A NOVEL PRODUCTION OF AMOXICILLIN USING WASTEPAPER

DISCRIMINATION IN PHAMACEUTICAL DEVELOPMENT IN THE UNITED STATE

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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

How does marketing affect pharmaceuticals' role in healthcare?

In the United States, sales of prescription drugs constitute the primary source of revenue for the pharmaceutical industry (Levy, 1994). The annual growth rate of retail prescription drug spending has been rising. In 2018 the growth rate was 3.8 percent; in 2019 it was 5.7 percent (Conti et al., 2021). Yet not all drugs are dispensed in a retail pharmacy (Conti et al., 2021). To market their drugs, pharmaceutical companies offer incentives and sponsor conferences and holidays as inducements to doctors (Hailu et al., 2021). Steep growth in prescription-drug spending burdens insurers, public health programs, and individual patients, imposing difficult choices about the allocation of limited healthcare dollars.

A Novel Production of Amoxicillin Using Wastepaper

In the U.S, how can the conversion of wastepaper feedstock to penicillin be sustainably implemented in pharmaceutical plants?

Eric Anderson of the Chemical Engineering Department is advising this team capstone project. Collaborators are Patrick Bruns, Justin Harrington, Shining Wang, and Nathan Ruppert.

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 highincome 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, 2017). 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 costeffective 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).

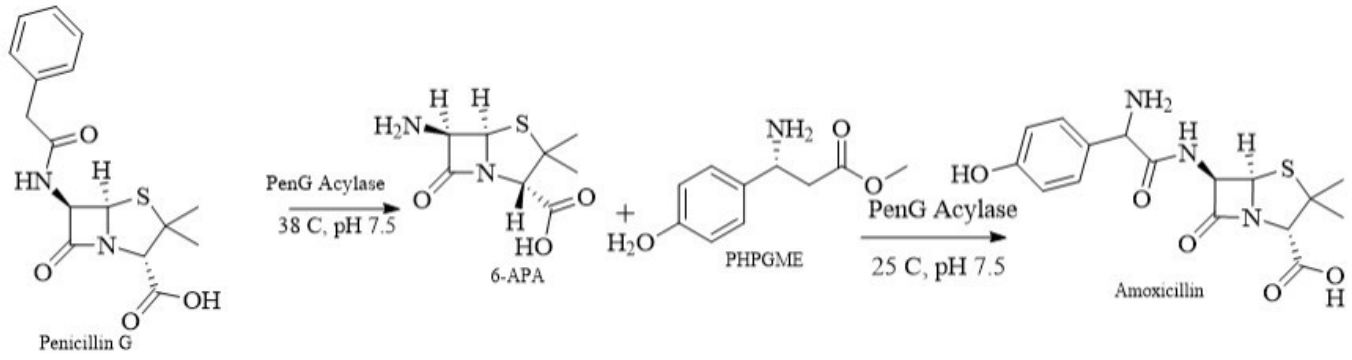

Figure 1: General Reaction Scheme for Amoxicillin Synthesis from PenG

The aim for this project is to design a plant to produce amoxicillin using wastepaper 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 wastepaper as a sustainable alternative could reduce capital costs and environmental footprint. Additionally, previous research has shown that wastepaper is a viable alternative feedstock for microbial fermentations (Nunes *et al*. 2020). 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 wastepaper (Nunes *et al*. 2020).

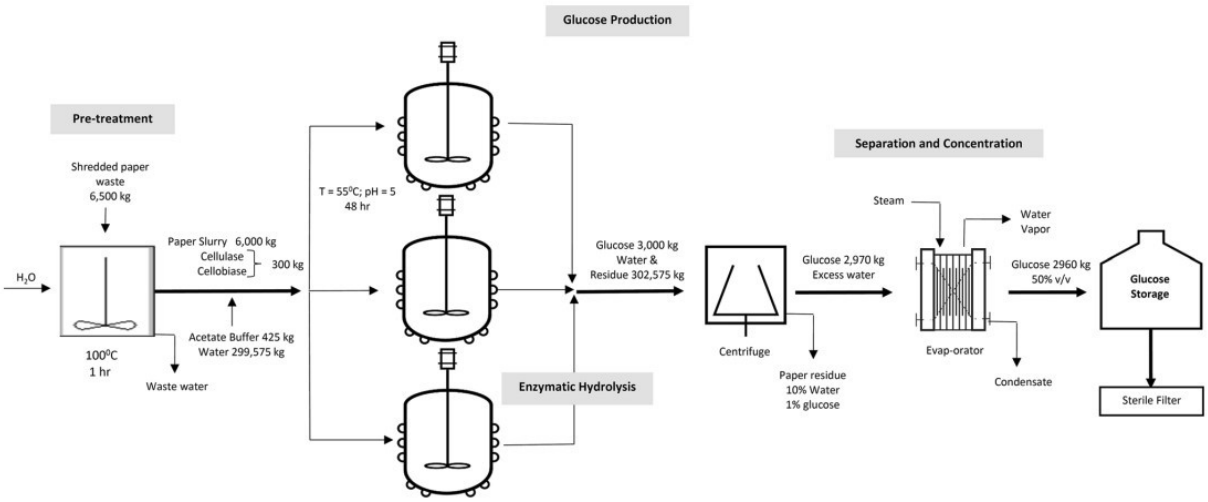

Figure 2: Process Flow Diagram for Production of glucose from wastepaper

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).

