DESIGN OF A SUSTAINABLE MANUFACTURING PROCESS TO PRODUCE PENICILLIN V USING WASTE PAPER AS A GLUCOSE FEEDSTOCK

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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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Summary

This project aims to determine the technical and economic feasibility of a large-scale penicillin VK manufacturing plant in South Africa. The novel aspect of the design is to use the conversion of waste paper to glucose as a carbon source for the synthesis process. The process of producing penicillin from waste paper is broken down into 3 main parts. The first step is the production of glucose from waste paper, followed by an upstream process involving the fermentation of *Penicillium chrysogenum* to produce penicillin. Lastly, a downstream process is designed to purify and crystalize penicillin V to penicillin VK crystals. The waste paper to glucose process consists of a pretreatment process using the liquid hot water method to remove impurities, followed by enzymatic hydrolysis of cellulose using cellulase to produce glucose. After hydrolysis, further purification processes such as centrifugation and evaporation were used to purify the glucose. The upstream and downstream process consists of multiple primary operations: fermentation, filtration, neutralization, centrifugation, extraction, distillation, and crystallization.

The design of unit operations was conducted via hand calculations using Microsoft's Excel, Aspen Plus, and MATLAB software programs. An economic analysis was facilitated by Microsoft's Excel, CAPCOST (Turton et al., 2017), and various websites.

The final product will be sold as an active pharmaceutical ingredient (API). The plant aims to produce 677.4 tonnes of glucose and 330.4 tonnes of penicillin VK powder annually to meet the market demand in Sub-Saharan Africa. The bulk selling price of penicillin VK per tonne used was $35,000.

The economic feasibility of the project was determined under the assumption that the life of the plant would be 20 years with an additional 2 years of construction during which the fixed

capital investment would be distributed equally and that a 10-year straight-line depreciation would be accurate. Using these conditions, the economic analysis of the project shows that the net present value after 20 years of operation is $23,159,773 and the internal rate of return (IRR) would be 15.35%. Because the IRR is above the recommended industry standard, this project is economically feasible.

1. Introduction

Two major economic patterns are apparent in the 21st century: the development of emerging economies and the transition of already-industrialized economies to become net carbon neutral. As emerging economies become more developed, they represent an exceptional opportunity for growth within the pharmaceutical industry. Emerging economies already represent 30% of the global pharmaceutical market, and that figure is expected to rise by the end of the 21st century. This growth projection is due to the characteristics of emerging economies: large populations, growing prosperity, and increased life expectancy. Additionally, emerging economies are prime markets for drug formulae that have been selling for decades, meaning that well-established antibiotics are ideal candidates for exploitation within emerging economies (Tannoury *et al*., 2017).

While the growth of the pharmaceutical industry means that increased production will be a profitable sector, the increased push for net carbon zero-emissions will lead to an increased focus on the emissions of the pharmaceutical industry. Recent studies have illuminated that the global pharmaceutical industry is 55% more carbon-intensive than the automotive industry. This statistic means that the pharmaceutical industry related activities emit 55% more carbon than the automotive industry does per dollar of revenue. Therefore, the industry will be of primary consideration for decarbonization to meet the target goal of 1.5℃ that was laid out in the Paris Climate Agreement and recently reiterated in the Glasgow Climate Pact. The global pharmaceutical industry needs to reduce its carbon output by roughly 50% relative to its 2015 levels to meet emissions targets for the 1.5℃ plan (Belkhir *et al*., 2019). To achieve the level of reduction, redesign efforts are necessary to decarbonize processes and create carbon credits for businesses.

To profit off of these major economic trends, the creation of a penicillin V manufacturing plant in South Africa has been proposed that will utilize the conversion of waste paper to glucose as a carbon source for the aerobic fermentation that is part of the synthesis process. Penicillin V was first discovered in 1948 and was created out of necessity for a broad-spectrum antibiotic with high bioavailability. This production method will assist in the decarbonization of the pharmaceutical industry while simultaneously allowing for cheap, safe, and pure drugs for sale in emerging economies. The high solubility, rate absorption, and stability of penicillin V under acidic conditions make it resistant to gastric pH, allowing the oral administration of this drug (Rolinson *et al.,* 2007). Penicillin V is 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).

2. Drug product explanation

The final product of the proposed process will be phenoxymethylpenicillin (penicillin V) powder as an API. Penicillin V is usually sold in its calcium or potassium salt form because of its higher absorption profile (DrugBank 2005). As a result, additional processing is required before the drug product can be distributed to consumers, but details are not covered in the report as it is outside the scope of this project.

Penicillin V is a member of the group of beta-lactam penicillin antibiotics with antibacterial activity. By binding to the penicillin-binding proteins (PBR) inside the bacterial cell wall, penicillin V disrupts bacterial cell wall synthesis. This mechanism, which is similar to that of all other penicillins, subsequently causes cell lysis and inhibits microorganism biosynthesis. Penicillin V is used to prevent and treat mild to moderately severe bacterial infections in the upper respiratory tract, skin, and soft tissues (Stuart *et al.* 2008).

3. Business scale and location

Even though penicillin V is on the World Health Organization's List of Essential Medicines, reports have shown that antibiotics shortages are prevalent in South African public sector hospitals, especially penicillins, with 80% of hospitals reported to experience shortages in the previous six months (Chigome *et al*., 2019). Additionally, Sub-Saharan African countries, including South Africa, have the highest burden of infectious disease, making the medicine shortage situation more concerning (Dheda *et al.,* 2017).

The use of paper products generates over 100 million tonnes of waste every year globally (Guo, 2018). To adapt to new environmental challenges stemming from increasing global waste paper recycling needs, the global waste paper trade pattern has been reforming rapidly in recent years. Noticeably, the African community, led by South Africa and Rwanda, has gradually formed independent communities to become the key nodes in the trade network (Ma *et al., 2021*).

A domestic penicillin V manufacturing plant that uses waste paper as the input carbon source can address the medicine shortage issue in South Africa while taking advantage of the abundance of waste paper from trading. Therefore, the proposed pilot plant will be built in South Africa. Based on total yearly prescriptions, 470 tonnes of amoxicillin are prescribed in the US annually. Under the assumption that emerging economies will have comparable pharmaceutical market demand to that in developed countries, the design is set to produce ⅛ of South Africa's estimated annual consumption, which is equivalent to 150,000 kg of penicillin V using backward conversion from amoxicillin to penicillin precursor. This plant will work for 300 days per year, producing an estimated 6,000 kg of penicillin per batch. The predicted duration of each batch is 7 days.

4. Previous Work

South Africa is a leading economy within Africa for recycling. Paper and fiber recycling in particular is already well developed with a network of agents collecting, baling, and transporting waste paper pre-existing within the economy. In 2017 South Africa generated 3.6 million tonnes of paper waste, 39% of which was recovered. These commercial recycling processes are predominantly focused on recycled paper goods. However, there is interest in a recycling stream focused on non-traditional products manufactured from recycled paper from companies like Averda (Averda).

Much literature exists that discusses processes for the production of glucose from biomass. While much of this literature is predominantly focused on fuel production from these carbon sources, the initial enzymatic hydrolysis step is the same as the proposed enzymatic hydrolysis. Levine *et al.* and Reese specifically did studies on the conversion of waste paper to glucose using cellulase enzymes at various temperatures, pH, pretreatments, and concentrations which can be utilized in the design of the enzymatic hydrolysis process (Levine *et al.,* 2010; Reese, 1956).

A similar design effort focuses on the conversion of waste paper to glucose as a feedstock to produce amoxicillin in Trinidad and Tobago. This provides an overall guidance for design decisions for both the conversion of waste paper to glucose and the fermentation of penicillin. In regards to the implementation of downstream processes for purification, a simulation by Carmichael & Petrides provided a basis for the design and recovery information of all processes (Carmichael *et al.,* 2020).

5. Discussion

5.1 Waste Paper to Glucose

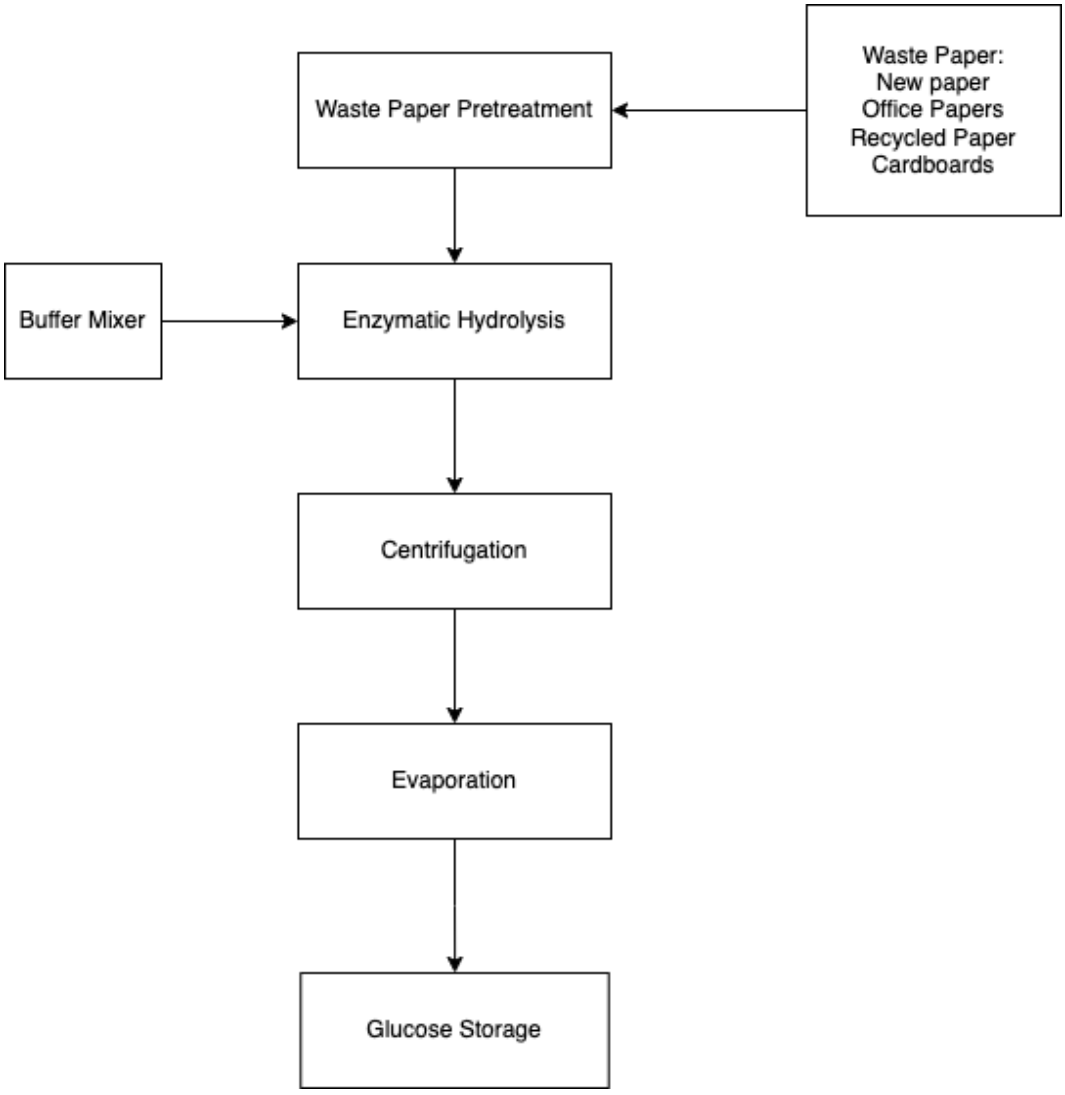

Figure 5.1-1 shows a generic process overview block flow diagram of converting waste paper to glucose .

5.1.1 Waste Paper pretreatment

Prior to hydrolysis, incoming recycled paper is pretreated and pulped. Pretreatment is a key step of cellulosic glucose production because it improves the hydrolytic efficiency of the process by removing contaminants like hemicellulose and lignin, as well as other impurities associated with waste paper such as dirt, inks, and oil. Additionally, pulping allows for greater exposure to terminal ends of the cellulose polymer chain, which is beneficial since cellulase can only hydrolyze glucose subunits from these terminal spots. Among the various pretreatment methods, hydrothermolysis using water has shown to be effective in removing and solubilizing hemicellulose. Liquid hot water pretreatment (LHW) of cellulosic biomass (waste paper) at a controlled temperature effectively dissolves hemicelluloses and some of the lignin while minimizing the formation of monosaccharides and further degradation of sugars to toxic substances during the pretreatment step. The cellulosic waste paper is also pulped to increase substrate access by hydrolytic catalysts when suspended in a mixture of water. After the paper is converted into a slurry, the mixture is screened to separate the pulp from the non-pulp material. The non-pulp materials which consist of hemicellulose, lignin, impurities, and wastewater are discharged out into wastewater treatment plants for recycling.

A drum pulper was used to pulp and screen the feedstock for this process since it has a relatively simple configuration and requires low energy consumption, which reduces running costs per ton of pulp. The ZG2500 drum pulper made by Leizhan was used for the design basis. In addition to the drum pulper, a ZDFD3 series single effect fiber separator was used for secondary screening of waste paper pulp by separating the impurities from the paper slurry needed for the enzymatic reactor. The paper slurry is assumed to be 88 w/w % of paper coming

out of screening equipment into the enzymatic reactor. Based on the production requirements of producing 150,000 kg of penicillin V annually, 1,680,000 kg of waste paper is processed annually. The pulper and screener will be kept at a temperature of 100 ℃ to help facilitate the separation of fibers in the waste paper.

To calculate the energy requirement for pulping, the specific heat capacity of the slurry using paper composition was estimated. Assuming that paper is fed at 17 ℃, which is the average annual temperature in South Africa, water was added at 100 ℃ and the energy required was calculated.

5.1.2 Enzymatic Hydrolysis

The objective of the hydrolysis unit is to convert the cellulose that makes up the waste paper into glucose via enzymatic hydrolysis. Cellulose is a crystalline homopolymer made of glucose monomers. Enzymatic hydrolysis was chosen over chemical hydrolysis since it has been identified as a "green" and environmentally friendly process. The cellulose polymer is degraded by cellulase to give the monomer glucose, which can, in turn, be used as a carbon substrate in the fermentation of *P.Chrysogenum* to yield penicillin V. The chemical reaction of converting cellulose to glucose is shown in Equation 5.1.2-1.

$$(C_6H_{10}O_5)n + nH_2O \rightarrow nC_6H_{12}O_6 \qquad \text{(Eqs. 5.1.2-1)}$$

Cellulases play a crucial role in generating glucose feedstock from cellulose. Cellulase is produced commercially using a fungus called *Trichoderma reesei*. For this project, large-scale purchases of cellulase produced from this fungus will be used for cellulose hydrolysis. *T. reesei* has been recorded as one of the most important commercial cellulase producers and has been widely used in a variety of industries (Hamdan *et al.* 2018). The amount of enzyme used is

determined based on the amount of cellulose present in the hydrolysate and the specific activity of the enzyme. The cellulase activity used is 10 FPU/g which is purchased from Henan Dongtai Pharmaceutical Co. Ltd.

A stirred tank batch reactor was modeled in which the paper slurry, cellulase, water, and acetate buffer are transferred into the tank to perform the reaction above. Acetate buffer was added to control the pH inside the reactor and to promote glucose conversion. The reactor conditions used were pH of 5.5 and operating temperature of 45-55°C. From the literature, it was found that a 55% conversion of cellulose to glucose is feasible with enzymatic hydrolysis, material balances were done to determine how much glucose, cellulose, and solid waste would come out of the reactor accounting for the mass of the water molecules lost during hydrolysis. For each batch process, including filling and draining the batch tank was assumed to take about 55 hours, with 48 hours being the reaction time. The target design conditions for enzymatic hydrolysis are summarized in Table 5.1.2-1.

Table 5.1.2-1. Enzymatic Hydrolysis Conditions

Temperature	45°C
Initial solids loading	10 wt% total solids
Residence time	48 hrs
Number of batch vessels	7
Size of batch vessels each	40 m^3
Cellulase loading	0.0565 kg of protein/ kg of paper

We propose a design for the enzymatic batch reactor that is a scaled-up operation from the design proposed by Palmqvist. The original design was for a 2.5 L reactor with a pitched-blade impeller. The blades are at an angle of 45°, with individual impeller diameter (D_i)

of 70 mm and width (w_i) of 20 mm pumping upwards (Palmqvist *et al.* 2011). To meet the demand for this project, seven 40,000L reactors will be needed per batch. Standard geometric proportions were used to calculate the dimensions of scaled-up reactors with the power to volume ratio kept constant relative to the lab-scale reactor. Standard geometry for enzymatic reactors follows the following rules of tank dimensions ratios.

$$D_t D_i = H D_i = 3 \text{ and } H D_t = 1 \quad \text{(Eqs. 5.1.2-2 and Eqs. 5.1.2-3)}$$

Where:

D_t = Tank diameter

D_i = Impeller diameter

H = Height of the tank

The power applied to the agitation system was calculated using equation 2-2, where the power consumption (P) is a function of power number (N_p), fluid density (ρ), Reynolds Number, geometric parameter such as the impeller diameter (D_i) and rotational speed (N).

$$P = N_p \rho N^3 D_i^5 \quad \text{(Eqs. 5.1.2-4)}$$

The resulting tank dimensions, number of impellers, impeller rotational speed and gassed flow rate to achieve the desired reaction are in Table 5.1.2-2.

