University of Pennsylvania
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April 18th, 2017

Dear Dr. John Crocker and Professor Bruce Vrana:

Enclosed is our proposal for the process design and financial performance of the low-cost production of *sofosbuvir*, a Hepatitis C drug patented by Gilead Sciences. The goal of this proposal is to design a process that would offer *sofosbuvir* at a cost significantly lower than the current price of $84,000 per treatment. The process design scales up reactions as outlined by patents submitted by Jiangsu Hanson Pharma Group in 2016 and Medivir in 2015. In order to meet the projected annual demand for 10 million patients worldwide, it is recommended that 100 batches per year be produced, with each batch generating 3,500 kilograms of *sofosbuvir*.

This report contains analysis of the market for *sofosbuvir* in the developing world, which defends our estimation of a 100 million patient market. This process requires an initial capital investment of $27 million and an annual operating cost of $568 million. Assuming the current market price of starting materials and utilities, the drug can be produced at a cost of $1,434/kg. If the drug is sold at $100 for a 12-week course of treatment, then the internal rate of return is projected to be 67.7%, making this a profitable venture after ten years of operation.

After thorough consideration, we submit this report for review with recommendations to build the facility to produce *sofosbuvir* to treat patients with Hepatitis C in low-income countries.

Sincerely,

Joseph Solomon

Cynthia Tong

Jake Hsu

Ryan Bliss

Low-Cost, Commercial Scale

Production of *Sofosbuvir*

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April 18th, 2017

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Section 4 - Abstract

Recent advances in antiviral therapeutics have produced highly effective small molecule drugs to treat Hepatitis C, a deadly infection of the liver. *Sofosbuvir*, a hepatitis C drug developed by Gilead Sciences, is a breakthrough treatment due to its low side effects and high cure rate. However, the cost of treatment is extraordinarily high, priced at $84,000 per treatment in the US. In response to backlash regarding the cost barriers in developing countries, Gilead has reached licensing agreements with generic pharmaceutical companies to produce the drug for markets in low-income countries such as India, Kenya, and Cuba among others.

The report describes a cost-effective, commercial scale process design for the production of *sofosbuvir*. The proposed production facility is designed to deliver 350,000 kg/year of the active pharmaceutical ingredient, enough to treat 10 million patients per year. The production will be completed over one hundred batches, requiring operation of 120 days/year. Assuming an 11-year period of operation, detailed economic analysis suggests that this is a profitable venture with an IRR of 67.7% and a NPV of $1.2 billion USD.

Keywords: sofosbuvir, hepatitis C, liver, drug production

Section 5 - Introduction and Objective Time Chart

5.1 Introduction

Hepatitis C is an infection of the liver that affects over 130 million people worldwide. While some patients do not exhibit symptoms, chronic infection can lead to severe liver damage, and there are approximately 700,000 deaths worldwide because of hepatitis-related complications each year[5-1]. The latency period of Hepatitis C Virus (HCV) is very long, and it can take several years for a HCV infection to become life-threatening in the form of hepatocellular carcinoma (liver cancer) or cirrhosis[5-2]. As a result, many patients will wait for medication to become more affordable. Recent advances in antiviral medications have produced anti-retroviral molecules that can eliminate the virus in infected patients, providing a much-needed cure for this condition.

Sovaldi (*sofosbuvir*) is a nucleotide analog drug produced by Gilead Sciences, which received FDA approval in 2013 for the treatment of HCV. Sovaldi is prescribed as a once-daily oral tablet for patients of all stages of HCV. A full course of treatment consists of 12-weeks of sofosbuvir (400mg) and a second-line antiviral. This treatment demonstrated cure rates as high as 97% in clinical trials. The World Health Organization (WHO) has included *sofosbuvir* in its List of Essential Medicines. Compared to previous HCV treatments, *sofosbuvir* is a breakthrough due to its once daily dosing, oral administration, low side effects, minimal drug-drug interactions, and high virologic response rates in patients with unfavorable baseline characteristics. Most patients treated with *sofosbuvir* show no signs of the HCV after three months[5-4].

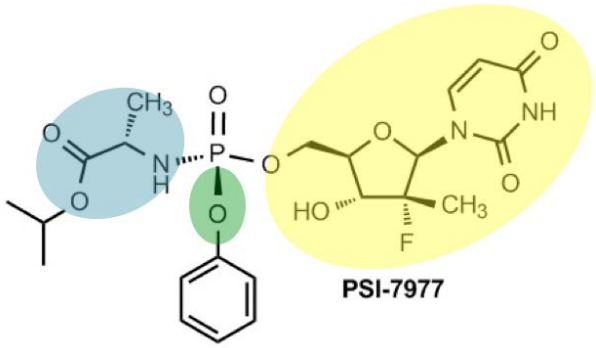

Figure 5-1 Sofosbuvir (PSI-7977) Molecular Structure

The molecule is chiral about the phosphate group, as indicated by the green highlighted group in Figure 5-1. PSI-7977 is the S-enantiomer, which is more actively metabolized. Its isomer PSI-7976 is metabolized with the same pathway. PSI-7977 has an EC90 of 0.28µM whereas PS-7976 has an EC90 of 2.96 µM, indicating that PSI-7977 is roughly 10 times more active. To prevent dosage issues, sofosbuvir is enantiomerically pure, consisting of only the PSI-7977 isomer. The phosphate group connects a modified uridine group (yellow) and a modified L-alanine group (blue).

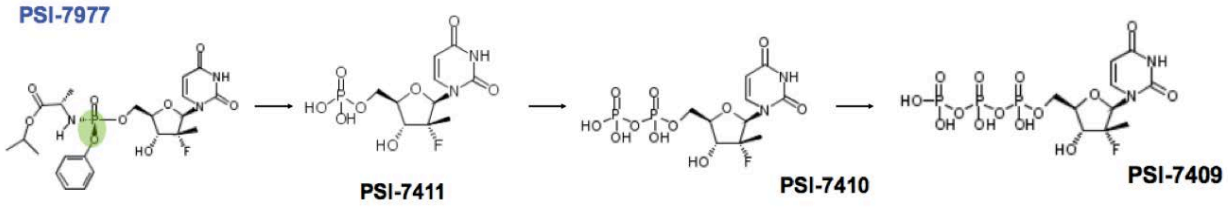

Figure 5-2 Metabolism of Sofosbuvir (PSI-7977) Prodrug into Biologically Active PSI-7409

HCV uses NS5B polymerase to replicate its viral RNA. NS5B is a reverse transcriptase, so it is a valuable antiviral target because reverse transcription is not used for any other function outside of viral replication. *Sofosbuvir* enters the body as a prodrug and is phosphorylated twice to become the active metabolite PSI-7409, as shown in Figure 5-2 above. The active metabolite then mimics uridine nucleotides and binds competitively with the NS5B polymerase to terminate the viral RNA chain. This inhibits HCV-RNA synthesis with minimal side effects, as the drug

does not bind with other substrates, given that reverse polymerase is not indigenous to the human body[5-5].

However, Sovaldi is one of the most expensive medications in the world. Currently, a 12-week course of treatment costs $84,000 in the US, making it the most expensive drug of 2016 [5-6]. The high price point in the United States and other first world markets is driven by the need to recuperate the costs of research and development, which were reported to be roughly $400 million. Given the average success rate of approximately 20% for R&D projects at pharmaceutical companies, the total costs to recuperate were approximately $2 billion. Currently, Gilead is aware that developing countries are unable to afford *sofosbuvir* at the price point previously discussed; however, HCV is a global humanitarian issue, and there is more to be discussed aside only from the high cost of the drug in developed countries. If Gilead could be reimbursed the costs of R&D, it is possible that the cost of the drug could drop in the developed world and the developing world, allowing for the global eradication of the deadly HCV. For instance, if Gilead were reimbursed by international governments or humanitarian aid organizations, the global cost of life-saving *sofosbuvir* could fall. While this discussion is beyond the scope of the design project, it is worth noting that the global eradication of a disease that claims the lives of millions annually is entirely feasible.

In response to this backlash, Gilead has reached licensing agreements with pharmaceutical companies to sell *sofosbuvir* at generic prices in 101 specified developing countries. The patent covers many developing countries with high incidence of HCV, but deliberately excludes middle income countries such as China and Brazil, which each have millions of Hepatitis C patients. Mylan, Cipla, and Natco Pharma have all acquired licenses to

manufacture the generic drug[5-4]. This project assumes operation as one of these generic companies.

We have been tasked with designing a process to produce *sofosbuvir* at a significantly reduced price. The goal is to provide the 12-week course of treatment for less than $100. This target is supported by the analysis of Andrew Hill and his group in the UK, who claim that sofosbuvir be produced for a price of $101 for a 12-week course of treatment[5-8]. The manufacturing facility will operate for ten years, as Gilead's patent period on *sofosbuvir* will end in 2028[5-9] and thus the licensing agreement will end.

5.2 Objective Time Chart

The goal of this project is to create a production process of *sofosbuvir* that is both affordable for patients in developing countries who need the drug and financially feasible for the drug manufacturer. The scope of this project includes analyzing the most profitable chemical routes to synthesize *sofosbuvir*, modeling unit operations to determine equipment needs, and costing all of the resources required in the process. As a general target, it must be profitable to sell the active pharmaceutical ingredient (API) for less than $3,000 per kilogram. Project leaders are Joseph Solomon, Cynthia Tong, Jake Hsu, and Ryan Bliss.

Deliverable	**Description**	**Date Accomplished**
Determine Chemical Synthesis Pathway	Read patent literature and discuss with consultants to determine the most efficient, cost-efficient process	February 10
Model Process Steps in ASPEN	Determine the equipment specifications to perform necessary reactions and separations with appropriate utility demands.	March 15

Schedule Operations in SUPERPRO	Model equipment operations in SUPERPRO and determine the scheduling of shifts	April 2
Determine Utility Requirements Needed	Size equipment (reactor vessels, distillation columns) and determine the heating and cooling costs.	April 4
Complete Financial Analysis	Calculate fixed and variable costs for the process and determine NPV and ROI	April 8
Complete Report		April 14

Endnotes

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Section 6 - Innovation Map

The low-cost process proposed in this report will yield a product that is bioequivalent to the API in Gilead Science's branded drug Sovaldi. As shown in the Innovation Map (Figure 6-1) below, *sofosbuvir* products (Sovaldi, Harvoni, Epclusa) and the new generation of oral HCV drugs (Daklinza, Zepatier, and Viekira) are significantly differentiated from the previous generation pegylated-interferon (Peg-INF) and ribavirin (RBV) treatments in that they are highly effective, easily administered, and lead to few side-effects. The key attribute that differentiates *sofosbuvir* drugs and other HCV drugs is that it is approved for multiple genotypes of HCV. This makes *sofosbuvir* an ideal treatment for HCV patients in developing countries because HCV genotypes vary greatly between geographic regions. More detailed explanation of the market analysis can be found in Section 7.

In terms of manufacturing process, many patented syntheses were considered. All synthesis patents considered required the expensive molecule 2'-deoxy-2'-fluoro-2'-methyluridine (methyluridine). Patents were screened based on a variety of factors, the most important of which were final yield and complexity of intermediate. Between the first two processes shown in Figure 6-1, the first synthesis was chosen because of its significantly higher yield. Between the first and third processes, the first was chosen because of the more straightforward synthesis of the intermediate. Detailed explanation of the process selection and design is presented in Section 16.

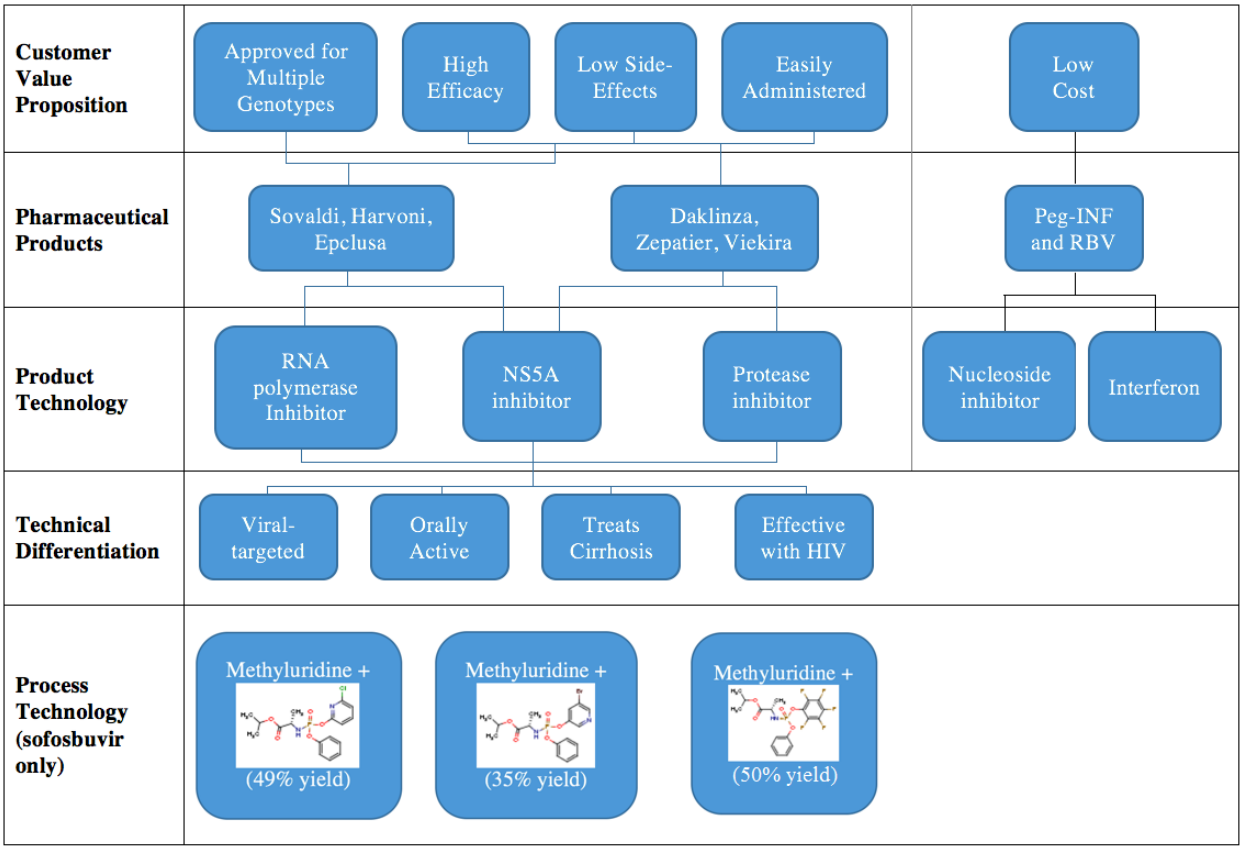

Figure 6-1 Innovation Map

Section 7 - Market and Competitive Analysis

7.1 Hepatitis C Market Analysis

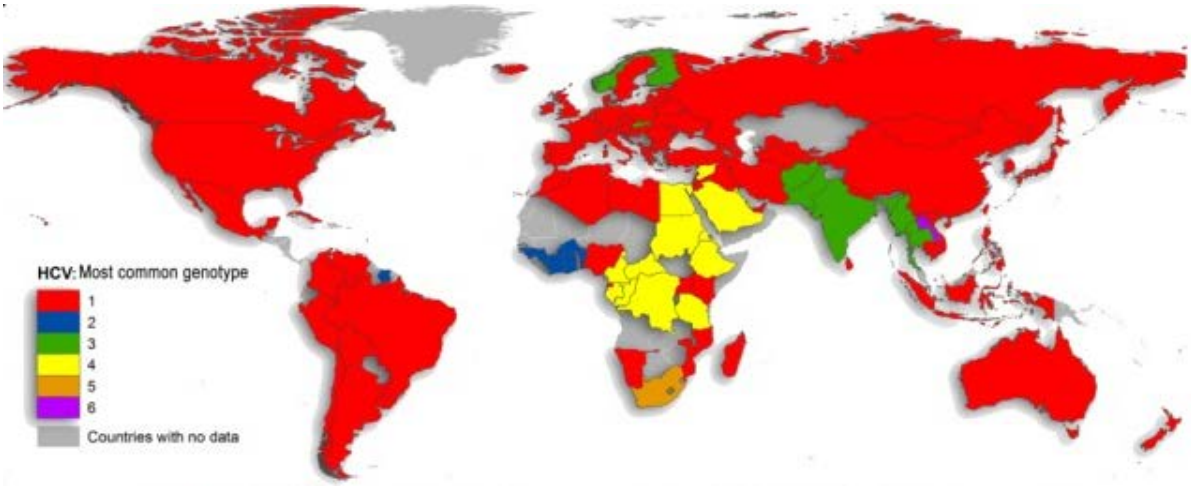

Figure 7-1 Hepatitis C Genotypes by Geography[7-1]

Treating HCV is uniquely challenging due to the high rates of mutation within the virus. Significantly differentiated viruses are categorized under separate genotypes. Currently, there are six genotypes of HCV enumerated 1 through 6. Each genotype may contain further sub-types. Genotype profiles can vary dramatically across geographic regions. In North America and Europe, genotype 1 is the most commonly observed among HCV patients for all genotypes, whereas India has high prevalence of genotype 3 and Africa has high prevalence of genotype 4.

HCV treatment can be further complicated by advanced disease progression into liver cirrhosis, simultaneous infection by multiple genotypes, and cross-infection with HCV and HIV. In later stages of HCV, characterized by liver cirrhosis, patients experience lower cure rates. For example, among patients treated with Daklinza, those who suffered from cirrhosis were cured at a rate of 58%, whereas those who did not were cured at a rate of 98%. Patients who have

multiple infections are often treated more aggressively with one or two additional antivirals. Overall, the global Hepatitis C market is fragmented by genotype and cross infection.

7.2 Pharmaceutical Hepatitis C Treatment Options

7.2.1 Pegylated-Interferon and Ribavirin

Before effective oral treatments of HCV became available, the preferred course of treatment was a combination therapy of pegylated-interferon and ribavirin. The combined treatment had a cure rate of 45% in genotype 1 and 80% in genotypes 2 and 3[7-2].

Pegylated-interferon (Peg-INF) mimics a protein in the body to fight off infection. It is typically delivered as a weekly injection, which must be administered by a doctor. This is not particularly desirable or convenient for patients because it creates barriers to treatment. Peg-INF can also lead to serious side effects such as fever, nausea, , and even autoimmune disorders. Peg-INF is most commonly prescribed in a combination treatment with RBV; however, it can also be used in combination with *sofosbuvir*. The use of Peg-INF has decreased in recent years more approved treatments have become available.

Ribavirin (RBV)[7-3] is an oral antiviral drug approved in 1998 for use in HCV combination treatments. The mechanisms of RBV are not well documented because of challenges involved in developing an in vivo HCV model; however, it is believed that RBV interferes with the replication of viral DNA and RNA. By itself, RBV has shown to have no effect on viral replication, so it is never used as a stand-alone treatment. RBV is currently marketed under several generic brands, making it a popular second-line antiviral.

7.2.2 New Oral Hepatitis C Treatments on the Market

As antiviral research matured, more pill-based treatments were approved by the FDA and became available on the market. These treatments were a significant improvement from the

previous generation of peg-INF and RBV treatments because the oral forms were easier to take and were associated with less severe side effects. The most well known of these HCV antivirals was *sofosbuvir*; however, there are several other notable drugs that serve a sizeable portion of the global HCV market.

Daklinza (*daclatasvir*)[7-4], developed by Bristol-Myers Squibb, is an inhibitor for the NS5A replication complex. It was first approved by the FDA in July 2015 for the treatment of genotypes 1 and 3 in combination with *sofosbuvir*. It has occasionally been used to treat genotypes 2 and 4. Daklinza is taken in the form of a once-daily oral tablet with 98% efficacy when used as a first line treatment.

In January 2016, Merck entered the HCV market with its own drug, **Zepatier (*elbasvir/grazoprevir*)**[7-5]. Zepatier is an oral first-line treatment for patients with genotypes 1 through 4. It can be administered with or without RBV in combination. After 12 weeks of treatment, patients were cured with over 97% success.

Viekira Pak/Viekira XR (*ombitasvir/paritaprevir/ritonavir/dasabuvir*)[7-6] was developed by Abbvie in December 2014 for patients with genotype 1. Viekira Pak is taken as two tablets: the first containing ombitasvir/paritaprevir/ritonavir, and the second containing dasabuvir. Abbvie followed up with Viekira XR, a single tablet version of Viekira Pak in July 2016. Among patients with genotype 1 without cirrhosis, Viekira Pak has a cure rate of 97% after a 12-week course of treatment.

7.2.3 Gilead Sciences Hepatitis C Portfolio

Gilead's blockbuster drug, Sovaldi (*sofosbuvir*)[7-7], changed the market of HCV treatments when it was approved in December of 2013. Its active drug, *sofosbuvir*, is a polymerase inhibitor that prevents the virus from replicating. It is taken as a daily oral tablet to

treat genotypes 1 through 4. Compared to its predecessors, Sovaldi boasted high cure rates as well as a wide viability; however, taking Sovaldi required combination treatments with peg-INF or RBV, which could be inconvenient.

Harvoni (*sofosbuvir/ledipasvir*)[7-8] was approved to Gilead's HCV portfolio in October 2014. At the time of approval, it was the first single pill treatment for patients with genotype 1. Unlike Sovaldi or Zepatier, Harvoni did not require co-administration with RBV or a second anti-viral. In phase 3 trials, 94% of patients treated with Harvoni were completely cured after 12 weeks.

Epclusa (*sofosbuvir/velpatasvir*)[7-9] was approved in June 2016 as the first oral tablet that could be used to treat all genotypes of HCV. Epclusa's treatment flexibility extends not only to genotypes but also to later stage patients with liver cirrhosis and patients with multiple infections. Among patients without cirrhosis, 98% were cured from HCF after 12-weeks of treatment with Epclusa. Epclusa used in combination with RBV resulted in similar cure rates among patients with cirrhosis.

