

# Optimization of the Production of Lofexidine

(Technical Report)

Capstone  
Presented to the Faculty of the  
School of Engineering and Applied Science  
University of Virginia

By

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March 23, 2020

On our honor as University students, we have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Capstone-Related Assignments.

Signed: \_\_\_\_\_

Approved: \_\_\_\_\_ Date \_\_\_\_\_  
Eric Anderson, Department of Chemical Engineering

## **Letter of Transmittal**

Under the advice of Professor Eric Anderson, we have designed a facility for the manufacture of lofexidine, an opioid withdrawal drug. The following document has been prepared to communicate the design specifications of the capstone design project.

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## I. SUMMARY

This technical project sets out to optimize the production of an opioid withdrawal medication, lofexidine. The U.S. is currently experiencing an opioid epidemic with estimates of more than 130 Americans dying each day after overdosing on opioids (National Institute of Drug Abuse, 2019). This research focuses on optimizing the production process to lower manufacturing costs and drive the sale price down, making lofexidine more available to a greater number of patients.

This up-scaled production of lofexidine was adapted from a lab-scale experiment detailed in a patent presented by Crook and Vartak in 2012. Production of impure lofexidine solution is performed using 3 batch reactors, 3 evaporators and 1 filtration. The lofexidine is then purified with an extractor, filtered and mixed with HCl to produce the pharmaceutically active salt form of lofexidine, lofexidine hydrochloride. These processes were modeled using Aspen Plus.

Economically, the process generates a yearly cash flow of roughly \$260 million at the current market price for lofexidine, but also returns a comfortable \$2.6 million profit if the price is cut 50-fold to \$2.30 per mg with a 19% internal rate of return after two years of production, assuming one year of sunk costs related to process validation. At the diminished price, lofexidine will become more appealing to consumers as its availability increases due to the lower achieved manufacturing costs.

However, before the process is officially adopted and implemented, several small scale experiments and pilot runs should be run to expand the library of property data on the compounds involved and develop a permanent plant schedule. The plant can be reprocessed for the remaining calendar months as a plant to manufacture antiviral drugs to help mitigate the severity of the COVID-19 pandemic or any small molecule pharmaceutical with similar scaling to the process outlined below.

## II. INTRODUCTION

Lofexidine, commercially known as Lucemyra, is a non-opioid withdrawal medication manufactured in the United States by US WorldMeds, LLC. According to the National Institute of Drug Abuse, U.S. overdose deaths involving opioids rose from 8,148 in 1999 to 47,000 in 2017 (National Institute of Drug Abuse, 2019). The United States Department of Health and Human Services declared the opioid crisis a national public health emergency in October 2017. Adverse symptoms stemming from the sudden discontinued usage, or withdrawal, of opioids, such as codeine, morphine, heroin, oxycodone, and hydrocodone, are often the principal factors in driving repeated misuse and eventual addiction (Juergens, 2019). Unfortunately, popular treatment plans, such as methadone, buprenorphine-nalaxone, and naltrexone, prescribe a less addictive opioid to treat the unpleasant problems that arise from long-term opioid withdrawal, involving a gradual tapering of the dosage prescribed until the patient has fully recovered (Juergens, 2019). The U.S. economic burden of the opioid epidemic -- including healthcare and substance abuse treatment cost, criminal justice and cost productivity -- was estimated to be over \$78.5 billion in 2013, while only \$2.8 billion was withdrawal treatment (National Institute of Drug Abuse, 2019). Among those afflicted with opioid addiction, only 19.7% seek treatment yearly, with many citing the main reason for avoiding treatment being the inability to afford the available treatments (Duncan, 2018). Lofexidine offers a nonaddictive non-opioid withdrawal treatment plan, but the price of treatment limits the accessibility for many patients in need. This technical project focuses on scaling up the production of lofexidine in order to drive down manufacturing costs and lower lofexidine prices.

Lofexidine was first sold in the United Kingdom to treat opiate withdrawal symptoms under the name Britlofex in 1992. However, doubts concerning the drug's effectiveness and value compared to clonidine delayed the United States from considering the medicine until a more substantive clinical study was submitted in 2016 (Rehman et al., 2019). FDA approval quickly followed in 2018, allowing it to be marketed under the name Lucemyra. Lofexidine became the first non-opioid opioid withdrawal medication to receive FDA approval. Clonidine, which is structurally similar to lofexidine, has been used off-label for decades to reduce opioid

withdrawals, but clonidine has serious side effects such as orthostatic hypotension and has not received FDA approval for opioid withdrawal treatment. Despite lofexidine's recent approval showing improved efficacy and safety over clonidine, lofexidine has not garnered much attention in the USA because clonidine is still cheaper by a factor of 80 and marketing has generally failed to entice investors (Solorio, 2018). Moreover, lofexidine's drug availability in the UK has suffered a sharp decrease since May 2018 due to manufacturing issues; supplies could not be imported from the other two principal manufacturers, China and the United States (Erskine, 2018). After successful scale-up of the intended process, lofexidine should be widely available at a more affordable price point.

### **III. PREVIOUS WORK**

There are four distinct, patented processes for the synthesis of lofexidine; each synthesis occurring at a laboratory scale. In the work of Biedermann et al. (1986), optically pure lofexidine is isolated through an amide dehydration, nitrile alcoholysis, imidazoline formation, and salification with hydrochloric acid using optically pure ethyl lactate as the starting material. However, the process involves 8 synthetic transformations with two high-vacuum distillation processes resulting in an overall yield of only 5%. U.S. Patent Number 4,518,783 follows a similar process, but obtains enantioselective lofexidine using a Lewis-acid mediated imidazoline formation. In this synthesis technique, the amidation from ethylene diamine is followed by a cyclization to imidazoline using the Lewis Acid  $\text{TiCl}_4$  with THF. This process returns an overall yield of 4% after 5 synthetic transformations, including a silica gel column chromatography step following the Lewis-acid catalysed formation of the imidazoline. In the work of Crassous et al., a related imidazoline is synthesized, m-nitrobiphenylene, through a Mitsunobu inversion of methyl lactate forming a substitute methyl ester, which is converted to an imidazoline by reaction with ethylene diamine in the presence of  $\text{AlCl}_3$ ; however, this process produces an enantiomeric excess of 72%, thus failing to yield a chirally pure product.

The insignificant overall yield and process complexity of the previous three synthesis techniques required a new method to obtain optically pure lofexidine using a process that improves the overall ease and yield of the previous work. Crooks and Vartak (2012) patented a

process to synthesize pharmaceutically active lofexidine through a series of reaction, crystallization, filtration, and separation steps starting with enantiomerically pure (-) methyl lactate. Methyl lactate is reacted with 2,6-dichlorophenol using triphenylphosphine and diisopropyl azodicarboxylate (DIAD) catalysts in a ether/hexane solvent mixture to yield an ethanoate intermediate, which is further converted to an ethanamide through treatment with ammonia. The third step of the synthesis involves the conversion of the ethanamide to an imino-ether intermediate through a direct electrophilic attack by a trimethyloxonium ion. This intermediate is subsequently reacted with ethylene diamine to produce (-) lofexidine. The resulting product is made pharmaceutically functional by mixing with aqueous hydrochloric acid. In the lab, the desired product is synthesized with an overall yield of roughly 64% - roughly triple that of the next best proposed process. The detailed unit operations and procedures of this patented process were adapted and scaled up by a factor of ~8 in an attempt to minimize production costs with the hope of increasing the drug's availability and consumer appeal.

#### IV. DISCUSSION

##### 1. Product Specifications

Lofexidine is a non-opioid, central alpha-2-adrenergic agonist prescription oral medication that works to block the release of norepinephrine, a hormone responsible for many of the most frequently experienced withdrawal symptoms. Before lofexidine, a majority of the recommended medications for management of opioid withdrawal were other opioids, with methadone and buprenorphine-naloxone being the most common (Food and Drug Administration, 2018). The propensity of patients struggling with opioid addiction to become addicted to these medications necessitated a non-addictive product for withdrawal management. The active ingredient in Lucemyra is lofexidine hydrochloride since the lofexidine molecule must be made into a pharmaceutically functional acid addition salt. The chemical formula for lofexidine hydrochloride is  $C_{11}H_{12}Cl_2N_2O \cdot HCl$  with a molecular weight of 295.6 grams per mole. The

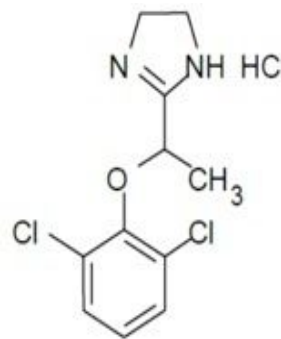


Figure 1: Molecular Structure of Lofexidine Hydrochloride



molecular structure of lofexidine hydrochloride is displayed in Figure 1. The desired purity of the lofexidine hydrochloride is greater than 98%.

In regards to the mechanism of action, lofexidine binds selectively to  $\alpha_2$  adrenergic receptors, acting as an agonist at the receptor normally targeted by norepinephrine (FDA, 2018). The activation of these  $\alpha_2$  adrenergic receptors leads to the inhibition of cyclic adenosine monophosphate (cAMP), which leads to potassium efflux, suppression of neural firing, and the inhibition of norepinephrine. Norepinephrine is related to alertness and energy, so the inhibition of norepinephrine can reduce heart rate, blood pressure and attenuate sympathetic stress response (FDA, 2018). Opioids also inhibit cAMP, and the discontinuation of opioid use results in rising levels of cAMP as opioid concentrations fall. This leads to an increase in norepinephrine release which is associated with withdrawal symptoms (FDA, 2018). The magnitude of these symptoms are associated with the length of opioid use because levels of cAMP will increase to compensate for opioid inhibition. Discontinuation of the opioid-driven inhibition often leads to higher levels of cAMP than normal and prolonged periods of greater amounts of norepinephrine than normal. Lofexidine works in opioid addicted individuals to bind to the selective  $\alpha_2$  adrenergic receptors, reducing the release of norepinephrine and moderating the symptoms of noradrenergic hyperactivity that resulted from the discontinuation of opioids. The selectivity of receptors that lofexidine binds with allows lofexidine to moderate the withdrawal symptoms without binding to the other opioid receptors that mediate opioid dependence and addiction (FDA, 2018).

Due to the public health need, lofexidine received fast approval in the UK in 1992 without significant data detailing drug efficacy or dosing. Since then, more studies have been conducted to prove the efficacy and safety of lofexidine for opioid withdrawal. Data collected on 1,074 opiate detoxifications conducted with lofexidine in the United Kingdom showed successful results in more than 60% of the subjects at a mean of 10 days of detoxification (Akhurst, 1999). The U.S. FDA approval of lofexidine was backed by a Phase 3 clinical development program with four studies involving 1,217 patients. Lofexidine demonstrated significant reductions in severity of acute opioid withdrawal and increased retention compared to the placebo (FDA, 2018). In addition to the efficacy, there is no current evidence that lofexidine has abuse potential

or addictive properties, giving it a significant advantage over opioid-based medications for opioid withdrawal (Gorodetzky et al., 2017). Additionally, clinical studies have shown that lofexidine resolves withdrawal symptoms sooner, resulting in a shorter treatment period compared to tapered dosing of methadone (Wakeman, 2018). In comparison to clonidine, lofexidine was found to be more effective in managing opiate withdrawal in accelerated detoxification without the risk of postural hypotension (Gerra et al, 2001).

Lucemyra dosing may vary depending on the patient needs, but typical dosing requires the patients to take three tablets, containing 0.18 milligrams of lofexidine, four times a day for five to seven days followed by a gradual reduction for two to four days (“Learn about Lucemyra (lofexidine),” n.d.). Lucemyra is sold in bottles containing 36 tablets costing \$787.11 per bottle. Therefore, Lucemyra costs roughly \$1,776 for a week of treatment.

## **2. Project Scale**

To estimate the scale of the project, the demographic of lofexidine must first be considered. More than two million Americans were affected by the opioid epidemic in 2018 according to a report from the Substance Abuse and Mental Health Services Administration; of those two million, only about 19.7% sought treatment (Lipari, 2018). Assuming that this project causes an increase in treatment capabilities, a 25% treatment rate is proposed. Of those being treated, there is also an assumption that only 20% of those treated for opioid withdrawal will use lofexidine as many substitution treatments currently use methadone. Therefore, only 100,000 treatments would be given per year.

As previously mentioned, a treatment consists of three 0.18 milligram tablets that are taken four times a day for seven days, followed by a gradually decreased treatment over two to four days (“Learn about Lucemyra (lofexidine),” n.d.). A standard treatment requires a minimum of 15.12 milligrams; the average realistic treatment is estimated at 22.5 milligrams (125 tablets), assuming 40-50% additional consumption during the gradually decreased treatment period. For 100,000 treatments at 22.5 milligrams per treatment, the yearly desired production of lofexidine is about 2.25 kilograms.

### 3. Social Implications

In the last decade, the opioid epidemic caused by the recreational misuse and abuse of opioids has reverberated throughout the world, affecting all ages and demographics. Beginning in 2010, unintentional overdose resulting from opioid dependence became the leading cause of death in the United States related to substance abuse, accounting for over 16,500 of the reported 40,000 drug overdose deaths (Beneitez & Ester Gil-Alegre, 2017). According to the 2010 National Survey on Drug Use and Health conducted by the Substance Abuse and Mental Health Services Administration, nearly 12 million people in the United States abused opioids in 2010, and roughly 2 million people reported their first recreational use of a prescription pain reliever that year. The same study details an increase in the annual patient admissions to opioid treatment facilities from 18,300 to 113,506 and a quadrupling in annual opioid related drug overdoses from 1998 to 2008. (Substance Abuse and Mental Health Services Administration, 2011).

Adverse symptoms stemming from withdrawal, or a sudden discontinued usage of opioids (such as codeine, dilaudid, and tramadol), are often the principal motivators for repeated misuse and eventual addiction (Juergens, 2019). The typical symptoms of withdrawal include muscle spasms, insomnia, anxiety, agitation, sweating, nausea, fluctuating blood pressure, and vomiting. These symptoms may chronically reappear for up to 24 months after the last dosage. Several medications have been manufactured in attempts to mitigate the afflictions experienced by opioid abusers, including clonidine, methadone, buprenorphine-naloxone, and naltrexone. The medication prescribed to opioid abusers often depends on the symptoms observed, the length/severity of addiction, and the subject's current physical and mental health (Juergens, 2019).

Financially, lofexidine is currently at a massive disadvantage. Clonidine (most commonly prescribed) costs only \$9 for a week's supply, while other major competitors buprenorphine-naloxone, methadone, and naltrexone cost \$115, \$126, and \$294 per week, respectively (National Institute on Drug Abuse, 2019). As seen in Section II, a week's supply of lofexidine may cost over \$1500. Lofexidine is the most effective drug to treat opioid withdrawal as it is not addictive and has the most manageable side effects. Unfortunately, the steep treatment cost of lofexidine is a significant barrier to recovery for opioid addicts. As seen in Section III, the

lofexidine production process of interest has a higher theoretical yield than present lofexidine manufacturing practices. Optimizing this process would allow for treatment cost reduction and help more opioid addicts to overcome difficulties associated with quitting.