Table 5.1.2-2: Enzymatic reactor dimensions and impeller specifications

N, rotational speed	500 rpm
Tank diameter ,D_t	3.7 m
Height of tank, H	3.7 m
Impeller diameter, D_i	1.2 m
Impeller height, H_b	1.2 m
Power per tank	68500 W

5.1.3 Buffer mixer

Research has shown that the addition of acetate buffers yielded the most optimal glucose conversion from copy paper and towel paper in an enzymatic treatment (Vynios *et al.* 2009). Specifically, the conditions used to optimize the enzymatic treatment were a 0.1 M concentration buffer and a constant pH value of 4.5. We plan to mix 0.1 M acetic acid and 0.1 M sodium acetate in a 1.3:1 volume ratio to prepare the acetate buffer solution with a target pH of around 4.5 because the two ingredients are readily available for bulk purchase in higher concentrations. The acid streams will be fed into a tank, where the homogenous acetate buffer solution is then fed into the enzymatic reactor with a buffer to paper slurry mix ratio of 50:1 based on the design proposed in a similar study (Nunes *et al.* 2020).

5.1.4 Centrifugation

The objective of the centrifuge is to separate the remaining paper residue, enzyme, and residual paper impurities from the bulk of the excess water containing glucose and acetate buffer. This separation is possible due to the phase and density differences between the liquid and the solids, where the solid density is greater than that of the fluid mixture. However, some glucose is lost since some of the water-glucose solutions gets entrained in the porous paper and exits the centrifuge equipment with the solids stream. The solid stream will exit via conveyor belts.

This is a transition step in the waste paper conversion step where the process switches from a batch process to a continuous process. The type of centrifuge we propose to use is a solid-bowl scroll-discharge centrifuge, which is also known as a continuous decanter centrifuge. It has a wide range of liquid-solid separation applications because of its capability to dewater

waste sludge (Records *et al.* 2001). The feed is separated by high gravitational forces, and a conveyor mounted within the bowl of the centrifuge transports the solids for further dewatering and ultimate discharge (Records *et al.* 2001). The chosen model for centrifugation is the GN 22 inch (550 mm) Decanter centrifuge (Model GNLW554ET-VFD). This model allows for a reasonable process time of 2.04 hrs to centrifugate the 260,000 L of reactor effluent operated at approximately 2,100 L/min.

5.1.5 Evaporator

The objective of the evaporator is to concentrate the glucose solution to a more easily-stored volume of liquid that can then be used in a fed-batch system while maintaining the appropriate concentration for the following *P.Chrysogenum* fermentation reaction. The feed into the evaporator will consist of a 5 wt.% glucose stream, with a concentrated 15 wt.% glucose stream out. Heat will be provided using condensed steam, and the evaporated steam byproduct will be utilized to heat the feed stream into the enzymatic reactor. To accommodate the batch size of our design, we propose to use SPX APV single effect evaporator, which has a maximum flow rate of 35,000 lbs/hr and a heat duty of 6,628 kWh/batch.

5.2 Upstream

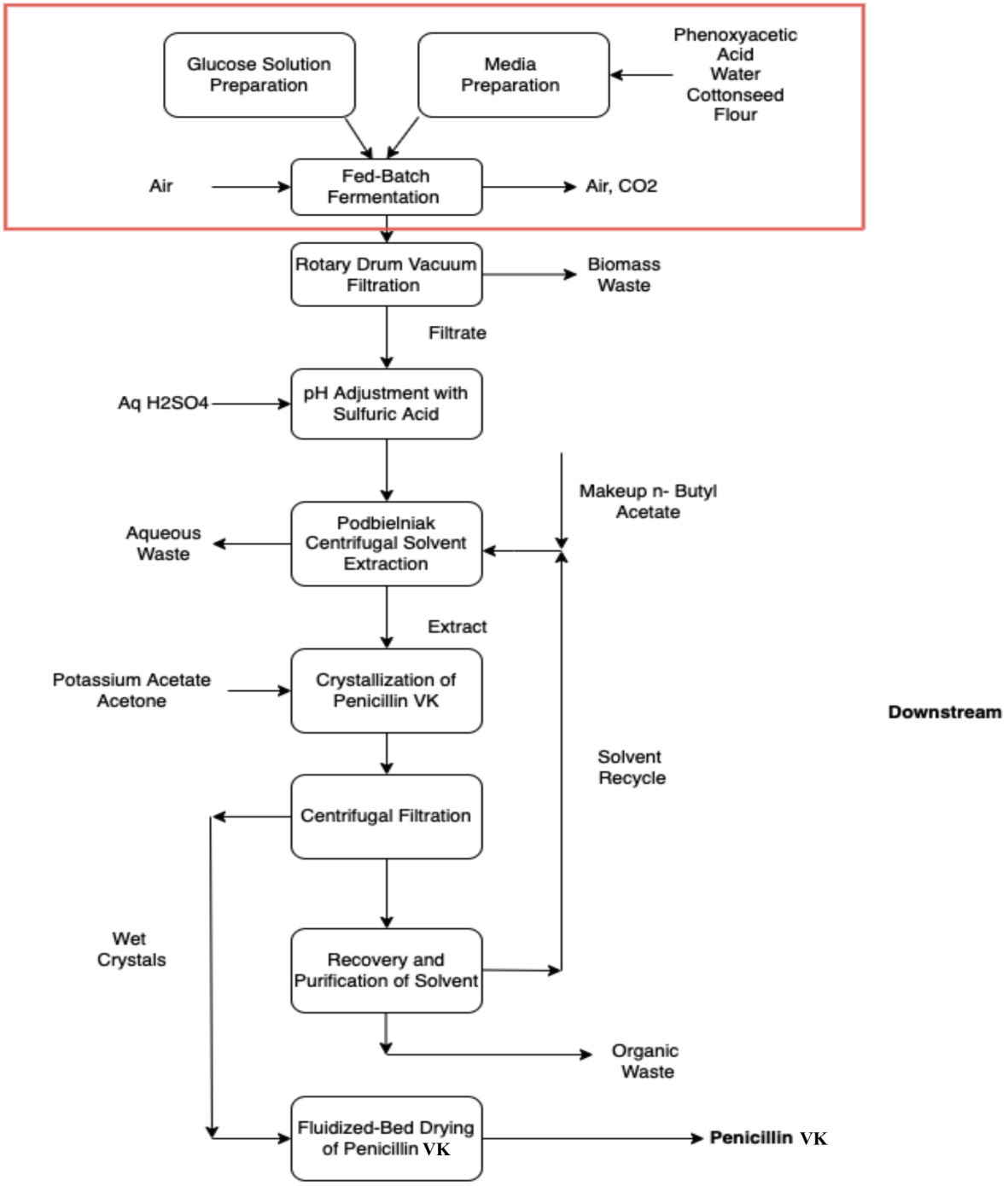

Figure 5.2-1 Block- Flow Diagram for Penicillin VK Process with the red line indicating the upstream process.

5.2.1 Cell Seed Train

The media composition used for this fermentation process was drawn from existing recommendations for optimized *P. Chrysogenum* growth shown in Table 5.2.1-1 (Moyer *et al.*, 1946). Corn steep liquor is a common additive that is used as a source of nitrogen for microbial growth. Other salts, sugars, and oils that have been shown to be necessary for the proper growth of *P. Chrysogenum* are listed in the table. For the purposes of later models, the properties of this media once diluted are assumed to be comparable to an equivalent volume of pure water. Glucose will serve as a primary carbon substrate for microbial growth and will be sourced from the upstream wastepaper degradation process. The bioreactor fermentation has been designed such that all of the glucose produced from a single batch of the degradation process is used in one fermentation batch. These batches include the seed train reactors as well as the 100,000 L fermenter. Phenoxyacetic acid will be added directly to the fermentation reactor since it is a precursor that is necessary for the production of penicillin V via metabolic processes. It will be added in proportion to the total amount of phenoxyacetic acid required corresponding with the volume of periodic fermentation broth additions.

Table 5.2.1-1: Composition of Fermentation Medium for *P. Chrysogenum* Growth

Component	Concentration (wt %)	Mass Required Per Batch (kg)
Corn steep liquor	3.5	3936.6
Lactose	3.5	3936.3
Glucose	13	13548.4
Potassium dihydrogen phosphate	0.4	449.5
Edible Oil	0.25	281.1
Water	N/A	90322.6
Phenoxyacetic acid	4.1	4600.0

Microbial growth kinetics were modeled using the Contois equation, which is commonly used to model fungal growth. This model is based on the idea that growth is limited by both the amount and access of biomass to carbon substrates. This principle results in a hyperbolic curve similar to that predicted by the commonly-used Monod model but with a half-saturation constant, K_s, that varies according to the biomass concentration, as shown in Equation 5.2.1-1.

$$\mu = \frac{\mu_{max} S}{K_s X + S} \quad \text{(Eq. 5.2.1-1)}$$

Where:

μ = specific growth rate (h^{-1})

μ_{max} = maximum specific growth rate (h^{-1})

S = Substrate concentration (g/L)

K_s = Half- Saturation constant

X = Biomass concentration (g/L)

The maximum specific growth rate and the half-saturation constant were 0.103 h^{-1} and 0.145 g/l, respectively, and were obtained from an experimental study (Bajpai *et al.,* 1980). Using these values, a modeled fermentation schedule was created using a fed-batch configuration with periodic additions of growth media. This model approximates the change in product concentration, substrate concentration, and biomass concentration within the bioreactor as demonstrated in Figure 5.2.1-1. Based on this model, the total penicillin V production quantity was calculated throughout the fermentation and is shown in Figure 5.2.1-1.

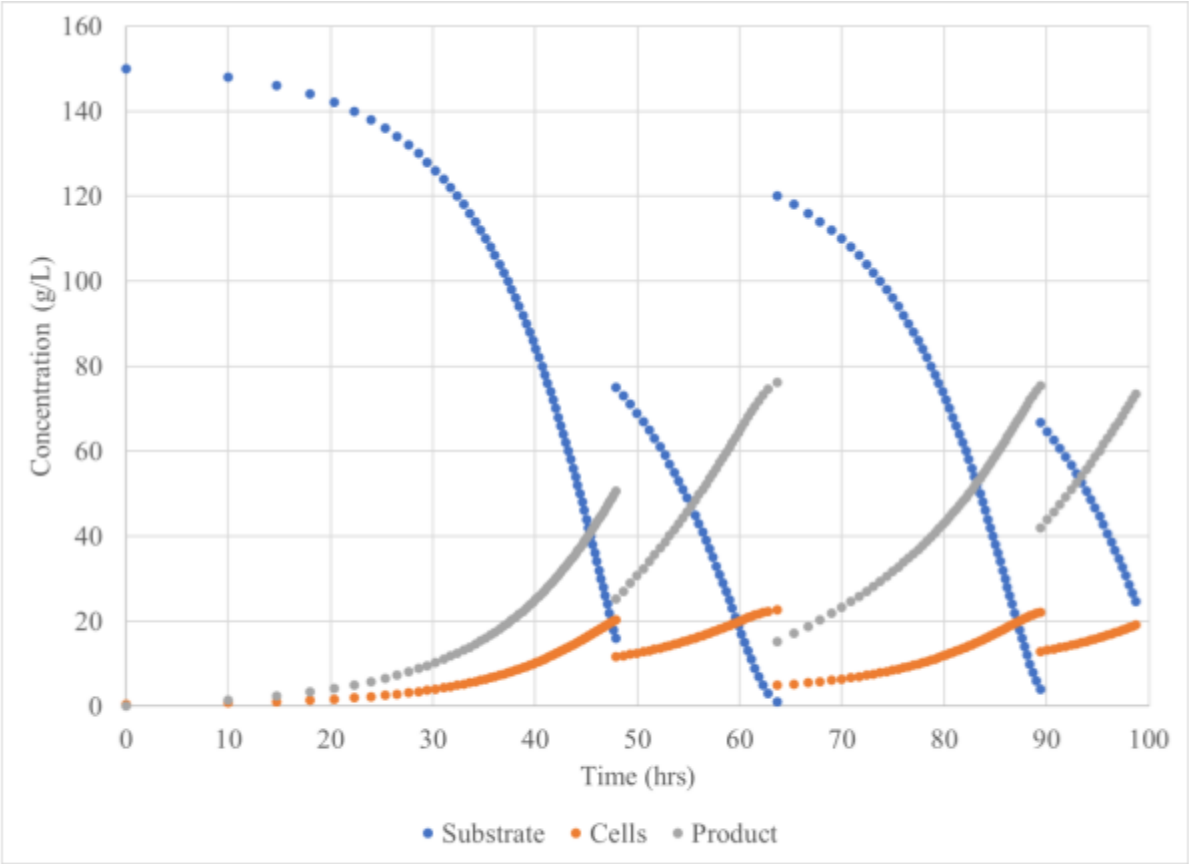

Figure 5.2.1-1: Model for Substrate, Biomass, and Product Concentration with Periodic Media Addition

The fermentation will begin using a seed train in which a 3 L shaker flask of *P. Chrysogenum* is cultured to the point where the biomass concentration is 25 g/L when measured by light diffraction. This flask will then be transferred to a 100 L bioreactor that will also be cultured until the biomass concentration is 25 g/L. Based on Figure 5.2.1-2, this fermentation will take 26 hours. The 100 L reactor contents will be transferred to a 100000 L jacketed reactor that will initially have only 5000 L of total liquid volume in it including the 100 L reactor contents. The compositions of the growth media in the two seed reactors will be the same as that of the final 100,000 L reactor with the exception that 4600 kg of phenoxyacetic acid will be added to the 100,000 L reactor for penicillin V production. This decision was made since current literature indicates that penicillin V production is increased in the presence of high biomass

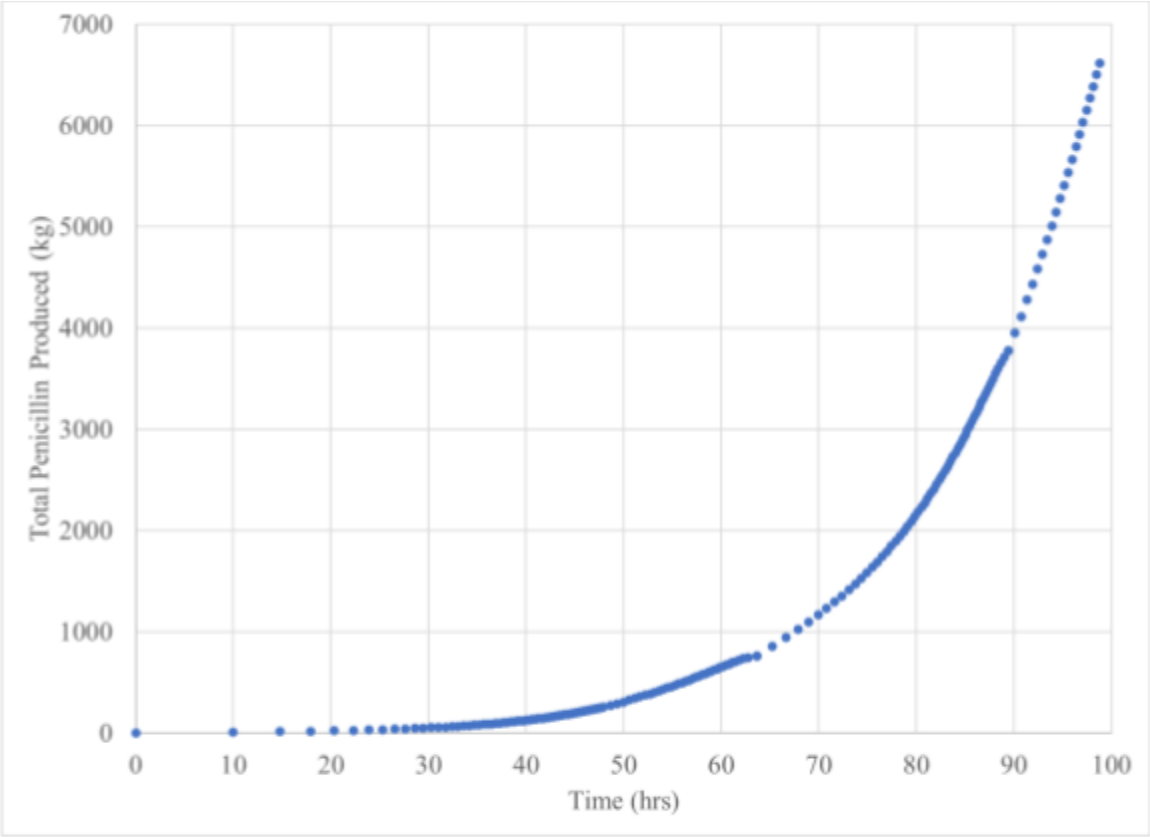

Figure 5.2.1-2 Production Schedule for Penicillin V

concentrations and limited carbon substrate (Muniz *et al.,* 2007). Based on these values, the initial biomass concentration in the 100,000 L reactor will be 2.5 g/L. After fermentation, the final concentration will be approximately 19 g/L. The final product concentration is 74 g/L. One important note that may be a flaw with the model used here is that it assumes the growth of cells is continuous and uninhibited by the presence of increasing concentrations of penicillin V. However, cell concentrations can often reach 40-50 g/L, so the model gives a relatively accurate depiction of the microbial growth (Pirt *et al.,* 1967).

Table 5.2.1-2: Time Schedule for Substrate and Phenoxyacetic Acid Addition

Time (hr)	Volume added (L)	Mass of Phenoxyacetic Acid (kg)
0	5,000	255.56
48	5,000	255.56
63	40,000	2044.44
89	40,000	2044.44

Table 5.2.1-3 shows the growth curve parameters used for the fermentation of *P. chrysogenum*.

Table 5.2.1-3: *P. Chrysogenum* Growth Model Parameters

μ_{max}	0.103 h^{-1}
K_s	0.145 g/L
$Y_{X/S}$	0.445 $g_{cells}/g_{substrate}$
$Y_{P/S}$	1.11 $g_{product}/g_{substrate}$
$Y_{X/O2}$	1.54 g_{cells}/g_{O2}

5.2.2 Fermentation Bioreactor

The 100 L and 100000 L reactors will be geometrically similar such that the dissolved oxygen concentration in both reactors is maintained at 20% of saturation. The dissolved oxygen and pH level are continuously monitored to provide the optimal environment for cells to grow. For the production schedule, the seed train and the expansion steps collectively take 5 days. Therefore, the entire upstream fermentation process lasts 6 days, factoring in time for shutting down and starting up.