7.3 Competitive Analysis

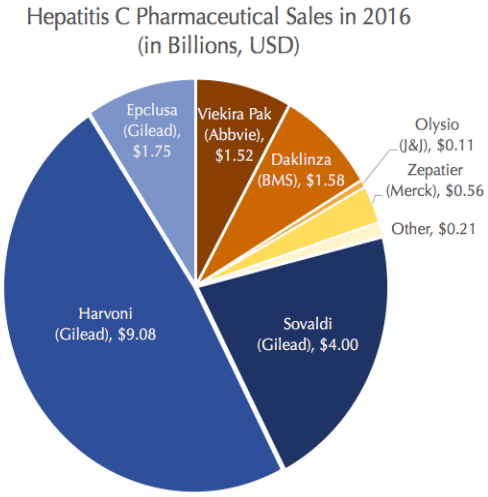

Figure 7-2 Global Hepatitis C Pharmaceutical Sales in 2016 Listed by Commercial Drug Name and Company[7-10, 11,12,13,14]

Although there are many options for HCV patients on the market, Gilead's set of *sofosbuvir*-based drugs are the clear market leaders. Currently, these drugs are considered the recommended first-line treatment for HCV patients of all genotypes and at all stages of progression. In 2016, Gilead Sciences held 79.8% of the HCV pharmaceutical market (Figure 7-2). Epclusa, Gilead's new combination drug, which launched mid-year 2016, is poised to take an even greater share of the market in 2017. Thus, demand for *sofosbuvir* will remain high. However, this is mainly the case in the developed world, because branded HCV drugs are unaffordable to patients in developing countries. Due to patent restrictions, patients with HCV in developing countries were previously limited to Peg-INF and RBV treatments. The new *sofosbuvir* licensing agreements will drastically change the HCV market in developing countries. Though Gilead's second-line antivirals ledipasvir and velpatasvir are protected under patent, *sofosbuvir* can be prescribed with ribavirin with similarly high efficacy. Given the restrictions

placed on the *sofosbuvir* licensing, *sofosbuvir* + ribavirin combination treatment is the best option for HCV patients in developing countries[7-7].

Under the terms of Gilead's generic licensing, generic manufacturers are able to produce and distribute *sofosbuvir* among 101 developing countries listed below in Table 7-1. These countries contain a large majority of HCV-infected individuals, totaling roughly 100 million patients. Thus, it is reasonable to estimate a maximum capacity of 10 million treatments produced per year over the next 12 years, while *sofosbuvir* is still on patent. Clinically, this will slow the spread of HCV in the most vulnerable populations. Financially, these large quantities of production will provide significant savings via the economies of scale. Once *sofosbuvir* comes off patent in 2028, this process will have had a significant advantage over new entrants in terms of brand recognition and optimization.

Table 7-1 Developing countries eligible for distribution of generic sofosbuvir product [7-15]

The licensing agreement encompasses the following countries:

Afghanistan	Comoros	Guinea	Marshall Islands	Paraguay	Tajikistan
Algeria	Congo, DR	Guinea-Bissau	Mauritania	Philippines	Tanzania
Angola	Congo, Rep.	Guyana	Mauritius	Rwanda	Timor-Leste
Antigua and Barbuda	Cook Islands	Haiti	Micronesia	Samoa	Togo
Bangladesh	Cote d'Ivoire	Honduras	Mongolia	Sao Tome & Pr.	Tonga
Benin	Cuba	India	Morocco	Senegal	Tunisia
Bhutan	Djibouti	Indonesia	Mozambique	Seychelles	Turkmenistan
Bolivia	Dominica	Kenya	Myanmar	Sierra Leone	Tuvalu
Botswana	Egypt	Kiribati	Namibia	Solomon Islands	Uganda
Burkina Faso	El Salvador	Kyrgyz Republic	Nauru	Somalia	Uzbekistan
Burundi	Equatorial Guinea	Lao PDR	Nepal	South Africa	Vanuatu
Cambodia	Eritrea	Lesotho	Nicaragua	South Sudan	Vietnam
Cameroon	Ethiopia	Liberia	Niger	Sri Lanka	Zambia
Cape Verde	Fiji	Libya	Nigeria	St. Vincent and the Grenadines	Zimbabwe
Central African Republic	Gabon	Madagascar	North Korea	Sudan	
Chad	Gambia	Malawi	Pakistan	Suriname	
	Ghana	Maldives	Palau	Swaziland	
	Guatemala	Mali	Papua New Guinea		

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Section 8 - Customer Requirements

The project is to design a process that will produce *sofosbuvir* at the commercial scale in India. The identified customers are patients with chronic Hepatitis C infections. To meet the demands of over 100 million patients in developing countries covered by the licensing agreement, the manufacturing output must be 350,000 kg per year. The cost of the drug must be no greater than $100 USD for a 35 gram, 12-week course of treatment. If the cost of the drug is too high, then patients who need this drug will not be able to afford treatment. Additionally, the process must produce the drug according to good manufacturing practices (GMP) standards, such as maintaining batch integrity and using high-purity raw materials. Ultimately, the finished drug product consists of both *sofosbuvir* and *ribavarinas* as a combination treatment, so the project must include both molecules. These customer requirements are classified as fitness-to-standard (FTS).

Section 9 - Critical-to-Quality Variables

Though this proposal focuses heavily on the process design aspect of sofosbuvir production, patient experience has also been seriously considered. Resources will be allocated to reducing barriers to patient access by maintaining low prices and optimizing distribution. High standards will be enforced to guarantee a high quality product by stringent quality control and precise dosing.

As mentioned previously, the main consideration for this project is price. The goal is to provide the drug at a price that is affordable to treat any patient. Because, the equipment units are designed around a specific patent, the process itself cannot be drastically changed. With this in mind, the team will be constantly monitoring the prices of starting prices. Procurement will seek to purchase the materials at cheaper prices as long as the same level of quality can be guaranteed. This is particularly true for methyluridine; currently, there are vendors in China who are offering the intermediate for sale at about $200 per kilogram. If this product can be verified for its purity, further price reductions may be available.

One important factor to our product is the purity of the sofosbuvir API. In order to guarantee patient safety, it is crucial that the purification process removes all undesirable contaminants, DCM, EA, and acetone in particular. According to the FDA, DCM is classified as a class 2 impurity, meaning that it has inherent toxicity and should be limited. The concentration limit for DCM is 600 ppm or 6 mg/day. EA and acetone are considered class 3 impurities, meaning they are less toxic and are not known to be human health hazards. Class 3 impurities are limited to less than 50 mg/day.[9-1] To enforce these safety standards, strict quality control will be conducted with each batch.

To prevent toxicity, each pill will be precisely dosed for 400 mg of *sofosbuvir* or 600 mg of ribavirin, the recommended daily dose for an adult being treated with the sofosbuvir + ribavirin combination.[9-2] Each pill will be formulated with distinct labels to avoid confusion. This will allow patients to easily keep track of their medication and avoid over-dosing. Furthermore, pills will be pressed with patient consumption in mind. Pills will be design to be as small as possible to be easily swallowed. Due to the language barriers that may exist, labels will be rigorously translated to enforce clarity and consistency.

Finally, the drug will be distributed with the geographic spread of our patients in consideration. Rather than focusing our efforts in distribution to individual pharmacies, it will instead be sold to national health agencies in the licensed developing countries or to international humanitarian non-profit organizations. These organizations have pre-established distribution channels, which will shorten the time to delivery.

Endnotes

9-1: US Department of Health and Human Services Food and Drug Administration (2012). Guidance for Industry: Q3C Tables and List. Retrieved from https://www.fda.gov/downloads/drugs/guidances/ucm073395.pdf.

9-2: Zeuzem, Stefan (2014). Sofosbuvir and Ribavirin in HCV Genotypes 2 and 3. N Engl J Med 2014; 370: DOI: 10.1056/NEJMoa1316145

Section 10 - Product Concepts

Currently, Gilead owns the only patent for a HCV treatment drug *sofosbuvir*. Gilead's brand name drug, *Sovaldi*, is sold in wealthier countries as are most, if not all, of their competitors in the Hepatitis C industry. For the purposes of the design project, our team is developing a generic, low-cost alternative to brand name drugs available via a license of the patent by Gilead for use in India. In that regard, there are no alternatives to product design, as the drug is protected by patent and non-generic drugs are cost prohibitive in developing countries.

Section 11 - Superior Product Concepts

As previously discussed, for the purposes of the design project, our team is developing a generic, low-cost alternative to brand name drugs available via a license of the patent by Gilead for use in India. In that regard, there are no alternatives to product design, as the drug is protected by patent and non-generic drugs are price prohibitive in developing countries.

Section 12 - Competitive Patent Analysis

As previously discussed, for the purposes of the design project, our team is developing a generic, low-cost alternative to brand name drugs available via a license of the patent by Gilead for use in India. In that regard, there is no competitive patent analysis, as our team is assuming that we are licensing the patent of Gilead Sciences in a market without brand-name competition.

Section 13 - Preliminary Process Synthesis

During the process synthesis analysis, various process flow diagrams were evaluated based on multiple patents, consultant recommendations, industrial scaling considerations and scheduling considerations. Each week, the product synthesis process was altered to minimize the cost of production of *sofosbuvir* and maintain a reasonably straightforward synthesis process. Initial assumptions were made regarding the scheduling, design and flow of the process so that our team could proceed accordingly. Subsequently, thorough patent analysis was performed to determine the optimal industrial synthesis route for *sofosbuvir*. Finally, synthesis processes were developed, altered and corrected throughout the term with the guidance of industrial consultants, external consultants, and close patent analysis.

The challenges throughout the semester were the scaling lab scale processes into industrial units. Our team concluded, among many other decisions discussed below, that chromatography and rotary evaporation were not viable at the industrial scale; industrial processes instead use large-scale liquid-liquid extraction and flash evaporation, respectively, in place of those two lab-scale processes. Flash evaporation vessels were modeled either as vacuum evaporation vessels or as distillation towers with multiple trays, operated at the ambient temperature vapor pressure of the solvent to avoid damage of the API. Furthermore, our group considered the process by which the soluble product would be purified and dried, deciding that the most relevant industrial scale analog of the lab scale process was a liquid-liquid extraction in a large, agitated wash vessel followed by drying in an anhydrous sodium sulfate packed bed. More complex process revisions are discussed herein. The overall goals of the process design were to find a synthesis route with a reasonable cost of raw materials and to scale the process

from lab-scale design in patents to an industrial-scale analog. The flow diagrams are available in Section 15 and the final processes are discussed in detail in Section 16.

13.1 Initial Considerations

The majority of early stage synthesis route prediction was born from exhaustive patent study. Most patents were extremely vague, as are their nature, which made the process of determining exact synthesis routes difficult initially. At the recommendation of industrial consultants and Dr. Crocker, it was determined that an appropriate route for patent "translation" was to choose R groups or solvents based on cost of raw materials, cost of removal and safety if the patent mentioned multiple R groups and solvents. Furthermore, the consultants recommended that our group should attempt to start with the lab scale process for the synthesis in the patents since there is often times an industrial scale parallel process. The obvious first step and goal was, then, to determine the process and/or synthesis route for producing *sofosbuvir* before discussing equipment in detail.

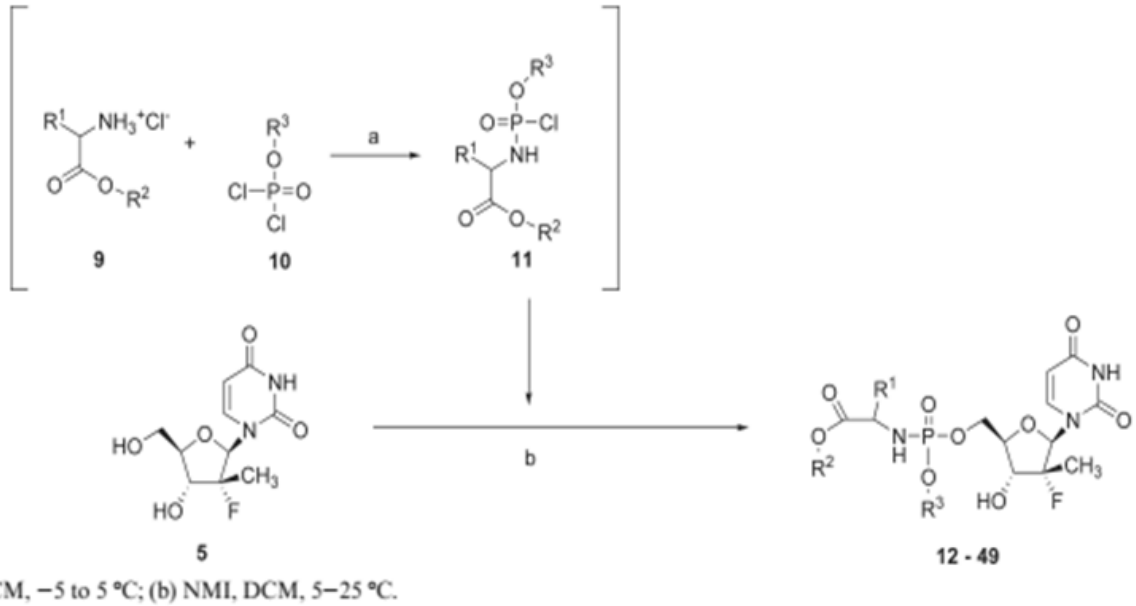
Our group concluded that it was safe to assume the use of a batch process since pharmaceutical standards require traceable batches the event of a contamination. Due to the chirality requirements of the sofosbuvir molecule, stereospecific and non-stereospecific processes were both considered. It was concluded that it is preferable to purchase the feedstock with the chiral center enantiomerically pure rather than separating after the reaction. Our group determined that the cost of R- and S- separation is prohibitive, so only stereospecific reactions were considered.

13.2 Synthesis Route Determination

Initial synthesis route determination was based on patents provided during the initial project proposal phase. Most patents were too vague regarding the synthesis route for *sofosbuvir*, mentioning only general routes between compounds of various R groups and chiral centers. Patent authors aim for their intellectual property to be as widely applicable as possible and purposefully neglect to identify specific solvents and functional groups. Our team decided to choose unspecified components based on cost and safety. In most cases, the pharmaceutical patents referenced to peer-reviewed papers where the synthesis process was more coherently outlined, so our team pivoted towards the peer-reviewed papers mentioned in the patents.

An article published in the Journal of Medicinal Chemistry, *Discovery of a Nucleotide Prodrug for the Treatment of Hepatitis C* by researchers Michael Sofia et al. was the first to be thoroughly reviewed for the process synthesis. The article detailed a synthesis route to obtain a family of molecules that could be directly converted to *sofosbuvir*. The paper discussed 3 major syntheses: a synthesis to produce methyluridine, a synthesis to produce an intermediate product, and the reaction of those two products to create a molecule in the family of molecules that could directly be translated to *sofosbuvir*. It is important to mention that the paper does not explicitly discuss the synthesis of the *sofosbuvir* as the final product, but does discuss the yields associated with the direct route synthesis from each of the molecules in the family of molecules described previously. Figure 13-1 presents an overview of the synthesis route described by the paper; the reaction pathway featured the use an amino acid ester (compound 9) and dichlorophosphate (compound 10) to create an intermediate product (compound 11), which would then react with a methyluridine (compound 5) to create one of many molecules that could be converted to *sofosbuvir* directly. Reactions a and b are conducted in the DCM as described in the figure.[13-1]

Scheme 2[a]



[a] NMI, DCM, −5 to 5 °C; (b) NMI, DCM, 5−25 °C.

Figure 13-1 Sofia et al. synthesis route

The paper determined that molecule 14, which has a structure similar to the final product in Figure 13-1, resulted in the best yield of the *sofosbuvir*. However, the paper revealed that the yields from each of the direct route molecules (compounds 12-49) were all fairly low, ranging from 10-25% yield of *sofosbuvir*. The overall synthesis from starting materials to *sofosbuvir* had a yield of 3%. This low yield concerned our group, but industrial consultants remarked that yields as low as 3% could be used in industry as long as the costs associated with that low of a yield are reasonable. Our team decided to move forward with an in depth analysis of this process.[13-1]

In order to determine the viability of the process described in the Sofia article, the raw material costs were analyzed to determine whether or not it would be possible to synthesize *sofosbuvir* for the target price. Raw materials 9 and 10 in Figure 13-1, amino acid ester and dichlorophosphate, were searched for on various chemical supplier websites in order to find a reasonable price point. Our team sought to find all raw materials for a total below $1,000 per kilogram of *sofosbuvir* product in order to obtain our objective price point. Preliminary research determined that the amino acid ester and dichlorophosphate were both reasonably priced and could be obtained for a price point well below the threshold of $1,000 per kilogram. However, our team determined that the price of methyluridine (compound 5) was constraining with a price point as high as $4000 per kilogram. This high price led our team to analyze the various processes described in the Sofia et al. article for the synthesis of methyluridine, but we soon determined that, again, the raw material costs for those syntheses were also quite cost prohibitive.

Our team, concerned by the high price point of this raw material, reached out to external industry experts to determine if an alternative synthesis of methyluridine was possible or a more

reasonable price was obtainable. Professor of Chemistry and Pharmaceutical Sciences at Howard University Joseph Fortunak advised our team that most companies currently producing *sofosbuvir* in India buy methyluridine directly from chemical manufacturers in China for prices much less than what our group was being quoted. Professor Fortunak recommended that we research the import-export data between China and India to find the realistic price for which we could purchase the methyluridine as a manufacturer in India. After researching import-export data between India and China, our team discovered that the imported methyluridine was much less cost prohibitive than previously thought, averaging $888 per kilogram in 2016. Our team also discovered that prices for our other raw materials were also less than previously estimated; all prices are discussed in the Section 14. After realizing the less prohibitive costs of the raw materials, the synthesis described by Sofia was reevaluated for its cost efficiency. While the costs of raw materials did decrease, the yield (3%), which had previously not been evaluated, proved to make the process impractical, as the total cost to obtain the necessary amount of *sofosbuvir* was well above the stated goal. Furthermore, many of the patents that referenced the Sofia et al. article mentioned chromatography separation of the final product and various intermediate products during the process. However, in meetings with industrial consultants our team was advised that chromatography processes are generally converted to adsorption towers. In order to determine the size of the adsorption tower needed, it was necessary to determine either the isotherm associated with the adsorption products or determine the mass or volume of silica gel used at the laboratory scale in order to scale the procedure up. Shorthand calculations revealed that the size of the tower would be too large to be reasonably affordable. The size and cost of the tower, together with the cost prohibitive yield of reaction and the industrial consultant

indication that adsorption is a rare industrial process led our group to decide to find a new synthesis route for *sofosbuvir*.

For help with the patent search, our team reached out to the University of Pennsylvania Chemistry department. Dan Wu recommended that our team use Reaxys, a chemistry synthesis software. Reaxys is a search tool that retrieves reaction data from journal literature and published patents. Given a compound it summarizes the reactions in which the compound was synthesized or reacted. These hits could be sorted based on yield. Starting with *sofosbuvir* as the end product, our team used Reaxys to back-synthesize until we reached starting molecules that could be purchased at reasonable prices. Synthesis reactions were selected in favor of high yields and simple intermediates. Reactions that included heavy metals were deliberately excluded because they would be difficult to remove in separation steps. Figure 13-2 displays the synthesis process determined using Reaxys to arrive at the final product *sofosbuvir*. Three total reactions are used each with yields ranging from 50 to 97%. With the higher overall yields, it was reasonable to assume the purchase of methyluridine given the prices from import data.

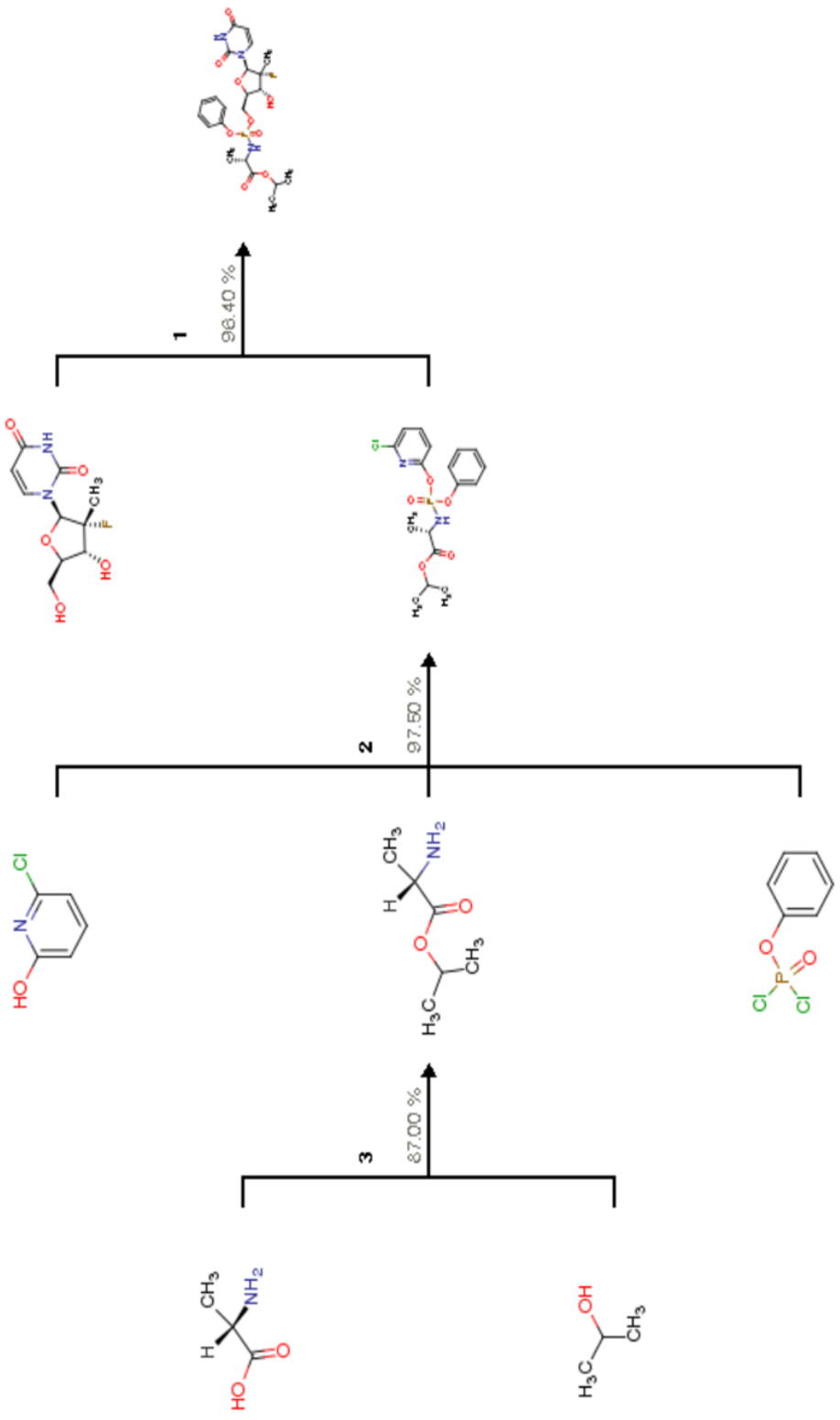


Figure 13-2 Reaxys Synthesis route

Reaction 3, the reaction furthest left in Figure 13-2, starts with raw materials isopropanol (IPA) and L-alanine to arrive at L-alanine isopropyl ester with an 87% yield. The L-alanine isopropyl ester from reaction 3 is then reacted with 2-chloro-6-hydroxypyridine and phenyl dichlorophosphate to yield Intermediate A1 with a 97% yield. Intermediate A1 is then reacted with methyluridine in reaction 1 to synthesize *sofosbuvir*. This reaction has a 50% yield, which is much higher than those seen in previous papers. The reactions featured many other solvents and catalysts that also factored into the costs associated with the process. Reaction 3 used IPA and thionyl chloride; reaction 2 uses the solvents dichloromethane (DCM) and N, N-diisopropyl ethylamine (DIEA); reaction 1 was catalyzed with zinc chloride in DIEA and tetrahydrofuran (THF). Additional washing buffers and drying agents were used to purify the product stream. These included ethyl acetate, ammonium chloride solution, salt water, hydrochloric acid, sodium carbonate/bicarbonate buffer and sodium sulfate. After researching the raw material costs via import data, the total cost for the synthesis was determined to be below the threshold. With the synthesis steps now reasonably determined for the process, it was possible to begin analysis of process equipment, timing and planning.

