**Design of a Sustainable Manufacturing Process to Produce Amoxicillin Using Waste paper as a Glucose Feedstock**

**The Publics of Pharmaceutical Activism**

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 Your Major

By

Justin Harrington

November 1, 2021

Kingsford Yeboah; Nathan Rupert; Patrick Bruns; Justin Harrington; Shining Wang

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

Sean Ferguson, Department of Engineering and Society

Eric Anderson, Department of Chemical Engineering

## Introduction

Treatable bacterial infections, such as pneumonia and bronchitis, lead to millions of deaths each year. One of the driving factors for this is the lack of access to antibiotics in the developing countries most affected by these diseases. Amoxicillin is the most commonly prescribed antibiotic, and the expansion of its production could lead to lifesaving drugs for those most at risk, either through pharmaceutical diplomacy or its production in developing countries (Dadonaite, 2018). Using a recently published paper that investigated the feasibility of a waste paper to amoxicillin plant in Trinidad and Tobago as a basis; my Chemical Engineering Capstone team aims to develop a modern amoxicillin plant that uses a novel process to convert waste to a substrate feed for the fermentation of penicillin producing fungi.

Although the expansion of the production of antibiotics could save lives internationally, the pharmaceutical systems that it expands, historically has been fraught with exploitation. In order to prevent further exploitation pharmaceutical activism has been employed to petition companies and government to fight for specific goals. I aim to develop a methodology for the analysis of previous U.S. pharmaceutical activists using the framework of Public and Participation; specifically, why they succeeded and why they were allowed to succeed. Then apply this methodology to modern day pharmaceutical activists supporting alternative medicines.

## Technical Topic

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, and up to $169/dose in high-income countries; thus low-middle-income countries are priced out of the vaccine as it is not subsidized. 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, 2018). One of the most effective antibiotic treatments for pneumonia is amoxicillin (Grant *et a*l. 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 (Nunes *et al*. 2020).

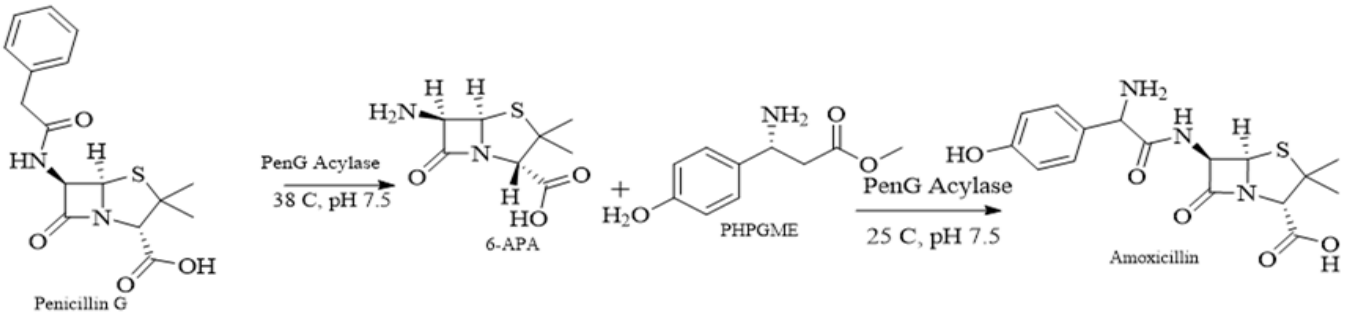


Figure 1: General Reaction Scheme for Amoxicillin Synthesis from PenG

The aim for this project is to design a plant to produce amoxicillin using waste paper as a carbon feedstock. Since a carbon source is required for microbial growth in fermentation processes and thus presents a major expense, the use of waste paper as a sustainable alternative could reduce capital costs and environmental footprint. Additionally, previous research has shown that waste paper is a viable alternative feedstock for microbial fermentations (Kühner, 2021). 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 glucose from waste paper (Nunes *et al*. 2020).