Due to the small scale of the equipment used in the lofexidine production process (no unit has more than 10 L fluid capacity), the entire facility detailed in the process flow diagram below could reasonably be contained in a large room around 15x8x6 meters (including walking space for operators). Installing this equipment in a building would not cause any social disruptions which are not considered later in environmental and safety discussions. Because the equipment will need full day oversight, it must be located in a building where consistent noise emanation is not an issue. As the equipment would only be producing lofexidine for about three months out of the year, in a realistic scenario the facility would be part of a larger chemical plant and most of the equipment would be repurposed for other drug production during the other nine months. After all, it does not make sense to hire equipment operators for only three months at a time – the pay grade and level of training required are far above the usual amount seen for seasonal work.

#### 4. Process Flow Diagram

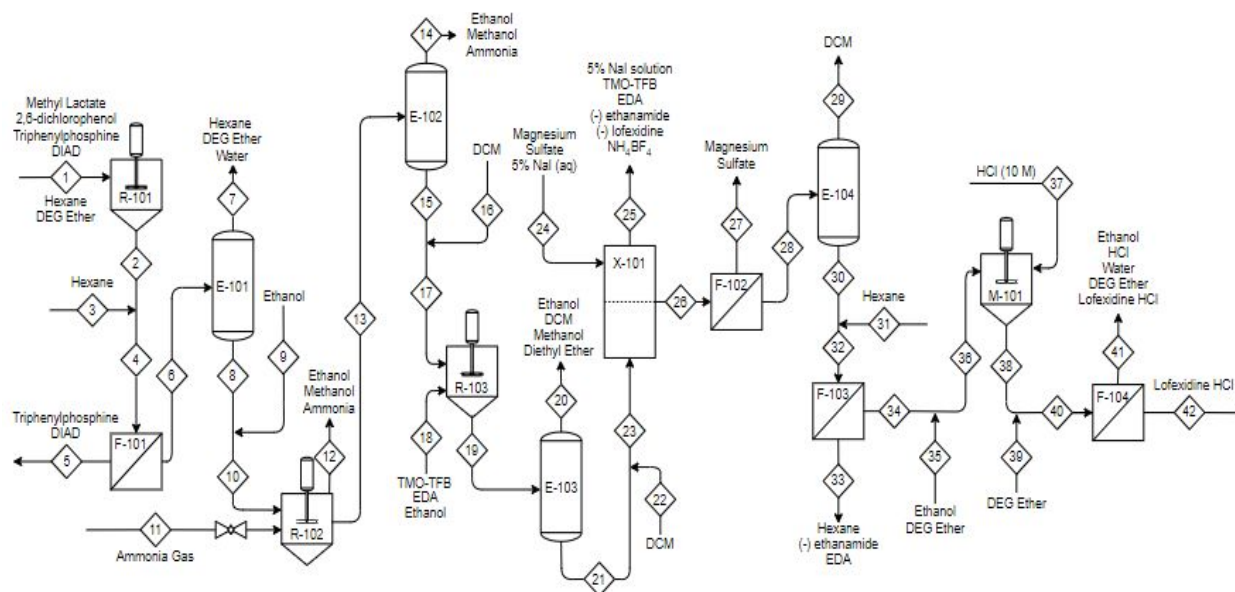


Figure 2: Process Flow Diagram of Lofexidine Production

## 5. Final Equipment Design

### A. Methyl Lactate Reactor R-101

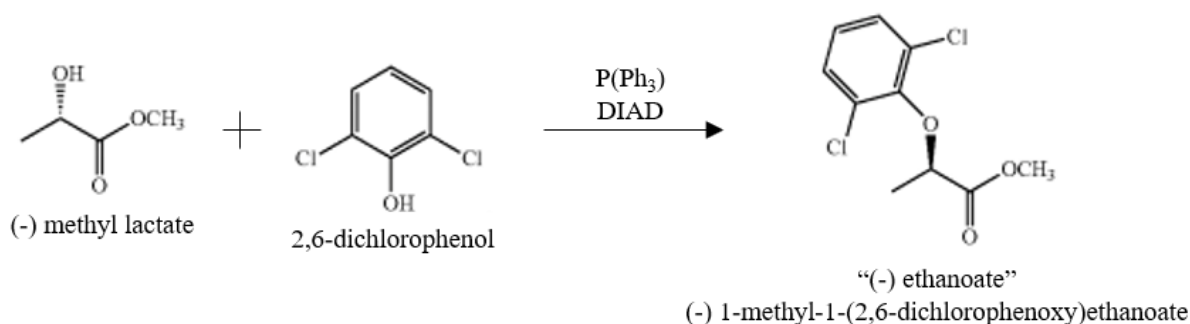


Figure 3: Chemical Reaction of Methyl Lactate Reactor

The esterification of (-) methyl lactate with 2,6-dichlorophenol to a (-) 1-methyl-1-(2,6-dichlorophenoxy)ethanoate intermediate (referred to herein as (-) ethanoate) is accomplished through a two-liter stirred tank reactor, as seen in Figure 3. The reactor was designed with A316 stainless steel, due to the lack of corrosive materials (Turton, 2018). The tank has a height:diameter ratio of about 2.5, with an interior diameter of 10.1 cm. The exterior diameter is 11.1 cm, for a wall thickness of 1.0 cm. The reagent stream (Stream 1) is comprised of 0.1055 kg (-) methyl lactate, 0.1655 kg of 2,6-dichlorophenol, 0.266 kg of triphenylphosphine, and 0.205 kg of diisopropyl azodicarboxylate (DIAD). The reagents are dissolved in a solvent mixture of 0.3375 kg hexanes (60%) and 0.4605 kg diethylene glycol (DEG) ether at 0°C. In accordance with the patent presented by Crook and Vartak (2012), the mixture is then warmed up to room temperature over the course of four hours; the initial cooling is done to mitigate potential hexane flash point concerns around an exothermic reaction.

In Aspen Plus V11, the reactor was modeled using the RSTOICH block with an operating temperature range of 0°C-25°C and an operating pressure of 0 barg. The reactor is mixed using a 7 cm diameter paddle impeller, which will require 0.353 W per reaction cycle (see Appendix for calculation). The reaction was modeled assuming 100% conversion of (-) methyl lactate due to the lack of literature providing a more suitable estimate. However, in a realistic reaction, some (-) methyl lactate will go unreacted; determining an accurate conversion rate would require experimentation. Heat generated by reaction was estimated by calculation at 56.2 kJ for each

cycle, and conductive heat transfer to the stainless-steel vessel from ambient air was calculated at 1296 J (see Appendix).

### *B. Solid-Liquid Filtration of Triphenylphosphine, DIAD and (-) ethanoate F-101*

The reaction product of R-101 (Stream 2) is diluted with 0.675 kg of hexanes (60%) following the completion of the reaction to double the mixture volume. Prior to this addition of hexane, the volumetric ratio of the nonpolar hexanes and polar aprotic ether was kept around 1:1 which allowed for a complete dissolution of all starting materials. This addition of hexane facilitates precipitation of triphenylphosphine and triphenylphosphine oxide from the reaction mixture as they are poorly soluble in hexane (Hu et al., 2009). After the additional hexane is added, the mixture is stirred in the R-101 vessel for 30 minutes and then sent to the filter. The purpose of this filtration step is to remove the catalysts triphenylphosphine and DIAD from the mixture.

A disposable microfilter is utilized for each cycle of the lofexidine manufacturing process. Unfortunately, this filtration was modeled as a basic separator (as opposed to a filter) in Aspen Plus due to restrictions around solids modeling without existing solubility data. In the filtration model for this step, some (-) ethanoate (0.01 kg) remains solid to account for the uncertain solubility of the intermediate in hexane. To prevent sizable entrainment losses of dissolved (-) ethanoate in the filter cake, the cake is washed with 0.54 kg of hexane. The two additions of hexane (totaling 1.215 kg) are designated Stream 3. The modeled filter cake (Stream 5) consists of 0.27 kg triphenylphosphine, 0.205 kg DIAD and 0.01 kg of (-) ethanoate solids, along with entrained liquids (assumed to be almost entirely hexane). Assuming entrained liquids comprise 50% of the filter cake mass, 0.485 kg of entrained hexane will leave with Stream 5. The filtrate product (Stream 6) contains around 0.46 kg ether, 0.24 kg (-) ethanoate, 0.018 kg water and 1.07 kg hexane.

### *C. Solvent Evaporator E-101 of Hexane, Diethylene Glycol Ethyl Ether and Waters*

A rotary evaporator is utilized to separate the product (-) ethanoate from the solvent mixture in Stream 6 consisting of hexanes, diethylene glycol ethyl ether and water. The

evaporator used to perform the separation has a 10 L receiving volume and is made from high borosilicate glass 3.3. The evaporator is set to operate at room temperature (25°C), at vacuum conditions of around 300 Pa. Vacuum conditions allow solvents' boiling point to be significantly lower than at ambient pressure (UCLA, 2010). Due to the cooling effects of evaporation, the evaporator has an internal water bath allowing for the load to remain at room temperature throughout the evaporation process. Maintaining room temperature prevents the solvents from freezing in vacuum conditions.

Evaporated solvents are collected in a separate chamber at ambient pressure which can be properly treated for disposal thereafter. The evaporator's rotational speed can vary from 10 to 130 rpm, depending on the desired rate of evaporation. Rotating the flask increases the surface area in which evaporation takes place, allowing for higher rates of evaporation to be achieved (UCLA, 2010). The expected rate of evaporation from the solvent evaporator is around 2.84 L and 5.68 L per hour for water and alcohol respectively. As hexane is more volatile than ethanol, the removal rate for alcohol vapors should be reasonably applicable to hexane evaporation: 1.07 kg of hexane is anticipated to evaporate within 30 minutes. However, DEG ether is significantly less volatile than water - the evaporation of 0.46 kg DEG ether may take up to one hour if the evaporation rate is  $\frac{1}{4}$  that of water.

In Aspen Plus V11, the rotary evaporator is modeled as a separator due to the lack of an evaporator model; the separator was the closest substitute to an evaporator in terms of purpose. The evaporation model assumes that all of the hexane, DEG ether and water are removed from the flask (solvent removals here are designated Stream 7) and none of the (-) ethanoate is evaporated. However, in a realistic rotary evaporator, some hexane and DEG ether is expected to be present in the product and trace amounts of (-) ethanoate will be lost when exiting with solvent vapors. It is important to identify a desired or tolerable concentration of (-) ethanoate in the product and quantify how much (-) ethanoate must be lost during evaporation to attain this threshold concentration.

#### D. Ammonia Reactor R-102

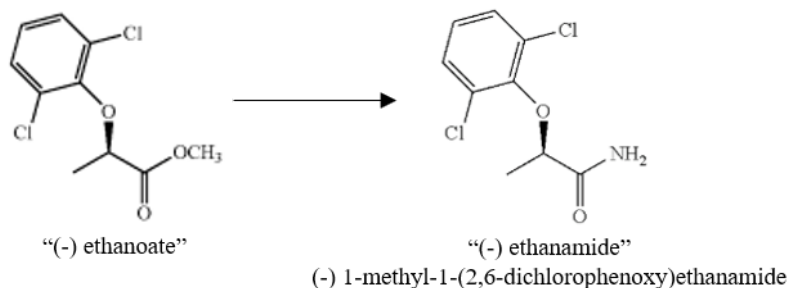


Figure 4: Chemical Reaction of the Ammonia Reactor

Conversion of the (-) ethanoate intermediate into (-) 1-methyl-1-(2,6-dichlorophenoxy) ethanamide intermediate (referred to herein as (-) ethanamide) is accomplished through a five-liter jacketed stirred tank reactor. The tank is made from A316 stainless steel due to lack of corrosive loadings (Turton, 2018). The tank has a height:diameter ratio of two, for an interior diameter of 15 cm. The exterior diameter is 16 cm, for a wall thickness of 0.5 cm. Each reactor batch cycle starts by loading Stream 10, made by combining the evaporator product (Stream 8, around 0.242 kg of (-) ethanoate) with solvent Stream 9 (2.43 kg of ethanol solution). This mixing occurs in the evaporator loading flask to minimize losses of (-) ethanoate during transfer. The reaction is performed in the range of 77-80°C (near the boiling point of pure ethanol) to provide the necessary heat for direct ester amidation (Marshall, 1944). In order to ensure the reaction occurs in the liquid phase at these temperatures, the vessel is pressurized to 1.5 bar.

Once Stream 10 is introduced to the reactor, the pressure is increased to 1.5 bar by loading compressed air. Once compressed, a stainless steel paddle impeller with a diameter of 7.5 cm is used to stir the solution at 75 rpm. The ethanol solution is warmed to 77°C by passing low pressure steam (~3 bar) through the reactor jacket. Using the specific heat estimated for the reaction mixture by Aspen Plus 11 (3070 J/kg °C), about 423 kJ of heat must be transferred to the vessel during the warming period, neglecting heat losses through the jacket exterior. Assuming an average steam pressure of 3 bar, with condensation enthalpy of 2163 kJ/kg and density of 1.65 kg/m<sup>3</sup> (Felder et al., 2005), a minimum 120 L (0.198 kg) of steam must condense in the jacket.

Using a basic jacket form of a 5 cm depth stainless steel shell with exterior insulation, 4 cm diameter exits on the side (for coolant and excess vapor) and 2 cm on the bottom (for



condensate), a steam flow rate of 2.25 L/s (3.71 g/s,  $Re \sim 1000$ ) will provide approximately 5.35 kW at the end of heating and 10.85 kW at the start. This will allow heating to be completed in around two minutes. Interior convective heat transfer coefficient was estimated using a correlation for 4-blade 45° pitched turbines detailed in Paul et al., (2004), whereas an external heat transfer coefficient was assumed to be 5000 W/m<sup>2</sup>C as suggested by Welty (2015).

Once the reaction mixture reaches 77°C, a sparger is used to introduce Stream 11 (0.03 kg of anhydrous ammonia) at a rate of around 0.5 L/min. This ammonia is drawn from a gas tank at 7.86 bar and decompressed to 1.5 bar using a globe valve. The loading of ammonia will take around 60 minutes, according to NH<sub>3</sub> density estimations in Aspen Plus 11. As the solubility limit for ammonia vapor in 2.43 kg ethanol at these conditions is around 27.5 g (estimated by Aspen Plus 11), the extra 2.5 g is used to supplement the overhead vapors to ensure the reaction stays saturated. In the event of pressure exceeding 2 bar, a relief valve is used to vent excess vapors to the waste processor which handles gas effluents from filter cake drying. In accordance with the patent by Crooks and Vartak (2012), the reaction is assumed to proceed to 88% conversion over four hours, producing Stream 13 which contains around 0.20 kg of (-) ethanamide and 0.0265 g of methanol products along with 0.01 kg ammonia and 0.029 kg (-) unreacted ethanoate in 2.40 kg ethanol. Overhead vapors (Stream 12) consisting of 0.0055 kg ammonia, 0.001 kg methanol, 0.03 kg ethanol, and air are also discharged to the waste processor at the end of reaction.