13.3 Process Development

For the purposes of flowsheet preparation, preliminary syntheses can be discussed on a reaction-by-reaction basis. As discussed above, the reaction synthesis selected for the process features three primary reactions. A key assumption our team made was that the reaction rates, volumes and order of reactions from the patents were directly scalable to the industrial scale. For simplicity, each reaction and its iterations will be discussed individually to highlight the changes made in each reaction more clearly and concisely.

13.3.1 Reaction 3 - Process 100

Reaction 3, herein Process 100, was developed from a patent by Medivir (Appendix A-2), which accounted for the described of L-alanine isopropyl ester.[13-2] The reaction required a dropwise addition of thionyl chloride to a suspension of L-alanine in IPA, which was stirred overnight at room temperature to yield L-alanine isopropyl ester. After the reaction step, the patent states that the product was "concentrated," which our team interpreted to be a crystallization to yield solid L-alanine isopropyl ester.

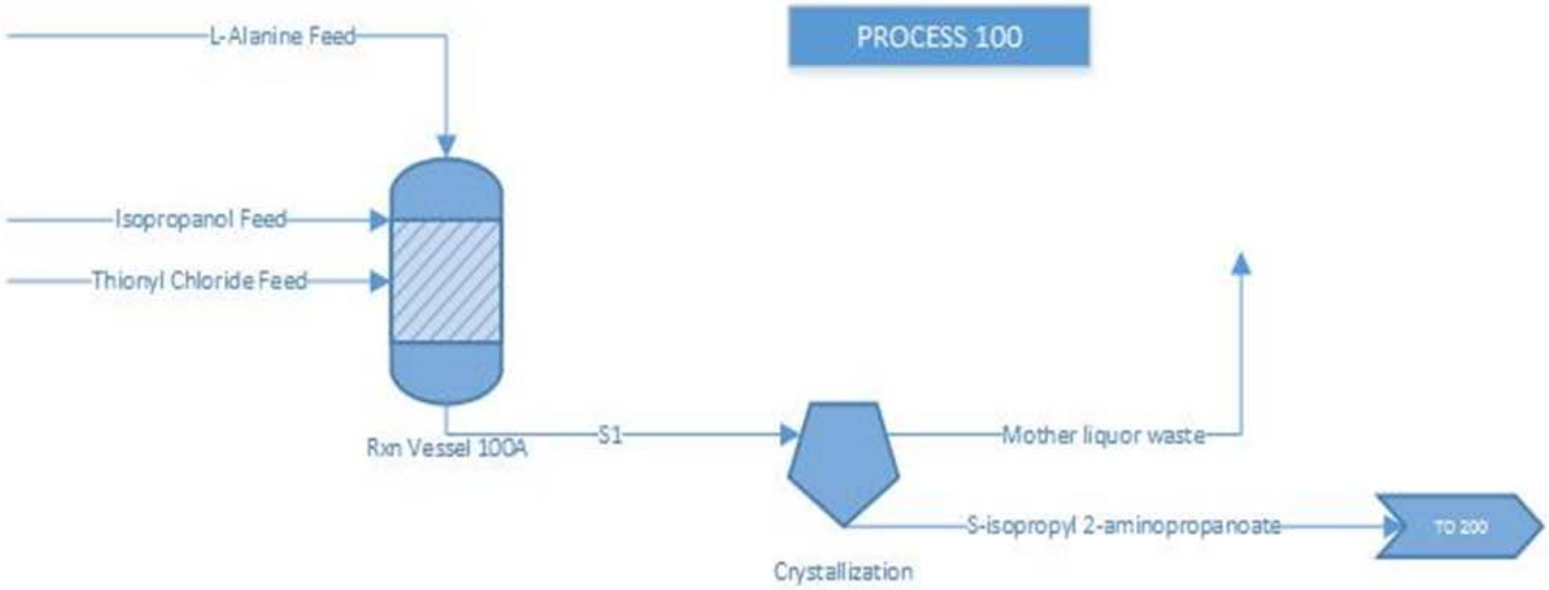


Figure 13-3 Process 100 flow diagram first iteration; initial patent interpretation and scaling

Process 100, visualized in Figure 13-3, used a single reaction vessel for the combination and reaction of the three raw material feeds, L-alanine, IPA and thionyl chloride. Those three raw materials were added to a reaction vessel according to the rates prescribed in the patent, by scaling based on the time of addition. After the appropriate reaction time, the product was removed from the system and crystallized to remove the main product as well as the mother-liquor waste.

Revisions were made to Process 100 and visualized in Figure 13-4. After discussing with industrial consultants and Dr. Crocker, our team revised our interpretation of the concentration step. Concentration is typically used in the final step of the process, not in intermediate reactions. The separation method by which the product was removed in Process 100 was changed to reflect the aforementioned conclusions. Given the aqueous suspension of product, it seemed prudent to use ultrafiltration to remove the suspended particulates from the solution for subsequent use. Furthermore, our team decided to add a storage tank to the process to regulate the addition of product to the next process, as the rate of ultrafiltration could be quite low.

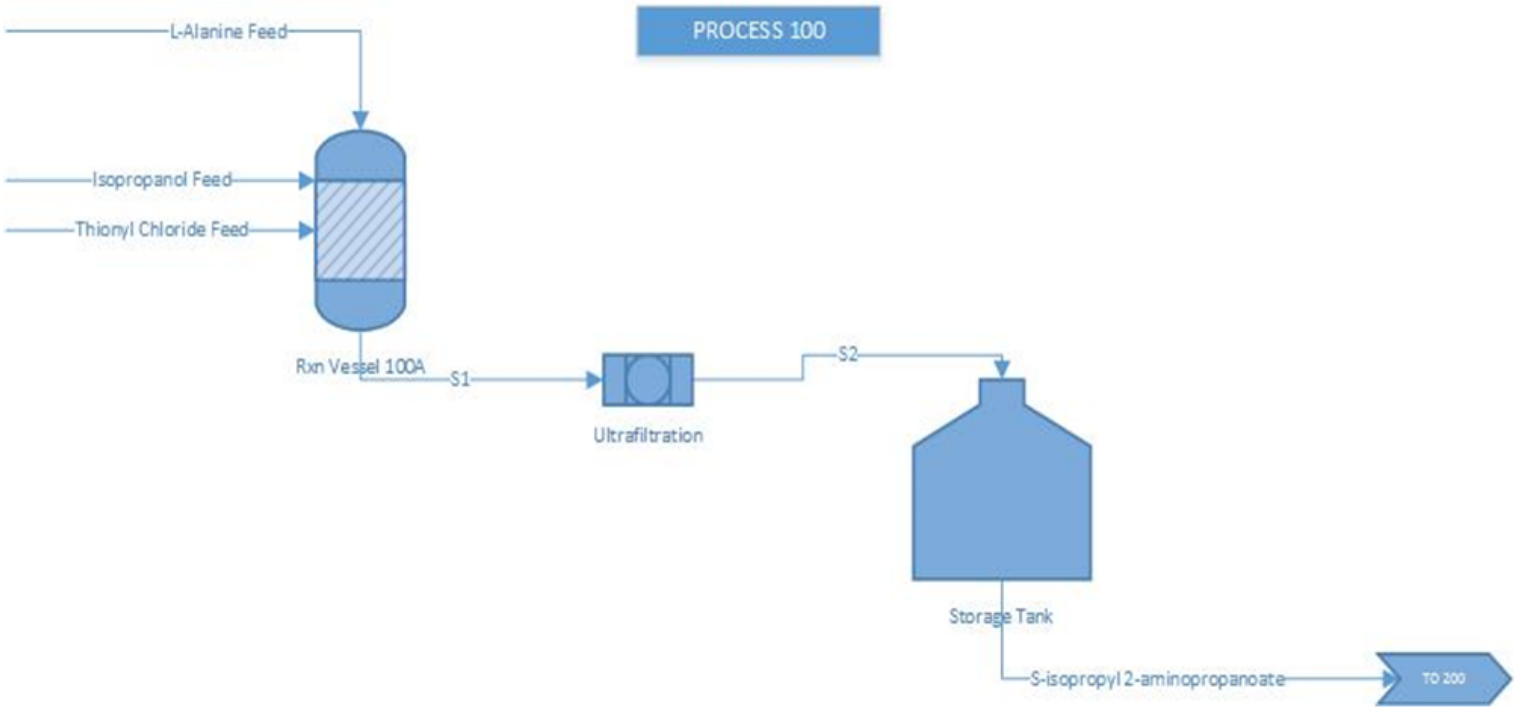


Figure 13-4 Process 100 flow diagram second iteration; addition of ultrafiltration and storage tank

After refining Process 100, visualized in Figure 13-4, our team discussed the new separation process with industrial consultants; our team concluded that ultrafiltration is extremely rare at the industrial scale, and is infeasible given the massive scale with which our process is operating. Given the total volume of the reaction, it is highly unlikely the time needed for ultrafiltration would be reasonable for the production time discussed for the entire supply of *sofosbuvir*. This was supported by the fact that solids are difficult to transfer from one process to the next, so a concentrated suspension of L-alanine isopropyl ester would be more convenient for the subsequent process.

After reviewing patent language, Process 100 was again revised, visualized in Figure 13-5; it was decided that rotary evaporation used at the bench scale could also be used at the industrial scale and was certainly more feasible than the use of ultrafiltration. Process 100 was revised to include a rotary evaporator, but other vessels remained the same.

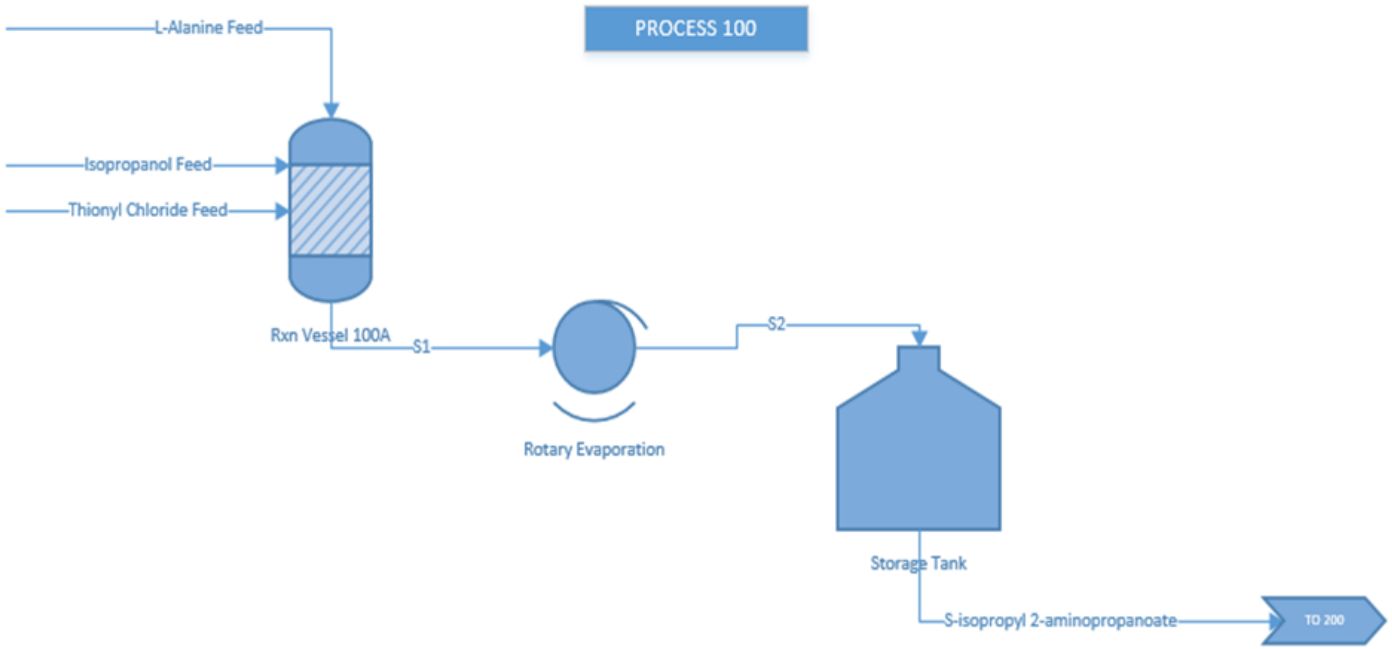


Figure 13-5 Process 100 flow diagram third iteration; addition of a rotary evaporator

After the third revision, Figure 13-5, our team reached out to Natalie Eyke, a chemical engineer at Merck with experience in small-molecules. Natalie advised our team that lab scale rotary evaporation is perhaps better adapted as a flash distillation to quickly remove solvent. Because IPA is relatively volatile, the solvent would be heated and removed from the solution resulting in a concentrated L-alanine isopropyl ester solution. However, our team was concerned that excessive heating could damage the product. The flash vessel was designed to operate as an evaporator unit, running at the vapor pressure of IPA at room temperature rather than using the vapor temperature at atmospheric pressure. The flash vessel design was incorporated in the subsequent flow diagram (Figure 13-6).

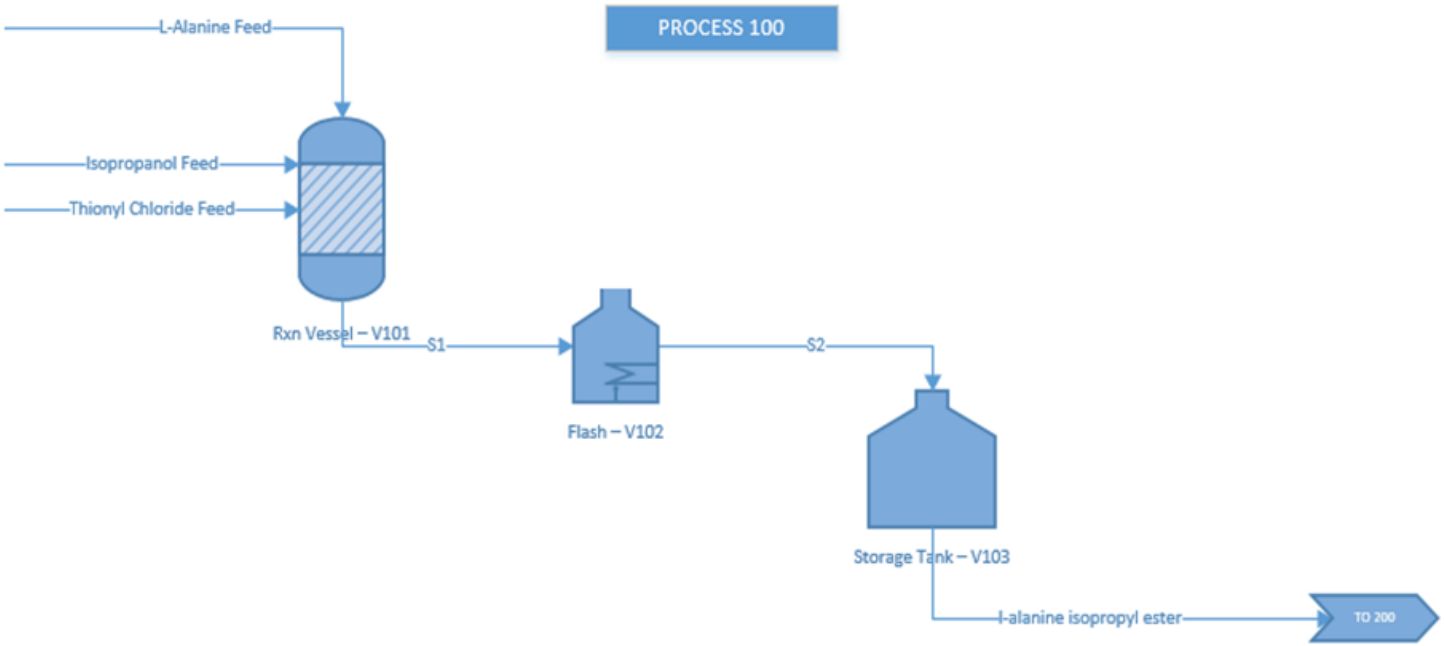


Figure 13-6 Process 100 flow diagram fourth iteration; addition of flash vessel for separation

Figure 13-6 depicts the last iteration before the finalized flow diagram for Process 100 was generated. In discussions with industrial consultants following the selection of the flash vessel, concerns regarding the collection, potential re-use, sale or wasting of the evaporated solvent arose. In order to return the distillate to the waste vessel or to the process, it had to be condensed back to a liquid state. Pharmaceutical processes rarely re-use solvents, as it interferes with batch integrity and introduces potential impurities to the process. In order to reduce the volume of waste or to sell the waste to a distributor who might purify it, our team decided to consider the use of a distillation column with multiple trays and a condenser and reboiler, to maximize the purity of IPA in the waste streams, as other liquids, namely unreacted thionyl chloride and side products, would be present in the stream. Furthermore, the low vapor pressure of IPA (0.04 bar) was a safety concern. These considerations are included in the final process flow diagram, presented in Section 15 and discussed in detail in Section 16.

13.3.2 Reaction 2 - Process 200

Reaction 2, herein Process 200, was developed from a patent by Jiangsu Hanson Pharma Group (Appendix A-3), which described for the production of Intermediate A1. The reaction required the addition of DCM, which would act as the main solvent in the process, to a vessel (V200A). Under nitrogen protection at -50° C, phenyl dichlorophosphate and DIEA were added and stirred before the L-alanine isopropyl ester from Process 100 was added. The solution reacted over 3-4 hours. In a separate reaction vessel (V200B) DCM was charged into the vessel before 2-hydroxy, 6-chloropyridine and DIEA were added. The mixture was stirred for 1-2 hours. After the contents of V200B were fully reacted, the contents of V200B were added to V200A to react for 6 hours. After the process was completed, the product was washed with a

combination of water and salt water to remove leftover reactants and then dried via anhydrous sodium sulfate. Intermediate A1 was then concentrated for use in Process 300.

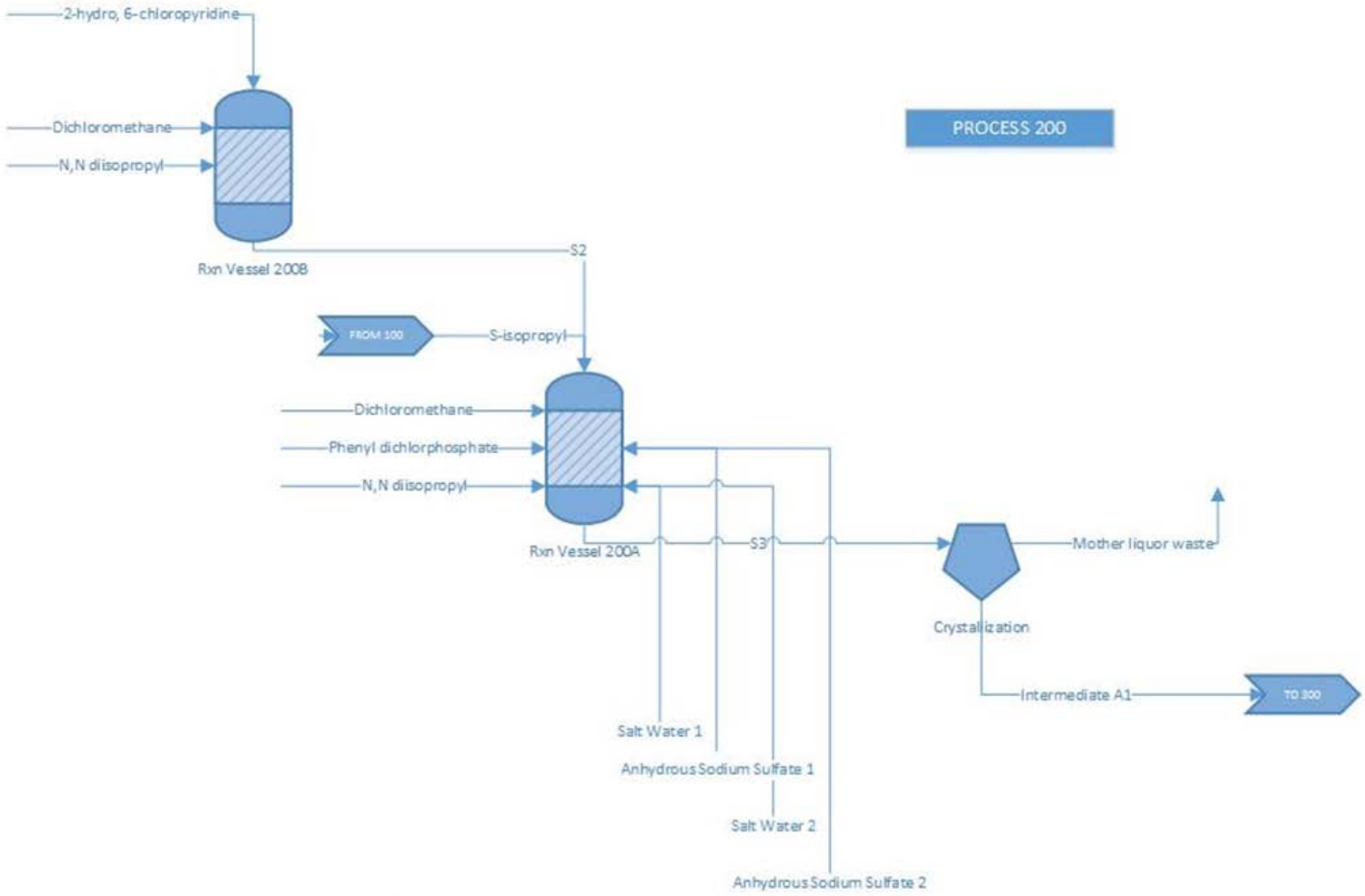


Figure 13-7 Process 200 flow diagram first iteration: development of process from patent scaling

Process 200, presented in Figure 13-7, initially featured the addition of V200B reactants to an independent vessel (Vessel 200B) to produce Intermediate A2. Meanwhile, V200A reactants were loaded into Vessel 200A and reacted the prescribed amount of time before the products of reaction V200B were added to V200A. After several hours of reaction, the final product is washed with cycles of salt water and dried with anhydrous sodium sulfate in vessel V200A before the final product was removed for crystallization.

