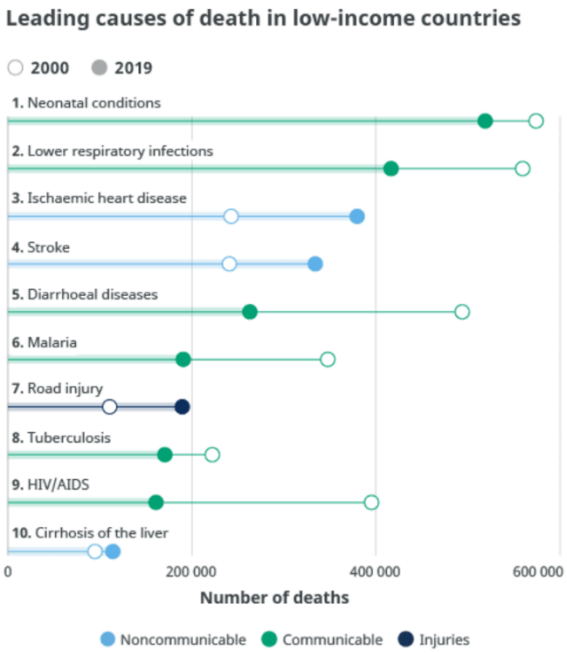

Figure 5: Causes of Death in low-income countries. This figure shows leading causes of death in low-income nations from 2000 and 2019 (World Health Organization, 2020a).

lower respiratory infection, such as Pertussis and Pneumonia. When looking specifically at low-income countries, as shown in figure 5, lower respiratory infections jump, becoming the second leading cause of death with just over 400,000 deaths per year. The vast majority of these death represent two populations, the elderly and children, whose immune systems are not able to effectively fight off these conditions. When considering just the young, more specifically children under 5 years old, pneumonia accounts for 14% of deaths (World Health Organization, 2019). These deaths are not equitably distributed across the world, however. Figure 6 shows the number of infant deaths from lower respiratory infections, and on it, two countries stand out: India and Nigeria. These two countries are part of greater regions afflicted with disease: Southern Asia and Sub-Saharan Africa. This project seeks to investigate these preventable deaths in specifically Sub-Saharan Africa.

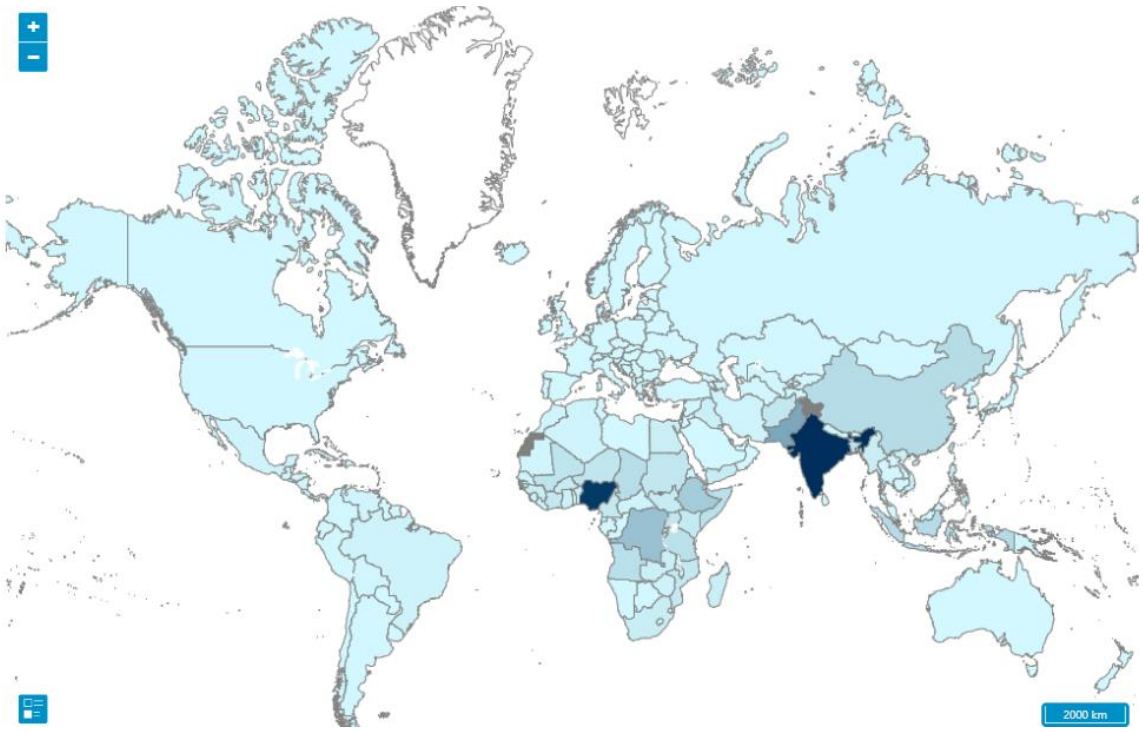

Figure 6: Infant Deaths from Lower Respiratory Infections. This figure shows a heat map of children aged 0-4 deaths due to lower respiratory infections (World Health Organization, 2020b).