The vapor-liquid mass transfer coefficient ( $k_L a$ ) for this process when operating the impeller at 75 rpm is around 26.06 h<sup>-1</sup> and the impeller power requirement is around 2.0 W, as estimated using correlations in Welty (2015). Reaction time being much greater than ammonia dispersion time is assumed to be a consequence of kinetic limitations. Heat of reaction for the amidation was estimated via Aspen Plus 11 at -33.15 kJ/mol using the RSTOICH block. Taking 88% conversion of (-) ethanoate, the heat generated during the reaction is 28.4 kJ. In order to maintain the reaction temperature within the specified range, water at 77°C is passed through the reactor jacket. This water may initially be circulated relatively quickly (250 mL/s) to fill/cool the jacket but flow will quickly be stagnated once the outlet temperature of the water falls below 77.3 °C. Assuming a full jacket, 4.36 L of water may rise by only 1.6 °C while absorbing the

entire heat of reaction, and the reaction vessel may only rise by 3.5°C. Even if the temperatures of the reaction mixture and jacket equalised at 77.3°C before the reaction began, heat transfer between a reaction mixture and a 5 cm ring of stagnant water differing by 1 °C is around 4.4 W, well above the estimated reaction heat generation rate (2 W), so the reacting vessel should reasonably be kept in the range 77-80°C by stagnant water.

#### *E. Solvent Evaporation of Ethanol, Methanol and Ammonia E-102*

The same rotary evaporator seen in the first evaporation process is used to remove methanol, ethanol, and ammonia from the R-102 effluent (Stream 13). Given all trace solvents are more volatile than ethanol, the evaporation of 2.4 kg ethanol is expected to take 40 minutes or less. As in the first evaporation, the separation is run at a temperature of 25°C (maintained by water bath) and a pressure of 300 Pa under vacuum conditions. Full separation is assumed, with the liquid product (Stream 15) comprising 0.029 kg (-) ethanoate and 0.20 kg (-) ethanamide. The evaporated solvents (Stream 14 - 2.40 kg ethanol, 0.0265 kg methanol and 0.01 kg ammonia) will enter an ambient pressure receiving flask where they will be stored for treatment and disposal. The low boiling point of ammonia may mean that some ammonia vapors do not condense upon expansion to ambient pressure; it is important to have an outlet for the solvent collection flask where non condensing vapors can be routed to dissolve in a wastewater tank for disposal.

As in the first evaporation, the solvent evaporator in this stage is modeled using a separator in Aspen Plus 11. The model assumes that all solvents are evaporated, leaving behind only nonvolatile products in the liquid stream. All successive evaporations are also modeled using this scheme, as there is only one physical evaporator unit used for this process. It is important to note that losses are to be expected in realistic evaporations, and more importantly trace solvents will be retained in the evaporating flask. While trace solvents may eventually be removed when washing filter cake products, it is important to allow for longer evaporating time if the presence of trace solvents will cause issues with subsequent steps of the process. A longer evaporating time will increase the purity of the evaporation product, but may also lead to significant losses, necessitating definition of threshold concentrations for evaporation products as

part of a cost/benefit analysis. As ethanol and methanol are both present in the following reaction, slightly incomplete evaporation is unlikely to be an issue for this specific separation.

#### F. TMO-TFB Reactor R-103

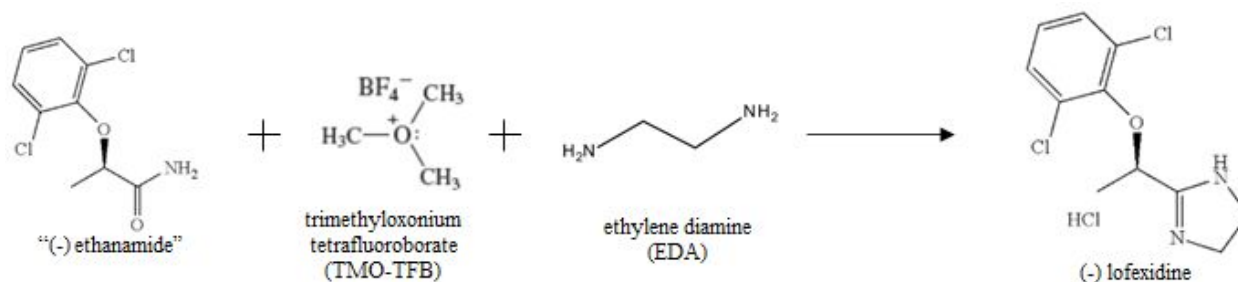


Figure 5: Chemical Reaction of TMO-TFB Reactor.

Following the evaporation of ammonia, methanol, and ethanol, 0.029 kg of unreacted (-) ethanoate and 0.20 kg of (-) ethanamide are dissolved within the evaporating flask using 6.01 kg of dichloromethane (DCM). The resulting solution is loaded into a 10 L stirred tank reactor, where the ethanamide is converted to an ionic imino-ether intermediate, which is further reacted into (-) lofexidine. The reactor is manufactured out of borosilicate glass, due to the presence of multiple ionic, corrosive materials (Turton, 2018), with an inner diameter of 20 cm, height of 32 cm, and tank thickness of 1 cm. Mixing is accomplished with a 4-blade A316 stainless steel paddle impeller coated in polyethylene with a paddle diameter of 9 cm. The reaction cycle begins by combining the DCM, ethanoate, and ethanamide stream (Stream 17) with 0.13 kg of trimethyloxonium tetrafluoroborate and stirring at 20 rpm for 36 hours at room temperature and atmospheric pressure. The imino-ether intermediate is formed through an electrophilic attack of the ethanamide oxygen from the trimethyloxonium ion, producing 0.04 kg dimethyl ether and 0.076 kg ammonium tetrafluoroborate as side products. After allowing the initial reaction to reach completion, 0.06 kg of ethylene diamine diluted in 1.23 kg of ethanol is added. The mixture is reacted for an additional 14 hours at ambient conditions using a stirring speed of 20 rpm. The ethylene diamine reacts with the imino-ester intermediate forming 0.19 kg of (-)

lofexidine and 0.023 kg of methanol. In accordance with the patent by Crooks and Vartak (2012), the extent of the combined reactions was assumed to be 85%.

The heat of reaction was estimated using Aspen Plus V11 with the RSTOICH reactor block and the available property estimation to be 32.47 kJ/mol. With a 0.733 molar extent for the reactions in series, the heat generated by the reaction was 23.8 kJ. Because the reaction occurs at room temperature over a two day span, the heat released to the plant was deemed negligible, as it will dissipate through the air during the 50 hours of operation, raising the temperature of the reactor at most 1°C. Using the appropriate correlations in Welty (2015), the power requirement for the 4-blade paddle impeller was estimated to be 0.035 W (see Appendix for calculation).

#### *G. Solvent Evaporation of Methanol, Ethanol, Dichloromethane and Dimethyl Ether E-103*

In this evaporation process, the aim is to remove volatile methanol, ethanol, dichloromethane and dimethyl ether present in the mixture, leaving behind (-) lofexidine, (-) ethanoate, EDA, ammonium tetrafluoroborate and imine intermediates. The output from the TMO-TFB reactor (Stream 19) contains around 0.029 kg (-) ethanoate, 0.023 kg methanol, 1.23 kg ethanol, 6.01 kg dichloromethane, 0.013 kg EDA, 0.04 kg dimethyl ether, 0.19 kg (-) lofexidine, 0.076 kg ammonium tetrafluoroborate and 0.043 kg of imine intermediate salts for each cycle. As DCM is more volatile than ethanol, the evaporation rate for alcohol vapors at the regular setting (25°C and 300 Pa) is used to estimate the overall operational time. Evaporation of 1.23 kg ethanol and 6.01 kg DCM is expected to occur within 80 minutes. The evaporated materials will be collected in the receiving flask for subsequent disposal. As with E-102, this evaporation contains a compound (dimethyl ether) that may not condense at ambient pressure, necessitating a vapor outlet from the receiving flask. Full separation of volatile from nonvolatile components will yield a liquid/solid product (Stream 21) consisting of 0.029 kg (-) ethanoate, 0.013 kg EDA, 0.19 kg (-) lofexidine, 0.076 kg ammonium tetrafluoroborate and 0.043 kg of imine intermediates.

Of the four evaporations in the lofexidine production process, this one is most important from a purity standpoint. The evaporation flask must be evaporated to dryness as the following

extractor could be sensitive to alcohols; a third phase forming with water and DCM would complicate the process. Additionally, the  $\text{NH}_4\text{BF}_4$  and imine salts are unlikely to dissolve well in DCM (but may dissolve in more polar ethanol) meaning there could be difficulties around determining when the evaporation is done. The number of potential trace compound complications necessitates extensive testing for the evaporation product; it is essential to identify the exact composition before proceeding on to the extractor.

#### *H. Extractor X-101*

To remove the salts and EDA from the product of E-103, a 10 L stirred vessel will function as a mixer-settler separating a DCM phase and an aqueous phase containing 5% sodium iodide by mass. Due to the corrosive properties of fluoroboric acid, borosilicate glass will be used to construct the liquid-liquid extractor. The extractor height:diameter ratio will be 1.2, for an interior diameter of 22 cm. Extraction cycles have four steps: 1) loading stream 24 to the extractor (1.6 kg of aqueous sodium iodide solution, 5% by mass), 2) mixing stream 21 (the product of E-103) with stream 22 (10 kg of dichloromethane) in the evaporation flask and loading the resulting solution (stream 23) to the extractor, 3) stirring the two phase solution for 20 minutes and 4) waiting 40 minutes for the phases to settle.

The two phases are mixed using a 15 cm high density polyethylene flat blade turbine impeller at 24 rpm, in accordance with heuristics described by Peters et al. (2003) for mixing immiscible liquids (1 kW of impeller power per  $\text{m}^3$  operating volume and a tip speed of at least 10 cm/s). The impeller power requirement is 11.0 W for a total energy input of 13.3 kJ over 20 minutes of mixing. Effects of potential reactions between EDA and imine intermediates in the water layer are ignored due to the low residence time (~1 hour) in the extractor. Even if all the EDA were to react after stream 26 was removed, it would still only raise the temperature of the stream by around 2 K.

All of the ionic compounds ( $\text{NH}_4\text{BF}_4$  and unreacted intermediates from the EDA reaction in R-103) are assumed to settle in the aqueous phase or emulsions within the DCM phase. Water can easily incorporate all the salts in the extraction whereas a limiting solubility for sodium

iodide in DCM is around 0.627 mmol/L (Namor et al., 1989). DCM/Water mass partition coefficients for the extraction were estimated in Aspen Plus 11 using the Decanter block. For (-) ethanoate, (-) ethanamide, and (-) lofexidine, these coefficients ranged between 0.246 and 0.25 (ratio of mass solute per mass of solvent). The corresponding coefficient for EDA was very low (0.002), meaning less than 200 mg of EDA would remain in the DCM phase. After extraction, the DCM layer (stream 26) was also estimated to contain around 0.117 kg (-) lofexidine and 0.018 kg of (-) ethanoate. In contrast, the aqueous layer (stream 25) was estimated to contain around 0.013 kg EDA, 0.073 kg (-) lofexidine, 0.011 kg (-) ethanoate, 0.076 kg  $\text{NH}_4\text{BF}_4$  salt, and 0.043 kg of unreacted ionic imine intermediates. To remove water emulsions from the DCM layer after settling, 0.05 kg of magnesium sulfate is added to stream 26 in storage.

It is likely that this description does not follow optimal mixing and settling times for this extraction; an additional experiment would be necessary to determine more advantageous operational times. One hour was used as a placeholder operational duration with  $\frac{2}{3}$  of time dedicated to settling in accordance with McCabe et al. (1993). Moreover, due to the limitations of Aspen Plus 11 surrounding electrolyte mixtures, mass partition coefficients used to characterize distributions of neutral compounds between the two phases were estimated while assuming pure water for the aqueous phase. Additional experiments would be necessary to determine an accurate partition coefficient respect to DCM and salt water; the patent by Crooks and Vartak (2012) suggests the true partition coefficient is much higher than the one used here (as they employed half as much DCM relative to saltwater). This experimental time could also be used to measure partition coefficients for other organic solvents relative to salt water in attempts to lower the volume of the organic phase for improved mixing.

### *I. Filtration of Magnesium Sulfate F-102*

A filtration step immediately following the extractor (X-101) is required to remove the drying agent (magnesium sulfate) from the solid product, as attempting to remove it after evaporation may prove exceedingly difficult. The extractor DCM product is passed through the same disposable membrane microfilter used to filter DIAD and triphenylphosphine. Again, this filtration was modeled as a basic separator (as opposed to a filter) in Aspen Plus due to

restrictions around modeling solids without existing solubility data. The inlet stream to the filter contains 10.02 kg of DCM solvent, 0.02 kg of unreacted (-) ethanoate, 0.117 kg of (-) lofexidine, and 0.05 kg of magnesium sulfate, designated Stream 26 in *Figure 2*. Once again assuming entrained liquids comprise 50% of the filter cake mass, the filter cake will contain 0.05 kg of entrained DCM. Assuming this entrained liquid also has the same composition as the filtrate, about one gram of (-) lofexidine is also captured. This filter cake (Stream 27) containing 0.05 kg DCM, 0.05 kg MgSO<sub>4</sub>, and 0.001 kg of (-) lofexidine is disposed of as solid waste. No DCM is used to wash this filter cake as the danger of adding extraction impurities back to the filtrate outweighs the benefit of recovering marginal entrainment losses. The filtrate product (Stream 28) contains roughly 9.97 kg DCM, 0.018 kg (-) ethanoate, and 0.116 kg of (-) lofexidine, the desired product.

#### *J. DCM Evaporator E-104*

The final evaporation stage of the production of lofexidine HCl involves removing the DCM solvent from the extractor output, leaving behind pure (-) lofexidine and other trace compounds present in the liquid residue (mostly (-) ethanoate). This evaporation is the last instance of DCM being used as a solvent in this process. Using the alcohol vapor removal rate, the evaporation of 9.97 kg of DCM is estimated to take approximately 90 minutes. However, practically evaporating this mixture to dryness under vacuum without incurring significant losses of (-) lofexidine is likely to be difficult as the mass of DCM is over 70 times greater than the mass of non volatiles. While removing as much DCM as possible is important to ensure that dissolved lofexidine is not washed out during the subsequent filtration step (which obtains (-) lofexidine as a solid), this need not be done entirely under vacuum. The next filtration step relies on (-) lofexidine crystallising from hexane that is lowered from 60°C to 25°C. Vacuum evaporation occurs at 25°C and 300 Pa, however DCM will also evaporate above 40°C at ambient pressure. The built in condenser unit of the rotary evaporator's vapor receiving chamber could be activated to stop boiling DCM from entering the receiving flask and mitigate potential backflow issues.

In a realistic scenario for this evaporation, a time frame might be specified where vacuum evaporation at 25°C would be switched to ambient evaporation at 60°C to minimize (-) lofexidine losses and prepare for the eventual warming of 2.06 kg hexane in the flask. As most of the liquid product is (-) lofexidine, it may be easier to visually monitor the evaporation progress than in E-102 or E-103. When assuming a full separation, the product (Stream 30) contains 0.116 kg (-) lofexidine and 0.018 kg (-) ethanoate. The 9.97 kg of DCM (Stream 29) is collected in the receiving flask and disposed of accordingly.