Revisions were made to the process, visualized in Figure 13-8, mainly to the separation methods and reaction vessel scheme. Conversations with industry consultants centered around the method by which the reaction vessels were used and ordered for the most efficient reaction process. The patent calls for a 2:1 volume ratio of V200A and V200B to create Intermediate A1, and it became clear that the volume required for Vessel 200A would be far too large, especially after wash steps. Because the wash steps effectively doubled the volume, the reactor would require double the original working capacity. Furthermore, our team found that washing in the same vessel could affect batch integrity, because the step would create a bottleneck and there would be no clean-in-place operation. Finally, as previously discussed for Process 100, crystallization is normally not used for intermediate products.

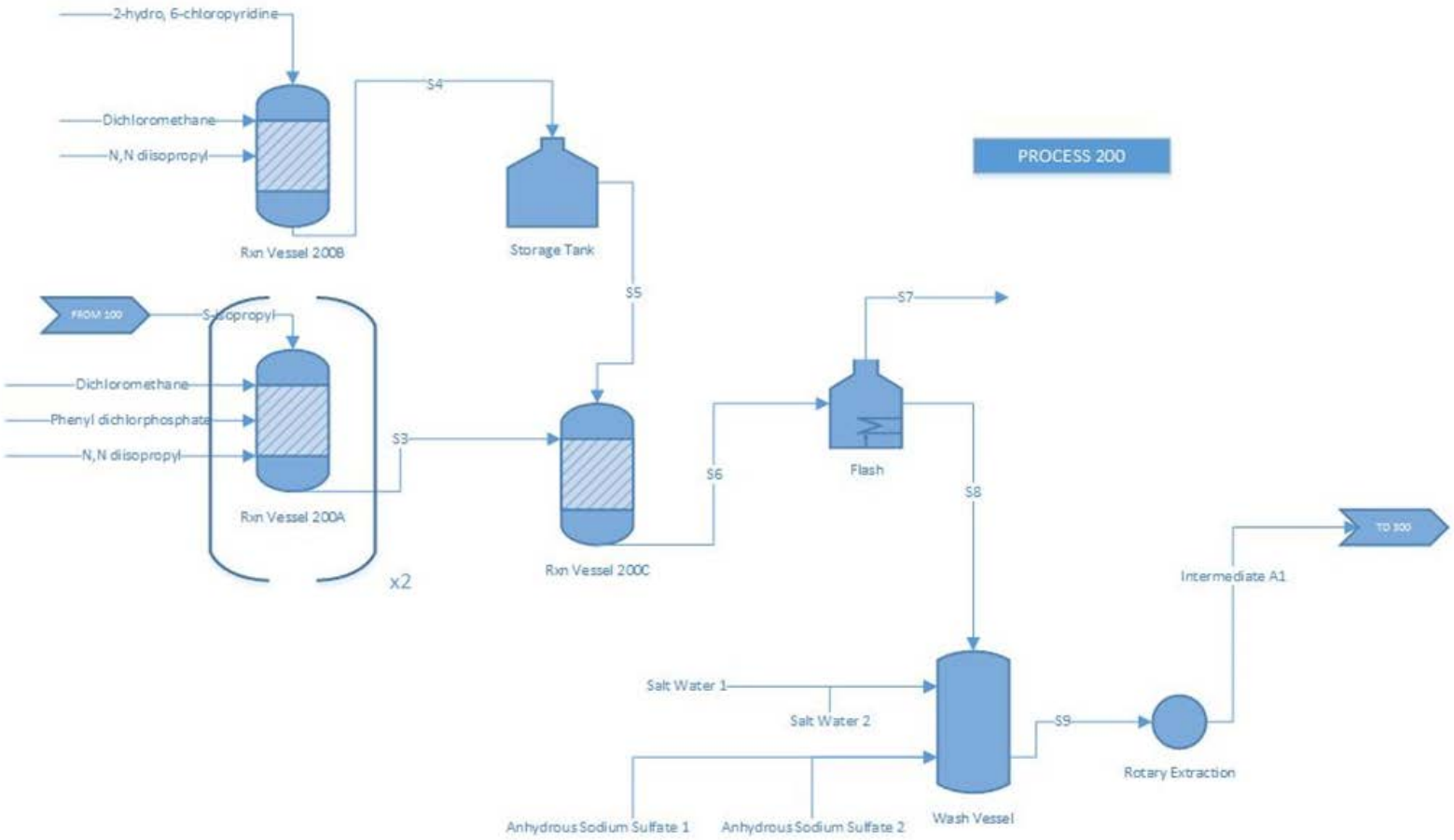


Figure 13-8 Process 200 flow diagram second iteration: refinement of process vessels and separations and optimization of scheduling

In order to account for the considerable volume required for the DCM, our team decided that running two reaction vessels in parallel was best, as it would allow for the bulk pricing and purchase of reactors of similar volume. L-alanine isopropyl ester from Process 100 is split evenly between the two reaction vessels and even quantities of the phenyl dichlorophosphate are reacted in the Vessel to yield Intermediate A2, which leaves in stream S3 in Figure 13-8. Simultaneously, 6-chloro, 2-hydroxypyridine is mixed with DCM and DIEA in Vessel 200B. During the development of the process in Superpro, it was clear that the scheduling of Process 200 was bottlenecked about the mixing occurring in Vessel 200B due to a long waiting period for Vessel 200A to load its product into Vessel 200C. In order to remove this bottleneck, a storage tank was added to the process to allow for cleaning- and sterilizing-in-place to take place before the next batch, which decreased the turnaround time. The products of both reactions are fed to a third reactor (V200C) to remove the bottleneck. Our team reasoned that without the third reaction vessel (V200C) the production timeframe might not be feasible, so the added costs of the vessel were necessary and acceptable. After the reaction was completed, industrial consultants suggested flash vaporizing off a significant portion of the DCM, which was simply a solvent in the process, to reduce the volume of product that would need be washed and reduce the volume of the wash vessel. After evaporating off a portion of the DCM, the product solution was charged to a wash vessel and washed with the two cycles of water and one cycle of salt water. Water was removed from the washed solution using sodium sulfate. Finally, rotary evaporation was used to concentrate the product, as we thought at the time that rotary evaporation was the best method of concentration. The concentrated Intermediate A1 was then fed to Process 300 for the final synthesis of *sofosbuvir*.

While Figure 13-8 made substantial progress for the process design of Process 200, our team made further considerations to refine the process, shown in Figure 13-9. As previously discussed for Process 100, Natalie Eyke our team that flash vessels are a better interpretation of rotary evaporation at the industrial scale. Taking into consideration the heat sensitivity of intermediate A1, the new flash vessel, as well as the flash vessel already involved in the process, was designed to flash the DCM at its vapor pressure at room temperature. The vapor pressure of DCM at ambient conditions is 0.54 bar, which is a reasonable operating condition for the flash vessels. Waste considerations were made for the process and the process flow diagram was revised to reflect solvent flash and condensation. Furthermore, industrial consultants revised a suggestion made in previous meetings regarding the flow rate between vessels. Previously, our team had been operating under the suggestion that vessels of 100 m^3 could be filled within about an hour, a flow rate of approximately 1500 L/min. After consideration, our team revised this assumption, realizing that 1500 L/min was actually quite. While possible if a large enough pump was used, our team decided to proceed with a lower flow rate of precisely 500 L/min. After investigating the effects this flow rate change had on the flow rate, it became clear that Reaction Vessel 200B, now renamed to V202, would no longer cause a bottleneck if the storage tank were not employed. Since the storage tank was now unnecessary to prevent a bottleneck in V202, our team decided to remove the tank to reduce equipment costs. To simplify process scheduling, parallel reaction vessels were removed.

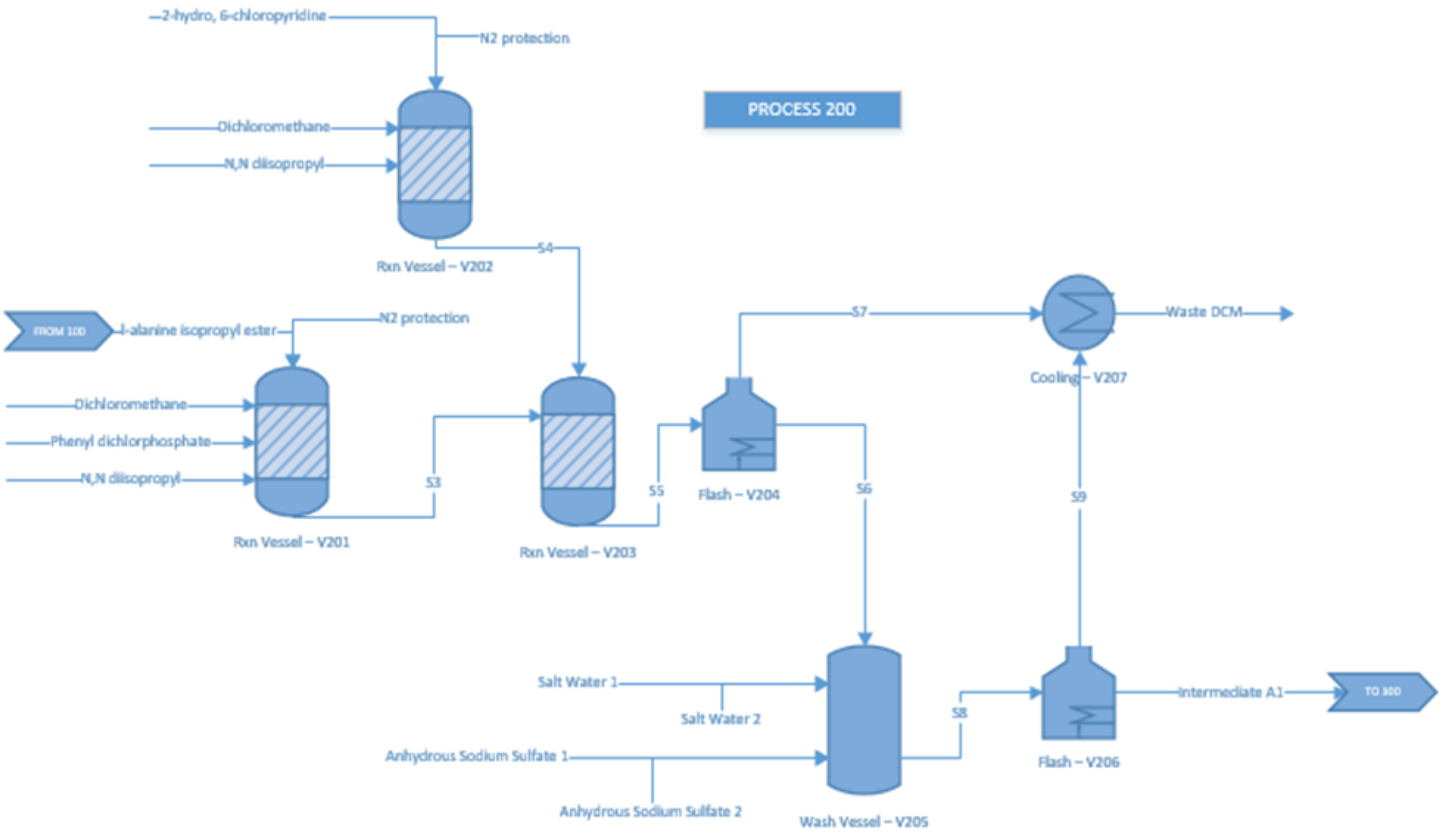


Figure 13-9 Process 200 flow diagram third iteration; addition of flash and condensation processes for DCM as well as explicit use of nitrogen protection

Figure 13-9 represents the last iteration before the finalized flow diagram for Process 200 was generated. While the process visualized in Figure 13-9 is reasonable, our team made additional revisions to address various aspects of the process. The reactor volumes of V201 and V203 would be too large to be reasonably purchased. Furthermore, our team determined that it was most likely that the anhydrous sodium sulfate drying was down outside the wash vessel, perhaps in a packed bed. These considerations are included in the final process flow diagram, presented in Section 15 and discussed in detail in Section 16.

13.3.3 Reaction 1 - Process 300

Reaction 1, herein Process 300, was developed from the same patent by Jiangsu Hanson Pharma Group (Appendix A-3), describing the synthesis of the final product, *sofosbuvir*. The patent called for the addition of solvent THF to the previously synthesized Intermediate A1. Once suspended, reactants methyluridine and DIEA were added to the reaction vessel along with a catalyst, zinc chloride. Under nitrogen protection, the reactor was heated to 60°C and the reaction proceeded for 15-40 hours. After reaction, the product stream was mixed with ethyl acetate and washed with various washing solvents: saturated ammonium chloride solution, 0.5 M hydrochloric acid, sodium carbonate/bicarbonate buffer, and saturated salt water. After the wash, water is removed from the organic phase by passing the solution over anhydrous sodium sulfate. The water-removed solution is concentrated and then crystallized using acetone and DCM. The initial process is visualized in Figure 13-10.

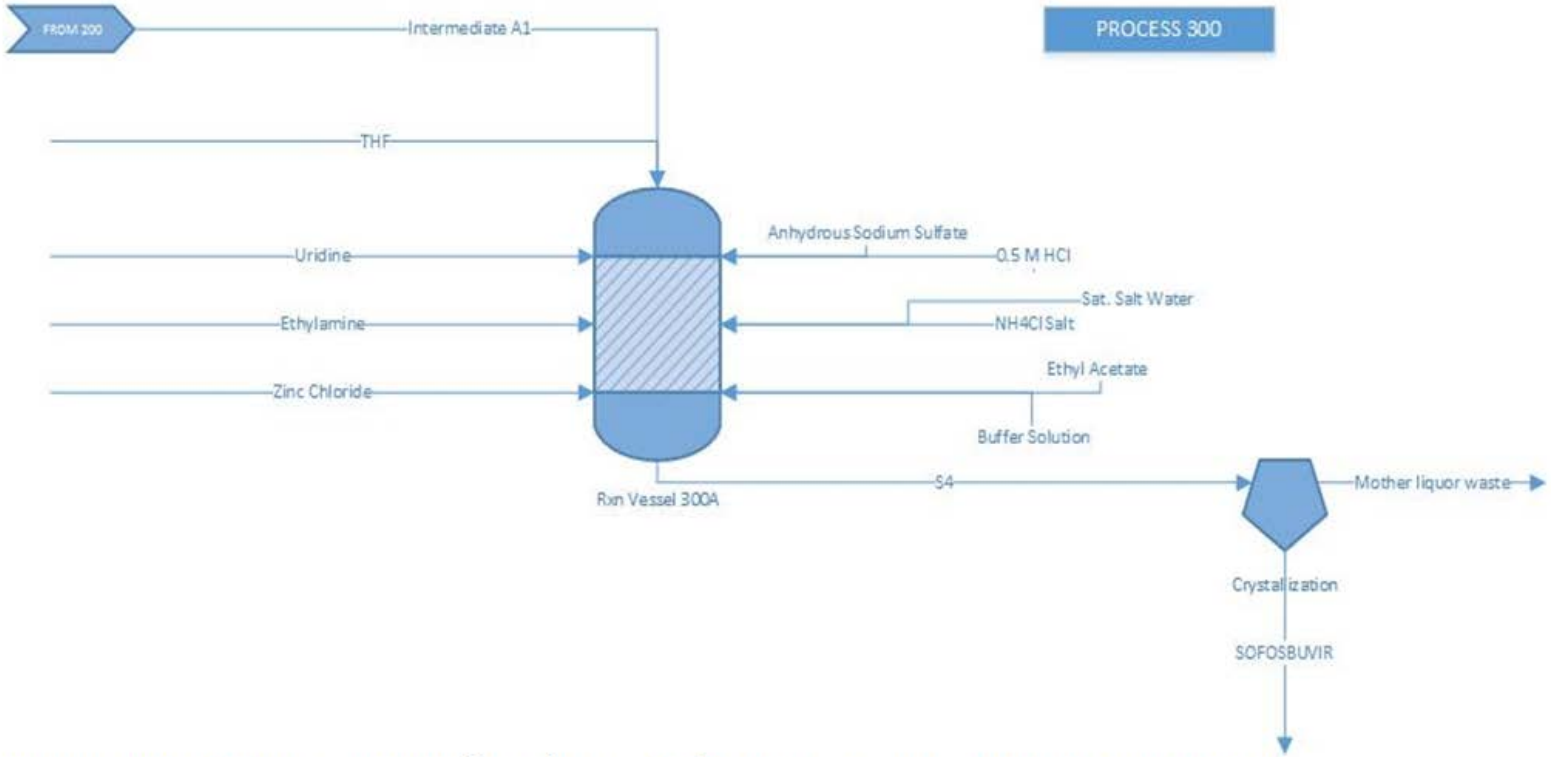


Figure 13-10 Process 300 flow diagram first iteration; patent interpretation

Similar to Process 200, the patent was initially interpreted to perform the reaction and wash steps within the same vessel, but this assumption was eventually ruled out, as it is would create a bottleneck and require excessively large reaction vessels; revisions for Process 300 were made in Figure 13-11. Again, our team was concerned that the massive wash volume required for the process would be too cumbersome for a reaction vessel and would be better suited for an independent wash vessel. The patent uses the vacuum evaporation to yield the "oily" product before crystallization to yield the nearly pure *sofosbuvir*. Process 300 was revised to include a separate wash vessel as well as a vacuum evaporation unit to reduce the volume of the solvent before crystallizing the final product. These changes are reflected in Figure 13-11.

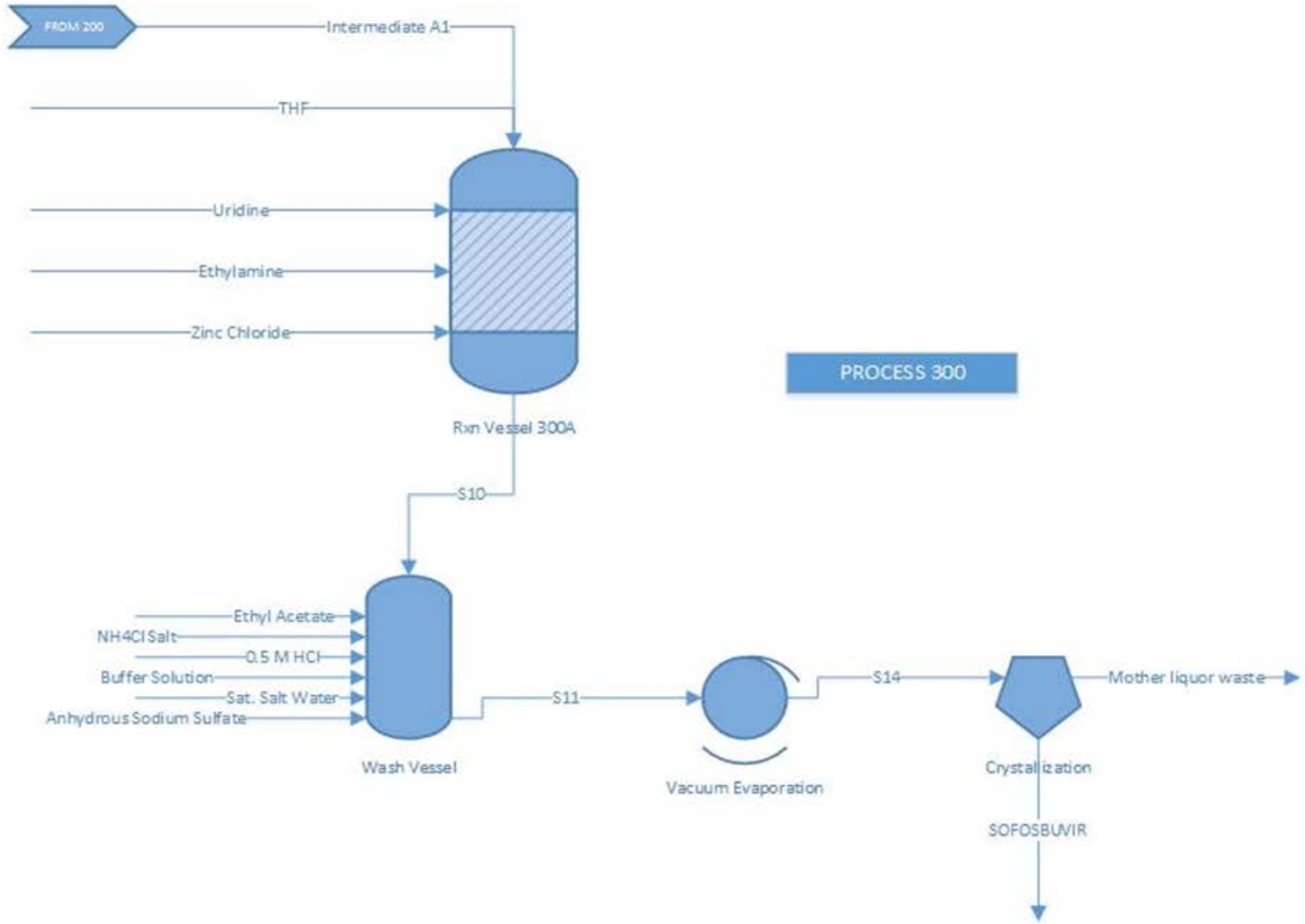


Figure 13-11 Process 300 flow diagram second iteration; addition of wash vessel and rotary evaporator

In subsequent meetings with industrial consultants, it became clear that the method by which solvents and products were dried with sodium sulfate was inherently different than our process reflected. Our process added the sodium sulfate to the wash vessel, when for practical purposes the product is run over a bed or through cartridges of sodium sulfate to remove water. After preliminary costing, it was clear that sodium sulfate cartridges would be cost prohibitive, and that using a necessary amount of sodium sulfate and then refreshing it after each batch with nitrogen purging would be more acceptable. Furthermore, Process 300 also changed in its volume reduction step, using the same method as Processes 100 and 200 wherein a flash vessel was used rather than rotary evaporation. The flash vessel was designed to run at ambient temperature and a pressure well below ambient, nearly 0.1 bar, the vapor pressure of the main solvents. Furthermore, a condenser was added after the flash unit to condense the solvent being vaporized for re-sale or disposal; these changes are reflected in Figure 13-12.