The production bioreactor has a 100,000 L working volume with a temperature of 25 ℃ and a pH of 6.5. Filtered air is fed to the bioreactor. Oxygen demands for the system were determined first by calculating the k_La using the steady-state assumption that oxygen uptake rate (OUR) is equal to the oxygen transfer rate (OTR), which results in Equation 5.2.2-1.

$$q_{O2}dX/dt = k_La\,(C_{O2}^{*} - C_{O2,min}) \quad \text{(Eq. 5.2.2-1)}$$

Where:

$q_{O2}dX/dt$ = Cell line-specific oxygen consumption rate (g_{O2}/L/hr)

q_{O2} = Oxygen biomass yield coefficient (g_{O2}/g_{cells})

X = *P. Chrysogenum* cell density (g_{cells}/L)

k_La = The oxygen transfer rate (h^{-1})

C_{O2}^{*} = The equilibrium oxygen concentration (g_{O2}/L)

$C_{O2,\,min}$ = The minimum oxygen concentration (g_{O2}/L)

Due to the nature of this equation and the constantly changing cell concentration in the reactor, the specific oxygen requirement of the system is constantly increasing. Using Equation 5.2.2-2, the k_La was determined to have a maximum value of 163 h^{-1}, since the other variables were found in the literature (Goldrick et al., 2015). After determining the required k_La of the system, the parameters for operating the bioreactor were determined using a design formula from Professor George Prpich's CHE 3347 course. The following equation used in the design was used to find the theoretical k_La of the system based on the impeller rotational speed and gassed flow rate (flow rate of air). These values were adjusted until an adequate k_La was achieved.

$$k_La = 0.6\left(\frac{P_g}{V}\right)^{0.4} v_s^{0.5} N^{0.5} \quad \text{(Eq. 5.2.2-1)}$$

Where:

k_La = oxygen mass transfer rate (h^{-1})

$\frac{P_g}{V}$ = power density (hp/1000L)

v_s = superficial gas velocity (cm/min)

N = impeller rotation rate (RPM)

The microbial and physical parameters, design target, and air supply inputs to the design formula are detailed in Table 5.2.2-1. The resulting tank dimension, number of impellers, impeller rotational speed and gassed flow rate to achieve the desired k_La are Table 5.2.2-1

Table 5.2.2-1: Bioreactor Parameters

Bioreactor Specifications	
Reactor Volume	100,000 L
Tank Radius	2.1 m
Impeller Radius	0.85 m
Impeller Type	Propeller, pitch twice diameter
Number of Impellers	3
Baffles	4, 0.21m
Solution Properties	
Density	997 kg/m^3
Viscosity	0.00089 Pa s
Temperature	25 C
Design Targets	
Total Penicillin	6616 kg
k_La	176.97 hr^{-1}
Air Supply	
p_{O2}	0.21 atm
Aeration to Volume Ratio	1 vvm
Q_g	90 m^3/min
Agitation	
Agitation Rate	100 RPM

To accommodate annual production targets, the bioreactor used for the fermentation of *P. Chrysogenum* will be a 100,000 L jacketed batch reactor. The reactor will have a diameter of 4.2 m and a height of 7.2 m, which will allow sufficient headspace for the fermentation when the maximum liquid volume of 90,000 L is reached. The reactor will be agitated at 100 RPM with 3 rushton turbine impellers each with a diameter of 1.7 m. The area of the cooling coils needed for the reactor will be 105 m^2. The vessel will be equipped with pH, temperature, dissolved oxygen, foaming and pressure sensors.

5.3 Downstream

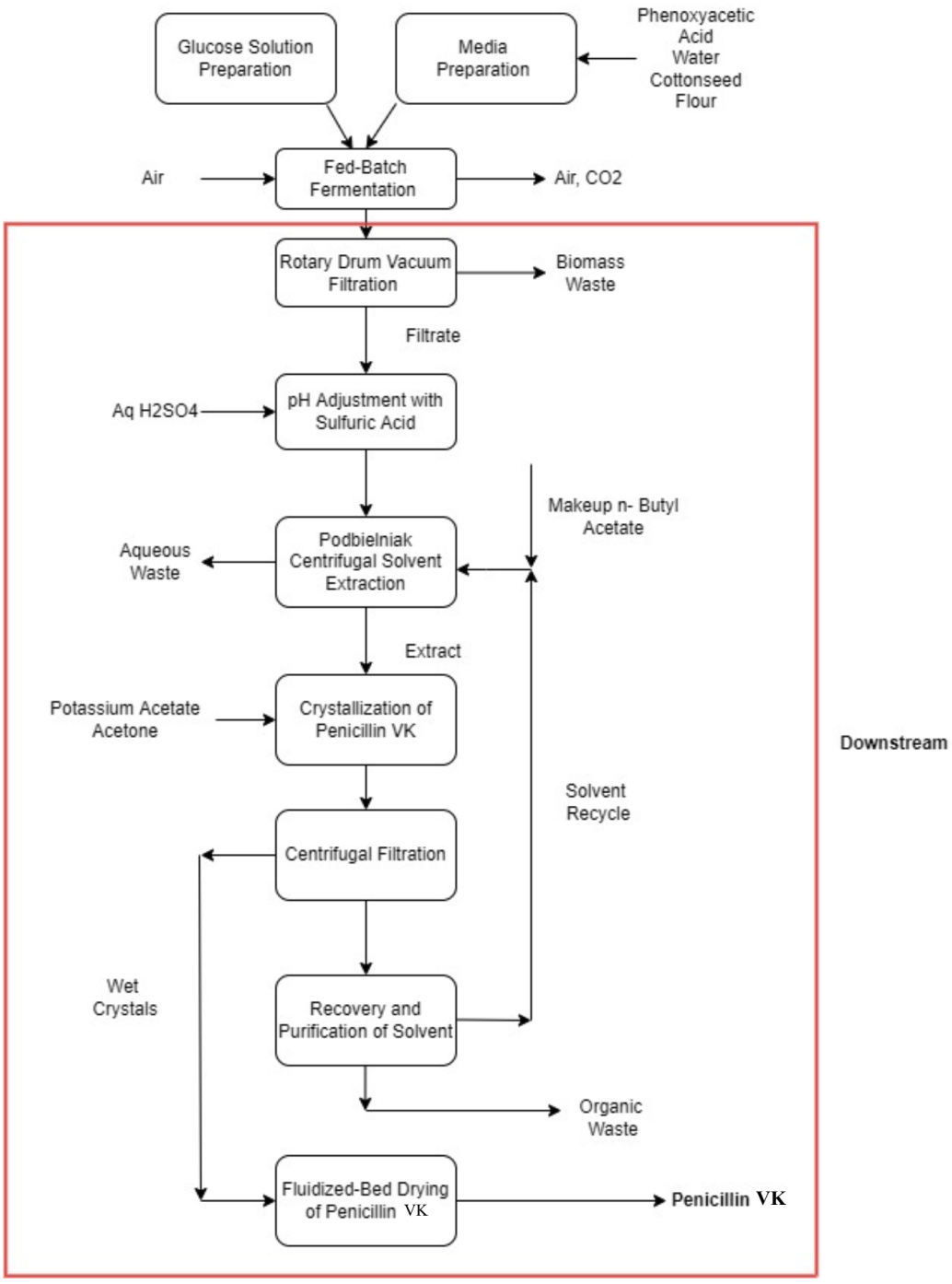

Figure 5.3-1 Block- Flow Diagram for penicillin VK process with the red line indicating the downstream process.

5.3.1 Broth Filtration

The first step in the recovery of penicillin V from the fermentation broth is the separation of cells from the liquid growth media. Since penicillin is produced extracellularly, it remains in the liquid phase and can be removed with a filtration step. For this separation, a continuous rotary vacuum filter is used to remove *P. chrysogenum* cells and other large debris from the growth media. The rotary vacuum filter operates continuously in which the biomass is captured in a concentrated cake. The filter cake is also washed with water in order to maximize the product recovery in the filtrate stream. An advantage of the rotary drum vacuum is that it has a lower operating cost since it is continuous and automated compared to other filtration methods. In this process, the filter runs continuously as fermentation batches are prepared.

In terms of design for the rotary vacuum, many factors were needed to determine an adequate size for the filter, such as the viscosity and density of the filtrate, solid-liquid ratio, size, and shape of the particles, and the pressure needed to ensure a sufficient filter rate of liquid. The chosen model for the rotary drum filtration was from a group called Andritz with a filtrate area of 2.8 m^2 and transmembrane pressure of 5 psig. It filters at a flux of 1000 L/m^2-h, to a cake porosity of 0.35 v/v. The wash solvent flowrate is 40.7 L/h. This specific unit was chosen because it can process a sufficient volume of fermentation broth in a reasonable time such that this step of the process will not bottleneck the downstream production of penicillin VK.

5.3.2 Filtrate Cooling and Acidification

To reduce penicillin degradation during the subsequent extraction step, the filtrate from the previous step is usually cooled to 2 ℃ using a simple heat exchanger. Because downstream penicillin solubility is extremely sensitive to the pH in the environment, the stream is acidified

by the addition of 10% sulfuric acid in order to increase solubility in organic solvents. The target pH for this step is 3.

5.3.3 Extraction of Penicillin with Solvent

Extraction of the filtrate is necessary to separate penicillin from the water before further processing. Countercurrent solvent extraction is the generally accepted process for this step. Liquid-liquid extraction is suitable because it can be utilized at low temperatures, has high selectivity, and is less expensive compared to distillation, evaporation, and membrane technology. In this process, we propose to use butyl acetate and potassium acetate to extract the desired product. The ideal equipment for the extraction is a continuous centrifugal extraction. Specifically, we will utilize a Podbielniak continuous extractor centrifuge to accomplish the countercurrent liquid-liquid extraction, where penicillin is extracted from the aqueous phase to a more thermodynamically stable organic phase consisting of butyl acetate. The organic phase is primarily composed of butyl acetate (32 %), potassium acetate (6 %), penicillin V (16%), and water (46%).

The aqueous waste stream consisting of mostly water and sulfuric acid from the centrifugal extractor is sent to a neutralization tank. To neutralize the waste stream before disposal, we propose to use a 50% Potassium hydroxide solution to neutralize the excess acid. The organic product stream is sent for additional downstream processing to separate and purify the penicillin product.

5.3.4 Crystallization of Penicillin V

To extract penicillin out of the organic phase, a crystallization technique is used since penicillin V is a crystalline powder. It is necessary to use crystallization in order to yield a highly pure penicillin V product and it is done through phase separation from an organic liquid phase to solid. For crystallization to begin, a supersaturated solution is required where there are more dissolved solids in the solvent than can ordinarily be accommodated at that temperature at equilibrium. We can achieve supersaturation by cooling, solvent evaporation, or by chemical reaction. For our process, supersaturation is achieved via a chemical reaction and cooling. Potassium acetate and acetone are added to the solvent, and penicillin V is crystallized as the salt from the solvent phase, with critical parameters including potassium concentration, pH value, penicillin concentration, and temperature. The chemical reaction is shown below in Equation 5.3.4-1.

$$C_{16}H_{18}N_2O_5S\,(aq) + CH_3CO_2K\,(aq) \rightarrow CH_3COOH\,(aq) + C_{16}H_{17}N_2O_5KS\,(s)$$

or

$$Penicillin\,V + Potassium\,Acetate \rightarrow Acetic\,Acid + Pencin - V - Crystal$$

(eq. 5.3.4-1)

The crystallization is assumed to be a one-phase process called primary nucleation. From research, the step is not fully understood but essentially primary nucleation is the growth of new crystals where a large supersaturation driving force is required to start the process. This will continue until the remaining solution concentration is at equilibrium. Often in commercial production, batch crystallization is used for polishing antibiotics, such as penicillin V. Batch crystallizers consist of tanks with stirrers and baffles. The design specifications are shown in the final design section of this report. The crystallizer is slowly cooled to about a temperature of 2°C

to produce supersaturation. Although the crystallization process results in high purity of the product, it can also be profoundly affected by trace impurities and batch crystallization can sometimes give poor quality, nonuniform products.

5.3.5 Centrifugal Filtration

A centrifuge is required to isolate the solid penicillin V precipitated from the previous crystallization step from the liquid phase. We propose to use a basket centrifuge in this step because of its high efficiency and low cost. Similar to regular centrifuges, a solid wall basket centrifuge uses centrifugal forces to separate liquid and solid materials. The feed is introduced into the rotating basket, where solids are pulled radially away from the liquid as the basket accelerates. The solid material is then collected along the inner wall of the basket, and the liquid flows over the wall as its volume increases and eventually gets collected along with the inner compartment and discharged by gravity. Additionally, the layers of fine mesh and coarse screens on the basket wall provide more opportunities for the separation of solid and liquid materials. The solids collected in the basket can be washed again with water to get rid of additional impurities adhering to the surface of the crystals.

With such equipment, we can separate a sizable amount of butyl acetate from the input stream and recycle the organic solution back to the centrifugal extractor step. Not only is it more economically favorable to recycle the solvent stream, the multi-functional equipment also allows for additional purification of the solids. Because the solids must be removed manually, this step will be a semi-batch process where a specified volume of liquid is fed in for each cycle.

5.3.6 Recovery and Purification of Solvent

Since the presence of acetone would draw penicillin V into the aqueous phase during the initial extraction of penicillin out of the fermentation broth, any residual acetone that needs to be separated from the butyl acetate and water before it can be recycled back into the centrifugal extractor. Additionally, the residual acetic acid from the basket centrifuge needs to be neutralized for better separation. In order to accomplish this, the recycle stream coming off of the centrifugal filtration is treated with potassium hydroxide for neutralization, followed by a distillation column to separate the acetone from the butyl acetate and water. The chemical reaction for neutralizing the stream is shown below

$$CH_3COOH + KOH \rightarrow CH_3COOK + H_2O$$

Acetic Acid + *Potassium Hydroxide* → *Potassium Acetate* + Water

(eq. 5.3.6-1)

The neutralized stream is then mixed with a makeup solvent stream and fed back into the centrifugal extractor.

The main process equipment in this step is the distillation column, which will have a total of 23 stages, a feed stage of 11 when counting from the top of the column, with a bottoms to feed ratio of 0.86, reflux ratio of 0.0704, a partial reboiler, and a total condenser. The bottom product will have a temperature exiting the column of 125.9 °C. This will then be cooled to a temperature of 50.0 ℃ before being combined with the solvent makeup stream. This system was then modeled in aspen and the concentration of acetone in the bottoms product was .00056% by mass acetone. To determine the height of the column, 16 mm PALL stainless steel packing was used with an HETP of 0.4 m. The final height of the column was 8.5 m with a diameter of 0.3 m.

5.3.7 Fluidized Bed Drying of Penicillin V

The final step in the downstream process involves drying the penicillin crystal collected from the solid basket centrifuge in order to lower the water content of the product for stability and transport. Because penicillin V can be sensitive to heat-induced degradation, the drying process will ideally be gentle and precise. As a result, we propose to use a fluidized bed dryer to reduce the moisture content of the pharmaceutical powder. The principle behind this equipment is that when particles are suspended (fluidized) by a pressurized flow of warm air, heat transfer takes place evenly between the wet solids and the hot gasses.

The objective of the design is to reduce the moisture content from 10% to 0.1% for the final storage of the API product before distribution. Assuming that the penicillin powders are porous and sufficiently wet to contain free moisture, the drying rate remains constant throughout the drying process. The water is evaporated out to a waste stream. The gas flow rate is calculated using the following equation:

$$G_g = \rho_g \mu_g A \qquad \text{(eq. 5.3.7-1)}$$

Where:

ρ_g: Density of gas (kg/m^3)

μ_g: Operating gas velocity or the multiple of the minimum fluidization velocity (m/s)

A: The cross-sectional area of the fluidized bed (m^2).

There are multiple mathematical models for modeling the fluidized bed dryer using different assumptions. Here, we scale up an operation proposed by Carmichael using a batch drying process with constant rate period and assuming only surface moisture is present. The drying time required is characterized by the following equation,

$$t_r = (X_o - X)M\lambda / G_g c_{pg}(T_{in} - T_{out}) \qquad \text{(eq. 5.3.7-2)}$$

Where:

$(X_o - X)$ = the change in moisture content (kg/kg),

λ = the latent heat of vaporization (J/kg),

M = the mass holdup of dry solid in bed (kg),

G_g = the gas flow rate of dry air (kg/s),

c_{pg} = the gas heat capacity (J/kg/K),

$(T_{in} - T_{out})$ = the change in air stream temperature (℃)

Using these design guidelines, the operating conditions appropriate for the scale of operation is detailed in Table 5.3.7-1 below, where the total power input represents the heat duty and the mechanical energy combined.

Table 5.3.7-1: Fluidized Bed Dryer Operating Conditions

Operation	**Batch**
Airflow rate (L)	6676
Pressure (atm)	1
Inlet air temperature (℃)	70
Outlet product temperature (℃)	35
Total power input (kWh)	3.7

5.4 Ancillary Equipment

The ancillary equipment needed in this design are centrifugal pumps and conveyor for general movement of fluids or components from one system to another, holding tanks between process steps, mixing tanks for buffers solution, and lastly heat exchangers.

5.4.1 Pumps

In order to accomplish needed flow rates for all streams, as well as pressure drops, centrifugal pumps will be used. The list of pumps utilized in the entire process is listed in Table 5.4.1-1. The design will incorporate two of each pump in order to have a contingency pump in case of failure. Therefore, a total of 42 centrifugal pumps will be purchased but 21 pumps will be used. All pumps were designed to be made of stainless steel. For each pump, the power required was calculated using Equation 5.4.1-1. To account for power loss due to efficiency, we will assume 70% shaft efficiency and 90% driver efficiency.

$$P_p = \frac{Qh}{\eta} \quad \text{(Eq. 5.4.1-1)}$$

Where:

P_p = Power (W)

Q = Flow rate (m^3/s)

h = Pressure head (Pa)

η = efficiency

The efficiency, η, is the product of shaft efficiency and driver efficiency. Based on the calculations, the total annual power requirement for all pumps will be approximately 4150 kWhr.