*K. Filtration to remove (-) ethanoate using Hexane F-103*

The product stream from the DCM evaporator consisting of 0.116 kg (-) lofexidine and 0.018 kg (-) ethanoate is mixed with 2.06 kg of heated hexane to allow for recrystallization of (-) lofexidine into pure white needles. Crystals of (-) lofexidine formed while lowering the temperature of this hexane mixture from near boiling to room temperature should be chemically and optically pure; this suggestion is supported by NMR spectra and optical rotation values presented in the patent by Crook and Vartak (2012). To ensure crystallization, the hexane is warmed to 60°C (near the boiling point) using the evaporator's heating element. This mixture is then slowly cooled to room temperature and sent to the filter where 0.116 kg of pure (-) lofexidine (Stream 34) is filtered out. 100% crystallization of (-) lofexidine was assumed in the absence of a more accurate value from the patent; additional experimentation is necessary to quantify the loss from dissolved (-) lofexidine in the filtrate.

The filter cake is washed with 0.51 kg hexane to displace potential (-) ethanoate dissolved in entrained hexane. Assuming a 50% filter cake mass of entrained liquid, the filter cake will also contain 0.116 kg of entrained hexane. The filter cake is air dried in an oven for approximately 30 minutes to prevent hexane contamination in the following mixer. This drying must take place in a chamber that is routed to the vapor waste processing lines to minimize leaking of hexane vapors. The liquid filtrate (Stream 33) contains 2.45 kg hexane and 0.018 kg of (-) ethanoate. This stream is disposed of, as discussed later in the waste management section.



A stainless steel vertical pressure leaf filter is utilized for this microfiltration batch filtration. Pressure leaf filters are widely used in the pharmaceutical industry for collection of the solids in solid-liquid filtration. Vertical leaf filters are preferred over horizontal leaf filters when working with flammable material (such as hot hexane), and they also allow for the more thorough cake washing when compared to horizontal leaf filters (Boegger Industrial, 2017). Vertical pressure leaf filters also provide high clarity, which is required for any pharmaceutical. The vertical pressure leaf filter in this process has a filter area of 1.95 m<sup>2</sup> with a cake volume of 0.07 m<sup>3</sup>, leaving room for additional hexane washing if necessary. This filtration will take place at room temperature and a pressure of 3 bar. The operating volume is 4.03 liters per cycle with an operating time of 1 hour per cycle.

#### *L. HCl Mixer M-101*

Pharmaceutical drugs are often made into their salt to enhance how the drug dissolves, boost its absorption into the bloodstream, and increase its effectiveness overall (Anderson, 2019). (-) Lofexidine is made into its hydrochloride salt form before it becomes available to patients. Hydrochloride is the most common drug salt.

Following the filtration, the 0.116 kg of lofexidine is mixed with 0.82 kg of DEG ether and 0.18 kg of ethanol. This ratio of ether to alcohol was adapted from the patent presented by Crook and Vartak in 2012. The pure (-) lofexidine is stirred in this ether and ethanol mixture until completely dissolved. After complete dissolution of the (-) lofexidine, 0.06 kg (0.052 L) of 10M HCl is added dropwise. The gradual addition of the concentrated aqueous solution allows for the precipitation of a microcrystalline hydrochloride salt of (-) lofexidine. Stirring the mixture to completion is assumed to take one hour. This assumption was scaled up from the recommended 10 minutes of stirring for the lab-scale amount of material found in the patent presented by Crooks and Vartak (2012). The outlet stream of this mixer (Stream 38) consists of 0.133 kg of lofexidine HCl, 0.82 kg of ether, 0.18 kg of ethanol and 0.04 kg of water per cycle, along with some trace amounts (<0.002 kg) of HCl.

The HCl mixing in this process is carried out in a 5L borosilicate glass mixer at ambient conditions. Borosilicate glass is used due to its chemical and thermal resistance. With the combination of (-) lofexidine, ether, ethanol and 10M HCl, the operating volume is 2.96 liters per cycle. The mixer vessel has a 17 cm diameter and 22 cm height. Using an impeller diameter of 8 cm and impeller speed of 60 rpm, the expected power requirement is 1.33 W (see Appendix for Calculation).

#### *M. Filtration for desired product F-104*

Once the HCl mixing is complete, the mixer output is diluted with 1.02 kg of DEG ether to precipitate the desired salt (lofexidine HCl). The same vertical vacuum leaf filter, with the same operating conditions, is used as described in *Section IV-5.K*, after the equipment is fully cleaned. In order to fully remove potential contaminants from the final product, the filter cake is washed with 1.54 kg of DEG ether; the two additions of DEG ether totaling 2.56 kg are designated Stream 39. Maintaining the prior assumption of entrained liquids occupying 50% of filter cake masses, the filter cake (Stream 42) consists of 0.133 kg of lofexidine HCl and 0.133 kg of entrained DEG ether. The filtrate (Stream 41) consists of 3.25 kg DEG ether, 0.18 kg ethanol, 0.04 kg water, and any trace HCl (~.001 kg). After filtration, the filtrate is disposed of as waste while the filter cake is dried with air in an oven to ensure that the final product is free of impurities.

Although the details of this operation are not included in this capstone, if the process was certified pharmaceutical grade, the 0.133 kg of lofexidine HCl per cycle would be sent to a ‘pill machine’ to form oral tablets with 0.18 mg of lofexidine HCl in each tablet. Active ingredient losses from sub-milligram dose packing are assumed to be approximately 15%. 20 cycles will produce 2.66 kg of delivered lofexidine HCl, which can be used to make 2.26 kg of pharmaceutically active lofexidine HCl; this fulfills the design quota of 2.25 kg stated in *Section IV-2*.

### *N. Storage and Flow Design*

The ammonia reactor effluent is stored in a 5 L chemical storage tank in order to cool it to 25°C. As its volume is low, it is designed as a tank on legs (Peters et al., 2002). It is constructed with A316 stainless steel, due to a lack of corrosive materials (Turton, 2018).

Due to the small scale and nature of the batch process, there is not a strong need for powerful pumps. Instead, to minimize costs, only weak peristaltic pumps will be required for the product stream (Stream 12) connected to the Ammonia Reactor (R-102) and the feed streams (Streams 4, 26, 32, 40) connected to the filters (F-101, F-102, F-103, F-104). For stream 12,  $2.23 \times 10^{-4}$  W are required to pump the effluent into the storage container (see Appendix for calculation). For stream 4,  $1.12 \times 10^{-4}$  W are needed to pump the feed stream of the first filter (see Appendix for calculation). For stream 26, 0.108 W are needed to pump the feed stream of the second filter (see Appendix for calculation). For streams 32 and 40, 0.281 W are required each to pump the feed streams of the second and third filters (see Appendix for calculation).

### *O. Coolant*

Coolant is required for two steps in the process: lowering the temperature of the methyl lactate reactor temperature to 0°C at the start of the reaction and cooling the ammonia reactor effluent to 0°C to promote crystallization of the (-) ethanamide reaction product. The coolant chosen is ethylene glycol, stored in a 10 L A316 stainless steel tank at -20°C using a single-stage refrigeration system with ammonia as the refrigerant. Each of the cooling steps will be completed with a cooling jacket surrounding the existing reactors. Using the specific heat estimated for the methyl lactate reactor feed mixture by Aspen Plus 11 (1442 J/kg K) and accounting for ambient air conduction, about 57.5 kJ of heat must be removed from the vessel during the cooling period. Assuming a glycol feed temperature of -20°C to the cooling jacket, with a specific heat of 2256 J/kg K (Welty, 2015), a minimum 1.7 kg of glycol must travel through the jacket. Using a basic jacket form of a 2.5 cm stainless steel shell with exterior insulation and 2 cm diameter exits on the side, a glycol flow rate of 0.79 L/min (see Appendix for calculation) will cool the feed mixture to 0°C in two minutes.

Once the ammonia reactor effluent has cooled to room temperature in the ancillary tank, it will be transferred back into the ammonia reactor, where it is cooled using the previously mentioned 5 cm insulated cooling jacket. Once again using the specific heat estimated for the ammonia reactor product mixture by Aspen Plus 11 (3070 J/kg K) and accounting for ambient air conduction, about 213 kJ of heat must be removed from the vessel during the cooling period. 5.89 kg of glycol is required to cool the mixture to 0°C, which will be accomplished in 5 minutes at a coolant flow rate of 1.2 L/min (see Appendix for calculation).

## 6. Plant Schedule

As discussed previously, the design quota calls for 20 cycles of the lofexidine production process. It is expected that each production cycle takes 95 hours, as outlined in *Table 1*. Note that experiencing losses higher than predicted throughout the report will necessitate more production cycles, but the individual cycle time will remain mostly unchanged.

*Table 1: Production cycle time requirements*

<b>Unit Cycle Time Scale</b>	
<i>Unit Operations</i>	
Methyl Lactate Reactor	4 hr
Ammonia Reactor	4 hr
TMO-TFB Reactor	50 hr
HCl Mixer	1 hr
10 L Filter	1 hr per pass (4 pass)
10 L Evaporator	Avg. 1 hr per pass (4 pass)
Extractor	1 hr
Total Unit Operation Time	68 hr
<i>Additional time for flow and cleaning</i>	

Storage and Flow	Avg. 1 hr in transitions (13)
Cleaning	1 hr for each step (14)
<b>Total Cycle Time</b>	<b>95 hr</b>

With a cycle time of 95 hours, the 20 cycles needed to produce the desired output will require 1900 man hours or roughly 79 days. Depending on how many cycle steps are run concurrently and how much maintenance is needed on the process vessels during operation, the entire yearly production should be completed in two to three months. Labor estimates will assume workers are paid three months for lofexidine production. Lofexidine production equipment and employees will be either outsourced to a different company or used to produce another small scale product for the remaining 9 months. Further discussion and decision making is recommended to determine the function of the facility space when lofexidine is not produced.

## 7. Environmental Concern and Waste Management

Along with any manufacturing production, the environmental concerns and waste management of the production of lofexidine HCl must be considered and dealt with properly. The table below, Table 2, summarizes the waste outputs for each unit operation of the process that produces waste and potential environmental concerns from these wastes.

*Table 2: Waste and environmental impact throughout the production process*

<b>Unit Operation</b>	<b>Waste (Per Cycle)</b>	<b>Environmental Impact</b>
F - 101	<i>Contents of the Filter Cake</i> <ul style="list-style-type: none"> <li>- 0.27 kg triphenylphosphine</li> <li>- 0.21 kg DIAD</li> <li>- 0.49 kg of entrained liquids (mostly Hexane)</li> </ul>	Triphenylphosphine and DIAD possess acute and chronic environmental toxicity in aquatic ecosystems.
E - 101	<i>Cooled Vapor Stream</i> <ul style="list-style-type: none"> <li>- 1.18 kg hexane</li> <li>- 0.35 kg ether</li> </ul>	Hexane was classified as a hazardous air pollutant in the U.S. Clean Air Act and it is regulated by the EPA. Hexane is a

	<ul style="list-style-type: none"> <li>- 0.018 kg water</li> </ul>	highly flammable organic compound. Hexane is also a threat to aquatic ecosystems if dumped in bodies of water. Ether is highly volatile, highly flammable and explosive in some cases.
R - 102	<i>Vapor Stream</i> <ul style="list-style-type: none"> <li>- 0.03 kg ethanol</li> <li>- 0.001 kg methanol</li> <li>- 0.0055 kg ammonia</li> </ul>	Pure ethanol is nontoxic and biodegradable. Ethanol is highly flammable. The negligible amounts of methanol and ammonia are not considered an environmental concern but will be dealt with as hazardous waste with the rest of this stream.
E - 102	<i>Cooled Vapor Stream</i> <ul style="list-style-type: none"> <li>- 2.40 kg ethanol</li> <li>- 0.027 kg methanol</li> <li>- 0.01 kg ammonia</li> </ul>	Environmental concerns for all components are previously discussed.
E - 103	<i>Cooled Vapor Stream</i> <ul style="list-style-type: none"> <li>- 6.01 kg dichloromethane</li> <li>- 1.23 kg ethanol</li> <li>- 0.04 kg dimethyl ether</li> <li>- 0.02 kg methanol</li> </ul>	DCM quickly evaporates to a gas and then degrades by reacting with air. Majority of DCM decomposes in the lower level of the atmosphere and does not reach the higher level of the ozone. The U.S. Clean Air Act does not regulate DCM as an ozone depleter. Environmental concerns with ethanol are previously discussed.
X - 101	<i>Aqueous Layer</i> <ul style="list-style-type: none"> <li>- 1.60 kg saltwater</li> <li>- 0.08 kg <math>\text{NH}_4\text{BF}_4</math></li> <li>- 0.07 kg (-) lofexidine</li> <li>- 0.04 kg imine intermediate</li> <li>- 0.01 kg EDA</li> <li>- 0.01 kg (-) ethanoate</li> </ul>	Salt water causes dehydration, foliage damage, and eventual osmotic stress damaging plant root growth. Saltwater intrusion leads to groundwater quality degradation. Added impurities introduce additional toxicity to wildlife.
E - 104	<i>Cooled Vapor Stream</i> <ul style="list-style-type: none"> <li>- 10.2 kg DCM</li> </ul>	Environmental concerns with DCM are previously discussed.
F - 102	<i>Liquid Stream</i> <ul style="list-style-type: none"> <li>- 2.45 kg hexane</li> <li>- 0.02 kg (-) ethanoate</li> </ul>	Environmental concerns with hexane are previously discussed. No additional concerns are predicted for (-) ethanoate.

F - 103	<i>Liquid Stream</i> <ul style="list-style-type: none"> <li>- 3.26 kg ether</li> <li>- 0.18 kg ethanol</li> <li>- 0.04 kg water</li> <li>- Trace HCl</li> </ul>	Environmental concerns for ether and ethanol are previously discussed.
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Due to the small scale of this production, none of the waste in the process is kept in-house and purified because the cost of purification is not worth the amount of material that could be reused. All of the waste management is outsourced to chemical waste management. Due to the environmental and human health concerns of the liquid waste in this process, all liquid waste will be labeled as hazardous. The hazardous liquid waste (condensed evaporator vapors, aqueous layer in the extractor and filtrates in F-102 and F-103) will be packed in strong containers with threaded lids and labeled with the contents. These containers will then be picked up by chemical waste management. The filtration, F-101, uses disposable microfiltration which leaves a filter cake on top of a disposable membrane that is hazardous due to the hexane. The disposal of this hazardous filter cake and one time-use membrane will be outsourced to a chemical waste management company as well.

## 8. Health and Safety

While the main purpose of the plant is to produce the desired output of lofexidine, it also has to follow a strict set of rules and regulations within the United States. The Occupational Safety and Health Act (OSH), passed in 1970, is a US labor law set by Congress to ensure worker and workplace safety in both the private sectors and the federal government in the United States (U.S.C et seq, 1970). The aim of OSH is to ensure employers provide workers with a workplace that is free from recognized hazards to both safety and health. As such, the objective of this section is to ensure the safety, environmental conditions and health of both personnel working at the plant and the people surrounding the production plant, such as the people residing near the plant. This is meant to minimize (if not eliminate) any dangers present, reduce the likelihood of accidents, and reduce the impact of accidents that do occur.