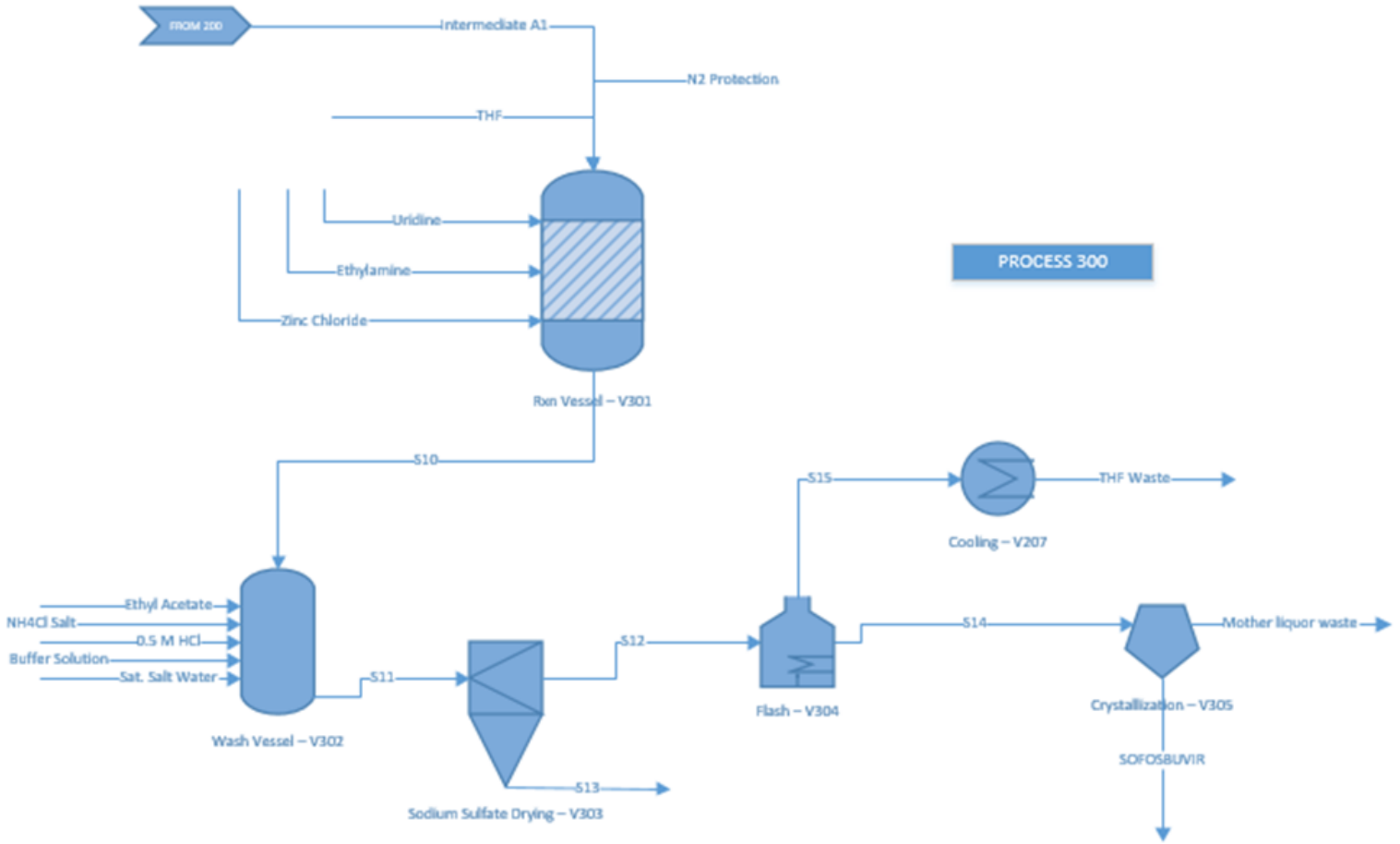


Figure 13-12 Process 300 flow diagram third iteration; addition of sodium sulfate drying bed as well as flash vessel and condenser

Figure 13-12 represents the last iteration before the finalized flow diagram for Process 300 was generated. In subsequent meetings, our team determined that the vacuum like pressure necessary in the flash vessel, was too low to be safely and economically operated; the use of a distillation column, much like Process 100, was considered. We reached out to Dr. Igor Dubovyk, a medical chemist at Pharmacyclics for better interpretation of the wash steps. Furthermore, the size and behavior of the crystallization unit were clarified with regards to the patent, as many consultants remarked that given the large volume of solvent remaining, it might be possible that the patent was referring to a centrifugal crystallization. These considerations are included in the final process flow diagram, presented in Section 15 and discussed in detail in Section 16.

Endnotes

13-1: Ross, B. S., Reddy, P. G., Zhang, H., Rachakonda, S., & Sofia, M. J. (2011). *Synthesis of Diastereomerically Pure Nucleotide Phosphoramidates*. The Journal of Organic Chemistry,76(20), 8311-8319. doi:10.1021/jo201492m

13-2: Medivir, A. (2015). Global Patent No. WO2015/56213. Geneva, Switzerland: The World Intellectual Property Organization (WIPO). *Synthesis of l-alanine isopropyl ester.*

13-3: Jiangsu Hanson Pharma Group Co., Ltd. (2015). P.R.C. Patent No. CN105461773. Beijing, China: State Intellectual Property Office of the People's Republic of China (SIPO). *Synthesis of Intermediate A1 and Sofosbuvir.*

Section 14 - Assembly of Database

The database of chemicals used throughout the process can be found in Appendix M as MSDS sheets. Reactants are listed in Appendix M-1 in alphabetical order; solvents, wash salts, desiccant, and catalysts are listed in Appendix M-2 in alphabetical order. The chemicals considered hazardous in this process are THF and ethyl acetate, both of which are highly flammable in the presence of oxygen. Prices for all chemicals are given in Table 14-1. Because of the large quantities needed for each batch, it was not feasible to obtain quotes from specialized chemical companies such as Sigma Aldrich. For entries that are sourced from "India Import/Export Data," the average recent import price of chemicals into India were used as the component price per kilogram[14-1]. This data can be found in Appendix G. Other vendors were found using Alibaba, which is a major exporter of pharmaceutical chemicals to India.

Table 14-1 Summary of Raw Material Prices and Vendor Sources

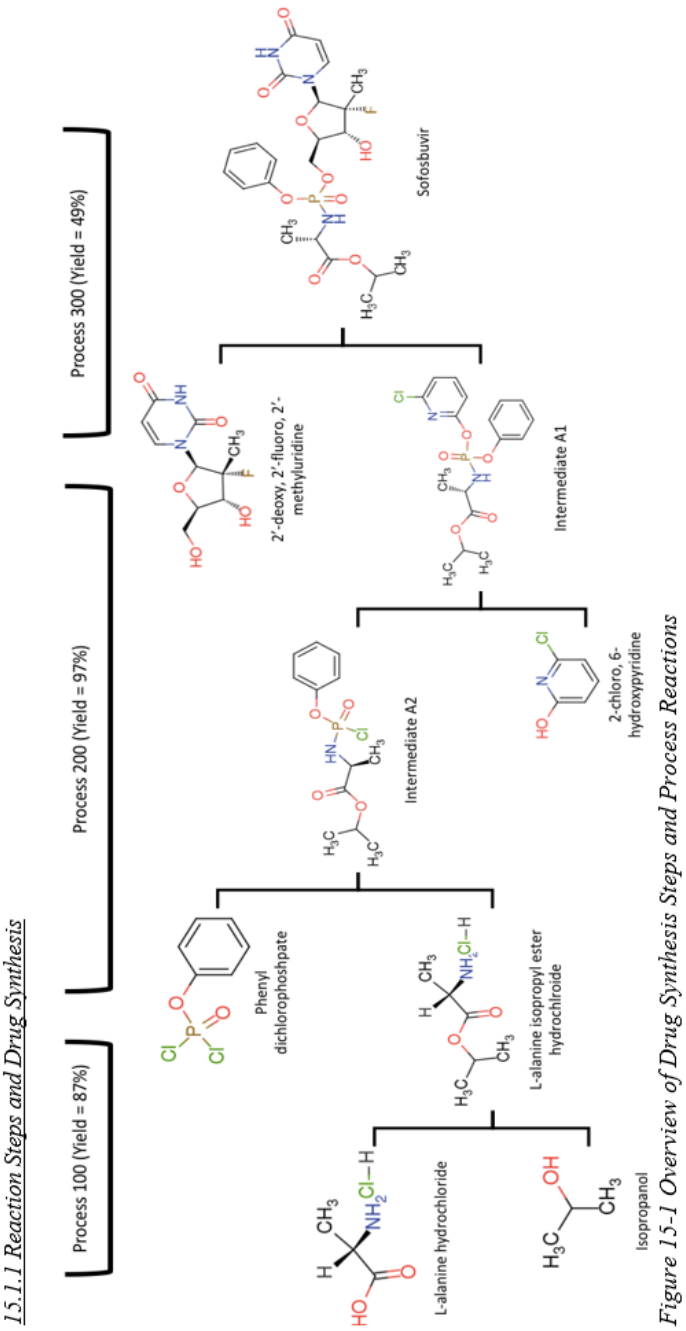
Component	Price ($/kg)	Source
L-Alanine hydrochloride	$4.34	India Import/Export Data
Isopropanol	$0.96	Qingdao HanHaiDa Import And Export Co., Ltd.
Thionyl chloride	$0.64	India Import/Export Data
Phenyl dichlorophosphate	$8.67	Haihang Industry (Jinan) Co., Ltd.
Dichloromethane	$0.42	Taizhou Ruibai Chemical Co., Ltd.
N,N-Diisopropylethylamine	$5.47	India Import/Export Data
2-Chloro-6-hydroxypyridine	$5.00	Jinan Finer Chemical Co., Ltd.
Saturated Salt Water	$0.01	India Import/Export Data
Anhydrous sodium sulfate	$0.10	India Import/Export Data
2'-deoxy-2'-fluoro-2'-methyluridine	$500-888	India Import/Export Data
Zinc Chloride	$0.90	Taian Health Chemical Co., Ltd.
Ethyl Acetate	$0.30	Shanghai Polymet Commodities Ltd.
Water for Injection	$0.12	India Import/Export Data
Ammonium chloride	$0.14	Dahua Group Dalian Guanlin International Trade Co., Ltd.
Hydrochloric Acid 0.5M	$0.15	India Import/Export Data
Sodium Carbonate	$0.20	India Import/Export Data
Sodium Bicarbonate	$0.22	Tianjin Huge Roc Enterprises Co., Ltd.
Sodium Chloride	$0.38	India Import/Export Data
Acetone	$0.60	India Import/Export Data
Nitrogen	$0.11	India Import/Export Data
Ethylene Glycol	$1.05	Indiamart
Propane	$0.40	India Import/Export Data
Ribavarin	$44.18	India Import/Export Data

Endnotes

14-1: Info Drive India (2016). *Import export data, export import data from customs*. Retrieved from infodriveindia.com

Section 15 - Process Flow Diagram and Material Balances

15.1 Process Flow Diagrams



15.1.1 Reaction Steps and Drug Synthesis

Figure 15-1 Overview of Drug Synthesis Steps and Process Reactions

15.1.2 Process 100

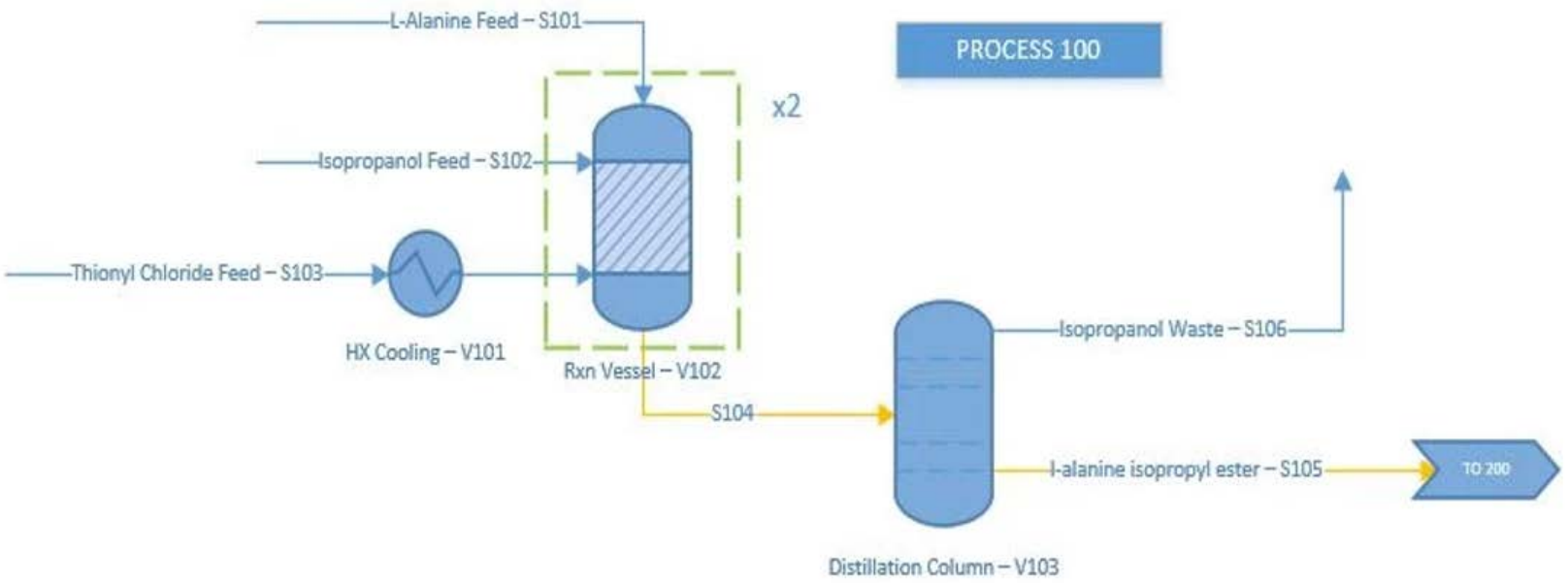


Figure 15-2 Process 100 Flow Diagram

15.1.3 Process 200

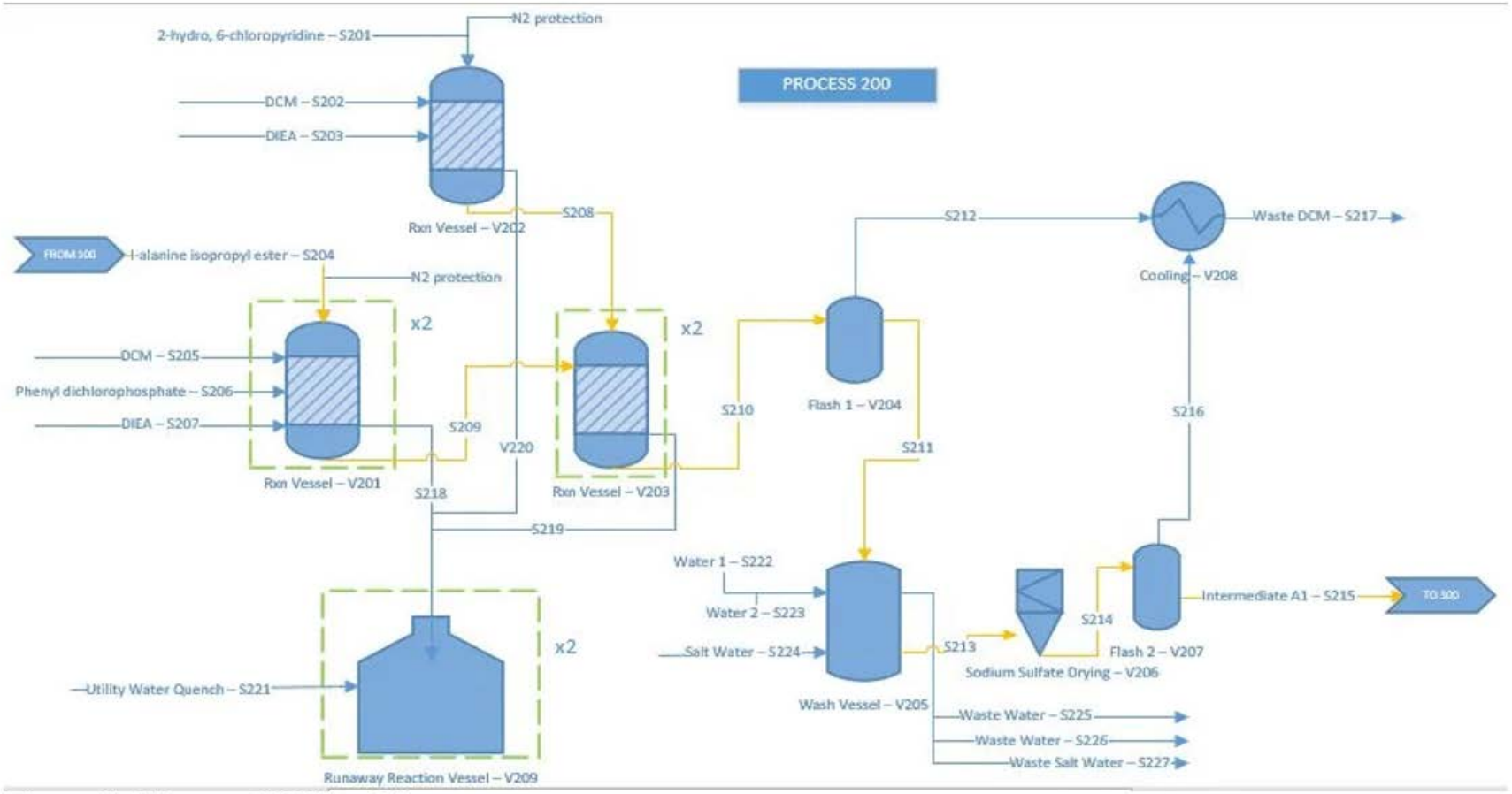


Figure 15-3 Process 200 Flow Diagram

15.1.4 Process 300

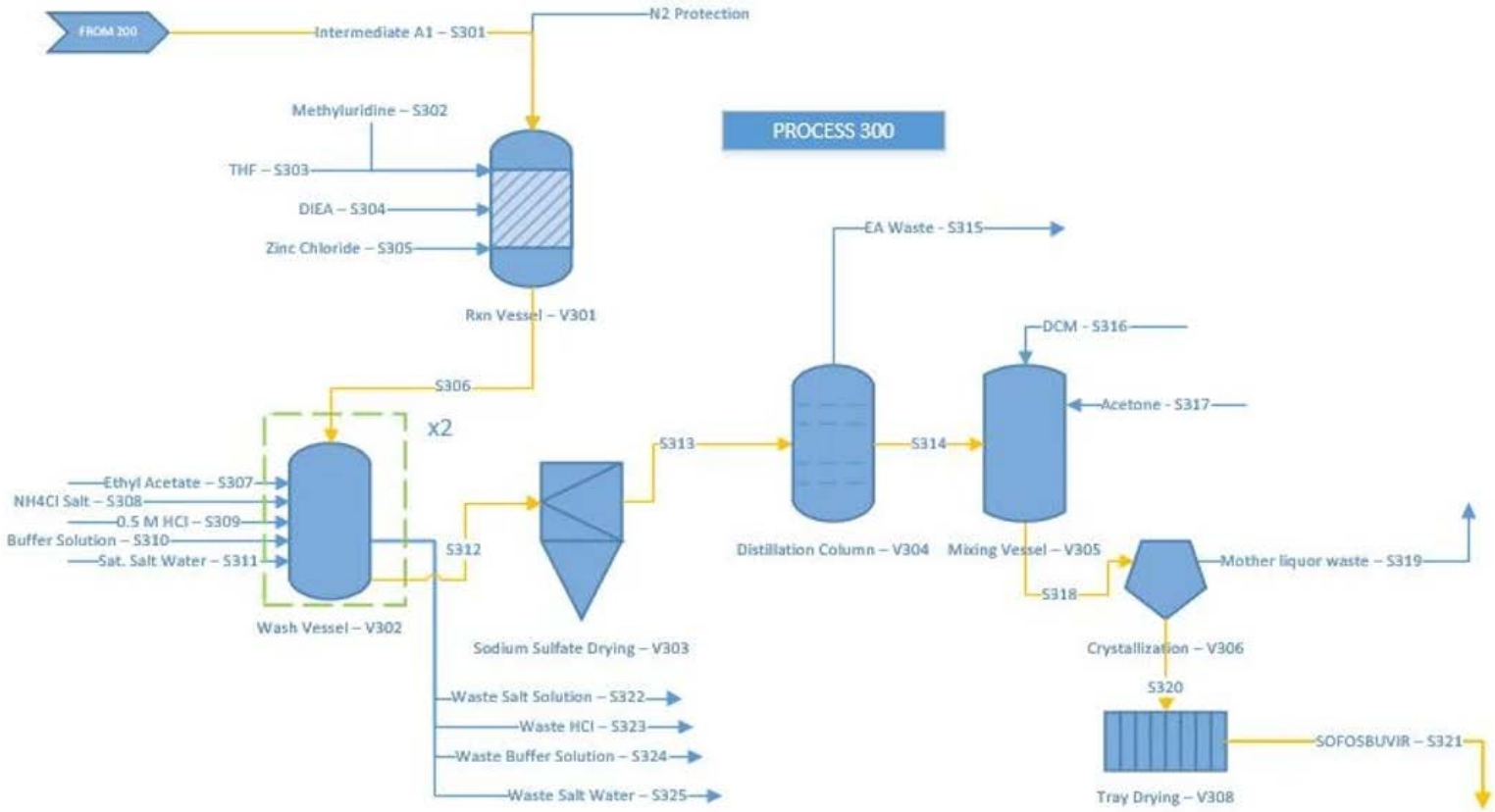


Figure 15-4 Process 300 Flow Diagram

15.2 Material Balances

Material Balances were calculated for each of the reactor units and summarized below. For Process 100, the synthesis of L-alanine isopropyl ester hydrochloride and its side products are summarized in Table 15-2. The synthesis is assumed to go to completion because the reaction and wash yield (87%) is rather high. Thus, it is reasonable to assume that any side products are negligible. The same assumption is extended to Process 200, whose reactions are summarized in Tables 15-2, 15-3, and 15-4. Though Process 300 has significantly lower yield (49%), the reaction step is assumed to reach completion because Intermediate A1 is fed in extreme excess.