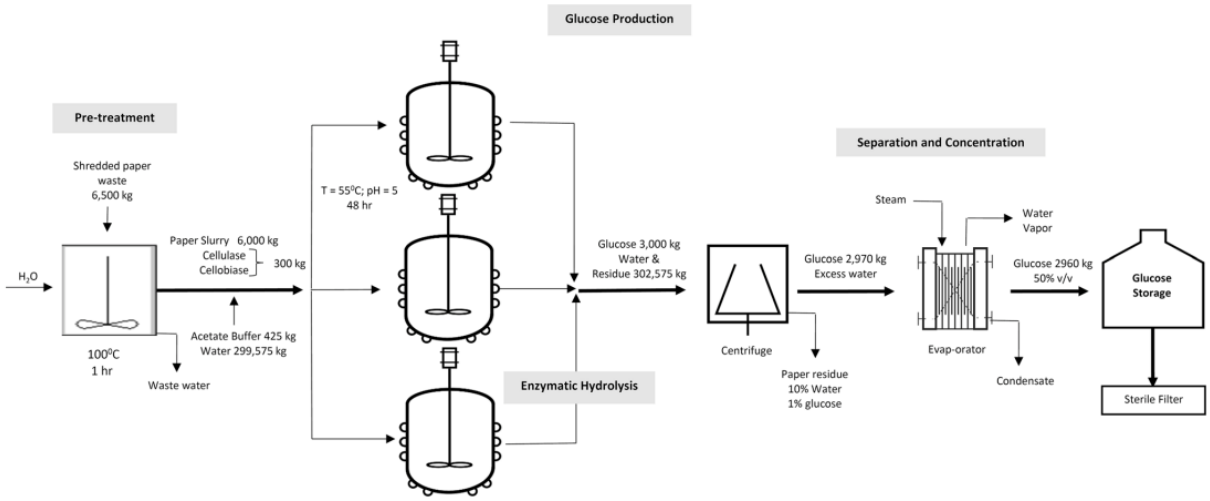


Figure 2: Process Flow Diagram for Production of glucose from waste paper

The glucose can then be used as the carbon-source feedstock for the fermentation step for PenG 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 (Nunes *et al.* 2020).