## A. Workplace Hazard Identification

Workplace hazards can be broadly classified under two main categories: Physical and Chemical. The following sections will further elaborate the two main types of hazards, providing examples of the hazards that can be commonly found within a typical industrial pharmaceutical production plant.

## B. Physical Hazard Evaluation

Physical hazards are factors within the environment, such as heat or noise, that can harm the body without necessarily touching it or having any form of contact. It is important to ensure physical hazards are kept in check for the consequences may often result in unneeded physical injuries, which can be dire at times. It is of the utmost importance that the workplace safety management team has a strict workplace practice policy to minimize the risk of such dangers from occurring. Table 3 below consists of a non-exhaustive list of the possible dangers that can arise, its related consequences and precautions to take to keep such risk at the minimum levels.

*Table 3: List of Physical Hazards (CSB, 2002)*

<b>Hazards</b>	<b>Description</b>	<b>Consequences</b>	<b>Precautions</b>
Fire Hazard	Outbreak of fire due to ignition of combustible chemicals or substances	Outbreak of fire can cause irreversible damage to equipment in the plant. May result in burns on personnel working in the plant at the time of the fire.	Ensure proper labelling of combustible chemicals with the fire hazard symbol and enforce strict practice of not having these chemicals near heat or ignition sources.



Reactive Hazard	Uncontrolled chemical reactions in industrial processes, mainly thermal runaways and chemical decompositions.	Such unwanted reactions can lead to outbreak of fires, explosion, and toxic gas releases.	Substitute highly volatile substances with alternatives that are less reactive. Changing the process parameters and condition can improve control of the hazards related to these chemicals
Explosion Hazard	Sudden and rapid increase in volume and release of energy in an extreme manner, usually accompanied with the generation of high temperatures and release of gases due to sudden change in pressure, temperature and phase.	May result in irreversible damage to equipment and properties, as well as injuries to personnel. In extreme cases, it might lead to death of personnel.	Ensure proper storage of chemicals. Make sure ventilation is working and adequate and monitor the air when using explosive materials in confined spaces.

There are many kinds of physical hazards present in an industrial production plant; it is important to identify and acknowledge as many physical hazards to the best of our abilities in order to ensure the safety of the workplace.

### **C. Chemical Hazards and Toxic Substance Evaluation**

Chemical hazards and toxic substances pose a wide range of health hazards, such as irritations and carcinogenicity, in addition to the potential physical hazards that can occur (US DOL, 1970). Each chemical has its own unique properties, flammability, reactivity and health risk. The dangers these chemicals and their reaction have on the plant and personnel are dependent on the types of chemicals that are involved in the reaction. The National Fire Protection Association (NFPA) has, in section 704 of the National Fire Code, specified a system for identifying the hazards associated with materials. The hazards identified for each chemical

follows a NFPA rating on each specific hazard: Health, Flammability and Reactivity. Table 4 below summarizes the NFPA ratings:

*Table 4: NFPA Ratings*

<b>NFPA Ratings</b>	<b>Health</b>	<b>Flammability</b>	<b>Reactivity</b>
NFPA 0	Normal Material	Will not burn upon ignition	Stable
NFPA 1	Slightly Hazardous	Will only burn upon ignition when temperature is above 200°F	Normally stable. May become unstable upon heating at high temperature
NFPA 2	Hazardous	Will burn upon ignition at temperature below 200°F	Exhibits violent chemical reactions
NFPA 3	Extremely Dangerous	Will burn upon ignition at temperature below 100°F	When exposed to shock and heat, chemical may undergo explosive decomposition
NFPA 4	Deadly	Will burn upon ignition at temperature below 73°F	Chemical may undergo explosive decomposition spontaneously

With the NFPA ratings in mind, Table 5 is a compilation of the respective NFPA ratings for all the raw materials used in the production of Lofexidine.

*Table 5: NFPA ratings of raw materials used in the production of Lofexidine*

<b>Chemical</b>	<b>Health</b>	<b>Flammability</b>	<b>Reactivity</b>
Dichloromethane	NFPA 1	NFPA 2	NFPA 0
Ethanol	NFPA 2	NFPA 3	NFPA 0

Diethylene glycol ethyl ether	NFPA 2	NFPA 2	NFPA 0
Hexane	NFPA 2	NFPA 3	NFPA 0
Anhydrous Ammonia	NFPA 3	NFPA 1	NFPA 0
2,6-Dichlorophenol	NFPA 2	NFPA 1	NFPA 0
(-) Methyl Lactate	NFPA 2	NFPA 1	NFPA 0
DIAD	NFPA 1	NFPA 1	NFPA 0
Triphenylphosphine	NFPA 2	NFPA 1	NFPA 0
TMO-TFB	NFPA 2	NFPA 2	NFPA 1
Ethylene Diamine	NFPA 2	NFPA 3	NFPA 0
Hydrochloric Acid	NFPA 3	NFPA 0	NFPA 1
Potassium Carbonate	NFPA 2	NFPA 0	NFPA 0

Table 6 below shows the NFPA ratings for the final product.

*Table 6: NFPA ratings for the final product of the production of Lofexidine*

<b>Chemical</b>	<b>Health</b>	<b>Flammability</b>	<b>Reactivity</b>
Lofexidine HCl	NFPA 3	NFPA 1	NFPA 0

#### **D. Occupational Safety and Control Measures**

In order to minimize the risk of exposure to hazardous materials, we opt to follow the hierarchy of controls as shown below.

Table 7: Hierarchy of Controls

Effectiveness (1 – Most Effective, 5 – Least Effective)	Methods
1	Elimination
2	Substitution
3	Engineering Control
4	Administrative Control
5	Personal Protective Equipment (PPE)

Given the specific nature of the production of Lofexidine, it is impossible to eliminate materials from the production process, neither is it possible to substitute necessary materials for other less hazardous materials for it may result in a completely different reaction. The only way to effectively lower the risk of exposure is to focus on engineering controls, administrative controls and the use of PPE.

### **E. Engineering Control**

Engineering controls are measures put in place to eliminate or reduce exposure to a chemical or physical hazard through the use or substitution of engineered machinery or equipment. Through the implementation of engineering control measures, we can effectively lower the exposure and risk of the hazards of all personnel in the industrial production plant. In our production plant for Lofexidine, we will be utilizing numerous controllers so that certain conditions such as temperature and pressure can be properly controlled. These controllers are expected to handle simple or slight deviations from the set points, as well as handle basic disturbances from the surrounding environment or other disruptive sources. The intended controllers are automated and simple enough for an operator in the plant to understand and properly operate it if necessary.

Below is a list of potential controllers that we will be utilizing within the production plant.

Table 8: Parameters and Controllers

Parameters	Type of Controller	Purpose
Temperature	Temperature Controller	To monitor any deviations in the temperature of the reactors so that it can be maintained within tolerable limits so as to ensure efficient production of lofexidine
Pressure	Pressure Controller	To monitor any deviations in the set pressure within the equipment so as to ensure there is no build-up of excessive pressure
	Relief Valve	To release vapor into the surroundings and relieve pressure build-up
All parameters	Alarm system	When the deviation is far beyond set point, the alarm system serves to warn operators on-site to a potential emergency and to allow operators to have ample time to remedy the situation.
	Sensor	To detect any leaks in any of the equipment, especially the reactors

## F. Administrative Control

Administrative controls are work practices such as the Standard Operating Procedure (SOP) set, written safety policies, rules, supervision, schedule and training to reduce the likelihood of prolonged exposure to hazards chemicals or situations, as well as reduce the impact of such exposure. To implement administrative control in the production plant for Lofexidine, we will be utilizing the following practices to ensure operators are well equipped with the necessary skills and knowledge to ensure workplace safety.

Table 9: Administrative controls implemented in the production of Lofexidine

Practices	Rationale
Proper Training for all operators	All operators that are part of the production line are expected to understand how to operate all machinery and equipment present in the production plant. They are also expected to know the proper practices, in the event of any unfortunate accidents, such as fire evacuation. As such, proper briefing must be conducted before production begins and mock drills, such as fire evacuation drills should be practiced at regular periods.
Re-training	Operators are required to undergo re-training to refresh on their skills and knowledge in operating the machineries, and to gain new knowledge on how to operate, especially when there are any upgrades done to the equipment.
Rotation of tasks	We will cycle operators between tasks so that they will not have repetitive motion injuries, due to complacency.
First-aid staff	Some of the operators will be first-aid certified and cycled between schedules in order to provide immediate on-site response to any injured personnel when needed.
Proper housekeeping	Reducing clutter around the workspace, properly labelling chemicals and keeping hazards materials always from ignition sources in proper storage can greatly reduce the risk of any accidents from happening.

### G. Personal Protective Equipment (PPE)

Apart from engineering controls and administrative control, we also expect operators to wear the necessary PPE when operating any machines or equipment. As the most basic form of protection, PPE is the first line of defense to any accidents in case it happens. As such, we will have gloves, lab coats, scrubbers and other basic PPE on-site in excess for the operators to use when working. The table below shows the different types of PPE needed on-site.

Table 10: List of PPEs that can be found in the plant

<b>PPE</b>	<b>Function</b>
Gloves	Protect hands from coming into contact with chemicals when handling chemicals, especially those that are corrosive in nature
Helmet	Protects the operators head from any potential falling objects
Lab Coat	Protects the body from splashes of chemicals, if any.
Respirator	Prevent excessive inhalation of toxic fumes
Safety Goggles	Protect eyes from chemicals spillage or splashes
Earplugs	Protect ears from loud noises from the reactors
Face Shield	Protect the face from chemicals

## **H. Dow Fire and Explosion Index (FEI) Analysis**

In this section, we will be doing a HAZOP analysis on the major equipment in the production plant. The analysis will be done based on the Dow Fire and Explosion Index (FEI). Dow FEI is a formal, systematic approach using a rating form that can provide relative ranking of the different hazard categories and provide for the estimate in monetary loss. It helps to predict the damage that might possibly happen but does not serve as the measurement to the safety of the plant. The Dow FEI is used to gauge the potential risk of each equipment in the plant.

According to the Dow FEI, a base factor of 1 is given to the General Process Hazards, F1, and the Special Process Hazards, F2. There are guidelines in the Fire & Explosion Index forms which use penalty factors that add up with the base factor when penalties are found during evaluation of the equipment. The Material Factor (MF) is then determined according to the

materials used by the equipment. MF is a value assigned by the National Fire Protection Association (NFPA), and due to the numerous materials that are involved in each equipment, we only take into consideration the material with the highest MF value. The FEI is then obtained by the following equation:

$$FEI = F1 \times F2 \times MF$$

From the FEI value, we can determine the Degree of Hazard of that equipment, based on the pre-set tiers found in the Dow Fire & Protection Index Hazard Classification Guide.

The table below shows the FEI for the reactors.

*Table 11: FEI value for reactors*

<b>Unit</b>	Methyl Lactate Reactor	Ammonia Reactor	TMO-TFB Reactor
F1	2.45	1.65	1.65
F2	1.25	3.02	1.6
MF	16	16	16
FEI	49	79.7	42.2
<b>Degree of Hazard</b>	Light	Moderate	Light

Given that the amount of raw materials needed is small and production per operating year is in a low quantity, the above-mentioned reactors posed a lower hazard level compared to a similar production line at a higher quantity of product.

### **I. Hazard and Operability (HAZOP) Analysis**

Next, a HAZOP study will be conducted for the above-mentioned reactors. This allows us to identify various potential hazards surrounding the reactors, consider the various causes, its consequences, and subsequently suggest recommendations to mitigate or resolve these consequences. By coming up with implementable recommendations, we can effectively reduce



the final risk ratings of the reactors, and hence reduce the overall risk of the plant. By conducting the HAZOP analysis, we are assuming that there are currently no forms of safety procedure and methods implemented, and all recommendations here are done before the construction of the plant.

The HAZOP Analysis will focus on 5 main areas listed in the Table below.

*Table 12: HAZOP Analysis of Impacts*

<b>Impact</b>	<b>Description</b>
Safety	Focuses on the physical health of personnel in the plant and the surrounding areas of the plant. This is inclusive of health impact by prolonged exposure to chemicals above threshold level and injuries
Process	Focuses on the quality of the process, both upstream and downstream. It is inclusive of the product quality and deviations from calculated timeframe
Equipment	Focuses on the equipment itself, whether there is damage done to the equipment in the plant, the frequency of required maintenance or replacement, which can potentially incur more cost.
Environment	Focuses on the environmental impact such as air and water pollution from the processes that are occurring in the plant.
Economic	Focuses on the profits and loss of the plant. It deals with the additional cost needed to ensure that the equipment is running at the lowest risk possible.

#### **i. Qualitative Risk Assessment (Crowl et al, 2011)**

The qualitative risk assessment involves the use of a Risk Rating Assessment Matrix to rank the various incidents. Both the severity (S) and likelihood (L) of a consequence happening is measured on a scale of 1 to 5 and the hazard calculated using the equation below. The following tables show the guidance for severity and likelihood, as well as the risk matrix.

Table 13: Guidance for severity rating

Level	Severity	Description
5	Catastrophic	Fatality, fatal diseases or multiple major injuries
4	Major	Serious injuries or life-threatening occupational disease (includes amputation, major fractures, multiple injuries, occupational cancer, acute poisoning)
3	Moderate	Injury requiring medical treatment or ill health leading to disability (includes lacerations, burns, sprains, minor fractures, dermatitis, deafness, work-related upper limb disorders)
2	Minor	Injury or ill-health requiring first-aid only (includes minor cuts and bruises, irritation, ill-health with temporary discomfort)
1	Negligible	Not likely to cause injury or ill-health

Table 14: Guidance for likelihood rating

Level	Likelihood	Description
1	Rare	Not expected to occur but still possible
2	Remote	Not likely to occur under normal circumstances
3	Occasional	Possible or known to occur
4	Frequent	Common occurrences
5	Almost certain	Continual or repeating experience

The Risk Matrix table below in summarizes overall Risk Rating (RR) values as a combination of likelihood and severity levels.

Table 15: Recommended 5x5 Risk Matrix with numerical and descriptive ratings

<b>Likelihood</b> → <b>Severity</b> ↓	Rare (1)	Remote (2)	Occasional (3)	Frequent (4)	Almost Certain (5)
Catastrophic (5)	5 (medium)	10 (medium)	15 (high)	20 (high)	25 (high)
Major (4)	4 (medium)	8 (medium)	12 (medium)	16 (high)	20 (high)
Moderate (3)	3 (low)	6 (medium)	9 (medium)	12 (medium)	15 (high)
Minor (2)	2 (low)	4 (medium)	6 (medium)	8 (medium)	10 (medium)
Negligible (1)	1 (low)	2 (low)	3 (low)	4 (medium)	5 (medium)

Ratings highlighted in green are acceptable RR values, with no additional risk control measurements necessary. Frequent reviews and continual monitoring of hazards are still required to ensure the RR values assigned are accurate and do not increase over time. Ratings highlighted in yellow are tolerable RR values. Evaluation of hazards must be done to ensure that the risk level is reduced to as low as reasonably practicable within a defined time period. The use of interim risk control measures can be implemented while longer term measures are being established, together with continual management attention. Ratings highlighted in red are non-acceptable RR values. These ratings must be reduced to at least the tolerable levels before production can commence. The use of interim risk control measures are not permitted and the risk control measures for this group should focus on engineering control means and above. Allow for risk control measures to be implemented to eliminate hazards and a mandatory

management review is required post-implementation of the risk control measures before work commences.