Table 15-1 Synthesis of L-alanine isopropyl ester hydrochloride in reactor V101

Reaction 1: $C_3H_7NO_2 \cdot HCl$ (L-alanine hydrochloride) + C_3H_7OH (Isopropanol) → $C6H_{13}NO_2 \cdot HCl$ (L-alanine isopropyl ester hydrochloride) + HOH
Reaction 2: $HOH + SOCl_2 \rightarrow 2HCl + SO_2$

Stream Number	**1**	**2**	**3**	**4**
Stream Description	L-Alanine In	IPA In	Thionyl Chloride In	Reactor V102 Out
Total Mass (kg)	4569	100108	8653	113330
		Component Mass (kg)		
L-Alanine	4569	0	0	590
Isopropanol	0	100108	0	98205
Thionyl Chloride	0	0	8653	4883
L-Alanine Isopropyl Ester Hydrochloride	0	0	0	5313
HCl	0	0	0	2311
SO2	0	0	0	2029
In - Out				0

Table 15-2 Synthesis of Intermediate A2 in reactor V201

Reaction: $C_6H_{13}NO_2 \cdot HCl$ (L-alanine isopropyl ester hydrochloride) + $C_6H_5PO_2Cl_2$ (Phenyl dichlorophosphate)→ $C_{12}H_{17}ClNO_4P$ (A2) + 2HCl

Stream Number	**8**	**9**	**10**	**11**	**12**
Stream Description	DCM In	Phenyl In	L-AIE In	DIEA In	Reactor V201 Out
Total Mass (kg)	149335	6634	5313	8041	169323
Component Mass (kg)					
DCM	149335	0	0	0	149335
Phenyl Dichlorophosphate	0	6634	0	0	0
L-Alanine Isopropyl Ester hydrochloride	0	0	5313	0	42
DIEA	0	0	0	8041	8041
Intermediate A2	0	0	0	0	9612
HCl	0	0	0	0	2293
In - Out					0

Table 15-3 Dissolution of 2-chloro, 6-hydroxypyridine in reactor V202

Stream Number	**13**	**14**	**15**	**16**
Stream Description	Pyridine In	DCM In	DIEA In	Reactor V202 Out
Total Mass (kg)	3705	76391	4021	84116
Component Mass (kg)				
DCM	0	76391	0	76391
DIEA	0	0	4021	4021
2-Chloro, 6-Hydroxypyridine	3705	0	0	3705
In - Out				0

Table 15-4 Synthesis of Intermediate A1 in reactor V203

Reaction: $C_{12}H_{17}ClNO_4P$ (A2) + C_5H_4ClNO (2-chloro, 6-hydroxypyridine) → $C_{17}H_{20}ClN_2O_5P$ (A1) + HCl

Stream Number	**12**	**16**	**17**
Stream Description	Reactor 1 out	Reactor 2 out	Reactor 3 out
Total Mass (kg)	169323	84116	253440
	Component Mass (kg)		
DCM	149335	76391	225726
L-Alanine Isopropyl Ester hydrochloride	42	0	42
DIEA	8041	4021	12062
Intermediate A2	9612	0	870
HCl	2293	0	3336
Hydroxypyridine	0	3705	0
Intermediate A1	0	0	11405
In - Out			0

Table 15-5 Synthesis of sofosbuvir in reactor V301

Reaction: $C_{17}H_{20}ClN_2O_5P$ (A1) + $C_{10}H_{13}FN_2O_5$ (methyluridine) → $C_{22}H_{29}FN_3O_9P$ (sofosbuvir) + C_5H_4ClNO (2-chloro, 6-hydroxypyridine)

Stream Number	**30**	**31**	**32**	**33**	**34**	**35**
Stream Description	M-uridine In	Int A1 In	ZnCl2 In	THF In	DIEA In	Reactor Out
Total Mass (kg)	3640	11143	2884	49778	2730	70174
			Component Mass (kg)			
Methyluridine	3640	0	0	0	0	0
Intermediate A1	0	11143	0	0	0	5565
Zinc Chloride	0	0	2884	0	0	2884
THF	0	0	0	49778	0	49778
DIEA	0	0	0	0	2730	2730
Sofosbuvir	0	0	0	0	0	7405
Pyridine	0	0	0	0	0	1812
In - Out						0

Section 16 - Process Description

In order to provide a much more cost-effective alternative to brand name Hepatitis C drugs, it was necessary to analyze various synthesis routes and methods to limit costs. Patent analysis, chemical synthesis route determination and raw material costing was a majority of process development, with the raw materials often being the key cost contributor on a per batch basis. Once a legitimate synthesis route was determined, it was necessary to recreate the often lab scale development processes on a commercial scale. Iteration of process steps, reaction routes, separation techniques and drying methods was necessary to develop an acceptable, commercial-scale process for the production of affordable *sofosbuvir*.

16.1 Chemical Synthesis

The synthesis of *sofosbuvir* was generated from an exhaustive patent analysis and search, described in detail in Section 13.2. Figure 15-1 visualizes the final, overall synthesis route for *sofosbuvir*, separated into four reactions carried out in three reaction processes. IPA, is used as a solvent for L-alanine hydrochloride, the salt of L-alanine ester. IPA is fed in excess to maximize the reaction yield, with the majority of the solvent left unreacted and distilled after the reaction step. The reaction is carried out in Process 100, discussed in Section 16.2, and yields, at 87%, L-alanine isopropyl ester for use in subsequent reactions.

The product of the first reaction, L-alanine isopropyl ester, is added to a reaction vessel in Process 200 with various solvents, including mainly DCM, and main reactant phenyl dichlorophosphate, fed in excess. The reaction yields phenyl(isopropoxy-L-alanine) phosphorochloridate, herein Intermediate A2, which is then added to a separate reaction vessel to a solution containing main reactant 2-chloro, 6-hydroxypyridine, which is suspended in DCM

from a previous reaction step. The two reactants yield a reactive intermediary referred to in the patent as Intermediate A1. The overall yield of the three reactions, all carried out in Process 200, is 97% and the Intermediate is fed to subsequent processes.

The most specialized chemical in the synthesis is used in the final reaction to produce *sofosbuvir*. The reactive Intermediate A1 is added to a reaction vessel with solvent THF with main reactant methyluridine. These two reactants yield *sofosbuvir* at 47% overall, the lowest of all yields, yet most efficient of all patents analyzed. Each of the reactions involves a complex series of separations, washes and drying phases, which are all discussed in detail in the remainder of Section 16.

16.2 Process 100

Process 100, whose development is discussed in detail in Section 13.3.1, was developed from a patent by Medivir, which accounted for the production of L-alanine isopropyl ester. The patent calls for the dropwise addition of thionyl chloride at 0°C to a suspension of L-alanine hydrochloride dissolved in IPA which is to be stirred overnight. Process 100, visualized in Figure 15-2, demonstrates three main vessel procedures. A heat exchanger, V101, is used to cool inlet thionyl chloride from ambient temperature to the prescribed 0°C for dropwise addition to the reaction vessel, V102. The heat exchanger is operated with coolant ethylene glycol, which is cooled between batches in a refrigerated chiller unit to -10°C. All three solvents are charged with pumps at 500 L/min into two parallel reaction vessels for the overnight reaction time, which was assumed to be 16 hours. All pumping speeds are maintained at 500 L/min unless otherwise noted. After the reaction is complete, the product is pumped continuously into a distillation column, V103, where the main solvent, IPA, is removed from the product L-alanine isopropyl ester; the distillation process was modeled in ASPEN using RADFRAC. The use of multiple

trays in the column allows for a purer overhead product of waste IPA. The purer IPA facilitates its resale to distributors for little or no cost, as it is then easily repurposed as pure IPA. Pharmaceutical processes do not recycle solvents or reagents, as this does not maintain batch integrity. The addition of trays to the column was non-cost prohibitive, so the generation of a pure overhead was a reasonable consideration; the overhead IPA is condensed using propane coolant again with a chiller unit cooled between batches. After distillation removes most of the solvent, the product, suspended in some IPA, is pumped into Process 200 for further synthesis. After each vessel is used, it is cleaned in place before the next batch begins. Vessel details and specifications can be found in Sections 18 and 19.

16.3 Process 200

Process 200, whose development is discussed in detail in Section 13.3.2, was established from a patent by Jiangsu Hanson Pharma Group Co, which described the production of Intermediate A1. The Process, which is visualized in Figure 15-3, features a series of vessel procedures to produce the final reactive intermediary, Intermediate A1, for the production of *sofosbuvir*. In two reaction vessels in parallel, V201, DCM is added under nitrogen protection and cooled to -50°C using liquid propane in cooling coils. The liquid propane coils are chilled between batches using a refrigerated chiller unit, as are all other coolants in Process 200. Phenyl dichlorophosphate, the main reactant in V201, is added and stirred for 15 minutes before the product of Process 100, L-alanine isopropyl ester, is added. While the L-alanine isopropyl ester is suspended in some remaining IPA, IPA and DCM are miscible and, thus, IPA was assumed to be an inert. All additional flow rates are 500 L/min unless otherwise noted and all materials are charged with pumps to avoid any inconsistency with gravity pumping. DIEA is added at a flow rate of 133 L/min, a scaling factor from the patent which called for dropwise addition. After the

addition of DIEA, the vessel temperature raises to around -5°C over the course of 3-4 hours. As the first reaction vessel, V201, begins its initial cooling step to -50°C, a second reaction vessel, V202 is loaded with DCM and 2-chloro, 6-hydroxypyridine under nitrogen protection and cooled to -10°C using liquid propane in coils. Again, DIEA is added to the vessel at a slower flow rate to account for lab-scale dropwise addition with constant stirring throughout its addition. After the addition of DIEA, the vessel temperature rises to approximately 0°C over the course of 1.5 hours, as the reaction is exothermic. Once V201 reached its ending temperature of -5°C, the contents of V201, which is run in parallel, were pumped to a third vessel, V203, which is also run in parallel. V203 is held at 0°C using liquid brine in coils while the contents of V202 are split evenly and pumped into V203 over the course of 15 minutes. Again, brine is chilled between batches in a refrigerated chiller unit. Once the addition of V202 contents is complete, V203 is stirred for six hours while the contents equilibrate to room temperature. A consideration made during the revisions of Process 200 was the possibility of a runaway chemical reaction, as each of the three reaction steps are significantly exothermic, raising 5-10°C every hour. To account for the possibility of a runaway chemical reaction, two runaway reaction vessels were attached to the 5 total reaction vessels with multiple pumps such that if the vessels began overheating, their contents could be emptied and quenched with utility water to avoid a highly exothermic meltdown.

After the reaction in V203 is complete, the contents of the parallel reactors are pumped into an evaporation vessel, V204, at a flow rate of 500 L/min. The evaporation vessel operates a de-facto flash vessel, though it serves to vaporize DCM at its ambient vapor pressure isothermally to avoid heating damage of the active. The vessel operates at 0.5 bar, just below the vapor pressure of DCM at ambient temperature. The evaporation serves two main purposes: it

drastically reduces the wash volume needed in subsequent procedures and it increases the overall evaporation of DCM in the process that would otherwise be fed to Process 300. V204 evaporates 71% of DCM, which is then condensed using a heat exchanger, V208, operating with chilled propane at -100°C. This propane is, similarly, refrigerated on a batch-by-batch basis in a chiller unit, with a sufficient flow rate and inlet temperature to completely condense the evaporated DCM, which can then be disposed of more affordably.

The now more concentrated product stream enters a wash vessel, V205, where it is washed two times with a pure water stream and one time with a salt water stream. The water and brine are up to 3x more polar than DCM[16-1], allowing for the removal of any polar impurities in the product as well as the removal of some DCM from the product stream. The washing agents are added to the vessel and mixed thoroughly before being removed with some amount of impurities, which call for their safe disposal, a consideration discussed in Section 23.1. After the various wash cycles, the product is pumped into a packed bed of drying agent sodium sulfate, V206. ASPEN simulations, in Appendix I, revealed that approximately 2% of water from the washes remains in the DCM and Intermediate A1 product stream. At an absorption ratio of 1.2 g water:1 g sodium sulfate, approximately 2,400 kg of sodium sulfate packing was required. The bed size was calculated with a void fraction of 0.55, as recommended by industrial consultants, as well as the consideration that sodium sulfate expands as it absorbs water. After the product drying is complete and the water is removed, the bed is emptied and replaced with fresh sodium sulfate, maintaining batch integrity and actually lower the cost of cleaning and sodium sulfate drying costs. The now “dry” product stream is pumped into a second evaporator vessel, V207 with similar operating conditions and stream results as V204. Again, 71% of DCM is evaporated, resulting in an overall volume reduction of 92% of the original solvent feed. The vapor overhead

is, again, condensed in heat exchanger V208 while the final product stream, which is the synthesized Intermediate A1 in a remaining volume of DCM, is pumped into Process 300. After each vessel is used, it is cleaned in place before the next batch begins. The specifications, sizes and number of all equipment in Process 200 can be found in Sections 18 and 19.

16.4 Process 300

Process 300, whose development is discussed in detail in Section 13.3.1, was developedfrom a patent by Jiangsu Hanson Pharma Group (Appendix A-4), which accounted for the production of the final product, *sofosbuvir*. Under nitrogen protection, a reaction vessel, V301, is charged, again at a constant pump flow rate of 500 L/min, with methyluridine, THF, DIEA and zinc chloride. The vessel is then sparged with nitrogen to remove any oxygen that may have been introduced during the process and Intermediate A1 is added to the vessel from Process 200, along with some leftover DCM; however, DCM and THF are miscible and DCM is even used in a later process step, so its presence was acceptable. The contents of the vessel are then heated to 60°C and reacted over "15-40 hours", per the patent; our team decided to react the contents for an overnight duration, 16 hours. After the reaction in V301 is complete the contents are split and transferred to a wash vessel, since the 1:1 wash volume would require a single vessel too large for practical purposes. The wash vessel, V302, is run in parallel and requires various washing agents added sequentially. Ethyl acetate (EA) is added to the product stream. EA and THF are miscible, but *sofosubvir* is more soluble in EA. Saturated ammonium chloride solution creates a phase separation with the EA phase containing *sofosbuvir*, and draws out DIEA. HCl is used to remove the zinc chloride catalyst and any remaining DIEA completely. Sodium carbonate and bicarbonate buffer is added to neutralize the HCl remaining in the rganic phase. Finally, the solution is washed with saturated salt water as a preliminary drying step to

remove water from the organic phase. These washes are performed as liquid-liquid extractions in the wash vessel.

The wash product is then pumped through a sodium sulfate packed bed, V303, much like Process 200. The two packed beds are similar in size and amount of packing material required, and like the packed bed in Process 200, V303 also uses fresh sodium sulfate for each batch. For both packed bed units V206 and V303, the Ergun equation was used to determine the pressure drop in the packed bed to determine the energy requirement of pumps into and out of the vessel. The dried product stream is subsequently pumped into a distillation column, V304, for reasons similar to Process 100, in that the vapor pressure of the main solvent, EA, is far too low for an evaporator vessel, but the recovery of solvent is still highly important to the procedure. The distillation process will occur continuously, as the batch flows out of the packed bed, much like the operation of the evaporators and distillation columns previously used as well. The liquid overhead EA is condensed using liquid propane coolant, which is refrigerated between batches in a chiller unit, and collected for waste disposal and/or resale; the concentrated bottoms product stream enters a final mixing vessel, V305, where solvents DCM and acetone are charged to assist in crystallization. After the solvents and concentrated product are agitated in V305, the contents are pumped out at a very low flow rate, approximately 80 L/min, into the crystallizer unit, V306. This flow rate into the crystallizer was selected based on the rate at which the unit could perform a continuous crystallization, as scaling a crystallizer was more cost intensive than most other equipment. During scheduling, the flow rate into the crystallizer was changed such that the mixing vessel, V305, became the bottleneck, assuring that the flow rate in to V306 was as low as possible. The crystallizer operates continuously for about 20 hours with 4 hours of downtime between batches. Finally, the wet crystals are pumped to a tray drying unit, V308, where the wet

crystals are dried over 30 mins until the remaining EA, DCM and acetone, all of which are extremely volatile, evaporate. The total area of the trays will be 50 square feet, based on the flow rate of the crystallized product out. Furthermore, the mother liquor waste is collected and disposed of properly. Tray drying will yield the final product, *sofosbuvir*, in solid form, ready for encapsulation and long term storage for sale. The specifications, sizes and number of all equipment in the overall process can be found in Sections 18 and 19.

Endnotes

16-1: Louisiana State University (2010). Polarity Index. Retrieved from http://macro.lsu.edu/howto/solvents/Polarity%20index.htm.

Section 17 - Energy Balance and Utility Requirements

For each batch of *sofosbuvir*, 197,000 kWh of energy are required. While this quantity appears to be a large amount, but the overall cost of energy utilities ($23,987 per batch) constitutes only a small portion of the total cost of *sofosbuvir*. Electricity was estimated to cost roughly $0.07 per kWh as noted in Table 17-1 of the Product and Process Design Principles textbook by Dr. Seider (Appendix F-1). This was a reasonable estimate for cost of electricity in India as it is consistent with the prices of $0.08 surveyed by Ovo Energy[17-1]. Furthermore, to encourage industry in India, the government will subsidize energy, so the cost could conceivably be lower than $0.07. The other major cost is for the regeneration of coolant, which is used in the condensers. These costs are interpolated from the data provided in Appendix F-1. More detailed breakdowns of the energy utilities for each individual process stage can be found in Tables 17.1-3 below.

Table 17-1 Utility Costs Per Equipment in Process 100

Unit	Function	Energy Requirement (kWh/Batch)	Cost ($/Batch)
V101 - $SOCl_2$ Heat Exchanger	Cooling	61	$19.70
V102 - Screw Conveyor	Transport	1	$0.06
V102 - Reaction Vessel	Stirring	92	$6.46
V103 - Distillation Column	Heating	44,181	$3,092.69
	Cooling	44,236	$7,154.96
Pumping	Transport	3	$0.23
Process 100 Total		**88,574**	**$10,274.11**

Table 17-2 Utility Costs Per Equipment in Process 200

Unit	Function	Energy Requirement (kWh/Batch)	Cost ($/Batch)
V201 - Screw Conveyor	Transport	1	$0.06
V201 - Reaction Vessel	Cooling	3,833	$1,705.07
	Stirring	35	$2.47
V202 - Screw Conveyor	Transport	1	$0.06
V202 - Reaction Vessel	Cooling	894	$289.35
	Stirring	18	$1.23
V203 - Reaction Vessel	Cooling	230	$47.50
	Stirring	68	$4.76
V204 - Flash	Heating	13,280	$929.60
V205 - Wash Vessel	Stirring	227	$15.88
Salt Water Tank	Stirring	16	$1.10
V207 - Flash	Heating	3,867	$270.69
V208 - Condenser	Cooling	18,284	$2,957.43
Total Pumping	Transport	16	$1.10
Process 200 Total		**40,770**	**$6,226.31**

Table 17-3 Utility Costs Per Equipment in Process 300

Unit	Function	Energy Requirement (kWh/Batch)	Cost ($/Batch)
V301 - Screw Conveyor	Transport	2	$0.13
V301 - Reaction Vessel	Heating	5,180	$362.57
V301 - Reaction Vessel	Stirring	90	$6.29
Buffer Tanks (Combined)	Stirring	27	$1.88
V302 - Wash Vessel	Stirring	113	$7.94
V304 - Distillation Reboiler	Heating	30,397	$2,127.81
V304 - Distillation Condenser	Cooling	30,533	$4,938.58
V305 - Mixing Vessel	Stirring	181	$12.67
V305 - Crystallizer	Heating	384	$26.88
Total Pumping	Transport	22	$1.51
Process 300 Total		**66,928**	**$7,486.26**
Overall Total		**196,273**	**$23,986.68**

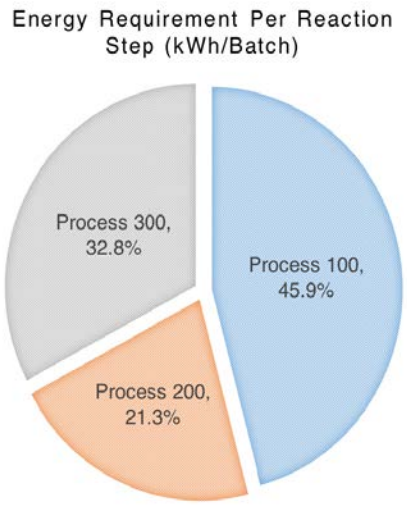


Figure 17-1 Percentage of total energy requirement (192,912 kWh per batch) broken down by section of process

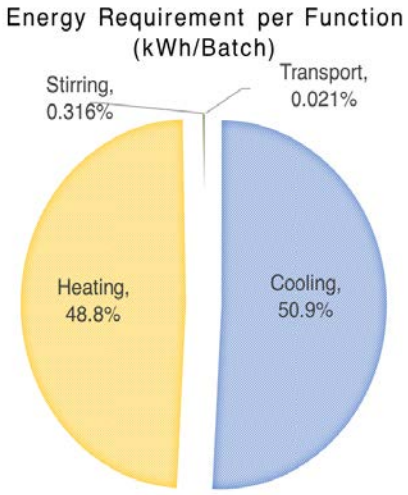


Figure 17-2 Percentage of total energy requirement (192,812 kWh per batch) broken down by energy use

17.1 Heating Utilities

Distillation columns and flash vessels were modeled in Aspen Plus using the RADFRAC and Flash2 units respectively (Appendix F). Overall, separation vessels require 91,700 kWh to

induce the separation. All heating will be accomplished using electricity, which costs $0.07 per kWh. As a result, it will cost $6,421 per day to heat the distillation columns and flash vessels.