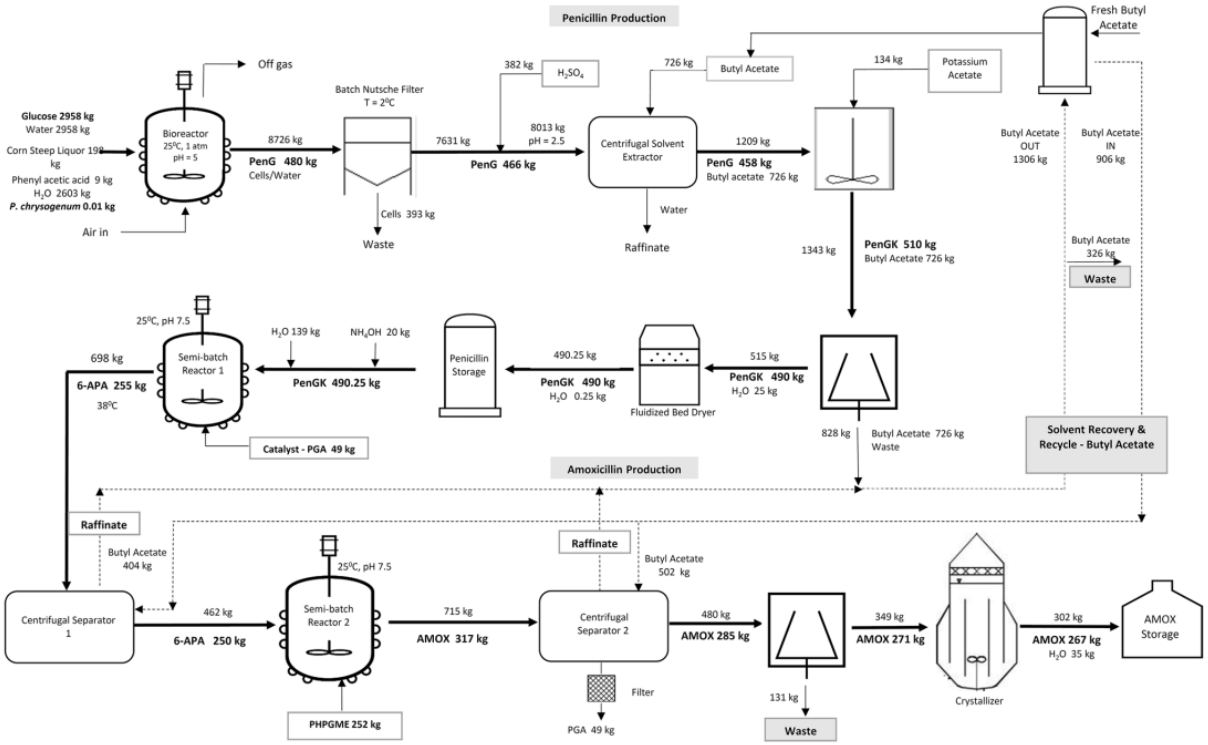


Figure 3: Process Flow Diagram for Production of Amoxicillin Via Fermentation

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. 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. All of this will be combined into a final design report which will contain material and energy balances; process equipment designs; economic analysis; and discussion of safety, environmental and social issues for the proposed facility.

## STS Topic

According to the CDC, in the past 30 days, roughly half of Americans have used at least one prescription drug, a 20% increase from 1988, and one in eight Americans have used five or more prescription drugs, a 320% increase from 1988 (CDC, 2021). Most Americans are intrinsically interlinked with the pharmaceutical system in some way whether it be through prescribed antidepressants, lifesaving cancer drugs, or daily vitamins. Every drug released represents a multitude of conflicting goals: the therapeutic benefits of treatment; hazardous side effects; profit and the economic impact of its sale on users and developers (Institute of Medicine of the National Academies, 2007). Balancing these differing goals can lead to vast social benefits that simultaneously benefit various stakeholders. Thus, the control of these systems should not uniquely be held by the companies that develop them or the companies responsible for their payment. Historically publics have fought to prevent this and advance progressive drug research and pharmaceutical policies using methods of public activism, called pharmaceutical activism (Batt *et al.* 2020). The purpose of this paper is

to investigate the publics participation in the pharmaceutical system, both at key historical points and today; specifically defining the publics that have been allowed to participate historically, the effectiveness of the mobilization of these publics within the pharmaceutical system, and applying this methodology to modern day pharmaceutical activists pushing for alternative medicine.

In order to understand the importance of publics in pharmaceutical activism, and its abilities or inabilities to affect the pharmaceutical system, one must observe historical examples for insight. One of the first instances of pharmaceutical activism can be traced back to the gilded age, specifically the role that women's groups played in the formation of the U.S. FDA (Goodwin, 1999). The exportation of food, drink, and medications from the house to factory during the gilded age was also accompanied by the adulteration of products and by false advertisements. Samuel Hopkins Adams in *The Great American Fraud* highlights the astroturfing campaigns that pharmaceutical companies pushed at the time "They see my advertising. They read the testimonials. They are convinced. They have faith in Peruna. It gives them a gentle stimulant and so they get well." (1905). This was compounded by the rampant political corruption during the gilded age, wherein the government would exclusively side with industrialists (Batt *et al,* 2020). Women, driven by these issues, fought for unadulterated products before prominent politicians, physicians, or even journalists did (Goodwin 1999). Their activism led to the creation of the Food and Drug Administration in 1906 with the passage of the 1906 Pure Food and Drug Act. While the women's groups of the gilded age were successful in

their activism the Drug manufacturers at the time fought back, successfully lobbying for the only required reported ingredients being opium, morphine, and alcohol (Batt *et al.* 2020). What made this movement successful while others that have come sense have not seen similar levels of success? What aspects of culture drove these women to mobilize against the pharmaceutical system?