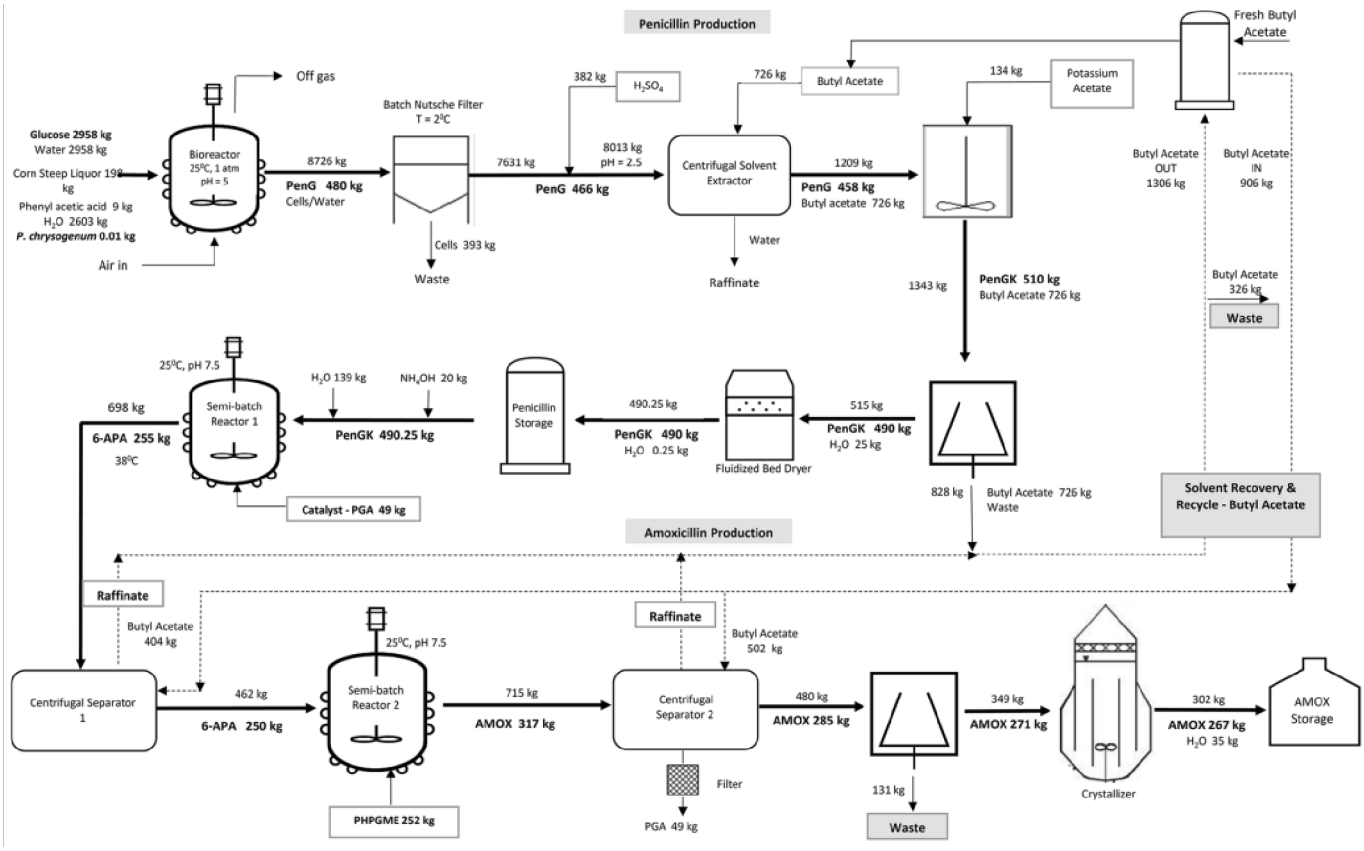

Figure 3: Process Flow Diagram for Production of Amoxicillin Via Fermentation

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.

Discrimination in Pharmaceutical Development in the United States

In the U.S., how have social groups sought to combat gender and racial discrimination in clinical trials for the development of pharmaceuticals?