Table 5.4.1-1: Pumps Utilized in Manufacturing Process

Pump ID	Flow Rate (m^3/hr)	Pressure head (atm)	Duration (hr/batch)	Power Per Batch (kWh)
Waste Paper to Glucose				
P-102	159.869	1.5	2.5	26.784
P-103	14.020	1	0.1	0.063
P-104	27.565	0.5	10	6.158
P-106	26.173	1	10	11.693
P-107	52.685	1	2	4.707
P-108	27.625	1	0.08	0.099
P-109	23.238	1	0.02	0.021
Upstream				
P-201	34.686	1.5	2	4.649
P-202	0.142	1	0.72	0.005
P-203	27.214	1.5	3.36	6.128
Downstream				
P-301	3.793	0.5	24	2.033
P-302	3.160	0.5	12	0.847
P-303	2.999	1.5	24	4.823
P-304	2.774	1	24	2.974
P-305	1.536	1	24	1.647
P-306	1.755	1	24	1.882
P-401	30.357	1	1.5	2.034
P-402	37.859	1	1	1.691
P-405	39.696	1	1	1.773
P-406	39.253	1.5	1	2.631
P-407 (Reflux)	0.025	1	24	0.027

5.4.2 Heat Exchangers

Throughout the process, several streams need to be cooled and heated using heat exchangers The list of heat exchangers utilized in the entire process is listed in Table 5.4.2-1. Heat duties were calculated using Aspen, and heuristics designs from Turton were used to determine heat-transfer coefficients and pressure. Finally, temperature differences were determined by using a minimum difference of 10 °C. Heat exchangers were designed and priced according to Equation 5.4.2-1. Of note, HE-302 requires a heat transfer media cooled below the freezing point of water, as such the water flowing through the heat exchanger is at risk of freezing; it was assumed that the water would not freeze due to freezing point depression from the solutes present in the water.

$$A = \frac{Q}{Uo*\Delta Tlm} \qquad \text{(Eq. 5.4.2-1)}$$

Where:

A=Area

Q=Heat Duty

Uo=Heat-Transfer Coefficient

ΔTlm=mean temperature difference

Table 5.4.2-1: Heat Exchangers utilized in Manufacturing Process

Heat Exchanger ID	Temperature in (°C)	Temperature out (°C)	Heat Transfer Media	Heat Duty (kW)	Duration (hr/batch)	Power Per Batch (kWh)	Area (m^2)	Shell Side Pressure (barg)	Tube Side Pressure (barg)
HE-101	18	100	Steam	5911.36	2.5	14778.4	172.30	5	5
HE-301	28	15	Cooling Water	-409.54	3.4	-1376.1	125.67	5	5
HE-302	16	2	Ethylene Glycol	-48.49	24.0	-1163.8	19.32	1.014	1.014
HE-Condenser	79	64	Cooling Water	-36.52	24.0	-876.6	0.85	1.014	1.014
HE-Reboiler	90	90	Steam	119.11	24.0	2858.7	42.46	5	5
HE-401	90	17	Cooling Water	-35.27	24.0	-846.5	2.61	1.014	1.014

5.4.3 Holding / Transfer Tanks

In between the processing steps; enzymatic hydrolysis, upstream, and downstream and after final formulation, tanks are used to hold materials or products. The tanks were designed to hold the volume capacity required for a batch with adequate headspace. All holding tanks are stainless steel for cleaning purposes. A total of 12 storage tanks are used within the process with residence time ranging from 10 minutes to 24 hours. The comprehensive list of holding and mixing tanks can be seen in Table 5.4.3-1.

Table 5.4.3-1: Tanks Specifications for holding, Mixing, and Waste Storage

Tank ID	Volume (L)	Quantity	Contents
Waste Paper to Glucose			
T-101	400,000	1	Water Storage
T-102	500	1	Acetic Acid
T-103	10,000	1	Glucose
T-104	14,000	1	Waste Paper
Upstream			
T-201	9,000	1	Pharmedium
T-202	53,000	1	Extra Glucose Storage
T-204	101,000	1	Fermentation Media
Downstream			
T-301	115,000	1	Products from fermentation
T-302	200	1	Sulfuric Acid
T-303	250	1	Sodium Hydroxide
T-401	10,000	1	Penicillin and Water
T-402	9,000	1	Crystal Penicillin

5.5 Final Recommendation for Design

5.5.1 Equipment Table and Process Flow Diagram

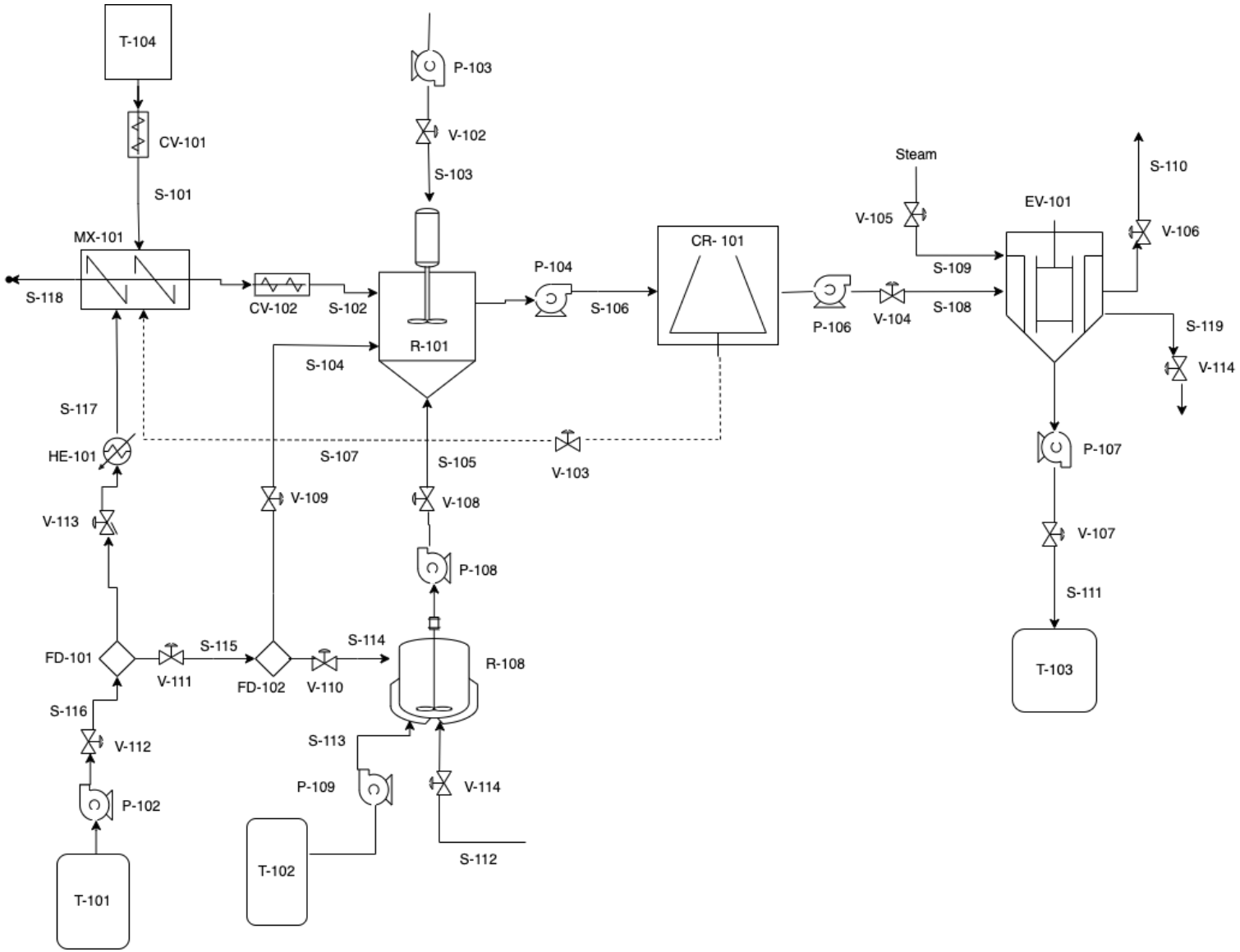

Figure 5.5.1-1. Process flow diagram of waste paper to glucose production

Table 5.5.1-1. Waste Paper to Glucose production Stream/ Equipment Identification

Stream/ Equipment Tag	**Specification**
MX- 101	Mixer for paper slurry
R-101	Enzymatic Reactor
R-108	Buffer Reactor or Mixer
CR-101	Decanter Centrifuge
EV-101	Evaporator
P-10#	Centrifugal Pumps
V-10#	Gate Valves
T-10#	Storage Tanks
HE-10#	Heat Exchangers
CV-10#	Conveyors
FD-10#	Flow Splitters
S-10#	Stream from one equipment to another

Footnote: # - represents the last digit associated with the equipment

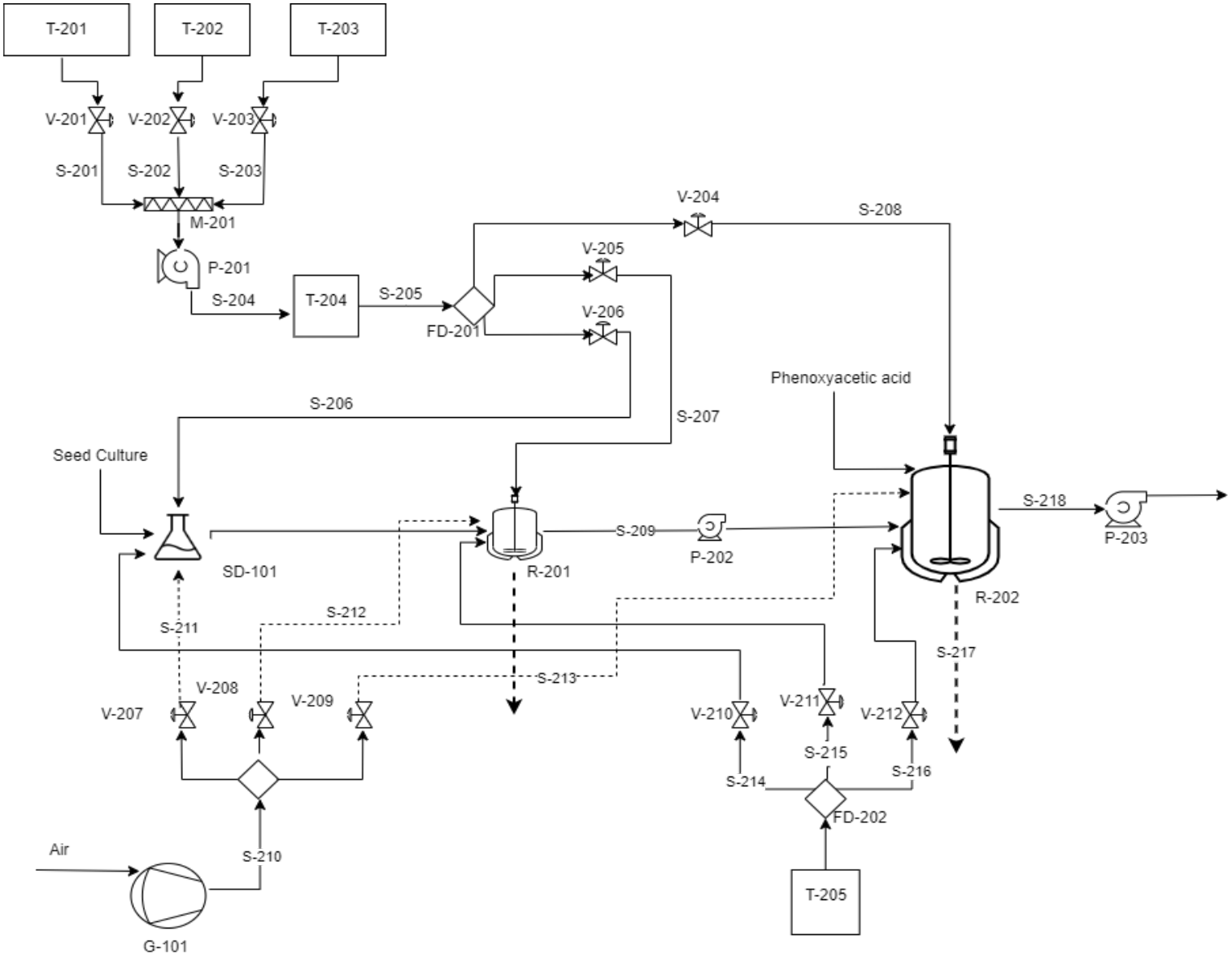

Figure 5.5.1-2: Process Flow Diagram for Seed Train and Bioreactor

Table 5.5.1-2. Waste Paper to Glucose production Stream/ Equipment Identification

Stream/ Equipment Tag	**Specification**
SD-101	3 L Seed Culture
R-201	100 L Seed Culture
R-202	100 m^3 Fermentor
G-101	Gas (Air) Compressor
P-20#	Centrifugal Pumps
V-20#	Gate Valves
T-20#	Storage Tanks
S-20#	Stream from one equipment to another
FD-20#	Flow Splitters

Footnote: # - represents the last digit associated with the equipment

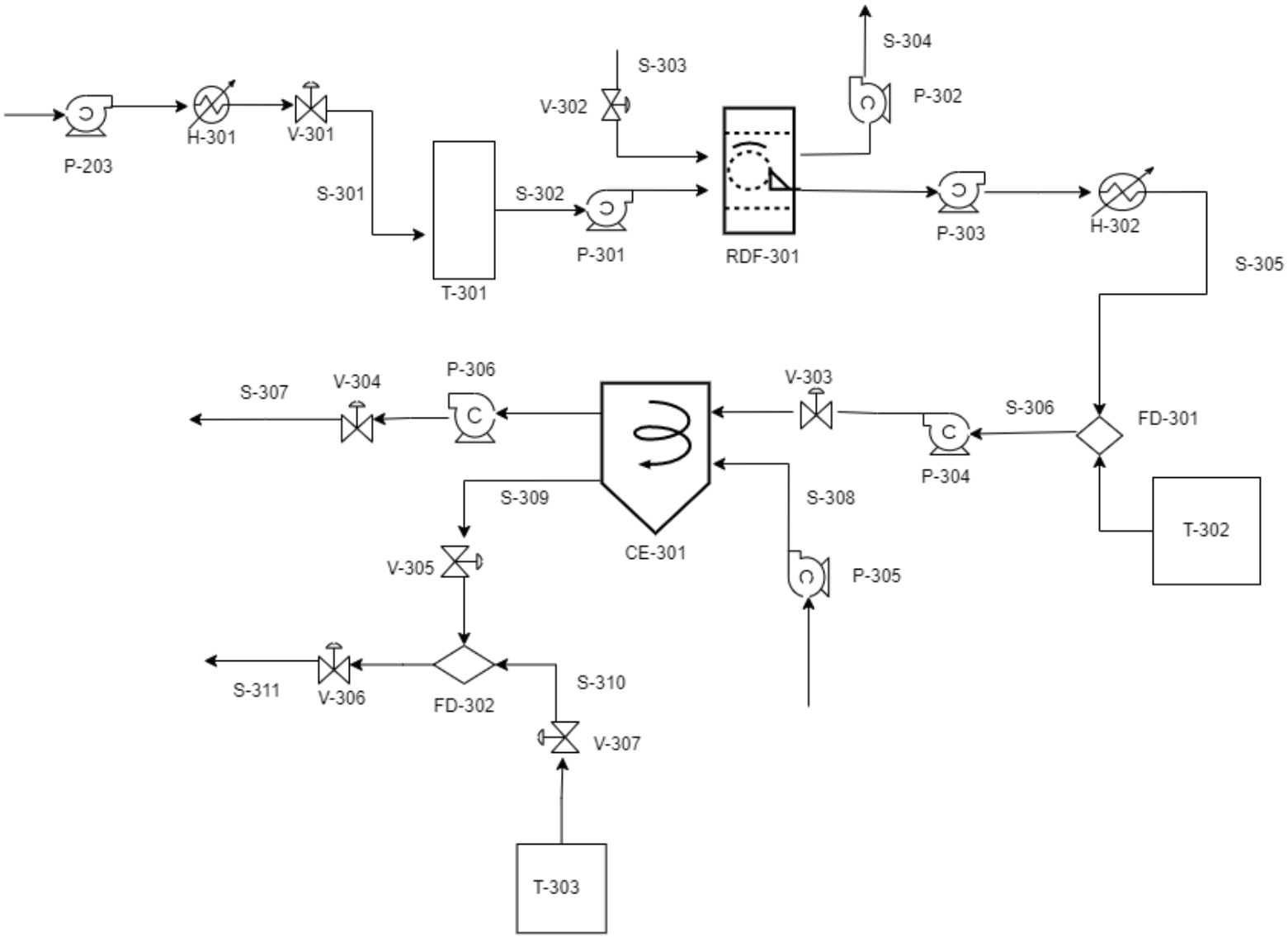

Figure 5.5.1-3 Process Flow Diagram for Rotary Drum Vacuum Filtration and Centrifugal Extraction

Table 5.5.1-3. Rotary Drum Vacuum Filtration and Centrifugal Extraction Stream/ Equipment Identification

Stream/ Equipment Tag	**Specification**
RDF- 301	Rotary Drum Filtration
CE-301	Centrifugal Extraction
P-30#	Centrifugal Pumps
V-30#	Gate Valves
T-30#	Storage Tanks
HE-30#	Heat Exchangers
FD-30#	Flow Splitters
S-30#	Stream from one equipment to another