For the Methyl Lactate Reactor, the most significant deviations that will likely cause accidents to happen were selected. The impact of each deviation was then studied and classified.

*Table 16: HAZOP Parameters for the Methyl Lactate Reactor*

Parameter	Deviation						
	Lower	Higher	No	Less	More	Other than	Reverse
Pressure		✓					
Temperature		✓					
Flow					✓	✓	

The analysis for the Methyl Lactate Reactor is summarized in the HAZOP table below.

*Table 17: HAZOP Table for Methyl Lactate Reactor*

Parameter	Deviation	Causes	Consequences	Impacts	S	L	RR
Pressure	Higher	1) Choking due to blockage within the pipes  2) Sudden increase in temperature of piping	1) Pressure exceeds the maximum pressure that can be handled and pipes are ruptured	Safety Process Equipment Environmental Economic	5	2	10

Temperature	Higher	1) Failure of cooling jacket. 2) Accumulation of heat within the reactor	1) Affects the product quality produced. 2) Higher pressure within the system	Safety Process Economic	3	2	6
Flow	More	1) Input of raw materials more than intended for each cycle	1) Overflowing the reactor is the amount input for the cycle is more than the volume of the reactor. 2) Higher reaction rates which leads to higher temperature and pressure within the reactor.	Process Economic	2	1	2
Flow	Other than	1) Impurities introduced into the input stream	1) Potentially having side reactions which may result in lower product quality and quantity. 2) Produce a whole different product which may be harmful to humans.	Process Economic	5	1	5

After identifying the potential areas of hazard, we came up with some recommendations to reduce the hazard levels for the Methyl Lactate Reactor.

*Table 18: Recommendations for improvement for Methyl Lactate Reactor*

<b>Parameter</b>	<b>Deviation</b>	<b>Recommendation</b>	<b>S</b>	<b>L</b>	<b>RR</b>
Pressure	Higher	1) Install insulations to pipes so it is less susceptible to changes in surrounding temperature. 2) Install a pressure sensor and a pressure control system to monitor the pressure closely. Connect it to an alarm so that operators on site can be notified immediately when it happens 3) Check the pipes for any potential blockage before running the cycle	5	1	5
Temperature	Higher	1) Run the cooling jacket before the start of the cycle to ensure it is working. 2) Install temperature probe connected to a main control system to constantly monitor the temperature of the reactor 3) Temperature sensors, connected to an alarm system, can be utilized to inform operators on site of this deviation.	3	1	3
Flow	More	1) Use flow sensors to cut of flow into the reactor once it reaches a certain height or volume in the reactor	2	1	2
Flow	Other than	1) Use a composition controller to detect and measure impurities that may be present in the feedstock before running the cycle.	5	1	5

For the Ammonia Reactor, the most significant deviations that will likely cause accidents to happen were selected. The impact of each deviation was then studied and classified.

*Table 19: HAZOP Parameters for the Ammonia Reactor*

Parameter	Deviation						
	Lower	Higher	No	Less	More	Other than	Reverse
Pressure		✓					
Temperature		✓					
Flow				✓	✓		

The analysis for the Ammonia Reactor is summarized in the HAZOP table below.

*Table 20: HAZOP Table for Ammonia Reactor*

Parameter	Deviation	Causes	Consequences	Impacts	S	L	RR
Pressure	Higher	1) The globe valve (Class 150) used is not operating at full capacity or is faulty	1) Pressure exceeds the maximum pressure that can be handled and rupture the pipes	Safety Process Equipment Environment Economic	5	2	10
Temperature	Higher	1) Accumulation of heat in reactor	1) Affects the product quality produced. 2) Higher pressure within the system	Safety Process Economic	3	2	6

Flow	Less	1) Blockage to the pipes entering the Ammonia Reactor	1) Affect product quantity, which might result in not obtain desired amount at the end of the process	Process Economic	3	1	3
Flow	More	1) Leftover side materials from the evaporator present that are not evaporated	1) Might result in potential side reactions with ammonia or ethanol, causing potential contamination to the desired product	Safety Process Economic	5	2	10

After identifying the potential areas of hazard, we came up with some recommendations to reduce the hazard levels for the Ammonia Reactor.

*Table 21: Recommendations for improvement for Ammonia Reactor*

<b>Parameter</b>	<b>Deviation</b>	<b>Recommendation</b>	<b>S</b>	<b>L</b>	<b>RR</b>
Pressure	Higher	1) Install insulations to pipes so it is less susceptible to changes in surrounding temperature. 2) Install a pressure sensor and a pressure control system to monitor the pressure closely. Connect it to an alarm so that operators on site can be notified immediately when it happens  3) Check the pipes for any potential blockage before running the cycle 4) Periodic maintenance of the globe valve to ensure proper operation.	5	1	5



Temperature	Higher	1) Install temperature probe connected to a main control system to constantly monitor the temperature of the reactor 2) Temperature sensors, connected to an alarm system, can be utilized to inform operators on site of this deviation.	3	1	3
Flow	Less	1) Check the pipes for any potential blockage before running the cycle	3	1	3
Flow	More	1) Use a composition controller to detect and measure components in the output of the organics evaporator before running the output in the ammonia reactor 2) Use flow sensors to cut of flow into the reactor once it reaches a certain height or volume in the reactor	5	1	5

For the TMO-TFB Reactor, the most significant deviations that will likely cause accidents to happen were selected. The impact of each deviation was then studied and classified.

*Table 22: HAZOP Parameters for the TMO-TFB Reactor*

Parameter	Deviation						
	Lower	Higher	No	Less	More	Other than	Reverse
Pressure							
Temperature		✓					
Flow						✓	

The analysis for the TMO-TFB Reactor is summarized in the HAZOP table below.

Table 23: HAZOP Table for TMO-TFB Reactor

Parameter	Deviation	Causes	Consequences	Impacts	S	L	RR
Temperature	Higher	1) Accumulation of heat in reactor	1) Affects the product quality produced. 2) Higher pressure within the system	Safety Process Economic	3	2	6
Flow	Other than	1) Impurities introduced into the input stream	1) Potentially having side reactions which may result in lower product quality and quantity. 2) Produce a whole different product which may be harmful to humans	Process Economic	5	1	5

After identifying the potential areas of hazard, we came up with some recommendations to reduce the hazard levels for the TMO-TFB Reactor.

Table 24: Recommendations for improvement for TMO-TFB Reactor

Parameter	Deviation	Recommendation	S	L	RR
Temperature	Higher	1) Install temperature probe connected to a main control system to constantly monitor the temperature of the reactor 2) Temperature sensors, connected to an alarm system, can be utilized	3	1	3

		to inform operators on site of this deviation.			
Flow	Other than	1) Use a composition controller to detect and measure impurities that may be present in the feedstock before running the cycle.	5	1	5

## J. Other Safety Measures

After identifying the associated risk with the three reactors in the plant, it is also important to focus on the bigger picture and come up with safety practices within the plant. Enforced compliance of these practices are of utmost importance as it is paramount to the safety of the personnel in and out of the production plant.

### i. Emergency Response Plan

In the unfortunate event of an accident occurring despite all the safety measures put in place, an emergency response plan is needed to ensure personnel know what to do in such an event. A non-exhaustive list of practices is summarized in the table below.

*Table 25: Emergency Response Plan*

<b>Accidents</b>	<b>Emergency Responses</b>
Contact with chemicals	Eyes: Immediately rinse eyes with excess water using an emergency eye wash station, located within the plant, until the person is fine. If irritation or pain persist, immediately seek medical assistance. Skin: Immediately wash of affected areas with excess water, using the emergency shower if needed. If contamination is on clothing, remove the contaminated clothing and wash thoroughly. Dispose of clothing accordingly if needed.

Spillage/Leakage of Chemicals	Switch off any ignition source nearby the area that can potentially cause a spark. Immediately contain the spillage/leakage with a spill kit, dressed in appropriate PPE. If the chemical is volatile, immediately open all windows and ventilation sources to dilute the chemical vapor and minimize inhalation of the chemical. In the unlikely case of a serious spillage, immediately evacuate the area and sound the alarm to notify other personnel in the area. Notify relevant authorities and departments for professional containment of the spillage/leakage.
Fire Outbreak	In the case of minor fires, operators can attempt to extinguish the fire using the available fire extinguishers. In the event of a major fire, sound the fire alarm and evacuate all staff to a safe location. Notify relevant authorities and the fire department to extinguish the fire.
Inhalation of chemicals	Immediately leave the area and move to the open where it is more ventilated
Ingestion of chemicals	Seek medical assistance immediately

Quarterly review of the accident occurrence and the emergency response plan will be conducted to better deal with subsequent accidents in the future.

## ii. Evacuation Plan and Protocols

In the event of a needed evacuation, strict protocols must be followed in order to minimize casualties and to account for all personnel in the plant. The protocols include:

- Ensure stairways and emergency exits are free from blockages and obstruction.

- Ensure emergency exit labels and emergency pathways are well-lit, powered by a separate power source, in the event the main source is cut off.
- An emergency evacuation route plan must be put up at prominent places for all personnel to see.
- Assigned fire and evacuation wardens are expected to help move personnel from danger to safe areas during the emergency. The warden-personnel ratio should not exceed 20.
- Multiple emergency evacuation assembly areas must be set up and areas utilized should pose the least hazard to personnel.
- Emergency evacuation drills are to be conducted biannually to ensure every personnel is well-aware of the movement plan to safety.

### **iii. Fire Response System**

In the plant, the fire response system includes a dedicated fire-fighting team and sprinkler systems.

The fire-fighting team is expected to have the basic knowledge of the use of a fire extinguisher and means to contain a small to moderate fire outbreak, until professional help arrives. In the event of a big fire, the fire-fighting team must know the relevant authorities to contact to minimize any lag time in responding to the fire.

A sprinkler system will also be set up throughout the plant. The purpose of the sprinkler system is to help the fire-fighting team contain the fire and minimize the spreading of the flames. In addition, in the event of major spillage of volatile chemicals or engulfing fumes from the fire, sprinklers can also help to knock down gas clouds and flush away hazardous spills.

## **V. ECONOMIC ANALYSIS**

The operational costs for the lofexidine production facility are estimated using correlations in Turton (2018) Table 8.2. There are five cost variables that the correlations use: Fixed Capital Investment (equipment costs), utilities, labor, waste treatment, and raw materials.

These fundamental variables each have their own individual estimation correlations within Turton (2018) - estimation of these five expense subsets is detailed below.

### 1. Fixed Capital Investment

Turton (2018) does not provide accurate correlations for most of the operational equipment due to the small process scale. A calculation for the leaf filter is provided in Appendix: Production Calculations; all other cost estimates are derived from obtained listings selling similar equipment. When agitated vessel listings did not include adequate corrosion-resistant impellers within the purchase package; custom polymer based impellers were assumed to incur a cost of \$1000 while steel paddle impellers incurred a cost of \$50. Note: no listing for a two liter jacketed/agitated stainless steel vessel could be found, so the cost of an equivalent glass vessel (without additional accessories) was used for the estimate. Six 10 L glass storage flasks were assumed necessary for transport of material between blocks (loading and/or unloading), along with a jacketed storage tank for cooling R-102 effluents. These flask prices were obtained from the same listing used to estimate the price of the evaporator.

*Table 26: Capital Equipment Cost*

<b>Equipment</b>	<b>Estimated Cost (USD)</b>	<b>Listing</b>
R-101	2300	Toolots
R-102	3000	Wehai Borui
R-103	6250	Columbia International
X-101	7250	R-103 with custom impeller
M-101	5275	Columbia International
Leaf Filter (10 L accomodation)	25020	n/a
Evaporator (10 L accomodation)	11300	Across International
Storage Flasks (6)	1380	Across International
Jacketed Storage Tank	1000	USA Lab

The total capital investment for essential equipment is 62775 USD.

Peters et al. (2003) provided estimates for installation-based capital costs based on the “delivered” equipment cost. Delivery fees are estimated at 10% of the purchase estimate; delivered equipment cost for this facility would be 69050 USD. Assuming that the lofexidine facility would be an expansion to an existing site, direct installation costs covered by the Peters text include equipment setup (40%), instrumentation (26%), yard work/construction (15%), electrical wiring (23%), piping (31%), land (6%) and housing (29%). The sum of these direct capital costs total 170% of the delivered equipment cost, leading to a total capital investment of 186440 USD. Indirect costs not covered in the Turton text are potential installation contingencies, estimated to incur an additional 8% capital investment costs - when contingencies are accounted for, the fixed capital investment is estimated at 201355 USD.

## **2. Waste Treatment, Utilities and Labor**

Waste treatment costs are estimated using the value of 2000 USD/1000 kg for solid/liquid hazardous waste disposal displayed in Turton (2018) table 8.3. The total hazardous waste from this process is around 609 kg, assuming an extra 2.2 kg of process water added to dissolve dimethyl ether and ammonia vapors that may not condense at room temperature after leaving the evaporator. This yields a total yearly waste treatment cost estimate of 1218 USD.

Utility costs are negligible for this process; the process only requires around 200 kg of process water, with fewer than 100 megajoules of required electricity, heating, and refrigeration duties. Total utility costs are anticipated to be less than 10 USD per year. Labor costs were estimated using Turton formula 8.3 for the average number of active operators, with the number of solid handling steps set to the allowable maximum of two. It is understood that this process has five solid handling steps, however using that value led to an unreasonable result of 28 active operators per shift. Using two solid handling steps yielded 12 active operators per shift, a more reasonable value for the facility’s small size. These 12 operators may include quality assurance and other R&D workers outside the equipment space who ensure continual process viability.

With 12 active operators per shift for three months, the total labor cost is estimated at 938000 USD - far greater than all other operational costs combined.

### 3. Raw Materials

When direct quotes from suppliers were not publicly available, bulk material costs for reagents and solvents were estimated from listings on Alibaba.com and Fisher Scientific for orders between 1-1000 kg (minimum orders were assumed to be acceptable for up to 15 times the yearly requirement). To meet the production specification for 2.25 kilograms (7.61 moles) of lofexidine hydrochloride per year, the mass requirement and bulk cost of each starting material and the final product are summarized in Table 27 (Appendix: Production Calculations).