Research on this topic will be presented as a scholarly article, with the primary objective being to analyze the global pharmaceutical market as it affects the availability of antibiotics in Sun-Saharan Africa. Actor-Network Theory will serve as the primary framework of analysis, which focuses on the interactions and relationships between different entities to explain social phenomena (Johnson, n.d.). A preliminary set of actors and networks can be seen in figure 6, which will serve as the starting point for analysis. The combination of these

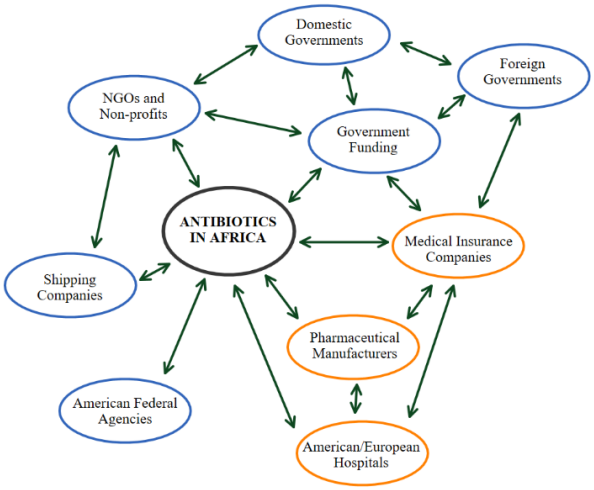

Figure 7: ANT for Antibiotics in Africa. This figure is a graphical representation of a proposed network of actors involved in the antibiotic crisis in Africa

actors forms the network that can help to understand and to explain the inequity present in global pharmaceutical trade.

REFERENCES

Akhavan BJ, Khanna NR, Vijhani P. Amoxicillin. [Updated 2021 Aug 17]. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482250/

Centers for Disease Control and Prevention (2019). Therapeutic Drug Use. Centers for Disease Control and Prevention. https://www.cdc.gov/nchs/fastats/drug-use-therapeutic.htm

Dadonaite, B. (2018, November 4). *Pneumonia*. Our World in Data. https://ourworldindata.org/pneumonia#citation

Grant, G. B., Campbell, H., Dowell, S. F., Graham, S. M., Klugman, K. P., Mulholland, E. K., Steinhoff, M., Weber, M. W., & Qazi, S. (2009). Recommendations for treatment of childhood non-severe pneumonia. *The Lancet Infectious Diseases*, 9(3).

Harvard Health Publishing. (2011). Drugs in the water. Harvard Health. https://www.health.harvard.edu/newsletter_article/drugs-in-the-water

Johnson, D. (n.d.) Social Construction of Technology. *Encyclopedia of Science, Technology, and Ethics.* 1791-1794, https://www.encyclopedia.com/science/encyclopedias-almanacs-transcripts-and-maps/social-construction-technology

Kasche, V. (1986). Mechanism and yields in enzyme catalyzed equilibrium and kinetically controlled synthesis of β-lactam antibiotics, peptides and other condensation products. *Enzyme and Microbial Technology*, 8(1), 4-16, https://doi.org/10.1016/0141-0229(86)90003-7

Mikulic, M. (2020, May 25). Pharmaceutical market worldwide revenue 2001-2018. Statista. https://www.statista.com/statistics/263102/pharmaceutical-market-worldwide-revenue-since-2001/

Nunes, J. J., Maharaj, R., Maharaj, V., Sedoo, T. A., Fernandes, L. J., & Holder, C. (2020). Waste Paper to Antibiotics: A Design and Feasibility Study of a Penicillin Production Facility in Trinidad and Tobago. Waste and Biomass Valorization, 11(6), 2581-2589.

Vynios, D., Papaioannou, D., Filos, G., Karigiannis, G., Tziala, T., & Lagios, G. (2009). Enzymatic production of glucose from wastepaper. *BioResources*, 4(2), 509-521, from https://ojs.cnr.ncsu.edu/index.php/BioRes/article/view/BioRes_04_2_0509_Vynios_PFKTL_Enzym_Prod_Glucose_Waste_Paper

World Health Organization. (2019). Pneumonia. World Health Organization. https://www.who.int/news-room/fact-sheets/detail/pneumonia

World Health Organization. (2020a). The top 10 causes of death. World Health Organization. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death

World Health Organization. (2020b). Number of deaths in children aged <5, by cause map. World Health Organization. https://www.who.int/data/gho/data/indicators/indicator-details/GHO/number-of-deaths