Footnote # - represents the last digit associated with the equipment

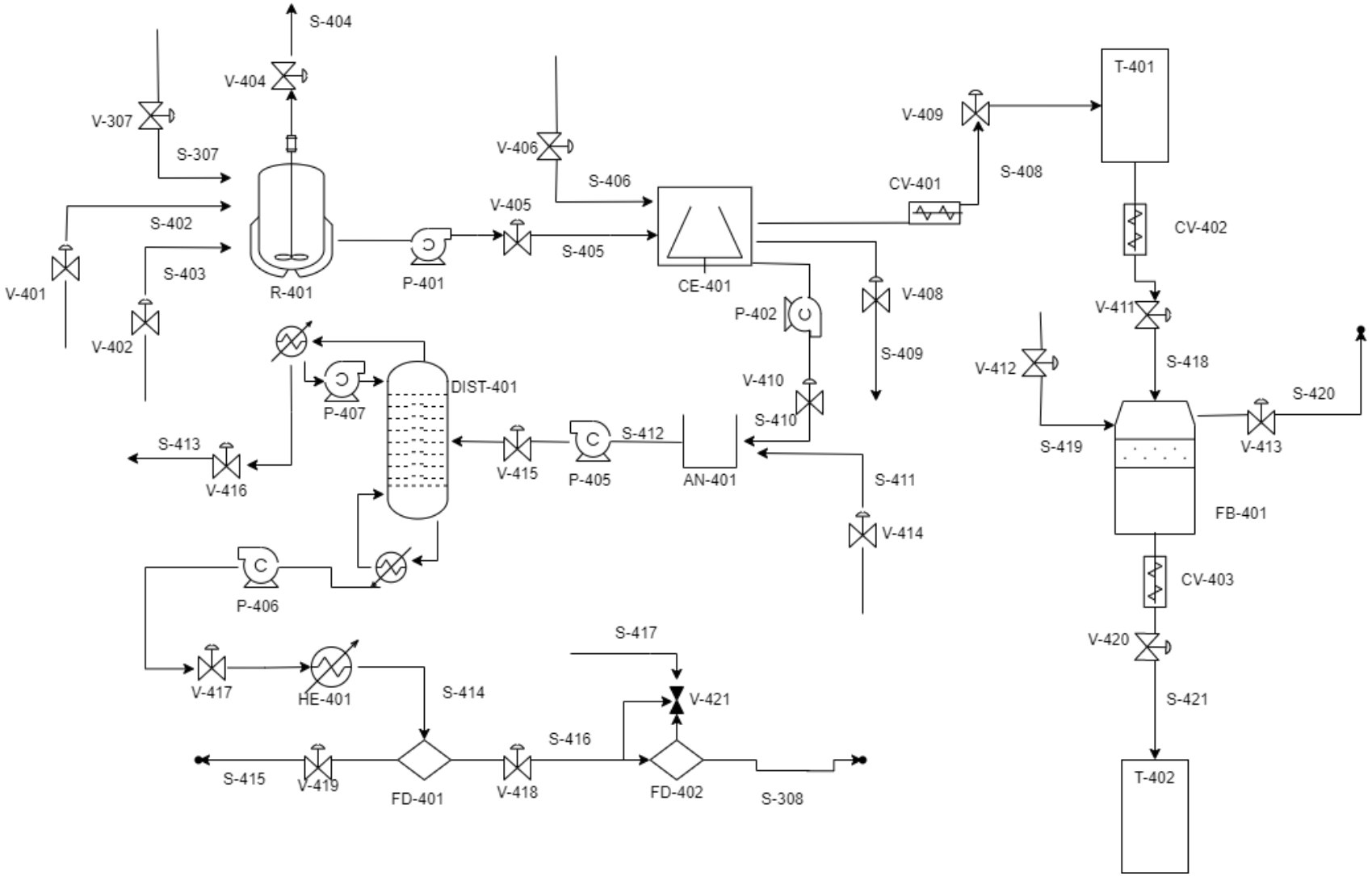

Figure 5.5.1-4 Process Flow Diagram for Re-extraction/ Crystallization, Distillation, Basket Centrifugation and Fluidized Bed Dryer.

Table 5.5.1-4. Re-extraction/ Crystallization, Distillation, Basket Centrifugation and Fluidized Bed Dryer Stream/ Equipment Identification

Stream/ Equipment Tag	**Specification**
R-401	Re-Extraction and Crystallizer
CE-401	Basket Centrifugation
AN-401	Acid Neutralizer
DIST-401	Distillation Column
FB-401	Fluid Bed Dryer
P-40#	Centrifugal Pumps
V-40#	Gate Valves
T-40#	Storage Tanks
HE-40#	Heat Exchangers
CV-40#	Conveyors
FD-40#	Flow Splitters
S-40#	Stream from one equipment to another

Footnote *# - represents the last digit associated with the equipment*

5.5.2 Waste Paper to Glucose

5.5.2.1 Waste paper pretreatment

Waste paper (S-101) and Hot liquid water (S-117) will be mixed in a mixer (MX-101) to make a paper slurry. The mixer is a drum pulper that is operated at a temperature of 100 ℃. We will be using the ZG2500 drum pulper made by Leizhan with a production capacity of 70-1400 tons /day. ZG2500 drum pulper is standard, grade 316 stainless, allowing mixing in the turbulent conditions. A ZDFD3 series single effect fiber separator is also used with the addition of the pulper for secondary screening of waste paper pulp by separating the impurities from the paper slurry needed for the enzymatic reactor. The waste products of the centrifuge (CR-101), mostly paper, is recycled back into the mixer to limit operational costs. Below is a table summarizing the composition of each stream entering and leaving the mixer (MX-101).

Table 5.5.2-1 Pretreatment of Paper (MX-101)

	Streams (Flows in kg/batch)						
Components	S-101	S-115	S-116	S-117	S-118	S-102	S-107
Paper	13,637.0	0	0	0	0	24,795.0	11,158.0
Water	0		399,672.1	154,970.0	153,340.0	3,244.0	1,614.0
Cellulase Enzyme	0	0	0	0	9.1	0	9.1
Glucose	0	0	0	0	0	0	0
Acetate Buffer	0	0	0	0	2.3	0	2.3
Total (kg/batch)	13,637.0		399,672.1	154,970.0	153,351.4	28,039.0	12,792.4

5.5.2.2 Buffer Mixer

To accomplish the pH requirement for the enzymatic reactor (R-101), 0.1 M of acetate buffer is required. Adequate amounts of sodium acetate (S-112), and water (S-114) is mixed with acetic acid (S-113) in a reactor (R-102) to make an acetate buffer. Table 5.5.2.2-1 shows the stream table for the acetate buffer Reactor (R-102). Table 5.5.2.2-2 shows the acetate buffer Reactor (R-102) specifications.

Table 5.5.2.2-1 Acetate Buffer Reactor (R-102) Stream Table

	Streams (Flows in kg/batch)			
Components	S-112	S-113	S-114	S-105
Sodium Acetate	1,372.0	0	0	0
Acetic Acid	0	488.0	0	0
Water	0	0	350.1	350.1
Acetate Buffer	0	0	0	1,859.9
Total (kg/batch)	1,372.0	488.0	350.1	2,210.0

Table 5.5.2.2-2 Acetate Buffer Reactor (R-102) specification

Rotational Speed (rpm)	200
Volume of reactor (m^3)	2.25
Tank Diameter (m)	1.42
Tank height (m)	1.42
Type of impeller	Rushton
Impeller diameter (m)	0.5
Width of impeller blade (m)	0.1
Height of impeller blade (m)	0.125
Residence Time (min)	6

5.5.2.3 Enzymatic Hydrolysis

The paper slurry (S-102), cellulase enzyme (S-103), and the acetate buffer (S-105) are transferred into a stirred tank reactor. Water (S-104) is added to decrease the concentration of paper from 88% to 10% of total solids. Based on the amount of glucose required to achieve the desired penicillin production quantity, 7 stirred batch tank reactors are needed. The reaction conditions are listed in Table 5.5.2.3-1. The tank dimensions, number of impellers, impeller rotational speed and gassed flow rate to achieve the desired reaction are in Table 5.5.2.3-2. Table 5.5.2.3-3 summarizes the composition of each stream entering and leaving the enzymatic reactor.

Table 5.5.2.3-1. Enzymatic Hydrolysis Conditions

Temperature	45°C to 55°C
Initial solids loading	10 wt% total solids
Residence time	48 hrs
Number of batch vessels	7
Size of batch vessels each	40 m^3
Cellulase loading	0.0565 kg of protein/ kg of paper

Table 5.5.2.3-2: Production Enzymatic Reactor Dimensions and Impeller Specifications

Volume, (m^3)	40
N, rotational speed, (rpm)	500
Tank diameter,(m)	3.7
Height of tank, (m)	3.7
Impeller diameter, (m)	1.2
Impeller height, (m)	1.2
Power per tank, (W)	68500

Table 5.5.2.3-3 Enzymatic Reactor (R-101)

	Streams (Flows in kg/batch)				
Components	S-102	S-104	S-105	S-103	S-106
Paper	24,795.0	0	0	0	11,157.7
Water	3,244.0	244,352.0	0	0	247,596.0
Cellulase Enzyme	0	0	0	1,402.0	1,402.0
Glucose	0	0	0	0	13,637
Acetate Buffer	0	0	1,859.9	0	1859.9
Total (kg/batch)	28,039.0	244,352.0	1,859.9	1402.0	275,652.6

5.5.2.4 Decanter Centrifuge

The decanter centrifuge chosen for this step is the GN 22 inch (550 mm) Decanter centrifuge (Model GNLW554ET-VFD). The rotational speed used is 3100 rpm with a terminal settling velocity of 5 cm/s. This model allows for a reasonable process time of 2.05 hrs to centrifugate the volume of reactor effluent at approximately 2,100 L/min. Below is a table summarizing the composition of each stream entering and leaving the centrifuge (CR-101). Table 5.5.2.4-1 shows the stream specifications around the centrifuge. The remaining enzymes in the liquids stream were assumed to contribute solely to biomass growth in the future penicillin fermentation; however, a separation system could be designed using membrane filtration.

Table 5.5.2.4-1 Centrifuge Streams (CR-101, Flows in kg/batch)

Components	S-106	S-107	S-108
Paper	11,157.7	11,157.7	0
Water	247,596.0	1,613.5	246,334.3
Cellulase Enzyme	1,402.0	9.1	1,392.9
Glucose	13,637.0	88.8	13,548.5
Acetate Buffer	1,859.9	12.1	1,847.8
Total (kg/batch)	275,195.9	12,792.4	263,123.5

5.5.2.5 Evaporator

The product coming out of the centrifuge (S-108) and subsequently into the evaporator (EV-101) consists of 5 wt% glucose. The evaporator is used to concentrate the glucose content to

15 wt% (S-111). The type of evaporator used is a single falling film evaporator. The SPX APV single effect evaporator is selected for our production requirement, which has a maximum flow rate of 35,000 lbs/hr and a heat duty of 19,011 kW/batch.

Table 5.5.2.5-1 Evaporator (EV-101)

	Streams (Flows in kg/batch)		
Components	S-108	S-110	S-111
Water	245,984.8	156,011.7	89,973.1
Acetate Buffer	1,847.8	0	1,847.8
Glucose	13,548.5	0	13,548.5
Cellulase Enzyme	1,392.9	0	1,392.9
Total (kg/batch)	263,123.5	156,011.7	106,762.3

5.5.3 Upstream

5.5.3.1 Fermentation

Cell seed culture of *P. chrysogenum* at 2.5 g/L is added to a shake flask (SD-101) along with a cell nutrient blend (S-206). This is allowed to ferment for 26 hours, then the contents are added to a 100 L bioreactor (R-201). Further cell media is added (S-207) and the cells are fermented for a further 26 hours. The resulting solution (S-209) is added to the primary 100,000 L bioreactor (R-202). The reactor is fitted with 4 baffles and is stirred with 3 propellers at 100 RPM. Air is supplied at 1 vvm, or 90 m^3/min. The reactor is maintained at 25 C using chilled water. Periodic additions of 150 g/L glucose and pharmedium (S-208) will be added at 32, 52, and 72 hrs from the start of the fermentation in volumes of 4000, 8000, and 77000 L respectively. After 96 hrs, the contents of the bioreactor are drained (S-218). Stream tables are summarized in the tables below.

Table 5.5.3.1-1: Seed Train Stream Table (Flows Around T-201 for Bioreactors, in kg/batch)

Components	S-201	S-202	S-204	S-205	S-206	S-207	S-208
Water	89,973.0	0.0	89,973.0	89,973.0	2.5	90.0	89,880.5
Glucose	13,458.0	0.0	13,458.0	13,458.0	0.4	13.5	13,444.1
Corn Steep Liquor*	0	3,937.0	3,937.0	3,937.0	0.1	3.9	3,933.0
Lactose*	0	3,937.0	3,937.0	3,937.0	0.1	3.9	3,933.0
Edible Oil*	0	281.1	281.0	281.0	0.0	0.3	280.7
Potassium dihydrogen phosphate	0	449.5	450.0	450.0	0.0	0.5	449.5
Total (kg/batch)	103,431	8,605.0	112,036.0	112,036.0	3.1	112.1	111,920.8
Footnotes	** - These components are stored together as solids in T-201, referred to as Pharmamedium onward* *+- Stream S-203 is a glucose makeup stream to account for variations in glucose yield from upstream enzymatic hydrolysis*						

Table 5.5.3.1-2: 100,000 L Fermentor Stream Table (R-202)

	Streams (Flows in kg/batch)		
Components	S-209	S-218	Phenoxyacetic Acid
Biomass	2.5	4,783	0.0
Glucose	12.5	918.0	0.0
Penicillin V	0	6,600	0.0
Water	90	79,200	0.0
Phenoxyacetic acid	0.0	92.0	4600
Pharmamedium	0.5	113.0	0.0
Total (kg/batch)	105.5	91,706	4,600

Table 5.5.3.1-3: Downstream Stream Tables- Fermentor to Storage Tank (T-301)

	Streams (Flows in kg/batch)	
Components	S-301	S-302
Biomass	4,783	4,783
Glucose	918	918
Penicillin V	6,600	6,600
Water	79,200	79,200
Phenoxyacetic acid	92	92
Pharmamedium	113	113
Total (kg/batch)	91,706	91,706

5.5.4 Downstream

5.5.4.1 Broth Filtration

The products out of the fermentor (S-302) are fed into a rotary drum vacuum (RDF-301). The filter removes the unnecessary biomass product (S-304). The rotary drum chosen for this step is Andritz with a filtrate area of 2.8 m^2. The flux will be 1000 L/m^2-h, leading to a volumetric flow rate of 2800 L/hr. It will be operated at a transmembrane pressure of 5 psig with a cake porosity of 0.35 v/v. Table 5.5.4.1-1 summarizes the composition of each stream entering and leaving the rotary drum. The units for the process are reported in kg/batch rather than L/hr to keep the simplicity of the material balance for the next unit operation. At this step of the process, it was assumed that most of the phenoxyacetic acid stayed with the product stream as a result of its high solubility in the aqueous product solution.

Table 5.5.4.1-1: Downstream Stream Tables- Rotary Drum Vacuum Filter (RDF-301)

	Streams (Flows in kg/batch)			
Components	S-302	S-303	S-304	S-305
Biomass	4,783	0	4,783	0
Glucose	918	0	0	918
Penicillin V	6,600	0	0	6,600
Water	79,200	18,967	33,271	64,895
Phenoxyacetic acid	92	0	31	61
Pharmamedium	113	0	0	113
Total (kg/batch)	91,706	18,967	38,085	72,474

5.5.4.2 Solvent Extraction

In the centrifugal extractor (CE-301), penicillin is extracted into butyl acetate (S-30). Before extraction, the biomass-free broth was acidified to a pH of around 3 using sulfuric acid (S-312) and cooled to minimize degradation during the extraction. The solvent extraction is conducted in a Podbielniak centrifugal extractor (POD). The POD has 2 equivalent number of extraction stages with an operating capacity of 30 m^3/ h and a rotational speed of 1500 rpm. The extract (S-307) is fed into a crystallizer and the raffinate (S-309) is sent into a waste treatment process. Table 5.5.4.1-2 shows the material balance for the centrifugal extractor.

Table 5.5.4.2-1 Centrifugal Extractor (CE-301)

	Stream (Flows in kg/batch)				
Component	S-312	S- 306	S-308	S-307	S-309
Glucose	0	918.4	0	0	918.4
Penicillin V	0	6,600.0	61.5	6,600.0	219.4
Water	0	64,895.0	19,487.0	19,358.0	64,852.0
Pharmamedium	0	113.0	0	0	0
Phenoxyacetic Acid	0	61	0	0	61
Sulfuric Acid	146.0	146.0	0	0	146.0
Acetone	0	0	0.2	0.2	0
Butyl Acetate	0	0	13,032.0	13,032.0	66.1
Potassium Acetate	0	0	2,450.0	2,450.0	0
Potassium Hydroxide	0	0	9.70	9.70	0
Total (kg/batch)	146.0	72,733.5	34,978.7	41,449.9	66,262

The raffinate (S-309) is sent to neutralizer for waste treatment. Potassium Hydroxide (S-310) , the neutralizing agent, is used at an excess for this reaction. The reaction is continuous with a residence time of one hour, under adiabatic conditions and pressure of 1.101 bar.

Table 5.5.4.2-2 Downstream Stream Tables- H_2SO_4 (FD-302)

	Streams (Flows in kg/batch)		
Components	S-309	S-310	S-311
Glucose	918.4	0	918.4
Butyl Acetate	66.1	0	66.1
Water	65,025.3	119.7	65,145.0
Phenoxyacetic Acid	61	0	61
Pharmamedium	115.8	0	115.8
Penicillin V	219.4	0	219
Sulfuric Acid	145.2	0	145.2
Potassium Hydroxide	0	119.7	119.7
Total (kg/batch)	66,551.0	239.4	66,790.4

5.5.4.3 Crystallization

Following solvent extraction, the extract (S-307) is reacted with potassium acetate (S-402) and acetone (S-403) to promote the crystallization of the potassium salt of penicillin V. The process reacts in a batch mode for 12 hours at a temperature of 2℃ and pressure of 1.520 bar. The crystallizer (R-401) has a vent stream (S-404) to allow air to exit at atmospheric pressure and temperature of 20 ℃. We assumed the conversion of penicillin V achieved is 99 %. Table 5.5.4.3-1 and Table 5.5.4.3-2 show the crystallizer (R- 401) specifications and summarize the composition of each stream. The crystallizer equipment design did not take into account crystal size distribution.