Table 27: Yearly Input and Product Requirements with Accompanying Costs or Prices

<b>Compound</b>	<b>Mass Required Per Year (kg)</b>	<b>Price (USD) Per Year</b>
<i>Materials</i>		
Diethylene Glycol Ethyl Ether	76.78	126.69
Ethanol	76.87	87.63
Hexanes (60 %)	82.45	82.45
Dichloromethane	320.65	192.39
Anhydrous Ammonia*	0.60	---
2,6-dichlorophenol	3.31	16.55
(-) Methyl Lactate	2.11	52.75
DIAD	4.10	410.00
Triphenylphosphine	5.32	255.36
TMO-TFB	2.53	2041.71
Ethylene Diamine	1.13	39.55
Hydrochloric Acid (10 M)	1.16	161.70



Sodium Iodide	1.60	40.10
Magnesium Sulfate	1.00	48.24
<b>Totals</b>	579.61	3555.12

\* Price quote for 4 kg tank of anhydrous NH<sub>3</sub> vapor could not be obtained; cost is neglected.

#### 4. Overall Operational Costs

Estimates for other miscellaneous costs such as property tax, maintenance, and royalties are outlined in Turton (2018) as a function of FCI, labor, raw materials, utility, and waste treatment costs. The overall operational cost of the lofexidine facility is estimated using Equation 8.2 which combines all the miscellaneous cost correlations, neglecting the effects of depreciation. From Appendix: Production Calculations, the overall cost is approximately 2,607,200 USD. Given the Fisher Scientific price of 93.40 USD/g for sub-pharma grade lofexidine HCl, this process would certainly not be financially viable unless certified for use by a pharmaceutical company, or if the number of active operators was reduced. In order to obtain this certification, more involved measurements would be necessary to obtain precise mass flows around each block, most importantly testing for impurities in the last two filter cakes and proper partition coefficients in the extractor.

Were the process to be pharmaceutically viable in the stated arrangement, about 15% of the lofexidine HCl would be lost in the eventual tablet formulation process, leaving 2.26 kg of active pharmaceutical product. At the contemporary price of 117 USD/mg, the yearly profit margins are on the order of hundreds of millions of dollars. The breakeven point would be around 1% of the contemporary price, and comfortable profits could be made at 2.30 USD/mg. Even assuming a full year of process labor sunk costs for legitimization in addition to the capital investment (~4 million USD), the internal rate of return is 19% after two years and 42% after three years assuming the full stock is sold at 2.30 USD/mg. With the opioid crisis not expected to abate soon, the price of lofexidine for treatment could reasonably be reduced by a factor of 50 if this process was viable. The multi million dollar risk to confirm the process as viable would be the primary obstacle to lower treatment prices, and prices may not become that low right away as

most of the initial profits would ostensibly offset other sunk costs at the larger plant housing the lofexidine facility.

## **VI. Conclusions and Recommendations**

From merely an economical standpoint, it is highly recommended that this process be scaled up to industrial levels using the equipment and procedure outlined in this project. At the current market price (\$117.46 per mg), this process would yield a yearly profit of roughly \$264 million per year at an operating schedule of only 3 months out of the year. Similarly, if the price was lowered by a factor of approximately 50 to \$2.30 per mg, the yearly revenue would be around \$2.59 million with an internal rate of return of 19% after two years and 42% after three years (assuming one year of process validation work). If sunk costs exceed 4 million USD, incremental price increases of \$0.50 per mg may be instated to recover viable return rates. A drug price of \$2.30 per mg would make total treatment costs roughly \$50, which rival the major competitors: clonidine at \$9 for a 30-day supply, or buprenorphine-naloxone, methadone, and naltrexone at \$115, \$126, and \$294 per week, respectively (National Institute on Drug Abuse, 2019). Furthermore, lofexidine is taken for a week at the prescribed dose followed by an additional week of gradual tapering of the prescribed dosage, while a majority of its competitors are taken consistently throughout the patient's life as symptoms persist. If this process is adapted successfully by a pharmaceutical company, the lowered consumer price will make the drug more accessible to the public, which in turn will make it a more popular treatment option among those dealing with opioid dependence and opiate use disorder.

However, there are several contentions pertaining to the certainty the process works, and thus several recommendations will be suggested for those deciding to pursue making this project a reality. To begin, there is very little property data available for many of the compounds and chemicals used in this proposed synthesis of lofexidine HCl. Therefore, there are many instances where assumptions were made to model and size the equipment necessary in the process. First, the heat of reaction for the three reactors of the process are estimated through Aspen Plus V11's property estimation system based on the structure, molecular weight, and boiling point of each compound. In order to obtain more accurate values for each heat of reaction, small scale

reactions should be run before the full scale equipment is sized to the above specifications. Similarly, smaller experiments should be run to determine solubility of the compounds, particle size, filter cake depth, and solvent entrainment for the filters proposed as each of the filters were modeled in Aspen as a separator operating at 100% efficiency. A similar assumption was made for the evaporators with each separation assumed to be 100%. Experiments to determine the vapor pressure and volatility of the more complex components would aid in creating a more accurate model, which could be used to design a piece of equipment that would guarantee the desired separation.

Lab-scale testing can also be conducted to determine replacement solvents used in the process, as chlorinated solvents pose toxicity risks if contaminated in the final product and are difficult to dispose of in waste management. Finally, Aspen was again used to estimate the partition coefficients of the liquid-liquid extractor. A laboratory scale extraction would yield far more accurate values for these coefficients which in turn would scale to a far more reliable piece of industrial equipment. After a reliable library of property data is assembled, a pilot run of the process will create an exact plant schedule, since the current schedule assumes process times for certain pieces of equipment, cleaning, material flow, and storage. All together, it is strongly recommended that several laboratory experiments are run along with a pilot test run before the equipment design and procedure outlined in this process is adopted.

If a future capstone team is looking to advance this project or scale the production of lofexidine HCl to an industrial scale in an attempt to help mitigate the opioid epidemic, it is strongly recommended that a different process with more available, detailed information is chosen. The patent by Crooks and Vartak (2012) is intentionally vague in the process procedure, which resulted in a number of procedural presumptions in this project that may prove to fail if implemented in a real life plant environment. If possible, the chosen process should include a detailed outline of the procedure with chemicals and compounds that have extensive property data available to prevent the need for the myriad of assumptions made in this project, leading to a more dependable, realistic final product.

Finally, there are several recommendations for the function of the plant for the remainder of the 9 months of the calendar year in which lofexidine is not being manufactured. In light of the current global COVID-19 pandemic, the plant can be repurposed for the production of hydroxychloroquine or Favipiravir, antiviral drugs thought to treat the coronavirus and other RNA viruses. However, because of the widespread applicability of the equipment, most small molecule pharmaceuticals can be made in the plant as long as the market demand matches the small scale capacity of the plant.

## **ACKNOWLEDGEMENTS**

We would like to formally recognize and acknowledge the following individuals for their help, advice, and guidance in the completion of this project.

Eric Anderson

Michael King

Giorgio Carta

Geoffrey Geise

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## APPENDIX

### R-101: Impeller Power

The density of the reaction mixture was estimated using Aspen Plus V11.

$$\text{Reynolds number: } (1.01\pi \text{ s}^{-1}) * (0.07 \text{ m})^2 * (938.0 \text{ kg/m}^3) / (0.002418 \text{ kg/ms}) = 6031.$$

At a Reynolds number of this magnitude, the flow of the reactor is considered turbulent. From Figure 30.7 on page 633 of Welty (2015), the power number for a flat-blade turbine was approximated as 7.

$$P_i = P_n * n^3 * \rho * d_b^5 = (7) * (1.01\pi \text{ s}^{-1})^3 * (938.0 \text{ kg/m}^3) * (0.07\text{m})^5 = 0.353 \text{ W}$$

### R-102: Heat Flow - Jacket Steam Loading

Thermal resistance: interior (neglecting conduction to overhead vapor)

Use correlation from Paul et al., 2004 (pg. 879) for 45° pitched blade turbine

$$h = (k/D) (.45) (\text{Re})^{.75} (\text{Pr})^{.15} (D/H)^{.15} - \text{neglect effects of viscosity ratio and impeller blade height}$$

$$\text{liquid coverage} = (768.69 \text{ kg/m}^3)^{-1} * (2.652 \text{ kg}) / .00530 \text{ m}^3 = 0.65$$

$$\text{liquid height} = 0.65 * 0.30 \text{ m} = .195 \text{ m}$$

$$\text{surface area contact} = 0.65 * 0.30 \text{ m} * 0.15 \text{ m} * \pi = 0.092 \text{ m}^2$$

$$\text{Re} = (2.5\pi \text{ s}^{-1}) * (0.075 \text{ m})^2 * (768.69 \text{ kg/m}^3) / (0.0004324 \text{ kg/ms}) = 78500$$

Aspen outputs:  $k = 0.1485 \text{ W/mK}$ ,  $\text{Pr} = 8.94$  (At 353 K) - neglect temperature dependence

$$h = ((0.1485 \text{ W/mK}) / (.15 \text{ m})) * (.45) * (78500)^{.75} * (8.94)^{.15} * (0.15 \text{ m}/0.195 \text{ m})^{.15} = 1630 \text{ W/m}^2\text{K}$$

$$\text{Resistance} = 1 / hA = ((1630 \text{ W/m}^2\text{K}) * (0.092 \text{ m}^2))^{-1} = 0.00667 \text{ K/W}$$

$$\text{Conductive resistance through tank: } R = \ln(D_{\text{out}} / D_{\text{in}}) / 2kL\pi$$

Welty 224:  $k = 17 \text{ W/mK}$  (At 353 K) - neglect temperature dependence overheating

$$\text{Resistance} = \ln(0.16/0.15) / (2 * 17 \text{ W/mK} * 0.30 \text{ m} * \pi) = 0.00204 \text{ K/W}$$

External resistance: Assume convective heat transfer coefficient = 5000 W/m<sup>2</sup>K (Welty 227)

$$\text{Resistance} = ((5000 \text{ W/m}^2\text{K}) * (0.151 \text{ m}^2))^{-1} = .00133 \text{ K/W (exterior conduction neglected)}$$

Total resistance = 0.010 K/W; temperature of 3 bar saturated steam = 133.5°C (Felder 646)

$$\text{Heat flow at start} = (133.5 - 25) \text{ K} / (0.010 \text{ K/W}) = 10850 \text{ W}$$

$$\text{Heat flow at end} = (133.5 - 80) \text{ K} / (0.010 \text{ K/W}) = 5350 \text{ W}$$

### R-102: Heat Flow - Jacket Water Loading

Internal and conductive tank resistance remains the same, resistance must be calculated for a 5 cm jacket of stagnant water.

Welty 738:  $k$  (Water, 350 K) = 0.671 W/mK - very stable over the range 350-355 K, assumed constant

$$R = \ln(D_{\text{out}} / D_{\text{in}}) / 2kL\pi = \ln(0.21/0.16) / (2 * \pi * 0.30 \text{ m} * 0.671 \text{ W/mK}) = 0.215 \text{ K/W}$$

Total resistance = 0.224 K/W

Heat flow =  $1 / (0.224 \text{ K/W}) = 4.46 \text{ W}$  per 1 K difference between reaction mixture and jacket

### R-102: Impeller Power / Mass Transfer Coefficient

At a Reynolds number of 78500, the mixture is in the fully turbulent regime. Use the power number of 2.3 shown for “paddle-type” impellers in turbulent flow (Welty 633).

$$P_i = P_n * n^3 * p * d_b^5 = (2.27) * (2.5\pi \text{ s}^{-1})^3 * (0.075 \text{ m})^5 * (768.69 \text{ kg/m}^3) = 2.03 \text{ W}$$

Use the correlation for coalescing air bubbles (Eq. 30-32) as mass transfer coefficient estimation

$$k_L a = (.026) * (P_i/V_L)^4 * (u_s)^5$$

$$\text{Superficial velocity: } u_s = (0.5 \text{ L/min}) / (\pi * (0.075 \text{ m})^2) * (1 \text{ m}^3 / 1000 \text{ L}) * (1 \text{ min} / 60 \text{ s}) = 0.000472 \text{ m/s}$$

$$k_L a = (.026) * (2.03 \text{ W} / 0.00345 \text{ m}^3)^4 * (0.000472 \text{ m/s})^5 = 0.00724 \text{ s}^{-1} (26.06 \text{ h}^{-1})$$

### R-103: Impeller Power

The reactor mixture is mostly composed of ethanol and DCM, prompting a weighted average of these two components' physical properties at room temperature.

$$\text{Reynolds number: } (0.67\pi \text{ s}^{-1}) * (0.9 \text{ m})^2 * (1227 \text{ kg/m}^3) / (0.0005229 \text{ kg/ms}) = 39,800$$

At a Reynolds number of this magnitude, flow within the reactor is considered turbulent. From Figure 30.7 on page 633 of Welty (2015), the corresponding power number was approximated as 2.3.

$$P_i = P_n * n^3 * p * d_b^5 = (2.3) * (0.67\pi \text{ s}^{-1})^3 * (1227 \text{ kg/m}^3) * (0.09\text{m})^5 = 3.49 \times 10^{-2} \text{ W}$$

### **X-101: Impeller Power**

Most of the mixture is DCM phase so DCM properties at room temperature are used.

$$\text{Reynolds number: } (0.8\pi \text{ s}^{-1}) * (0.15 \text{ m})^2 * (1300 \text{ kg/m}^3) / (0.0004133 \text{ kg/ms}) = 178000$$

The mixture is fully turbulent, use the power number of 7 shown for flat blade turbines in turbulent flow (Welty 633).

$$P_i = P_n * n^3 * p * d_b^5 = (7) * (0.8\pi \text{ s}^{-1})^3 * (0.15 \text{ m})^5 * (1300 \text{ kg/m}^3) = 10.97 \text{ W}$$

### **HCl Mixer M-101**

Most of the mixture is ether, so ether properties at room temperature are used.

$$\text{Reynolds number: } (0.08 \text{ m})^2 * (2\pi \text{ s}^{-1}) * (713 \text{ kg/m}^3) / (0.000224 \text{ kg/ms}) = 128000$$

This Reynolds number means the mixture is fully turbulent. Paddle impellers are used for this mixture. Using *Figure 30.7* in Welty, the power number for turbulent flow with paddle impellers is estimated at 2.3.

$$P_i = P_n * n^3 * p * d_b^5 = (2.3) * (2\pi \text{ s}^{-1})^3 * (713 \text{ kg/m}^3) * (0.08\text{m})^5 = 1.33 \text{ W}$$

### **Coolant**

Specific heat capacity of ethylene glycol: 2.256 kJ/kg\*K (Welty, Appendix I)

Density: 1077 kg/m<sup>3</sup>

### Methyl Lactate Reactor

Cooling time = 2 minutes

Heat Removal Requirement from Methyl Lactate Reactor:

$$q_m = m * C_p * \Delta T = 1.56 \text{ kg} * 1442 \text{ J/kg*K} * -25 \text{ K} = -56238 \text{ J}$$

Ambient Air Conduction:

$$q_r = 2 * \pi * l * k * (T_i - T_0) / \ln(r_o/r_i)$$

$$k \text{ (ambient air, 300 K)} = 2.6240 \times 10^{-2} \text{ W/mK}$$

$$q_r = 2 * \pi * (0.25 \text{ m}) * (2.6240 \times 10^{-2} \text{ W/mK}) * (273 \text{ K} - 298 \text{ K}) / \ln(1.1) = -10.8 \text{ W}$$

$$q_{r,\text{tot}} = -10.8 \text{ W} * 120 \text{ s} = -1296 \text{ J}$$

Total heat removal requirement:

$$q = q_{r,\text{tot}} + q_m = -56238 \text{ J} + -1296 \text{ J} = -57534 \text{ J}$$