In V301, reaction to synthesize *sofosbuvir* occurs at 55°C and is operated overnight. Based on Aspen HeatEx calculations, 5,180 kWh of heating is required to increase the temperature of the vessel from 25°C to 55°C and to maintain that temperature over 16 hours. At a cost of $0.07 per kWh, V301 costs $363 per day.

For both evaporation and reaction, electricity was used as the heating mechanism instead of steam utility, because it is both cheaper and enables better control of the temperature fluctuation. A thermocouple installed in the vessel provides feedback to a PID controller that will maintain the temperature the distillation column and the flash vessel as solvent is removed.

17.2 Cooling Utilities

The largest energy requirement is regenerating coolant for the condensers and cooling the reactors. Cooling energy duties were simulated with Aspen Plus for the relevant solvents. Condenser heat duties were modeled using RADFRAC for the V103 and V304 distillation columns and using HeatX after the flash vessel V207. All condenser units were designed for total condenser, so the distillate stream can be stored and disposed. Based on the amount and final temperature of cooling necessary, either ethylene glycol or propane was selected to be the refrigerant (Appendix F-2).

Reactor V201 containing DCM was cooled to -50°C before the start of the reaction to prevent side reactions. Since the final temperature is low, propane was selected as the refrigerant. The heat capacity of propane (98 J/mol-K) is comparable to that of DCM (102 J/mol-K), so it can be used without creating a pinch point. To cool the DCM from 25°C to -50°C, 3,833 kWh would be removed via propane. To accomplish this cooling, the process requires a utility of

154,682 kg of propane refrigerated to -100°C, pumped through the system at 708 L/min for a total cooling time of 3.8 hours. The utility cost of refrigerating propane to -100°C is $10 per ton-day, yielding a total cost of $1,705 per day for cooling in reactor V201 (Appendix F-1).

Reactor V202 is cooled to -10°C prior to operation. Assuming that the 2-Chloro-6-hydroxypyridine does not affect the heat capacity of the DCM solvent, 894 kWh of cooling is required to cool the DCM solution from 25°C to -10°C. To cool V202, 26,249 kg of propane refrigerant are cooled by the propane chiller to -100°C. Propane is pumped through the cooling jacket over the course of 4.9 hours. Refrigerating propane to -10°C costs $10 per ton-day, yielding a total cost of $289 per day for cooling V202.

Reactor V203 is cooled from room temperature to 0°C and maintained at the temperature while transferring in the contents of reaction vessel V201. To accomplish this cooling, 230 kWh of energy is removed via chilled brine over 15 minutes. Refrigerating brine to -18°C costs $2.25per ton-day, yielding a total cost of $47.50 per day for the cooling of V203.

For reactors V201, V202, and V203, a thermocouple inside the reactor will detect temperature as the system cools. When the setpoint temperature is reached, the response with shut the valve for incoming refrigerant. This will prevent the waste of refrigerant used to cool the reactor below the setpoint or maintain the temperature once equilibrium is reached.

17.3 Pumps and Screw Conveyors

Pumps used for charging starting materials and transferring materials from one reactor to the next were modeled in Aspen Plus using the Pipe and Pump units. Flow calculations followed the following assumptions. Solvents flowed at 500 L/minute through stainless steel tubing with inner diameter of 0.15 meters. Since most tanks are roughly one story tall, the pipe had a length of 20 meters and an elevation change of 3 meters. Thus, the pump needed to compensate for

roughly 0.3 bars of pressure drop. This amounted to 0.431 kW per hour (Appendix F-3). Because the energy utility of pumps was so small, pump utilities were combined for each step of the process. Out of 197,800 kWh of energy required per batch, only 41 kWh was needed for pumping all the fluids.

Transport of the solid materials L-alanine, phenyl dichlorophosphate, 6-chloro-2-hydroxypyridine, and methyluridine were done via screw conveyor. Screw conveyors allow for controlled transport of the solid reactants. The energy utility of the twin screw conveyor was estimated using Appendix F-3 referenced from the Journal of Agricultural Science. At a rotation speed of 600 rpm and 12 mm of clearance, the conveyor would require 0.451 kW of power to transport solids. Altogether the screw conveyors require 5 kWh of electricity per batch. The total energy of transport is 46 kWh per batch, which is only 0.02% of the total energy utilities.

17.4 Agitators

Agitator requirements were estimated by the Agitator Power Calculator by CheCalc[17-2]. Calculations for the reactors were modeled a pitched blade agitator with 0.3 D/T ratio at a scale of 4. D/T ratio, the ratio between the agitator diameter and the tank diameter, typically ranges between 0.2 and 0.6. The scale of 4 was chosen because the organic solvents have similar viscosities and specific gravities. In comparison, the wash vessels (V205 and V302) were modeled with a scale of 8, because they require high velocities to mix the two immiscible fluids completely before separation occurs. The power of reactor agitators was roughly 10 kWh, whereas the power of larger wash agitators was much higher at 40 kWh. A summary of the agitator power

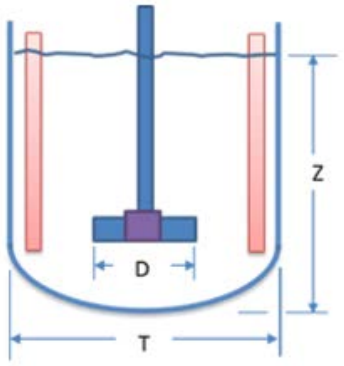


Figure 17-3 Dimensions of agitator with respect to the mixing vessel.

requirements are summarized in Table 17-4 presented below. The individual power requirement as solved by the program was multiplied with the operating time of the reactor to obtain the agitator energy utility.

Table 17-4 Summary of Agitator Power Requirements

	V101	**V201**	**V202**	**V203**	**V301**
Batch Volume (m^3)	100	85	85	125	80
Fluid	IPA	DCM	DCM	DCM	THF
Density (kg/m^3)	786	1330	1330	1330	889
Dynamic Viscosity (cP)	2.04	0.413	0.413	0.413	0.48
Diameter (m)	1.5	1.43	1.43	1.63	1.4
Agitator Speed (rpm)	52.87	55.82	55.82	49.08	56.95
Reynolds Number	773,362	6,123,009	6,123,009	6,962,981	3,451,020
Power (kW)	5.77	8.82	8.82	11.33	5.62

Endnotes

17-1: OVO Energy (2016). *Average electricity prices around the world: $/kWh*. Retrieved from https://www.ovoenergy.com/guides/energy-guides/average-electricity-prices-kwh.html

17-2: CheCalc (2015). *Agitator Power: Calculates agitator speed and power requirement for a given reactor geometry and mixture properties*. Retrieved from http://checalc.com/solved/agitator.html.

Section 18 - Equipment List and Description

18.1 Equipment List

Table 18-1 General Equipment

Equipment Description	Unit Number	Number of Units	Vendor
Vessel Agitator	V102/V201/V202/V203/V204/V301/V302/V307	12	N/A
Centrifugal Pumps	S102/S103/S104/S105/S106 S202/S203/S204/S205/S207/S208/S209/S210/S211/S212/S213/S214/S215/S216 S301/S303/S304/S306/S307/S308/S309/S310/S311/S312/S313/S314/S315/S316/S317/S318/S319	42	Flowserve
Propane Chiller	Chiller-Propane	1	Johnson Controls
Screw Conveyer	S101/S201/S206/S302/S305	5	N/A

Table 18-2 Process 100 Equipment

Equipment Description	Unit Number	Number of Units	Vendor
Heat Exchanger	V101	1	N/A
100,000L Reaction Vessel	V102	2	N/A
Distillation Column	V103	1	N/A
Ethylene Glycol Chiller	Chiller-EG	1	Johnson Controls

Table 18-3 Process 200 Equipment

Equipment Description	Unit Number	Number of Units	Vendor
85,000 L Reaction Vessel	V201	2	N/A
85,000L Reaction Vessel	V202	1	N/A
140,000L Reaction Vessel	V203	2	N/A
Flash Vessel	V204/V207	2	N/A
400,000 L Wash Vessel	V205	1	N/A
Packed Bed Drying Vessel	V206	1	N/A
Condenser (Heat Exchanger)	V208	1	N/A
100,000L Runaway Reaction Vessel	V209	2	N/A
Brine Chiller	Chiller-Brine	1	Johnson Controls

Table 18-4 Process 300 Equipment

Equipment Description	Unit Number	Number of Units	Vendor
120,000L Reactor	V301	1	N/A
192,000L Wash Vessel	V302	2	N/A
60,000 L Packed Bed Drying Vessel	V303	1	N/A
Flash Vessel	V304	1	N/A
160,000L Mixing Vessel	V305	1	1
Crystallization Unit	V306	1	Thermal Kinetics
Dryer	V307	1	N/A
Belt Conveyer	S320	1	N/A

18.2 Equipment Selection

Equipment units were selected based on the maximum efficiency of the process with advice from industrial consultants as well as specific vendors. Units were chosen to comply with GMP production.

18.3 Common Units

Pumps

Centrifugal pumps are used to transfer fluids throughout the process. In the reactor processes, the power of the pump is approximately 5 hp. The pumps operate at room temperature with a maximum flow rate of 500 L/min. The purchase cost of each pump is $4,936, as determined using the equipment costing spreadsheet. There are a total of 10 pumps for Process 100, 22 pumps for Process 200, and 10 pumps for Process 300.

Agitator

The Agitator is a component of each reaction vessel and wash vessel. The vessel costs were determined separately, as the vessel costs were computed using the pressure vessel cost equations. The agitator is necessary to keep the reactor contents well mixed in terms of reactant concentration and temperature. The agitator power is 15 hp, and this was determined based on the volume of the reactor contents and the intensity of mixing necessary. The agitator cost was determined to be $19,216 using chapter 23 of Product and Process Design Principles[18-1] .

Chiller (Ethylene Glycol/Brine/Propane)

The chillers for each of the refrigerants are used to remove heat from the refrigerants so they can be used in heat exchange functions to cool the process. These chillers use water for cooling, and their refrigeration capability is evaluated in calculations shown in Appendix C. The costs for the ethylene glycol, brine, and propane chillers were determined to be $4,000, $26,200, and $378,500, respectively.

Screw Conveyors S101/S201/S206/S302/S305

Screw conveyors will be used to feed solid materials into reactor vessel, including 2'-deoxy-2'-fluoro-2'-methyluridine and zinc chloride. Separate units will be used for each feed material to maintain GMP standards. The diameter of the conveyer will be 20 inches, and the length will be 30 feet. The purchase cost, as determined using Table 16.32 of Process Design Principles, is $15,748.

18.4 Process 100 Equipment Description

Heat Exchanger V101

The heat exchanger is used to cool the thionyl chloride from ambient temperature (25°C) to 0°C before it enters the reaction vessel. Patent literature states that this step is necessary in producing the L-alanine isopropyl ester. This exchanger uses shell and tube geometry, and ethylene glycol as the coolant. The area of the exchanger is about 25 square meters, and the ethylene glycol exits the exchanger at 4.8°C. This heat exchanger will cost $36,110, as determined using the equipment costing spreadsheet. A pressure relief valve will be used to maintain safe operation.

Reaction Vessel V102

The reaction vessel is used for the production of L-alanine isopropyl ester. The reaction vessel is charged with isopropyl alcohol, thionyl chloride, and L-alanine hydrochloride. The unit will be agitated at room temperature overnight to facilitate the reaction. The unit is made of stainless steel, and temperature and agitation are controlled with PID controls. The tank has a volume of 100,000L and a working volume of 75,000L. The cost is approximately $189,207, as determined using the equipment costing spreadsheet for a pressure vessel.

Distillation Column V103

The distillation column is used to concentrate the L-alanine isopropyl ester product from the unconsumed reactants and side products. The distillation column will have three stages, and will operate at reflux ratio of 3.0 and a bottoms-to-feed ratio of 0.04. The reboiler temperature will be kept low (46°C) to avoid degradation of the product. The column sizing was determined using chapter 13 of Process Design Principles (Seider, 2016). Calculations are shown in Appendix C. The column material will be stainless steel, and the purchase cost will be $249,823.

18.5 Process 200 Equipment Description

Reaction Vessel V201

This reaction vessel will combine phenyl dichlorophosphate, DCM, DIEA, and the L-alanine isopropyl ester from Process 100. The reaction vessel is made from stainless steel with a volume of 85,000L. In addition to jacketing for temperature control, there will be cooling coils to maintain the -50°C temperature necessary for the reaction. Additionally, a turbine agitator will be used to mix the reactor contents. The purchase cost of this reactor is $178,144. Two identical reactors will operate in parallel, and the reactants will be split evenly between the two vessels.

Reaction Vessel V202

This reaction vessel will react 2-chloro-6-hydroxypyridine, DCM, DIEA to produce a reaction intermediate that is to be reacted with the products of V201. The reaction vessel is made from stainless steel with a volume of 85,000L, and is jacketed for temperature control. Using the equipment costing spreadsheet the estimated purchase cost is $178,144.

Reaction Vessel V203

This reaction vessel will combine the products of V201 and V202 to produce Intermediate A1. The reactor will be jacketed for temperature control, and the reactor volume will be 140,000L. Additionally, the vessel will have a agitation turbine to induce mixing. The material will be stainless steel, and the purchase cost is $222,075.

Flash Vessel V204/V207

The flash vessel will be used to remove DCM from the product stream of V203 to reduce the volume of product that enters the wash vessel. The vessel will operate at 25°C and 0.50 bar, and the material will be stainless steel. One flash vessel will be used immediately after completion of the reaction, and another identical flash vessel will operate after sodium sulfate drying. Using the equipment costing spreadsheet the purchase cost of the flash vessel is $55,007.

Wash Vessel V205

The wash vessel's purpose is to add salt water to the product of V203. This process is necessary to purify the product intermediate A1. The vessel volume will be 400,000L and its material will be stainless steel. The washes will be performed at room temperature and ambient pressure, and thermal jacketing will be used for temperature control. Modeling the wash vessel as a pressure vessel, the estimated cost is $361,004.

Packed Bed Drying Vessel V206

The packed bed drying vessel will use anhydrous sodium sulfate to selectively absorb water from the product mixture. Between batches, the resin will be removed and the vessel can be cleaned using clean-in-place procedures. The anhydrous sodium sulfate will need to be replaced for each new batch as the sodium sulfate has limited absorption capacity. The vessel material will be stainless steel, and the estimated purchase cost is $72,082.

Condenser/Heat Exchanger V208

A heat exchanger will operate using propane as the refrigerant to condense the distillate product of the flash vessel. The exchanger geometry will be shell and tube with 12 feet long tubes, and the material will be carbon steel and stainless steel. The total area of heat transfer is 1614 ft^2 and the purchase cost is $75,569.

Runaway Reaction Vessel V209

The runaway reaction vessel will be used as a safety measure because process 200 involves exothermic reactions. The vessel will be filled with room temperature water. Reactor contents can be rapidly pumped into the runaway vessel in the event of a runaway reaction. The vessel material will be stainless steel and the volume is 100,000L. The purchase cost is $189,207.

18.6 Process 300 Equipment Description

Reaction Vessel V301

This reaction vessel will react methyluridine, DIEA, and intermediate A1 to produce the final product, *sofosbuvir*. The reaction vessel will use both an outer temperature jacket and internal heating coils for temperature control as the reaction is performed at higher temperature

(55°C). The material will be stainless steel and it will have a volume of 120,000L. The purchase cost will be $193,445.

Wash Vessel V302

The wash vessel will use various buffers and salt solutions to wash the product of V301. This step is necessary to purify the final product *sofosbuvir*. The vessel volume required will be 192,000L, and two vessels will be necessary per batch. Temperature control will not be necessary in this vessel. The material to be used is stainless steel, and the estimated cost of the vessel is $253,955.

Packed Bed Drying Vessel V303

Anhydrous sodium sulfate is used as a resin in a packed bed vessel to remove water from the organic phase after the wash. Sodium sulfate is a drying agent that will selectively absorb the water from the mixture, and this is part of the purification process. The purchase cost of the vessel is $48,091.

Distillation Column V304

A distillation column will be used to remove much of the solvent from the mixture leaving the drying vessel. Ethyl acetate will be removed in the distillate, while the product *sofosbuvir* will leave in the bottoms product. The column will operate at a reflux ratio of 3.0 and a bottoms-to-feed ratio of 0.085. The column will have two stages, and the column will operate at 0.15 bar. Stainless steel will be used as the material and the purchase cost of the column is $107,690.

Mixing Vessel V305

A mixing vessel will be used to mix acetone, DCM, and the bottoms product of the distillation column before feeding to the crystallization unit. The mixing vessel will agitate its

contents for 10 minutes before transferring the contents to the crystallizer. The vessel volume will be 160,000 L and the material will be stainless steel. The purchase cost was determined to be $237,160.

Crystallization Unit V306

A crystallization unit will be used to obtain the final product as crystals. A mixture of the product *sofosbuvir*, DCM, and acetone will be combined in the crystallizer. The crystallization unit will handle a flow rate of 5000L per hour. The cost is approximately $750,000 as determined by contacting the vendor directly.

Drying Batch Tray V307

A batch drying tray will be used to dry the final product after crystallization. The drying tray will use electrical heating to evaporate the remaining DCM from the *sofosbuvir* crystals. The tray will have an area of 50 square feet, and will operate at 39°C, the boiling temperature of DCM. The purchase cost is $17,301.

Belt Conveyer S320

A belt conveyer will be used to transport the solid *sofosbuvir* crystals from the crystallizer to the drying unit. The belt conveyer will have dimensions of 30 inches by 30 feet, and will operate only as the crystallizer produces *sofosbuvir* crystals. Using Table 16.32 of Process Design Principles, the purchase cost of the belt conveyer is $21,960.

Endnotes

Seider, W.D. (2016). Product and process design principles: synthesis, analysis and design. New York, NY: John Wiley & Sons.

Section 19 – Equipment Specification Sheets

Heat Exchanger V101

Description and Function: Heat exchanger uses ethylene glycol to cool thionyl chloride before it enters the reactor. Thionyl chloride is specified to enter the reactor at 0°C, so it must be cooled accordingly. For safety, the heat exchanger will have a pressure relief valve.

Vendor: N/A

Operation: Continuous

Materials Handled:

Input	Flow Rate (L/min)	Inlet Temperature (°C)	Outlet Temperature (°C)
Ethylene Glycol	500	-10	4.9
Thionyl Chloride	500	25	0

Characteristics:

Material	Carbon Steel
Area	25 m^2
Heat Duty	73571 cal/s
Tube length	12 feet
Sterilization	CIP
Tube Outer Diameter	1.5 in
Tubes	60

Operating Conditions:

Pressure	1.1 bar

Purchase Cost:

$36,110

Reference Page:

N/A

Reactor Vessel V102

Description and Function: 100,000L reactor used to produce L-alanine isopropyl ester in the first synthesis step. The reactor vessel will be temperature controlled to maintain the reaction conditions described in the patent literature. All contents of the tank will be pumped to V102 for separation by distillation. For safety, a pressure relief valve will be incorporated.

Vendor: N/A

Operation: Batch

Materials Handled (split in half across two identical vessels):

Input	Quantity (kg)
L-alanine hydrochloride	4568
Isopropyl Alcohol	99882
Thionyl Chloride	8642

Characteristics:

Material	Stainless steel
Working Volume	100,000 L
Total Volume	70,000 L
Sterilization	CIP

Operating Conditions:

Temperature	25°C
Pressure	1.1 bar

Purchase Cost:

$189,207

Reference Page:

N/A

Distillation Column V103

Description and Function: Distillation column used to separate L-alanine isopropyl ester product from isopropyl alcohol and thionyl chloride. The column will operate with three trays with reflux ratio set to three and bottoms to feed ratio of 0.04. The bottoms product will be pumped to V103 for storage. For safety, the column will have a pressure relief valve.

Vendor: N/A

Operation: Continuous

Materials Handled:

Input	Quantity (kg)
L-Alanine	295
Isopropanol	49101
Thionyl Chloride	2441
L-Alanine Isopropyl Ester	2656
HCl	1156
SO2	1014

Characteristics:

Material	Stainless steel
Diameter	15 ft
Height	31 ft
Sterilization	CIP
Spacing between stages	24 in
Tray Type	Valve

Operating Conditions:

Reflux Ratio	3.0
Stages	3
Bottoms to feed Ratio	0.04
Reboiler Temperature	320.8 K
Condenser Temperature	295.8 K

Pressure	0.06 bar
Foaming?	No Foaming

Purchase Cost:

$249,823

Reference Page: N/A

Ethylene Glycol Chiller

Chiller-EG

Description and Function: This chiller uses water cooling to absorb heat from the refrigerant, ethylene. The ethylene glycol is used as a refrigerant in V101.