Similar groups have arisen since, during the 1980s and 1990s the AIDS epidemic devastated multiple communities throughout the U.S.; The formation of the AIDS movement led to one of the most integrated research topics in medicine (Sismondo, 2010). Public engagement in the scientific process led to a distinctive sub movement within pharmaceutical activism. The AIDS movement successfully changed areas of research, such as preventing the use of placebo in clinical trials for drugs that were shown to prevent the replication of the virus, even leading their own clinical trials outside of the main pharmaceutical system (Epstein, 1996). At the same time the pharmaceutical system has failed to meet core demands of the AIDS movement, primarily the development of a vaccine, which was originally predicted to take two years to develop in 1984 (NIH). What barriers prevented the success of the AIDS movement and the pharmaceutical system in combatting the AIDS epidemic? What differences can be recognized in the makeup of the core groups behind the AIDS movement and the women's groups of the gilded age, and how did this play into the successes of the publics?

The questions proposed can be best answered using the framework of Public and Participation. This framework is characterized primarily by an analysis of the "processes by which different aspects of participation are defined or constructed" it is influenced heavily by the analysis of the shortcomings of public understanding of science and the interplay of the lay person and the way in which experts and policymakers dismiss the public due to a lack of scientific knowledge (Hess & Sovacool 2020). Using this framework, I will strive to identify the publics that have participated in social movements, and further determine the role that the differing characteristics of each group played in the amount of success that they were able to achieve. Finally applying this methodology to modern day activists who push for alternative medicines such as essential oils, homeopathy, and refusal of vaccines will allow for the determination of why this specific movement has been successful when more scientifically based movements have failed.

## Next Steps

The group will immediately start working on the Design Bases Memorandum in which a location, scale, and concrete process will be chosen. This will be completed by November 12. Following this the group will design the process and calculate parameters and design specifications throughout. Individuals will be assigned tasks during weekly meetings, working through each individual process step will be developed together. Professional help will be sought by experts at the University, such as Professors Giorgio Carta and Michael King.

For my personal STS project, I have already checked out *The Pure Food, Drink, and Drug Crusaders, 1879*-1914 by Lorine Goodwin and *Protecting America's Health* by Philip Hilts. I plan on reading them in order to develop a wide knowledge of the differing publics that have participated in pharmaceutical activism in the past. Further I have identified several target groups that participate in pharmaceutical activism for alternative medicines and have contacted several vocal members of the community with the purpose of interviewing them, specifically anti-vaccine group supporters. I am currently awaiting permission, and further plan to identify alternative medicine discussion boards to determine what the publics surrounding pharmaceutical activism for alternative medicines are.

## References


Adams, S. H. (1905). The great american fraud ...: A series of articles on the Patent Medicine Evil, reprinted from Collier's weekly ...: Also the patent medicine conspiracy against the freedom of the press. P.F. Collier & Son.

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/

Batt, S., Butler, J., Shannon, O., & Fugh-Berman, A. (2020). Pharmaceutical ethics and grassroots activism in the United States: A social history perspective. Journal of Bioethical Inquiry, 17(1), 49–60. https://doi.org/10.1007/s11673-019-09956-8

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

Epstein, S. (1996). Impure science: Aids, activism, and the politics of knowledge. Univ. of California Press.

Gindi, R. Health, United States, 2019. 2021.

Goodwin, L. S. (1999). The Pure Food, Drink, and Drug Crusaders: 1879-1914. McFarland.

Hess, D. J., & Sovacool, B. K. (2020). Sociotechnical matters: Reviewing and Integrating Science and Technology Studies with energy social science. Energy Research & Social Science, 65, 101462. https://doi.org/10.1016/j.erss.2020.101462

Institute of Medicine of the National Academies. (2007). Pharmaceuticals: The Good and the Bad. In Informing the future: Critical issues in health (pp. 13–13). essay.

Kühner, S. (n.d.). *Feedstock costs - bioboost*. Retrieved November 1, 2021, from https://www.bioboost.eu/uploads/files/bioboost_d1.1-syncom_feedstock_cost-vers_1.0-final.pdf.

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.

Sismondo, S. (2010). The Public Understanding of Science. In An introduction to science and technology studies. essay, Wiley-Blackwell.

U.S. Department of Health and Human Services. (n.d.). History of HIV vaccine research. National Institute of Allergy and Infectious Diseases. Retrieved October 18, 2021, from https://www.niaid.nih.gov/diseases-conditions/hivvaccine-research-history.