Table 5.5.4.3-1 Crystallizer reactor dimensions and impeller specifications

Type	Stirred Reactor
Volume (m^3)	45
Tank diameter (m)	3.9
Height of tank,(m)	3.9
Impeller diameter, (m)	1.29
Impeller height, (m)	1.2
Rotational Speed, rpm	250
Impeller type	Angled Pitch-blade

Table 5.5.4.3-2 Re-extractor/Crystallization Unit (R-401)

	Stream (Flows in kg/batch)				
Component	S-307	S-402	S-403	S-404	S-405
Acetone	0.22	0	2,308	0	2,308
Acetic Acid	0	0	0	0	1,110
Butyl Acetate	13,032	0	0	0.05	13,032
Nitrogen	0	0	0	40.5	0
Oxygen	0	0	0	12	0
Potassium Acetate	2,450	152	0	0	815
Penicillin V	6,600	0	0	0	66
Penicillin VK crystals	0	0	0	0	6,952
Potassium Hydroxide	10	0	0	0	0
Water	19358	0	18	0	19,652
Total(kg/batch)	41440.22	152.0	2,326.0	52.55	43,934.0

5.5.4.4 Centrifugal Filtration

For this process, a basket centrifuge (C-401) with water washing (S-406) then produces a crystal cake containing only 5 wt% moisture. The basket centrifuge chosen for this step is HZ 180/7.1 Andritz basket centrifuge with a filtrate area of 7.07 m^2. The basket inside diameter is 1.8 m with a length of 1.25 m. The maximum speed of the centrifuge is 840 rpm with a process time of one hour for each batch. Table 5.5.4.# shows the stream table for the basket centrifuge. The solid product separated (S-408) is fed to a fluidized bed dryer (FB-401). For the liquid separation products, stream (S-409) is sent to waste water treatment and stream (S-410) which mostly contains butyl acetate is sent to a solvent recovery system.

Table 5.5.4.4-1 Basket Centrifuge (C-401)

	Stream (Flows in kg/batch)				
Component	S-405	S-406	S-408	S-410	S-409
Acetic acid	1,110.0	0	0	1,089.0	22.2
Acetone	2,308.0	0	0	2,263.0	46.2
Butyl Acetate	13,032.0	0	0	12,771.0	260.5
Pen VK	6,952.0	0	6,945.0	7.0	0
Pen V	66.0	0	0	64.7	1.3
Potassium Acetate	815.0	0	0	798.5	16.3
Water	19,652.0	22,973	765.3	19,274.0	22,586.0
Total (kg/batch)	43,934.0	22,973	7710.3	36267.2	22932

5.5.4.5 Fluidized Bed Drying

In the fluidized bed dryer (FB-401), the penicillin is dried with inlet air (S-419), and the final product (S-421) is sent to storage tank T-402 using screw conveyor since the stream mostly consists of solid material. A purge stream (S-420) is designed to release the moisturized air. A wash step in the basket centrifuge removes the majority of other solvents, leaving a small amount of water and penicillin V. The breakdown of stream composition is shown below in Table 5.5.4.5-1. By suspending the API crystals with 70℃ warm continuous air flow pressurized to 4 bar, the process reduces the moisture content of API from 10% to 0.1%, extending the duration of storage. Other process parameters are detailed in Table 5.5.4.5-2 below.

Table 5.5.4.5-1 Fluidized Bed Dryer (FB-401)

	Stream (Flows in kg/batch)			
Component	S-418	S-419	S-420	S-421
Nitrogen	0.0	5075.7	5075.7	0
Oxygen	0.0	1540.9	1540.9	0
Water	765.3	0	757.6	7.65
Pen VK	6,945.5	0	69.5	6876.0
Total (kg/batch)	7710.8	6615.9	7443.7	6883.7

Table 5.5.4.5-2 Fluidized Bed Dryer Operating Conditions

Operation	Batch
Airflow rate (L)	6676
Pressure (bar)	4
Inlet air temperature (℃)	70
Outlet product temperature (℃)	35
Power input (kWh)	392

5.5.4.6 Recovery and Purification of Solvent

For the solvent recovery process, the filtrate (S-410) from the centrifugal filtration (C-401) is discharged and neutralized in an acid neutralizer (AN-401). The neutralization is performed to quench all the acetic acid from the stream and potassium hydroxide, the neutralizing agent, is used in excess. The material balance for the neutralizer is shown in Table 5.5.4.6-1. Table 5.5.4.6-1 also includes the material balance representation of the acid-base reaction in the molar unit for components involved in the reaction. Notably, potassium acetate becomes present in a higher quantity during this step since the pH of the solution rises. The mole balances are present to show that the material balance is satisfied. The products from the neutralizer are then sent to a continuous distillation column (DIST-401) to separate the butyl acetate, and acetone. The distillate product stream (S-413) contains acetone along with a small amount of butyl acetate. The bottom stream (S-414) contains butyl acetate, potassium acetate and water. The material balance and operation parameters for the distillation column is shown in Table 5.5.4.6-1 and Table 5.5.4.6-2. Table 5.5.4.6-4 shows the material balance for a purge stream that will be used to release any buildup of material while also allowing for material

balances to close more easily during theoretical calculations. Notably, there is a small amount of penicillin VK present in this stream as a result of purification limitations in previous unit operations. The small amount of penicillin VK crystals are able to leave in this stream due to the physical orientation of the stream, in which it is assumed that gravity will sufficiently aid in the removal of the crystalline solids. The butyl acetate (S-416) is reused in the extraction process. Fresh butyl acetate (S-417) is added to stream (S-416) in order to accommodate the required amount of butyl acetate needed for the solvent extraction process. The material balance for this process is shown in Table 5.5.4.6-5.

Table 5.5.4.6-1 Acid Neutralizer (AN-401)

	Stream (Flows in kg/batch)			**Stream (Flows in kmol/batch)**		
Component	S-410	S-411	S-412	S-410	S-411	S-412
Acetic acid	1,089	0	0	18.1	0	0
Acetone	2,262	0	2,262			
Butyl Acetate	12,771	0	12,771			
Potassium Acetate	799	0	2,579	8.14	0	26.3
Penicillin V	64.7	0	64.7			
Penicillin VK	6.95	0	6.95			
Potassium Hydroxide	0	1,027	10.2	0	18.3	0.182
Water	19,274	733	20,333	1071	40.7	1130
Total(kg/batch)	36,267	1760	38,027			

Table 5.5.4.6-2 Distillation Column (DIST-401)

	Stream (Flows in kg/batch)		
Component	S-412	S-413	S-414
Acetone	2,262	2,262	0.2
Butyl Acetate	12,771	1,772	10,998
Potassium Acetate	2,579	0	2,579
Penicillin V	64.7	0	64.7
Penicillin VK	6.95	0	6.95
Potassium Hydroxide	10.2	0	10.2
Water	20,333	809	19,524
Total(kg/batch)	38,027	2,645	33,184

Table 5.5.4.6-3 Distillation column operational parameters.

Feed Quality (q)	1
Reflux Ratio	0.86
Number of Actual Stages	23
Feed Stage	11
Tray Efficiency	80 %
Packing material	16 mm PALL stainless steel packing
HETP (m)	0.4
Height of the column	8.5
Condenser	
Temperature	61.5 ℃
Agent	Cooling Water
Partial Reboiler	
Temperature	125 ℃
Agent	Steam (High Pressure)

Table 5.5.4.6-4 Purge (FD-401)

	Stream (Flows in kg/batch)		
Component	S-414	S-415	S-416
Acetone	0.2	0	0.2
Butyl Acetate	10,998.0	549.9	10,448.5
Potassium Acetate	2,579.0	128.9	2,450.0
Penicillin V	64.7	3.2	61.5
Penicillin VK Crystals	6.95	6.9	0
Potassium Hydroxide	10.2	0.5	9.7
Water	19,524.0	976.2	18,547.8
Total(kg/batch)	33,184.0	1,665.8	31,518.2

Table 5.5.4.6-5 Makeup Mixing (FD-402)

	Stream (Flows in kg/batch)		
Component	S-416	S-417	S-308
Acetone	0.2	0	0.2
Butyl Acetate	10,448.5	2583.5	13,032.0
Potassium Acetate	2,450.0	0	2,450.0
Penicillin V	61.5	0	61.5
Potassium Hydroxide	9.7	0	9.7
Water	18,547.8	939.2	19,487.0
Total(kg/batch)	31,517.7	3,522.7	35,040.4

5.5.5. Batch Production Schedule

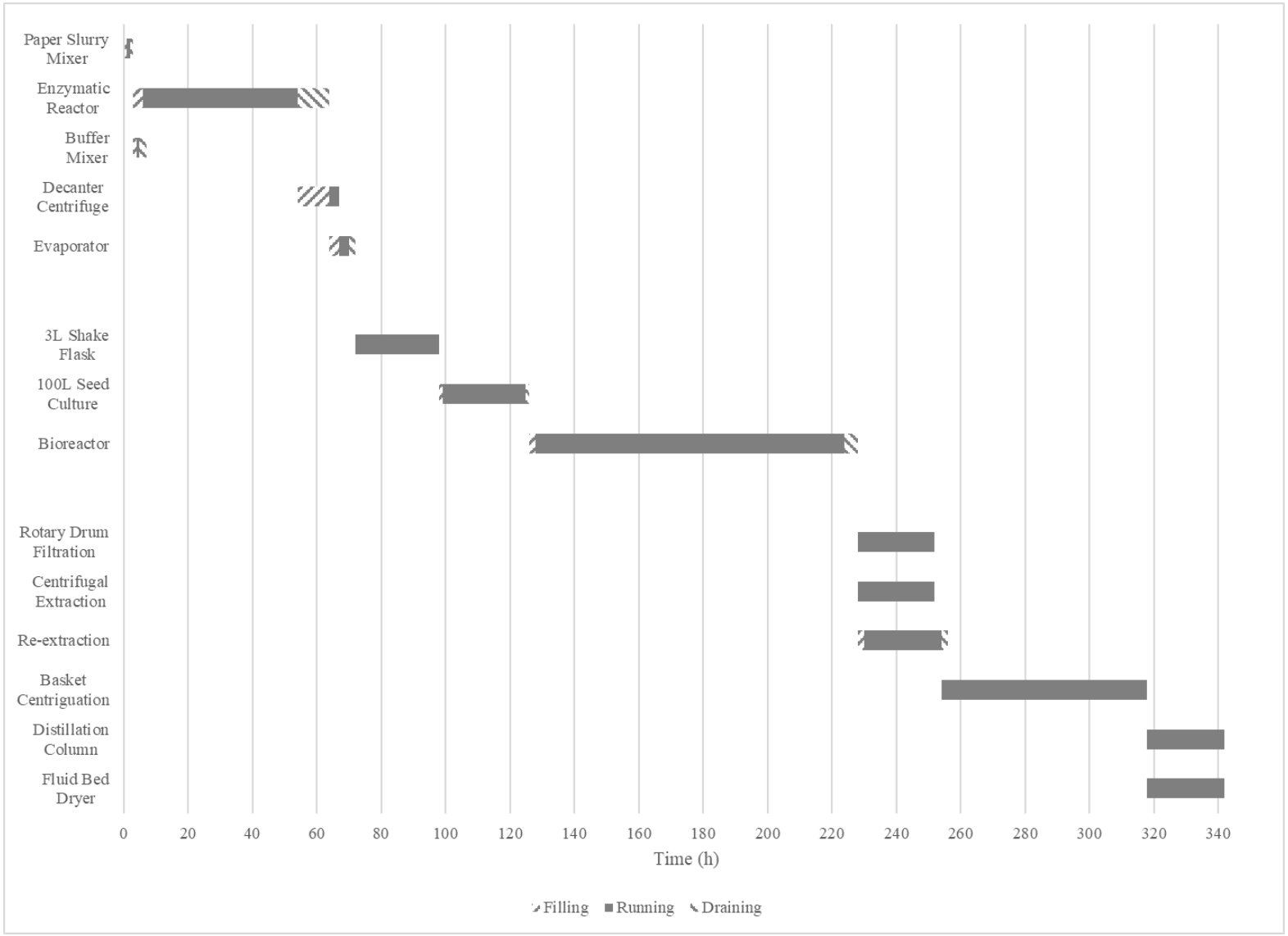

Figure 5.5.5-1: Start Up (Series) Production Schedule

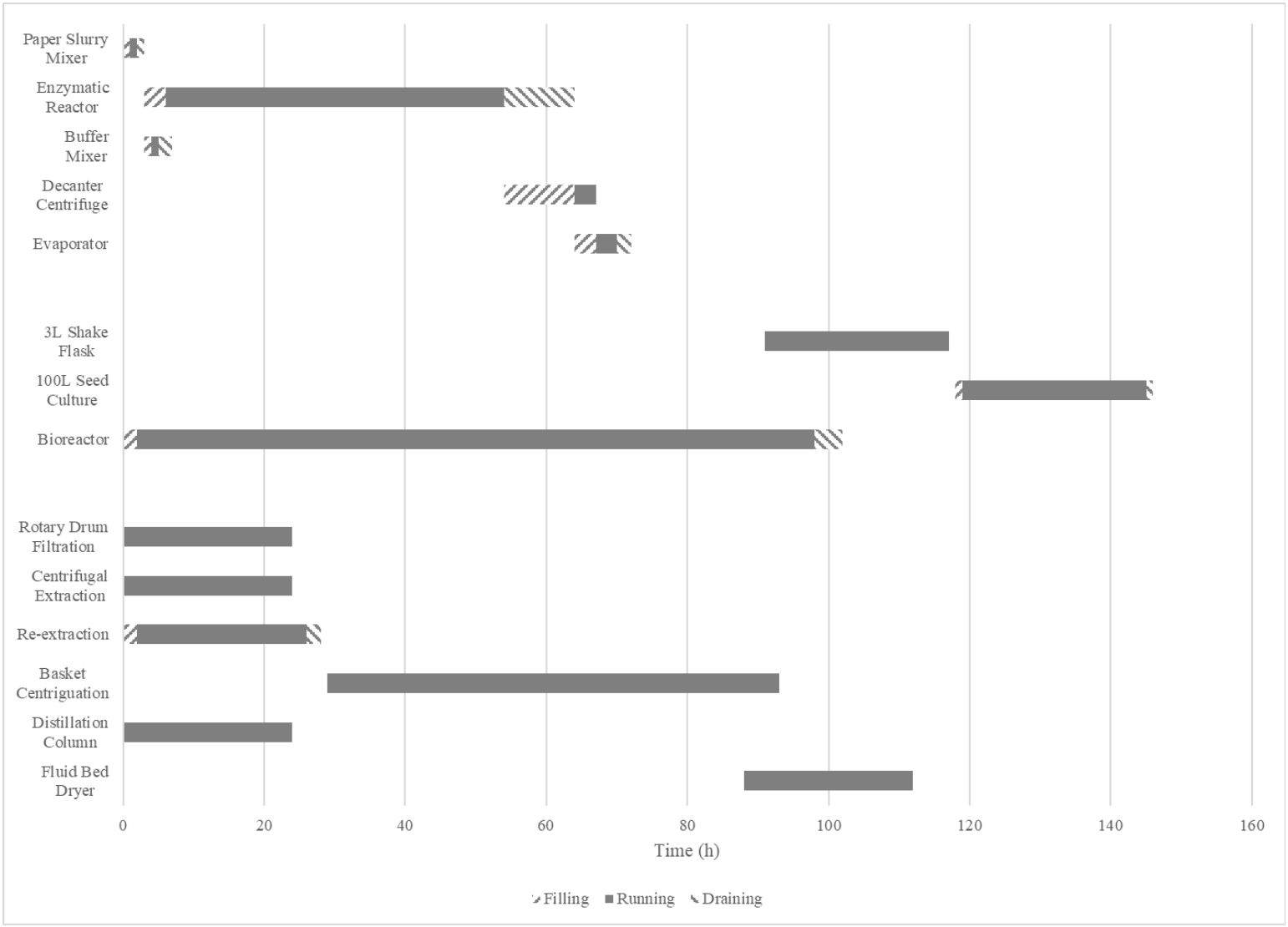

Figure 5.5.5-2: Parallel Production Schedule

Each batch yields 6876 kg of Penicillin V. Therefore, 22 batches are required to meet the 150,000 kg annual production goal. When the facility is first starting production, all operations will be conducted in series. The bioreactor must run after the glucose has been produced, and no downstream processing can be conducted until the fermentation is completed. This startup process timeline is shown in Figure 5.5.5-1. After the initial series batch, many operations can be streamlined to run in parallel, thereby increasing the number of batches that can be made in a given time period. Assuming three active batches at a time (one in glucose production, one in bioreactor fermentation, and one in downstream processing), the time required for a singular batch is reduced. This parallel operating schedule is shown in Figure 5.5.5-2. Since each batch of Penicillin V takes a total of 7 days, accounting for processes that can be run in parallel, this production goal can easily be achieved. Assuming 300 days of operation per year, it is feasible to run 48 batches of penicillin production per year which yields a total of 330,000 kg of penicillin VK annual.