Lack of diversity in drug development is an important issue. Data from testing on patients reveals that efficacy and safety may differ among population subgroups depending on several factors, including sex, race/ethnicity, and genetic background (Clark et al., 2019). Gender and racial discrimination persist in clinical trials. According to the Food and Drug Administration (FDA), African Americans and Hispanics comprise 12 and 16 percent of the total US population respectively, but account for only 5 and 1 percent of clinical trial participants (FDA, 2017). Advocacies, government agencies and some pharmaceutical companies are aiming to improve diversity in drug development in the United States.

Biopharmaceutical companies, such as Eli Lilly and Bristol Myers Squibb, are incorporating more African American in clinical trials. They have collaborated with the National Medical Association and National Hispanic Medical Association to increase enrollment of racially and ethnically diverse volunteers in U.S clinical trials, and to educate physicians and

patients about the importance of diversity. They are also working with other organizations committed to the same goal. To increase diversity in clinical trials, Eli Lilly is recruiting minority investigators (Eli Lilly, n.d). Eli Lilly states, “people are more likely to volunteer for a trial if the investigator speaks their native language or is familiar with their culture” (Eli Lilly, n.d). According to Eli Lilly, there has already been some improvement in minority participation (Eli Lilly, n.d). In 2020, Bristol Myers Squibb committed expanding health equity and clinical trial inclusion (McGrail, 2021). Acknowledging that social determinants of health perpetuate health disparities and inequities, the company has announced that it has allocated $50 million in grants over the next five years to promote disease awareness and education in underserved patient populations (McGrail, 2021).

The FDA recently released a strategic plan to advance regulatory science, aimed to increase the diversity of clinical trial participants. The agency is encouraging drug and biologics sponsors to broaden enrollment criteria and to avoid unnecessarily excluding participants (Schneider, 2020). The agency stated, “Unnecessary exclusion of participants such women and minorities may lead to a failure to discover important safety information about the drug after approval” (Schneider, 2020). In 2016, the FDA launched the Diverse Women in Clinical Trials initiative in partnership with the National Institute of Health (NIH) office of Research on Women’s Health to promote clinical trial participation from women from all ages and ethnicities (FDA, 2018). The initiative includes a Partner Social Media Toolkit (FDA, 2018) that helps women, policymakers, and researchers encourage participation in trials by women of all ages and ethnicities (FDA, 2018).

For example, with the toolkit, a consumer tweeted, “Help yourself and women like you. Learn why it’s important for #Hispanic women to join #clinicaltrials” to bring awareness to Hispanic women (FDA, 2018).

Past exploitation of racial and ethnic groups in medical research has left a legacy of distrust, which can deter participation in clinical trials. Investigators must make a concerted effort to overcome this history of distrust. The National Bioethics Research Initiative (NBRI) has developed a project called Building Trust. Through training and educational programs, it strives to increase the participation of minorities in public health and biomedical research (University of Maryland). The project’s curricula serve minority communities, particularly those whose residents endure significant health disparities, and investigators, research staff, and health professional students (University of Maryland). The project stresses the need for transparent communication. Most importantly, the conversion must take place on a level the patient can relate to without condescension. Community-Based Participatory Research (CBPR) can rebuild trust, educate patients, and raise awareness (De las Nueces, 2012). CBPR supports collaborative interventions that involve scientific researchers and community members to address diseases and conditions disproportionately affecting health disparity populations (De las Nueces, 2012). Trial sponsors and investigators have developed new paths to diversity by eliciting the support of trusted community leaders. Several studies targeted African American participants through black churches, black community events, and beauty salons. In 2017, at the Healthy Churches National Conference of 400 people, the Association of Black Cardiologists (ABC), and Boston Scientific Corporation (BSC) raised awareness about the role churches can take to eliminate disparities and increase diversity in clinical trials (ABC, 2017). The theme of the event was, “Faith and Public Health: Leading Together to Find Solution!”. Dr. Brewer of ABC promotes conversations at

familiar venues, saying "when you're asked" to enroll in a clinical trial "by your pastor, or church member, that's where the trust comes from" (ABC, 2017). Dr. Brewer also urges that they practice self-care and model healthy lifestyles, as they are influential in their faith communities (ABC, 2017).

The Eliminating Disparities in Clinical Trials Project (EDICT) named unreliable transportation as a major barrier to both participation and retention in clinical trials. Continuum Clinical is indirectly involved in clinical trials. It helps clients overcome the challenges associated with conducting multinational patient recruitment campaigns (Continuum Clinical, n.d.). Continuum partnered with Lyft to provide free transportation to patients' drug trials (Continuum Clinical, n.d). For participants who cannot afford to get to the appointment, Lyft recently partnered with Axovant Sciences to provide transportation. They have served elderly women enrolled in an Alzheimer's clinical trial in California (Resendez, 2016). This novel partnership model may be adapted to serve other marginalized communities.

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