Coolant required:

$$m = q / (C_p * \Delta T) = 57.534 \text{ kJ} / (2.256 \text{ kJ/kg} * \text{K} * (15 \text{ K})) = 1.7 \text{ kg}$$

$$V = 1.7 \text{ kg} * (1077 \text{ kg/m}^3)^{-1} * (1000 \text{ L/m}^3) / 2 \text{ min} = 0.79 \text{ L/min}$$

### Ammonia Reactor Effluent

Cooling time = 5 minutes

Heat Removal Requirement from Methyl Lactate Reactor:

$$q_m = m * C_p * \Delta T = 2.70 \text{ kg} * 3070 \text{ J/kg} * \text{K} * -25 \text{ K} = -207225 \text{ J}$$

Ambient Air Conduction:

$$q_r = 2 * \pi * l * k * (T_i - T_o) / \ln(r_o / r_i)$$

$$k \text{ (ambient air, 300 K)} = 2.6240 \times 10^{-2} \text{ W/mK}$$

$$q_r = 2 * \pi * (0.3 \text{ m}) * (2.6240 \times 10^{-2} \text{ W/mK}) * (273 \text{ K} - 298 \text{ K}) / \ln(1.07) = -18.3 \text{ W}$$

$$q_{r,\text{tot}} = -18.3 \text{ W} * 300 \text{ s} = -5490 \text{ J}$$

Total heat removal requirement:

$$q = q_r + q_m = -207225 \text{ J} + (-18.3 \text{ W} * 300 \text{ s}) = -212715 \text{ J}$$

Coolant required:

$$m = q / (C_p * \Delta T) = 212.715 \text{ kJ} / (2.256 \text{ kJ/kg} \cdot \text{K} * (15 \text{ K})) = 5.89 \text{ kg}$$

$$V = 5.89 \text{ kg} * (1077 \text{ kg/m}^3)^{-1} * (1000 \text{ L/m}^3) / 5 \text{ min} = 1.2 \text{ L/min}$$

### **Pump Calculations**

#### Filtration (F-101)

Stream 4:

$$P = (50662.5 \text{ Pa}) * (2.21 \times 10^{-9} \text{ m}^3/\text{s}) = 0.000112 \text{ W}$$

#### Ammonia Reactor

Stream 12:

$$P = (150000 \text{ Pa} - 100000 \text{ Pa} + 50662.5 \text{ Pa}) * (2.22 \times 10^{-9} \text{ m}^3/\text{s}) = 0.000223 \text{ W}$$

#### Filtration (F-102)

Stream 26:

$$P = (50662.5 \text{ Pa}) * (2.14 \times 10^{-6} \text{ m}^3/\text{s}) = 0.108 \text{ W}$$

#### Filtration (F-103)

Stream 32:

$$P = (300000 \text{ Pa} - 100000 \text{ Pa} + 50662.5 \text{ Pa}) * (1.12 \times 10^{-6} \text{ m}^3/\text{s}) = 0.281 \text{ W}$$

#### Filtration (F-104)

Stream 40:

$$P = (300000 \text{ Pa} - 100000 \text{ Pa} + 50662.5 \text{ Pa}) * (1.12 \times 10^{-6} \text{ m}^3/\text{s}) = 0.281 \text{ W}$$

### **Raw Materials Cost Estimation**

#### Initial esterification and amidation

Main reagents: 1 eq. 2,6-dichlorophenol, (-) methyl lactate,  $(\text{Ph})_3\text{P}$  and DIAD

Solvents deployed for  $\frac{1}{4}$  mole reagents: 125 mL ether, 750 mL ethanol, 575 mL hexanes.



### Formation of (-) lofexidine

Reagents: 1 eq. TMO-TFB, 1.1 eq. EDA, 1 eq. (-) ethanamide

Solvents used for 1/9 mole (-) ethanamide: 1100 mL DCM, 200 mL ethanol, 500 mL hexanes.

### Preparation of (-) lofexidine HCl salt

Reagents: 1 mol (-) lofexidine, 1.1 eq. aqueous HCl (10 M)

Solvents deployed for 1/25 mole (-) lofexidine: 20 ml ethanol, 330 ml ether.

### Solvent requirements for production of one mole (-) lofexidine HCl

**DEG Ether Cost:**  $(76.78 \text{ kg/yr}) * (1.65 \text{ USD/kg}) = 126.69 \text{ USD}$  (“Diethylene Glycol Diethyl Ether”, 2019).

**Ethanol Cost:**  $(76.87 \text{ kg/yr}) * (1.14 \text{ USD/kg}) = 87.63 \text{ USD}$  (Turton, 2018).

**Hexanes Cost:**  $(82.45 \text{ kg/yr}) * (1 \text{ USD/kg}) = 82.45 \text{ USD}$  (“Hexane 110-54-3”, 2019).

**DCM Cost:**  $(320.65 \text{ kg/yr}) * (0.6 \text{ USD/kg}) = 129.39 \text{ USD}$  (“Methylene Chloride, 99.5% 75-09-2”, 2019).

**NaI Cost:**  $(30.84 \text{ L/yr}) * (1.04 \text{ kg/L}) * (.05 \text{ kg NaI / kg solution}) * (25 \text{ USD/kg}) = 40.10 \text{ USD}$  (“Sodium Iodide 7681-82-5”, 2020).

**2,6-dichlorophenol Cost:**  $(3.31 \text{ kg/yr}) * (5 \text{ USD/kg}) = 16.55 \text{ USD}$  (“2,6-dichlorophenol 87-65-0”, 2019).

**(-) methyl lactate Cost:**  $(2.11 \text{ kg/yr}) * (25 \text{ USD/kg}) = 52.75 \text{ USD}$  (“Methyl (S)-(-)-lactate/C4H8O3 ...”, 2019)

**DIAD Cost:**  $(4.10 \text{ kg/yr}) * (100 \text{ USD/kg}) = 410 \text{ USD}$  (“2446-83-5”, 2019).

**(Ph)<sub>3</sub>P Cost:** (5.32 kg/yr) \* (48 USD/kg) = 255.36 USD (“Triphenylphospine, 98%”, 2019.)

**TMO-TFB Cost:** (2.53 kg/yr) \* (807 USD/kg) = 1089.45 USD (“Trimethyloxidanium Tetrafluoroborate”, 2019.)

**EDA Cost:** (1.13 kg/yr) \* (35 USD/kg) = 39.55 USD (“Factory wholesale high quality ethylenediamine ...”, 2019.)

**HCl Cost:** (1.17 kg/yr) \* (0.855 L/kg) \* (161.7 USD/L) = 161.70 USD (“Hydrochloric Acid 34-37%”, 2020).

**MgSO<sub>4</sub> Cost:** (1.0 kg/yr) \* (48.24 USD/kg) = 48.24 USD (“Magnesium Sulfate, Anhydrous”, 2020).

## Utilities

### Evaporator

*E-101:* (300 W) \* (16 min \* (60 s/1 min)) \* (1 GJ/1 × 10<sup>9</sup> J) = 2.88 × 10<sup>-4</sup> GJ.

*E-102:* (300 W) \* (32 min \* (60 s/1 min)) \* (1 GJ/1 × 10<sup>9</sup> J) = 5.78 × 10<sup>-4</sup> GJ.

*E-103:* (300 W) \* (47.7 min \* (60 s/1 min)) \* (1 GJ/1 × 10<sup>9</sup> J) = 8.59 × 10<sup>-4</sup> GJ.

*E-104:* (300 W) \* (81 min \* (60 s/1 min)) \* (1 GJ/1 × 10<sup>9</sup> J) = 1.46 × 10<sup>-3</sup> GJ.

*Total:* 2.88 × 10<sup>-4</sup> GJ + 5.78 × 10<sup>-4</sup> GJ + 8.59 × 10<sup>-4</sup> GJ + 1.46 × 10<sup>-3</sup> GJ = 3.18 × 10<sup>-3</sup> GJ.

Cost: 3.18 × 10<sup>-3</sup> GJ/cycle \* 18.72 USD/GJ = 0.0596 USD/cycle. (Turton, 2018)

0.0596 USD/cycle \* 20 cycles/yr = 1.19 USD per year.

### Heat Flow

*Steam:* (423 kJ) \* (1 GJ/1 × 10<sup>6</sup> kJ) = 0.000423 GJ.

$(0.000423 \text{ GJ/cycle}) * (2.03 \text{ USD/GJ}) = 0.000859 \text{ USD/cycle. (Turton, 2018)}$

$(0.000859 \text{ USD/cycle}) * (20 \text{ cycles/yr}) = .017 \text{ USD per year.}$

*Water:*  $(28.4 \text{ kJ}) * (1 \text{ GJ}/1 \times 10^6 \text{ kJ}) = 2.84 \times 10^{-5} \text{ GJ.}$

$(2.84 \times 10^{-5} \text{ GJ GJ/cycle}) * (1.523 \text{ USD/GJ}) = 4.33 \times 10^{-5} \text{ USD/cycle. (Turton, 2018)}$

$4.33 \times 10^{-5} \text{ USD/cycle} * (20 \text{ cycles/yr}) = 8.65 \times 10^{-4} \text{ USD per year.}$

### Refrigeration

$(56238 \text{ J} + 212715 \text{ J}) * (1 \text{ GJ}/1 \times 10^9 \text{ J}) * (8.49 \text{ USD/GJ}) = 0.00228 \text{ USD/cycle. (Turton, 2018)}$

$(0.00228 \text{ USD}) * (20 \text{ cycles/yr}) = 0.05 \text{ USD per year.}$

### Impeller Power

*R-101:*  $((2.00 \text{ W} * (1 \text{ kW}/1000 \text{ W})) * 4 \text{ h}) = 0.00800 \text{ kWh.}$

*R-102:*  $((2.03 \text{ W} * (1 \text{ kW}/1000 \text{ W})) * 4 \text{ h}) = 0.00812 \text{ kWh.}$

*R-103:*  $((0.0349 \text{ W} * (1 \text{ kW}/1000 \text{ W})) * 50 \text{ h}) = 0.00175 \text{ kWh.}$

*X-101:*  $((10.97 \text{ W} * (1 \text{ kW}/1000 \text{ W})) * 1 \text{ h}) = 0.01097 \text{ kWh.}$

*M-101:*  $((1.33 \text{ W} * (1 \text{ kW}/1000 \text{ W})) * 2 \text{ h}) = 0.00266 \text{ kWh.}$

*Total:*  $(0.00800 \text{ kWh}) + (0.00812 \text{ kWh}) + (0.00175 \text{ kWh}) + (0.01097 \text{ kWh}) + (0.00266 \text{ kWh}) = 0.03150 \text{ kWh.}$

*Cost:*  $(0.03150 \text{ kWh/cycle}) * (0.0674 \text{ USD/kWh}) = 0.00212 \text{ USD/cycle. (Turton, 2018)}$

$(0.00212 \text{ USD/cycle}) * (20 \text{ cycles/yr}) = 0.04 \text{ USD per year.}$

## Pump

$$R-102: ((0.000112 \text{ W} * (1 \text{ kW}/1000 \text{ W})) * 1 \text{ h} = 1.12 \times 10^{-7} \text{ kWh.}$$

$$F-101: ((0.000223 \text{ W} * (1 \text{ kW}/1000 \text{ W})) * 1 \text{ h} = 2.23 \times 10^{-7} \text{ kWh.}$$

$$F-102: ((0.108 \text{ W} * (1 \text{ kW}/1000 \text{ W})) * 1 \text{ h} = 0.000108 \text{ kWh.}$$

$$F-103: ((0.281 \text{ W} * (1 \text{ kW}/1000 \text{ W})) * 1 \text{ h} = 0.000281 \text{ kWh.}$$

$$F-104: ((0.281 \text{ W} * (1 \text{ kW}/1000 \text{ W})) * 1 \text{ h} = 0.000281 \text{ kWh.}$$

$$\text{Total: } (1.12 \times 10^{-7} \text{ kWh}) + (2.23 \times 10^{-7} \text{ kWh}) + (0.000108 \text{ kWh}) + (0.000281 \text{ kWh}) + (0.000281 \text{ kWh}) = 6.70 \times 10^{-4} \text{ kWh.}$$

$$\text{Cost: } (6.70 \times 10^{-4} \text{ kWh/cycle}) * (0.0674 \text{ USD/kWh}) = 4.52 \times 10^{-5} \text{ USD/cycle. (Turton, 2018)}$$

$$(4.52 \times 10^{-5} \text{ USD/cycle}) * (20 \text{ cycles/yr}) = 9.04 \times 10^{-4} \text{ USD per year}$$

## **Leaf Filter Cost Estimation**

Use Turton Appendix A to estimate the cost of a Leaf Filter Apparatus with 1.95 m<sup>2</sup> filter.

$$\text{Base cost (Eq. A-1): } 10^{\{3.8187 + .6235 \log (1.95) + .0176 [\log (1.95)]^2\}} = 10100 \text{ USD}$$

Bare module factor (Table A.7): 1.65

CEPCI adjustment index: 596/397 (“Economic Indicators”, 2019).

$$\text{Purchasing cost (Table A.5): } [C_B F_{BM} A_i] = (10100 \text{ USD}) (1.65) (596/397) = 25020 \text{ USD}$$

## **Labor Costs**

$$\text{NOL} = (6.29 + 31.7*(2 \text{ solid handling steps})^2 + 0.23*(14 \text{ nonparticulate steps}))^{0.5}$$

= ~11.7 operators per shift. (Turton, 2018)

Operating Labor = (4.5) \* (11.7 operators per shift) / 4 = ~14

14 \* 67000 USD/yr = 938,000 USD per year. (Turton, 2018)

### **Overall Cost of Manufacturing**

$0.81 C_{\text{ovr}} = C_{\text{RM}} + C_{\text{UT}} + C_{\text{Waste}} + 2.215 C_{\text{Labor}} + 0.146 C_{\text{FCI}}$  [Turton (2018) Equation 8.2]

Neglect utility costs

$C_{\text{ovr}} = \{3555 + 1218 + 2.215 (938000) + 0.146 (201355)\} / 0.81 = 2607200$

### **Internal Rate of Return**

Internal rates of return satisfy the equation  $0 = [C_n / (1+r)^n]$ , from 0 to n operating years. The IRR describes the necessary discount factor for the present investment to have no value.  $R_n$  is the net cash flow for year n; the “revenue” for year zero is total sunk costs.

Assuming a sunk cost of 4 million USD covering equipment and process verification:

A stock of 2.26 kg sold for 2.30 USD/mg will generate revenue of ~5,198,000 USD. Subtracting the manufacturing cost of 2,607,200 USD yields a yearly cash flow of 2,590,800 USD.

2 year IRR:  $4000000 = [2590800 / (1+r)] + [2590800 / (1+r)^2]$ ;  $r = .191$  (19.1%)

3 year IRR:  $4000000 = [2590800 / (1+r)] + [2590800 / (1+r)^2] + [2590800 / (1+r)^3]$ ;  $r = .423$  (42.3%)