6. Economic Analysis

6.1. Equipment Purchase

Costs associated with purchasing equipment were determined using several resources, including quotes from vendors, heuristics designs from Turton, and an Excel spreadsheet from the Analysis Synthesis and Design of Chemical Processes (Turton *et al.* 2018). Because the Excel spreadsheet was created in 2017, the prices were adjusted using an average Chemical Engineering Plant Cost Index (CEPCI) of 708 from 2021 to reflect a more accurate representation of current pricing. Table 6.1-1 to Table 6.1-3 below details the breakdown of all purchased equipment cost by production stage and unit operations. All equipment purchased are made of stainless steel when the option is available. All pumps purchased include a spare unit in case of unexpected maintenance issues. The total cost for purchasing equipment is $5,320,989.15.

Table 6.1-1 Summary of Purchased Equipment in the Glucose Production Stage

Stage	Unit Operation	Equipment	Quantity	Unit Cost ($)	Cost ($)
Waste paper to glucose	Wastepaper Pretreatment	Mixer (MX-101)	1	$27,954.24	$27,954.24
		400,000 L Tank (T-101)	2	$115,265.54	$230,531.07
		Heat Exchanger (HE-101)	1	$164,590.41	$164,590.41
		Screw Conveyor (CV-101)	1	$20,000.00	$20,000.00
		Pump (P-102)	2	$32,918.08	$65,836.16
	Enzymatic Hydrolysis	Enzymatic Reactor (R-101)	7	$250,804.43	$1,755,631.00
		Pump (P-104)	2	$6,779.56	$13,559.11
	Buffer Mixer	Mixer (R-108)	1	$11,926.27	$11,926.27
		500 L Tank (T-102)	1	$82,337.00	$82,337.00
		Pump (P-109)	2	$6,779.56	$13,559.11
	Centrifugation	Centrifuge (CR-101)	1	$38,059.57	$38,059.57
		Pump (P-106)	2	$6,779.56	$13,559.11
	Evaporator	Evaporator (EV-101)	1	$401,025.83	$401,025.83
		Pump (P-107)	2	$6,779.56	$13,559.11
		10,000 L Tank (T-103)	1	$83,137.75	$83,137.75

Table 6.1-2 Summary of Purchased Equipment in the Upstream Stage

Stage	Unit Operation	Equipment	Quantity	Unit Cost ($)	Cost ($)
Upstream	Bioreactor	4 L Shake Flask (SD-101)	1	$3,448.56	$3,448.56
		Tank (T-201)	1	$83,052.84	$83,052.84
		Tank (T-202)	1	$86,748.29	$86,748.29
		Tank (T-204)	1	$90,758.55	$90,758.55
		Pump (P-201)	2	$10,933.51	$21,867.01
		Pump (P-202)	2	$9,966.86	$19,933.73
		Pump (P-203)	2	$10,541.62	$21,083.25
		Intermediate Fermentor (R-201)	1	$6,661.99	$6,661.99
		Fermentor (R-202)	1	$438,907.75	$438,907.75
		Air Filter	1	$22,719.14	$22,719.14

Table 6.1-3 Summary of Purchased Equipment in the Downstream Stage

Stage	Unit Operation	Equipment	Quantity	Unit Cost ($)	Cost ($)
Downstream	Filtration	Rotary Drum Filter (RDF-301)	1	$46,634.01	$46,634.01
		115,000 L Tank (T-301)	1	$91,923.74	$91,923.74
		Pump (P-301)	2	$9,966.86	$19,933.73
		Pump (P-302)	2	$9,966.86	$19,933.73
		Pump (P-303)	2	$9,966.86	$19,933.73
		Heat Exchanger (HE-301)	1	$137,158.67	$137,158.67
		Heat Exchanger (HE-302)	1	$74,588.19	$74,588.19
	Acidification	200 L Tank (T-302)	1	$82,312.18	$82,312.18
		Pump (P-304)	2	$9,966.86	$19,933.73
	Solvent Extraction	Centrifuge (CE-301)	1	$41,851.04	$41,851.04
		250 L Tank (T-303)	1	$47,046.73	$47,046.73
		Pump (P-305)	2	$9,966.86	$19,933.73
		Pump (P-306)	2	$24,427.31	$48,854.61
	Crystallization	Crystallizer (R-401)	1	$269,042.39	$269,042.39
		Pump (P-401)	2	$6,779.56	$13,559.11
	Basket Centrifugal Filtration	Centrifuge (C-401)	1	$133,923.32	$133,923.32
		10,000 L Tank (T-401)	1	$83,137.75	$83,137.75
		Stirred Mixer	1	$11,926.27	$11,926.27

		(AN-401)			
		Screw Conveyor (CV-401)	1	$20,000.00	$20,000.00
		Pump (P-402)	2	$10,188.93	$20,377.86
	Solvent Recycling	Distillation Column (DIST-401)	1	$28,697.86	$28,697.86
		HE-Condenser	1	$10,763.69	$10,763.69
		HE-Reboiler	1	$89,479.70	$89,479.70
		Distillation Reflux Pump (P-407)	2	$11,479.14	$22,958.28
		Heat Exchanger ((HE-401)	1	$10,763.69	$10,763.69
		Pump (P-405)	2	$10,502.44	$21,004.87
		Pump (P-406)	2	$11,168.63	$22,337.27
	Fluidized Bed Dryer	FBD (FB-401)	1	$39,459.55	$39,459.55
		9,000 L Tank (T-402)	1	$83,052.84	$83,052.84
		Screw Conveyor (CV-402)	1	$20,000.00	$20,000.00
		Screw Conveyor (CV-403)	1	$20,000.00	$20,000.00
		Air Filter	1	$22,719.14	$22,719.14

6.2 Operating Costs

The operating costs include labor cost, raw materials cost, and utilities cost. In the process proposed, there are 6 particulate solids steps (1 solid mixer, 2 centrifuges, 1 rotary drum vacuum filter, 1 shake flask, and 1 fluidized bed dryer) and 15 nonparticulate steps (5 reactors, 1 evaporator, 1 centrifugal extractor, 1 distillation column, and 6 heat exchangers) in total. According to equations provided in the Turton textbook, the total number of operators required per shift for such an operation is 34, and the total number of operators required to be hired is 153. Based on guiding principles from Turton, the total number of supervisors required for 153 operators is 16. Using an average chemical plant operator cost of $10,012.32 in South Africa as stated on payscale.com and assuming that supervisors have a salary that is twice as much as that of an operator, the total cost of labor per year is $1,852,279.20.

Raw material costs were collected from various online vendors for bulk purchases. The majority of the vendors were based in China since price quotes from companies in that area were found to be cheapest. For the scope of this project, the cost of transporting raw materials was not included in the purchase price. In reality, the cost of transporting these materials may be rather significant. A summary cost of each raw material along with the quantity required for the penicillin V manufacturing process is shown in Table 6.2-1 below.

Table 6.2-1 Raw Materials Cost

Material	Amount/batch (kg)	Annual Amount (kg)	Total Cost $
Paper	13637	654576	-$65,457.60
Water	175055.2	8402649.6	$10,047.42
Cellulase	1402	67296	$672,960.00
Sodium acetate	1,372	65856	$65,856.00
Acetic Acid	488	23424	$18,130.18
Water	350.1	16804.8	$20.09
Air for Fermentor (scf)	286020	14301000	$4,290.30
Corn Steep Liquor	3937	196850	$98,425.00
Lactose	3937	196850	$39,370.00
Phenoxyacetic Acid	4600	230000	$825,063.33
$K_2H_2PO_4$	449.5	22475	$1,123.75
Edible Oil	281.1	14055	$1,405.50
H_2SO_4	146	7300	$1,293.78
Butyl Acetate	2252.66	112632.91	$39,421.52
Potassium Acetate	152	7600	$11,400.00
Acetone-Water	2308	115400	$97,397.60
USP Water	22973	1148650	$6,867.46
Evaporator Air (scf)	167500	8375000	$2,512.50
Potassium Hydroxide	1,037	51835	$44,837.28
Pharmamedium	13204.6	660230	561195.5
Total Cost			**$2,436,159.60**

Utility costs were also calculated using unit price estimates from Turton *et al.* Power usage from pumps was calculated based on the required flow rate for the relevant stream and estimated pressure drop for that stream. These pressure drops were estimated using design heuristics from Turton as well. Utility costs are summarized in Table 6.2-2 below.

Table 6.2-2 Utility Costs

Equipment	Utility	Requirement/ batch	Batch Cost	Annual Cost
Pumps	Power (kWh)	82.6	6.69	$334.69
MX-101	Power (kWh)	5.5	0.44	$22.21
HE-101	Steam (kg)	14,778.4	260.16	$13,007.95
CV-101	Power (kWh)	19.8	1.60	$80.19
R-101	Power (kWh)	479.5	38.84	$1,941.98
CV-102	Power (kWh)	39.6	3.20	$160.18
R-108	Power (kWh)	0.0	0.00	$0.04
CR-101	Power (kWh)	5,610.0	454.41	$22,720.50
EV-101	Steam (kWh)	6,628.4	536.90	$26,845.08
Fermentor Agitation	Power (kWh)	5,520.3	447.14	$21,462.73
Fermenter Cooler	Chilled Water (kg)	484,405.6	9,817.93	$471,260.79
RDF-301	Power (kWh)	96.0	7.78	$373.25
HE-301	Chilled Water (kg)	1,376.1	2.14	$102.72
HE-302	Ethylene Glycol (kg)	1,163.8	1,349.98	$64,799.22
CE-301	Power (kWh)	2,110.2	170.92	$8,204.36
CE-401	Power (kWh)	1,605.8	130.07	$6,243.51
AN-401	Power (kWh)	470.6	38.12	$1,829.66
CV-401	Power (kWh)	17.0	1.38	$66.10
HE-Condenser	Cooling Water (kg)	876.6	17.77	$852.77
HE-Reboiler	Steam (kg)	2,858.7	50.32	$2,415.57
HE-401	Cooling Water (kg)	846.5	14.90	$715.11
FB-401	Power (kWh)	3.7	0.30	$14.52
CV-402	Power (kWh)	17.0	1.38	$66.10
CV-403	Power (kWh)	17.0	1.38	$66.10
Waste Handling	Waste			$29,025.95
Total Cost				**$672,611.28**

6.3. Total Capital Investment

6.3.1 Fixed Capital Investment

Fixed Capital Investment (FCI) represents the cost to build a manufacturing facility ready for operation. Typically, FCI includes physical and construction assets such as factories and machineries as well as other fixed costs of the piping, instrumentation, and utilities installation. The guiding principles for different costs are calculated following the guiding principles outlined in Plant Design and Economics for Chemical Engineers (Peters *et al.* 2017). The cost estimation guidelines include a 20% margin of error depending on the actual design process. The breakdown of FCI is shown below in Table 6.3.1-1 with corresponding rules used to estimate the cost. The total Fixed Capital Investment sums up to $25,381,132.26.

Table 6.3.3-1 Fixed Capital Investment Breakdown

Categories	FCI Breakdown Guiding Principles	% of FCI	Value
Direct Cost	65-85% of FCI	67.92%	$17,239,940.05
Equipment Purchase (PE)	15-40% of FCI	20.96%	$5,320,969.15
Installation	25-55% of PE	7.34%	$1,862,339.20
Process Piping	10-80% of PE	8.39%	$2,128,387.66
Instrumentation and Controls	8-50% of PE	5.24%	$1,330,242.29
Electrical	10-40% of PE	4.19%	$1,064,193.83
Buildings, process and auxiliary	10-70% of PE	8.39%	$2,128,387.66
Service facilities and yard improvements	40-100% of PE	12.58%	$3,192,581.49
Land	4-8% of PE	0.84%	$212,838.77
Indirect Cost	15-35% of FCI	32.08%	$8,141,192.21
Engineering and Supervision	5-30% of Direct Costs	8.83%	$2,241,192.21
Legal expenses	1-3% of FCI	1.97%	$500,000.00
Construction	10-20% of FCI	13.79%	$3,500,000.00
Contingency	5-15% of FCI	7.49%	$1,900,000.00
TOTAL FCI	Direct + Indirect Costs		**$25,381,132.26**

6.3.2 Working Capital

In addition to the fixed capital investment that is used to construct the plant, working capital is required to maintain the plant operations. Specifically, this capital is used in maintaining inventories and cash flow on hand. Because this is not a fixed expenditure, the full amount can be recovered when the plant shuts down. As specified in the Peters textbook, the working capital is usually 10% to 20% of the Total FCI. Assuming an average of 15%, the

working capital is $3,807,168.84. By selling part of the purchased equipment and recovering some of the working capital after the life of the plant, we assume a salvage value of $6,864,050.20 for future economic analysis.

6.3.3 Cash Flow Analysis

Different scenarios were modeled to assess the economic feasibility of the plant using the estimations for FCI and operating costs. These costs are summarized in Table 6.3.3-1 and Table 6.3.3-2. The annual revenue from selling the final API product is summarized in Table 6.3.3-3.

Table 6.3.3-1 Initial Investments for Penicillin V Production

FCI	$25,381,132.26
Working Capital	$3,807,169.84
Total Investment	$29,188,302.09
Yearly Depreciation	$2,538,113.23

Table 6.3.3-2 Operating Costs for Penicillin V Production

Expense Label	Cost
Labor	$1,852,279.20
Utilities	$672,611.28
Materials	$2,436,159.60
Total	$4,961,050.08

Table 6.3.3-3 Revenue Estimate for Penicillin V Production

Revenue Estimate	
Pen VK Unit Price	$35/kg
Pen VK Production	6876 kg/batch
Batch Revenue	$240,660
Annual Revenue	$11,551,680

To conduct the cash flow analysis, a series of assumptions were made regarding the plant's operation. Firstly, the life of the plant was assumed to be 20 years with an additional 2 years of construction. The FCI was distributed equally between these two years. Additionally, the first year of operation would be at half production capacity and the working capital of the plant would be spent in this year. Finally, a 10-year straight line depreciation was assumed in order to distribute tax credits from the FCI over a longer period of time.

Using these conditions, a Discounted Cash Flow (DCF) model was created using a discount rate of 8% to find the Net Present Value (NPV) of the plant's operation. From this number, the Internal Rate of Return (IRR) was also calculated by finding the discount rate at which the NPV was $0, as shown in Equation 6.3.3-1.

$$0 = NPV = \sum_{n=0}^{N} \frac{CF_n}{(1 + IRR)^n}$$

Equation 6.3.3-1: IRR Calculation Using Yearly Cash Flows

Where: CF_n = Cash Flow in year *n*

IRR = Decimal Discount Rate of Cash Flow

NPV = Net Present Value

Using South Africa's corporate tax rate of 27%, the yearly cumulative cash position was calculated and is shown in Figure 6.3.3-1.

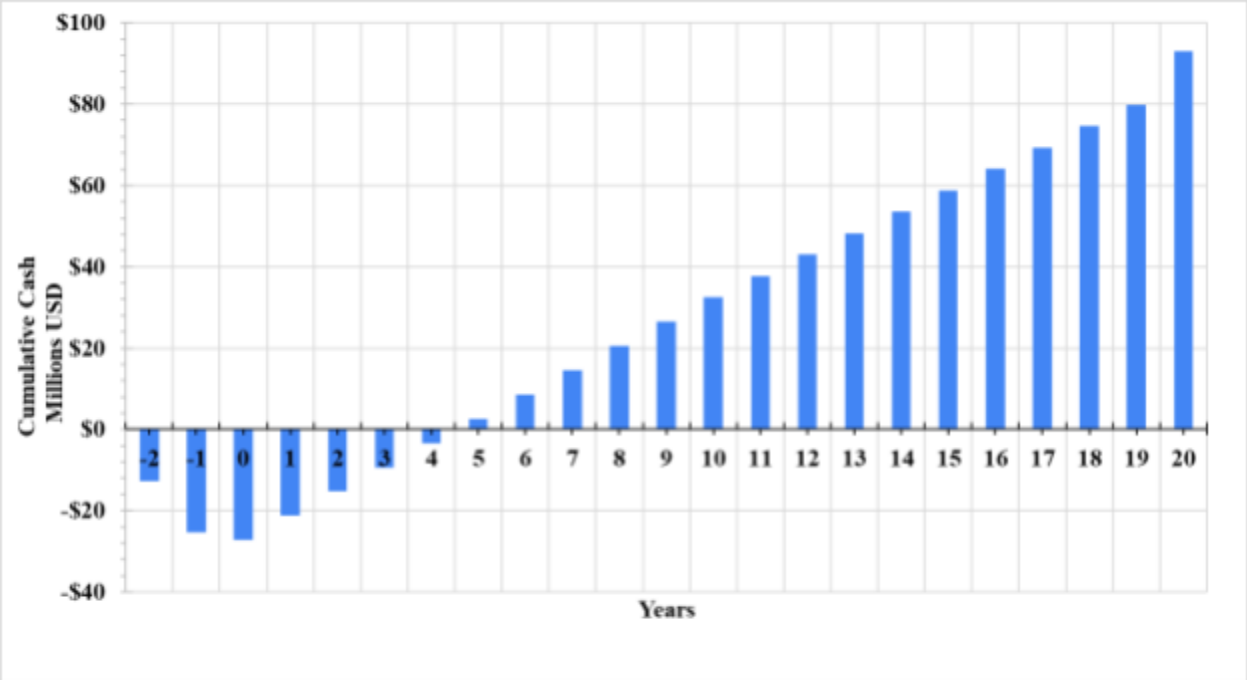

Figure 6.3.3-1 Cumulative Cash Position with 8% Discount (No Approval Period)

This graph shows that the plant would break even with the FCI between the fourth and fifth year of operation. A graph of the yearly present value throughout the life of the plant is shown in Figure 6.3.3-2. In this scenario, the NPV after 20 years of operation was $23,159,773 and the IRR would be 15.35%.

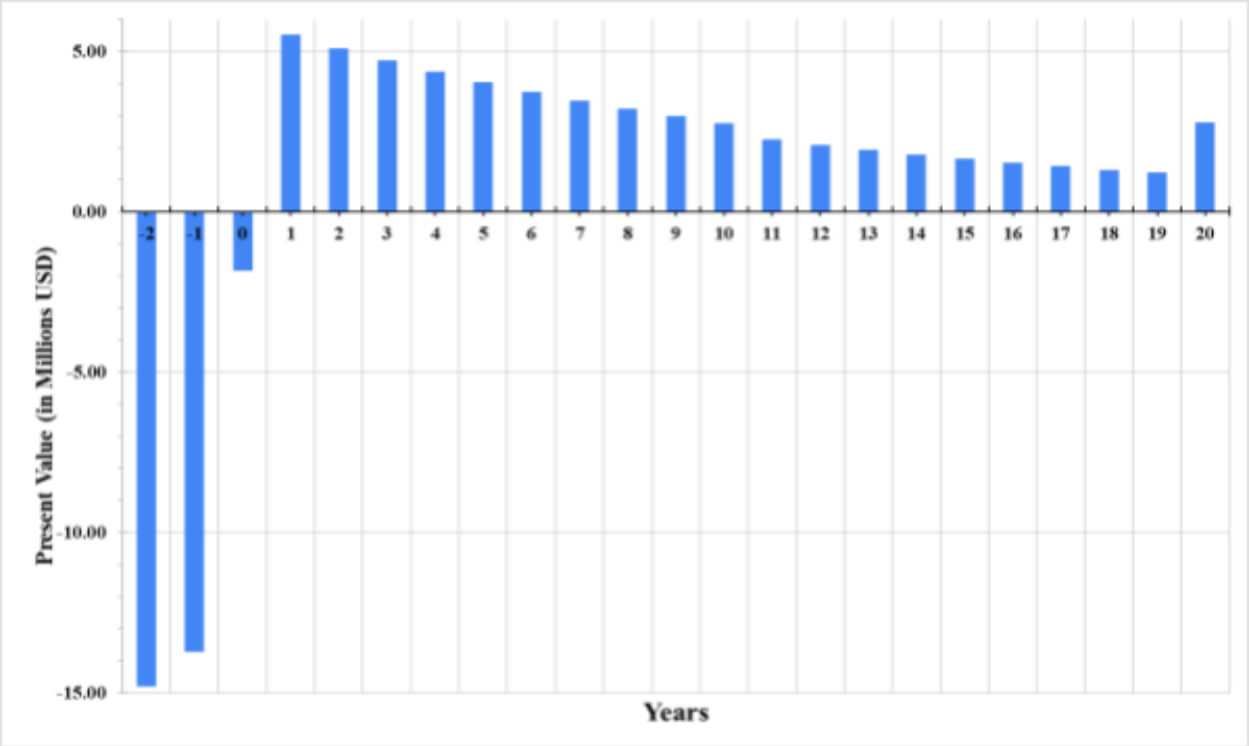

Figure 6.3.3-2 Annual Income Adjusted to Present Value (8% Interest, No Approval Period)

In the pharmaceutical industry, it is very common to have a regulatory holdup period before selling a product in order to ensure end-user safety. Therefore, a second economic forecast was evaluated in which a 5-year regulatory approval period was required before the plant could move forward with operation. In this scenario, no revenue was accumulated for the first five years after construction of the plant, but the life of the plant after construction was still 20 years. All other characteristics of the plant remain unchanged from the first scenario, including a 10-year straight line depreciation tax exemption that begins in the first year of plant operation. Figure 6.3.3-3 shows a graph of the cumulative cash position for the second scenario.

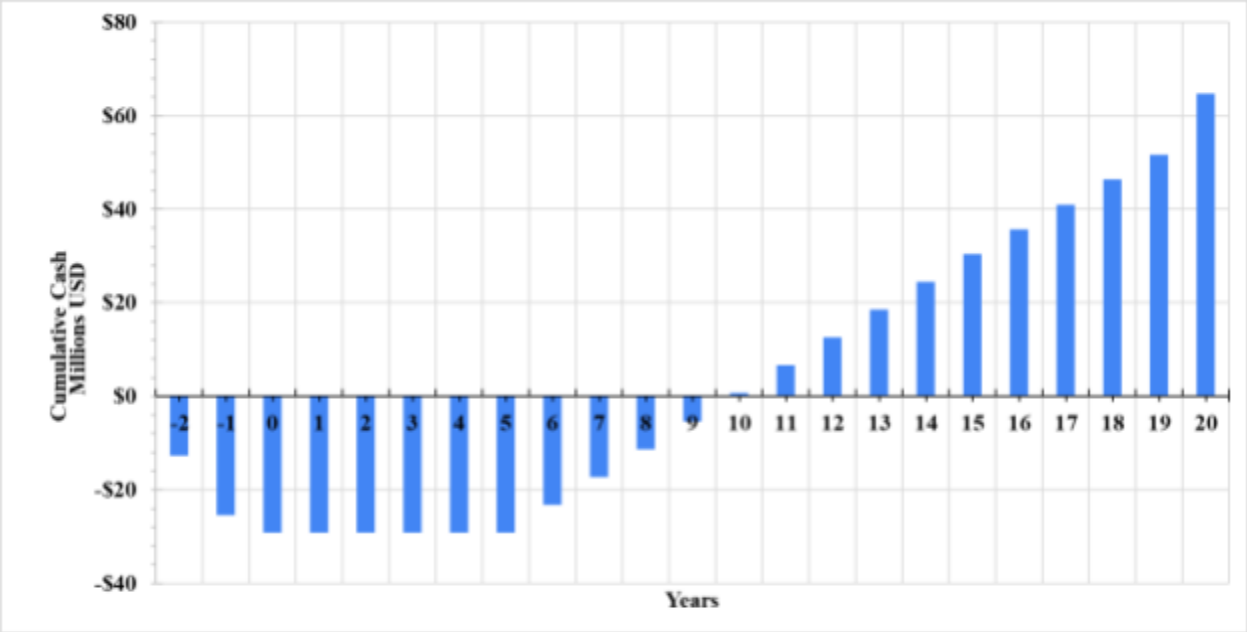

Figure 6.3.3-3 Cumulative Cash Position with 8% Discount and a 5-Year Approval Period

Figure 6.3.3-4 shows the present value each year as the plant progresses for the second scenario.

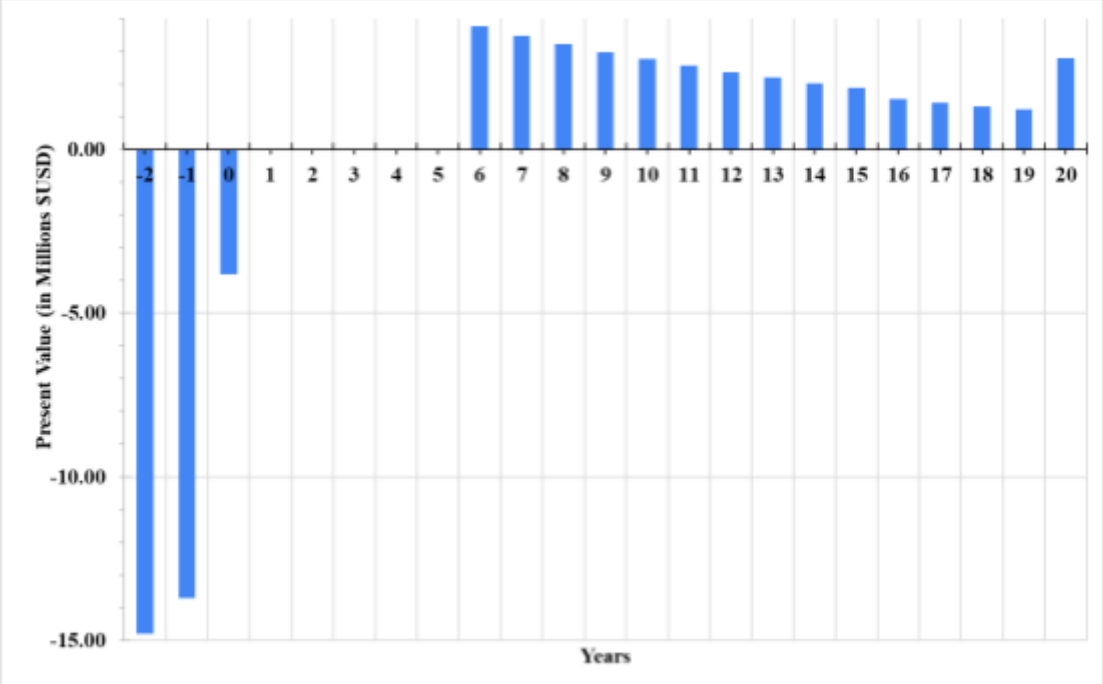

Figure 6.3.3-4 Present Value With 5-Year Approval Period (8% Discount Rate)

Interestingly, the NPV of the plant in this situation is $3,232,259 with an IRR of 8.79%. This shows that the profitability of the plant sharply decreases as with the presence of a regulatory approval period. However, these values still indicate a positive return on investment. Additionally, this scenario represents an extremely long approval period and therefore can be thought of as a minimum return on investment. The basis for this idea stems from the fact that the methods for producing penicillin V have gone unchanged for multiple decades. Consequently, it is likely that the approval period for this plant would be expedited or shortened greatly. Therefore, the team expects that forecasting the plant operation as not having an approval period is a plausible and more accurate scenario than the 5-year approval period.

Based on these economic forecasts, the team would recommend that the design move forward with implementation since the venture is profitable within a reasonable timeframe using realistic model assumptions.

7. Safety, Environmental, and Social Considerations

Due to the inherent difference in end users between most chemical processes and the pharmaceutical industry, there is a higher burden of product sterility as it is administered directly to the human body. Since the process is designed for the wholesale of penicillin VK powder for further processing and formulation, strict product controls do not necessarily need to be maintained at the same level as one designed for consumer use. Regardless, the process is designed to assure sterility through the use of filters for streams entering the fermentation and downstream processes, use of appropriate PPE, and quality control. Operator contact with the process will be limited as much as possible to prevent contamination of the process. Further, due to the hazardous nature of several process steps, operators will be trained in safe operating and handling procedures before being assigned to specific process steps.

A major process hazard associated with the design of the process arises due to the use of sulfuric acid. In the event of a spill, sulfuric acid is highly corrosive and produces hazardous vapors. From inherently safer design principles, the system will not use more than 300 kg of sulfuric acid per batch, and large volumes will not be stored. A second major process hazard arises from both acetone and n-butyl-acetate which are used in large volumes and are both extremely flammable liquids and vapors. To prevent this, the chemicals will be stored in conditions where the vapor percentage within the air does not rest between 2% and 13% by using floating roof storage tanks. Additionally, since the storage of acetone and butyl acetate is relatively large, their storage tanks will be protected with dikes to mitigate the consequences of a chemical release. Since the solvent recycle distillation heats acetone as its distillate product, a flare will be installed to allow for mitigating action in the case of an emergency. Since the amount of sulfuric acid stored on site is less than the OSHA threshold quantity of 453 kg, the

plant would not need to be covered by the OSHA PSM Standard for hazardous chemicals. This situation is ideal for reducing the breadth of regulatory requirements to which the plant would otherwise be subjected.

Two major social concerns arise from the implementation of this process, which include water usage in the context of the current South African drought and pharmaceutical inequity issues. South Africa is currently recovering from a countrywide water crisis, wherein reservoirs had declined to 20% of storage capacity and it represented one of the largest pending environmental crises in the world. Reservoirs have since been refilled to 95% of their storage capacity, however the threat of water shortages still remains. Consequently, there is a risk of water restrictions affecting the process. At the highest level of water restrictions, the process would need to reduce its consumption by 45%, which would severely reduce the scale of the batches and could lead to unfavorable economic conditions. Pharmaceutical inequity is also prevalent throughout the global south, which includes South Africa. In order to address this issue, the process is being designed such that the express goal of production is for the South African market, rather than the international one.

In regards to environmental concerns for this process, major wastes include the large amounts of water waste produced from glucose production and various washing steps throughout the process; the overall environmental impact is also reduced by the elimination of a large waste paper stream in the form of the enzymatic hydrolysis and the associated reduced need for sugar throughout the process. These waste streams will be treated at approved disposal plants and were accounted for as an extra waste cost in the economic analysis. Additionally, the waste stream holding various solvents coming out of the basket centrifuge (CE-401) toward the end of the process poses an environmental threat that will be dealt with by disposing of chemicals properly

in accordance with regulatory guidelines. Additionally, solvents such as butyl acetate and potassium hydroxide pose a health and aquatic hazard and will also be transported to an appropriate waste disposal plant.

8. Conclusions and Recommendation

This design encompasses the production and purification of penicillin V in South Africa using waste paper as a carbon substrate source. The use of waste paper helps to reduce the environmental impact of the production process and provide a solution for waste disposal issues in the South African region. Placing the plant in South Africa was decided upon to reduce existing inequalities regarding access to antibiotics.

Initially, the project was set to produce 150,000 kg of penicillin V. However, the team found that a total of 330,000 kg of penicillin V API could be produced annually after designing the upstream process. Production is designed to span 7 days per batch, with 48 batches annually. This gives a total of 336 manufacturing days in a year.

The plant production capacity captures one fourth of South Africa's estimated annual consumption and creates $11.5 million in annual revenue. The project is predicted to have an IRR of 15.3 % over 20 years of operation. This project was deemed economically feasible based on the IRR and the NPV both being positive when calculated using realistic assumptions about the venture.

This project was executed over a relatively short period of time to emulate a design scenario in industry. As a result, certain technical and logistical assumptions were made to reduce the scope of the design in order to make the design doable in the time period allotted for the project. Therefore, some recommendations can be made to either increase the accuracy of the design or to reduce the estimated costs of the venture.

The group made an assumption that the waste products generated from the waste paper pretreatment step such as lignin are decomposed by mechanical mixing (carried out by the mixer MX-101) and heat treatment. Any residual amounts of these pollutants in the glucose solution

were assumed to not interfere with the viability of the fermentation. In reality, an issue may arise in which a buildup of unreacted waste causes issues with the purity of the glucose solution that prevents efficient production of penicillin VK. A recommendation for better design in this respect would be to design some kind of periodic pollutant reduction system or to add in an extra paper processing step such that lignin and other contaminants can be reliably removed from the paper slurry. One method to offset the increased cost of adding this part of the process would be to sell the lignin waste, as there are companies that are developing renewable polymers using lignin monomers (Epps, *n.d.*).

Another recommendation for better design within waste paper processing would be to figure out a way to recover the cellulase enzyme after the hydrolysis reaction. Doing this would help to reduce the amount of enzyme needed annually since kinetic data shows that cellulase activity should persist for multiple batches at an acceptable level (Gusakov *et al.,* 1987). However, this recovery operation would be difficult since the enzyme has a similar size and solubility to glucose, which would make solvent extraction and membrane filtration more expensive and potentially unviable.

In modeling the growth kinetics of *P. Chrysogenum*, an assumption was made that the cell biomass concentration would continue to increase throughout the duration of the fermentation. This simplification is likely not representative of a realistic scenario. Instead, biomass would likely plateau at some point during the process and begin to decrease, which would be the expected behavior with increasing concentrations of an antibiotic in solution. In the model used here, cell biomass reached the upper limit of reasonable concentrations mentioned in literature using the Contois model, but a more accurate model could produce more realistic allocations for cell and product concentrations. Such a model could be a structured model in

which the biomass growth of *P. Chrysogenum* is modeled separately based on specific function for the cell (Goldrick *et al.,* 2015).

A further step would be to utilize a second distillation column to separate the acetone from the top of the solvent recovery distillation column and recycle this back into the system. This would reduce the total amount of acetone used per batch, reducing capital costs; simultaneously, recycling acetone would reduce the total amount of acetone that would need to be disposed of.

After the fermentation broth is filtered in the rotary drum vacuum filter, the aqueous solution carrying penicillin V is cooled to 2℃ to preserve stability of the molecule. Since a reasonable differential to drive heat exchange is 10 ℃, the stream is at risk of ice buildup within the cooler. It was assumed that this would not occur due to freezing point depression from solutes present in the water. In the future, the mix of solutes should be tested in order to determine the degree to which this conjecture holds true. Separately, cooler designs exist that scrape away ice buildup within the system, which would alleviate this issue.

The particle size distribution of the crystallization step was not considered as having a significant effect on the efficacy of the final API. A more comprehensive process design would be to acquire data for the particle sizes of the product and ensure that different morphologies would not be an issue for this production.

9. Acknowledgements

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10. Table of Nomenclature

Symbol	Definition	Units
A	Cross-sectional area	m^2
V	Volume	m^3
D_i	Impeller diameter	m
D_t	Tank diameter	m
H	Height of tank	m
H_b	Impeller height	m
N	Rotational speed	rpm
μ	Specific growth rate	h^{-1}
μ_{max}	Maximum specific growth rate	h^{-1}
μ_g	Operating gas velocity	m/s
S	Substrate concentration	g/L
K_s	Half-saturation constant	Unitless
X	Biomass concentration	g/L
$Y_{X/S}$	Biomass yield	$g_{biomass}/g_{substrate}$
$Y_{P/S}$	Product yield	$g_{product}/g_{substrate}$
$Y_{X/O2}$	Biomass to oxygen yield	$g_{biomass}/g_{oxygen}$
$q_{o2}dX/dt$	Cell line-specific oxygen consumption rate	g_{O2}/L/hr
q_{o2}	Oxygen biomass yield coefficient	g_{O2}/g_{cells}
k_La	Oxygen transfer rate	h^{-1}
C_{O2}^*	Equilibrium oxygen concentration	g_{O2}/L
$C_{O2, min}$	Minimum oxygen concentration	g_{O2}/L
v_s	Superficial gas velocity	cm/min
P_g/V	Power density	hp/L

ρ_g	Density of gas	kg/m^3
λ	Latent heat of vaporization	J/kg
M	Mass	kg
c_{pg}	Gas heat capacity	J/Kg/K
G_g	Gas flow rate	kg/s
T	Temperature	℃
P	Power	W
Q	Volumetric flow rate	m^3/s
h	Pressure head	Pa
η	Efficiency	Unitless

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