Vendor: Johnson Controls

Operation: Continuous

Materials Handled:

Material	Input (L)
Ethylene Glycol	50,000

Characteristics:

Material	Stainless Steel
Power	10 tons

Operating Conditions:

Cooling Method	Water
Temperature	-10°C

Purchase Cost:

$4,000

Reference Page:

N/A

Reaction Vessel V201

Description and Function: 85,000L reactor used to produce a reaction intermediate in process 200. The reactor vessel will be temperature and pressure controlled to maintain the reaction conditions described in the patent literature. Cooling will be provided using cooling coils with propane as the refrigerant. All contents of the reactor will be combined with the product of V202 in a third reaction step in V203. To ensure safe operation, the vessel will have a pressure relief valve, and the vessel will be nitrogen padded to prevent side reactions with oxygen.

Vendor: N/A
Operation: Batch
Materials Handled (split in half across two identical vessels):

Input	Quantity (kg)
DCM	149,335.08
Phenyl Dichlorophosphate	0
L-Alanine Isopropyl Ester hydrochloride	42.02963693
DIEA	8,041.12
Intermediate A2	9612.172131
HCl	2292.849779

Characteristics:

Material	Stainless Steel
Working Volume	60,000 L
Total Volume	85,000 L
Sterilization	CIP

Operating Conditions:

Temperature	-50 to -10°C
Pressure	1.1 bar

Purchase Cost:
$178,144
Reference Page:
N/A

Reaction Vessel V202

Description and Function: 85,000L reactor used to produce a reaction intermediate in process 200. The reactor vessel will be temperature and pressure controlled to maintain the reaction conditions described in the patent literature. Cooling will be provided using cooling coils with propane as the refrigerant. All contents of the reactor will be combined with the product of V201 in a third reaction step in V203. To ensure safe operation, the vessel will have a pressure relief valve, and the vessel will be nitrogen padded to prevent side reactions with oxygen.

Vendor: N/A

Operation: Batch

Materials Handled (split in half across two identical vessels):

Input	Quantity (kg)
2-chloro-6-hydroxypyridine	3705
DCM	76,342
DIEA	4020

Characteristics:

Material	Stainless Steel
Working Volume	60,000 L
Total Volume	85,000 L
Sterilization	CIP

Operating Conditions:

Temperature	-10 to 0°C
Pressure	1.1 bar

Purchase Cost:

$178,144

Reference Page:

N/A

Reaction Vessel V203

Description and Function: 140,000L reactor used to produce intermediate A1 in process 200. The reactor vessel will be temperature and pressure controlled to maintain the reaction conditions described in the patent literature. The reactor vessel will be jacketed to provide the necessary cooling. All contents of the reactor will be sent to a flash vessel (V204) for purification of product. To ensure safe operation, the vessel will have a pressure relief valve, and the vessel will be nitrogen padded to prevent side reactions with oxygen.

Vendor: N/A

Operation: Batch

Materials Handled (split in half across two identical vessels):

Input	Quantity (kg)
V201 Product	171670
V202 Product	84067

Characteristics:

Material	Stainless Steel
Working Volume	98,000 L
Total Volume	140,000 L
Sterilization	CIP

Operating Conditions:

Temperature	0 - 25°C
Pressure	1.1 bar

Purchase Cost:

$222,075

Reference Page:

N/A

Flash Vessel V204

Description and Function: Flash vessel to separate DCM from the product intermediate A1. Due to the relatively high vapor pressure of DCM at room temperature, the flash process does not manipulate temperature; only pressure is reduced in the flash vessel.

Vendor: N/A

Operation: Continuous

Materials Handled:

Input	Quantity (kg)
DCM	204886
Intermediate A1	21481

Characteristics:

Material	Stainless Steel
Diameter	7 ft
Length	22 ft
Feed flow rate	500 L/min
Sterilization	CIP

Operating Conditions:

Temperature	25°C
Pressure	0.5 bar

Purchase Cost:

$55,007

Reference Page:

N/A

Wash Vessel V205

Description and Function: The wash vessel introduces saturated salt water to wash away polar impurities such as phenyl dichlorophosphate. The vessel has an agitator to improve mixing. Temperature control is not necessary in this step.

Vendor: N/A

Operation: Batch

Materials Handled:

Input	Quantity (kg)
DCM	58858
Intermediate A1	21361
Saturated Salt Water	201027

Characteristics:

Material	Stainless Steel
Total Volume	400,000 L
Working Volume	280,000 L
Feed flow rate	500 L/min
Sterilization	CIP

Operating Conditions:

Temperature	25°C
Pressure	1.1 bar

Purchase Cost:

$361,004

Reference Page:

N/A

Drying Packed Bed V206

Description and Function: Packed bed with anhydrous sodium sulfate to remove water from the product mixture. The sodium sulfate selectively absorbs water in the mixture.

Vendor: N/A

Operation: Continuous

Materials Handled:

Input	Quantity (kg)
DCM	58858
Intermediate A1	21361
Saturated Salt Water	4026

Characteristics:

Material	Stainless Steel
Diameter	6ft
Length	12.4ft
Resin	Anhydrous Sodium Sulfate
Feed flow rate	500 L/min
Sterilization	CIP

Operating Conditions:

Temperature	25°C
Pressure	2.4 bar
Void Fraction	0.55

Purchase Cost:

$72,082

Reference Page:

N/A

Flash Vessel V207

Description and Function: Flash vessel to further remove DCM from Intermediate A1. The flash vessel will also be fed trace amounts of water that are not able to removed by sodium sulfate drying.

Vendor: N/A

Operation: Continuous

Materials Handled:

Input	Quantity (kg)
DCM	58858
Intermediate A1	21361
Saturated Salt Water	10

Characteristics:

Material	Stainless Steel
Diameter	7
Length	22
Feed flow rate	500 L/min
Sterilization	CIP

Operating Conditions:

Temperature	25°C
Pressure	0.5 bar

Purchase Cost:

$55,007

Reference Page:

N/A

Heat Exchanger (Cooling) V208

Description and Function: This heat exchanger uses ethylene glycol to condense the distillate of V204 and V207. The distillate is mostly DCM, and condensing to liquid allows the material to be discarded as liquid organic waste.

Vendor: N/A

Operation: Batch

Materials Handled:

Input	Inlet Flow rate (L/min)	Inlet Temperature (°C)	Outlet Temperature (°C)
DCM	500	25	21
Propane	500	-100	21

Characteristics:

Material	Stainless Steel/Carbon Steel
Area	1614 ft^2
Exchanger Design	Shell and Tube
Tube Length	20 ft
Tube Outer Diameter	1.5 in
Number of Tubes	206

Operating Conditions:

Pressure	0.5 bar

Purchase Cost:

$67,473

Reference Page:

N/A

Runaway Reaction Vessel V209

Description and Function: This runaway reaction vessel is necessary to address safety concerns. Process 200 involves exothermic reactions that may release excessive heat in the event of a runaway reaction. This vessel will contain cold water that can absorb the energy release by the reaction, preventing a runaway reaction from causing damage to the process.

Vendor: N/A

Operation: Batch

Materials Handled:

Input	Quantity (kg)
Water	20,000
V201 Contents	0-60,000

Characteristics:

Material	Stainless Steel
Volume	100,000L

Operating Conditions:

Temperature	25°C
Pressure	0.5 bar

Purchase Cost:

$189,207

Reference Page:

N/A

Brine Chiller

Chiller-Brine

Description and Function: This chiller uses water cooling to absorb heat from the refrigerant, brine. The chiller operates continuously to cool the brine which is used as a refrigerant for V203.
Vendor: Johnson Controls
Operation: Continuous
Materials Handled:

Material	Input (L)
Brine	82000

Characteristics:

Material	Stainless Steel
Power	65 tons

Operating Conditions:

Cooling Method	Water
Temperature	0°C

Purchase Cost:
$26,158
Reference Page:
N/A

Reaction Vessel V301

Description and Function: Reaction vessel to produce final product *sofosbuvir*. Reactor will operate at 55C for 16 hours. Reactor contents will be pumped to V302 for washing to purify product.

Vendor: N/A

Operation: Batch

Materials Handled:

Input	Quantity (kg)
2'-deoxy-2'-fluoro-2'-methyluridine	3639
Intermediate A1	11142
DIEA	2729
Zinc Chloride	2883
THF	49784

Characteristics:

Material	Stainless Steel
Working Volume	84,000 L
Total Volume	120,000 L
Sterilization	CIP

Operating Conditions:

Temperature	55°C
Pressure	1.1 bar

Purchase Cost:

$193,445

Reference Page:

N/A

Wash Vessel V302

Description and Function: Wash vessel introduces ethyl acetate, HCl, and saturated salt water to wash the product before further purification steps. The vessel will agitate contents to improve washing.

Vendor: N/A

Operation: Batch

Materials Handled (split across two identical vessels):

Input	Quantity (kg)
Sofosbuvir	3499
THF	49784
Ethyl Acetate	100466
Saturated Salt Water	55993
HCl	55993
Ammonium Chloride	19597

Characteristics:

Material	Stainless Steel
Working Volume	140,000 L
Total Volume	192,000 L
Sterilization	CIP

Operating Conditions:

Temperature	25°C
Pressure	1.1 bar

Purchase Cost:

$253,955

Reference Page:

N/A

Drying Packed Bed V303

Description and Function: Packed bed uses anhydrous sodium sulfate to selectively absorb water and remove it from the product.

Vendor: N/A

Operation: Continuous

Materials Handled:

Input	Quantity (kg)
Sofosbuvir	3499
THF	49784
Ethyl Acetate	100466
Saturated Salt Water	55993
HCl	55993
Ammonium Chloride	19597

Characteristics:

Material	Stainless Steel
Diameter	3.4 ft
Length	13.6 ft
Resin	Sodium Sulfate
Resin Mass	2100 kg
Sterilization	CIP

Operating Conditions:

Temperature	25°C
Pressure	2.4 bar

Purchase Cost:

$48,091

Reference Page:

N/A

Distillation Column V304

Description and Function: Distillation column used to separate ethyl acetate from the *sofosbuvir* product. The column will operate with two stages with reflux ratio set to three and bottoms to feed ratio of 0.085. The distillate will be discarded as waste while the bottoms product will be further processed by crystallization. The column sizing calculation is shown in Appendix C.
Vendor: N/A
Operation: Continuous
Materials Handled:

Input	Quantity (kg)
Methyluridine	1587
Intermediate A1	7997
THF	27418
Sofosbuvir	3684
Ethyl Acetate	100452
Water	2500

Characteristics:

Material	Stainless steel
Diameter	8 ft
Height	29 ft
Sterilization	CIP
Plate Spacing	24 in

Operating Conditions:

Reflux Ratio	3.0
Stages	2
Bottoms to feed Ratio	0.085
Reboiler Temperature	310.8 K
Condenser Temperature	293.9 K
Pressure	0.159 bar
Foaming?	No Foaming

Purchase Cost:
$137,659
Reference Page: N/A

Mixing Vessel V305

Description and Function: Mixing vessel to combine acetone, DCM, and oily bottoms product of distillation column.

Vendor: N/A

Operation: Batch

Materials Handled:

Input	Quantity (kg)
Sofosbuvir	3499
Acetone	8845
DCM	70760
Ethyl Acetate	10045

Characteristics:

Material	Stainless Steel
Sterilization	CIP
Working Volume	120,000 L
Total Volume	160,000 L

Operating Conditions:

Temperature	25°C
Pressure	1.1 bar

Purchase Cost:

$237,160

Reference Page:

N/A

Crystallization Unit V306

Description and Function: Crystallization unit introduces acetone and DCM to crystallize *sofosbuvir* as a purified final product.

Vendor: Thermal Kinetics

Operation: Batch

Materials Handled:

Input	Quantity (kg)
Sofosbuvir	3500
Acetone	8845
DCM	70760
Ethyl Acetate	10045

Characteristics:

Material	Stainless Steel
Model	Custom
Sterilization	CIP

Operating Conditions:

Temperature	25-30°C
Flow Rate	5000L/hr
Pressure	1.1 bar

Purchase Cost:

$750,000

Reference Page:

N/A

Batch Tray Dryer V308

Description and Function: Drying equipment removes residual DCM from *sofosbuvir* crystals. Operation is at 39°C, the boiling point of DCM.

Vendor: N/A

Operation: Batch

Materials Handled:

Input	Quantity (kg)
Sofosbuvir	3500
DCM	170

Characteristics:

Material	Stainless Steel
Sterilization	CIP
Area	50 ft^2

Operating Conditions:

Temperature	39°C
Pressure	1.1 bar

Purchase Cost:

$17,301

Reference Page:

N/A

Belt Conveyer S320

Description and Function: Belt conveyer is used as solids-handling equipment to transport solid *sofosbuvir* crystals, still wet with DCM, from the crystallizer to the dryer.

Vendor: N/A

Operation: Continuous

Materials Handled:

Input	Quantity (kg)
Sofosbuvir	3500
DCM	170

Characteristics:

Material	Stainless Steel
Sterilization	CIP
Length	30 ft
Width	30 in

Operating Conditions:

Temperature	35°C
Pressure	1 bar

Purchase Cost:

$21,960

Reference Page:

N/A

Screw Conveyers

Description and Function: The screw conveyer is used to add solid material to the reaction vessel, as solid materials cannot be transported by pressure-driven flow. The conveyer will handle crystalline solids and add them to V102, V202, and V301. Specifically, streams S101, S201, S206, S302, and S305 are transported using screw conveyers.

Vendor: N/A

Operation: Continuous

Materials Handled:

Input	Mass (kg)
2'-deoxy-2'-fluoro-2'-methyluridine	3639
Zinc Chloride	2883

Characteristics:

Material	Stainless Steel
Conveyer Length	30 feet
Conveyer Diameter	20 in

Operating Conditions:

Pressure	1.1 bar
Temperature	25°C

Purchase Cost:

$11,902

Reference Page:

N/A

Centrifugal Pumps

S101/S102/S103/S104/S105/S106

S201/S202/S203/S204/S205/S206/S207/S208/S209/S210/S211/S212/S213/S214/S215/S216

S301/S302/S303/S304/S305/S306/S307/S308/S309/S310/S311/S312/S313/S314/S315/S316/S317/S318/S319

Description and Function: Pumps create a pressure drop across the length of a pipe to induce pressure-driven flow of material.

Vendor: N/A

Operation: Batch

Characteristics:

Material	Ductile Iron
Flow Rate	500 L/min

Operating Conditions:

Temperature	25°C
Pressure Change	0.3-2 bar

Purchase Cost:

$4,936 per pump

Reference Page:

N/A

Agitator for Vessels

V101/V201/V202/V203/V205/V301/V302/V305

Description and Function: Agitator helps mix materials within reactors and wash vessels. Reaction vessels were priced using the pressure vessel model, so agitators are priced separately.

Vendor: N/A

Operation: Batch

Characteristics:

Material	Stainless Steel
Motor Hp	15 hp

Operating Conditions:

Temperature	-50 to 25°C
Pressure	1.1 bar

Purchase Cost:

$19,216

Reference Page:

N/A

Propane Chiller

Chiller-Propane

Description and Function: This chiller uses water cooling to absorb heat from the refrigerant, propane. The chiller operates continuously to cool the propane which is used as a refrigerant for V201, V202, and for the condensers of distillation columns V103 and V304.

Vendor: Johnson Controls

Operation: Continuous

Materials Handled:

Material	Input (kg)
Propane	1,546,400

Characteristics:

Material	Stainless Steel
Power	950 tons

Operating Conditions:

Cooling Method	Water
Temperature	-100°C

Purchase Cost:

$378,500

Reference Page:

N/A

Section 20 - Equipment Cost Summary

This section contains tables of equipment cost summaries for each process (100, 200, 300) including unit number, purchase cost of one unit, and the number of units needed. Equipment costing spreadsheets used to determine purchase costs are included in Appendix B. The crystallizer cost was determined by directly contacting the vendor. Additionally, equipment costs were rounded to the nearest $100 given the limited accuracy of equipment costing data.

Table 20-1 General Equipment

Equipment Description	Unit Number	Purchase Cost per Unit	Number of Units	Vendor
Vessel Agitator	V101/V201/V202/V203/V301/ V304	$19,200	12	N/A
Centrifugal Pumps	S101/S102/S103/S104/S105/S1 06 S201/S202/S203/S204/S205/S2 06/S207/S208/S209/S210/S211/ S212/S213/S214/S215/S216 S301/S302/S303/S304/S305/S3 06/S307/S308/S309/S310/S311/ S312/S313/S314/S315/S316/S3 17/S318/S319	$5,000	42	Flowserve
Propane Chiller	Chiller-Propane	$378,500	1	Johnson Controls
Screw Conveyer	S101/S201/S206/S302/S305	$15,800	5	N/A

Table 20-2 Process 100 Equipment

Equipment Description	Unit Number	Purchase Cost per Unit	Number of Units	Vendor
Heat Exchanger	V101	$36,100	1	N/A
100,000L Reaction Vessel	V102	$189,200	2	N/A
Distillation Column	V103	$249,800	1	N/A
Ethylene Glycol Chiller	Chiller-EG	$4,000	1	Johnson Controls

Table 20-3 Process 200 Equipment

Equipment Description	Unit Number	Purchase Cost per Unit	Number of Units	Vendor
85,000 L Reaction Vessel	V201	$178,200	2	N/A
85,000L Reaction Vessel	V202	$178,200	1	N/A
140,000L Reaction Vessel	V203	$222,100	2	N/A
Flash Vessel	V204/V207	$55,000	2	N/A
400,000 L Wash Vessel	V205	$361,000	1	N/A
Packed Bed Drying Vessel	V206	$72,100	1	N/A
Condenser (Heat Exchanger)	V208	$67,500	1	N/A
100,000L Runaway Reaction Vessel	V209	$189,200	2	N/A
Brine Chiller	Chiller-Brine	$26,200	1	Johnson Controls

Table 20-4 Process 300 Equipment

Equipment Description	Unit Number	Purchase Cost per Unit	Number of Units	Vendor
120,000L Reactor	V301	$193,500	1	N/A
192,000L Wash Vessel	V302	$254,000	2	N/A
Packed Bed Drying Vessel	V303	$48,100	1	N/A
Distillation Column	V304	$137,700	1	N/A
160,000L Mixing Vessel	V305	$237,200	1	N/A
Crystallization Unit	V306	$750,000	1	Thermal Kinetics
Drying Unit	V307	$17,300	1	N/A
Belt Conveyer	S320	$22,000	1	N/A

Section 21 - Fixed Capital Investment

This chapter describes the fixed capital investment, consisting of the equipment purchase and installation costs as well as the total permanent investment cost, which includes construction and plant startup. To calculate costs, the Profitability Analysis-4.0.xls spreadsheet by Brian K. Downey (2008) was used.

21.1 Equipment Costs

21.1.1 Unit Bare Module Costs

Purchase costs, as determined in Chapter 20, were used to calculate the bare module cost for each piece of equipment. The bare module cost for the entire process was then computed using the costs of individual pieces of equipment. The equipment cost is concentrated in Processes 200 and 300, which require several large reaction and wash vessels. The total general equipment Bare Module Costs is $1,547,000, the total Process 100 Bare Module Costs is $2,732,000, the total Process 200 Bare Module Costs is $8,302,000, and the total Process 300 Bare Module Costs is $6,387,000. The Bare Module Factors and Costs are tabulated below in Tables 21.1, 21.2, 21.3, and 21.4. The Total Bare Module cost is $18,976,000.

Table 21-1 General Equipment

Equipment Description	Unit Number	Purchase Cost per Unit	Number of Units	Bare Module Factor	Total Bare Module Cost	Vendor
Vessel Agitator	V101/V201/V202/V203/V301/V304	$19,216	12	1.5	$345,900	N/A
Centrifugal Pumps	S101/S102/S103/S104/S105/S106 S201/S202/S203/S204/S205/S206/S207/S208/S209/S210/S211/S212/S213/S214/S215/S216 S301/S302/S303/S304/S305/S306/S307/S308/S309/S310/S311/S312/S313/S314/S315/S316/S317/S318/S319	$4,936	42	3.3	$684,100	Flowserve
Propane Chiller	Chiller-Propane	$378,500	1	3.17	$1,199,900	Johnson Controls
Screw Conveyer	S101/S201/S206/S302/S305	$15,748	5	2	$157,500	N/A
Sprinklers	N/A	$1.61/ft^2	100,000 ft^2	3.21	$517,000	N/A

Total General Equipment Cost = $2,904,400

Table 21-2 Process 100 Equipment

Equipment Description	Unit Number	Purchase Cost per Unit	Number of Units	Bare Module Factor	Total Bare Module Cost	Vendor
Heat Exchanger	V101	$36,100	1	3.17	$114,500	N/A
100,000L Reaction Vessel	V102	$189,200	2	4.16	$1,574,200	N/A
Distillation Column	V103	$249,800	1	4.16	$1,039,300	N/A
Ethylene Glycol Chiller	Chiller-EG	$4,000	1	3.21	$12,800	Johnson Controls

Total Process 100 Equipment Cost = $2,741,000

Table 21-3 Process 200 Equipment

Equipment Description	Unit Number	Purchase Cost per Unit	Number of Units	Bare Module Factor	Total Bare Module Cost	Vendor
85,000 L Reaction Vessel	V201	$178,144	2	4.16	$1,482,200	N/A
85,000L Reaction Vessel	V202	$178,144	1	4.16	$741,100	N/A
140,000L Reaction Vessel	V203	$222,075	2	4.16	$1,847,700	N/A
Flash Vessel	V204/V207	$55,007	2	4.16	$457,700	N/A
400,000 L Wash Vessel	V205	$361,004	1	4.16	$1,501,800	N/A
Packed Bed Drying Vessel	V206	$72,082	1	4.16	$299,900	N/A
Condenser (Heat Exchanger)	V208	$67,473	1	3.17	$213,900	N/A
100,000L Runaway Reaction Vessel	V209	$189,207	2	4.16	$1,574,200	N/A
Brine Chiller	Chiller-Brine	$26,200	1	3.17	$83,100	Johnson Controls

Total Process 200 Equipment Cost = $8,201,600

Table 21-4 Process 300 Equipment

Equipment Description	Unit Number	Purchase Cost per Unit	Number of Units	Bare Module Factor	Total Bare Module Cost	Vendor
120,000L Reactor	V301	$193,445	1	4.16	$804,700	N/A
192,000L Wash Vessel	V302	$253,955	2	4.16	$2,112,900	N/A
Packed Bed Drying Vessel	V303	$48,091	1	4.16	$200,100	N/A
Distillation Column	V304	$137,659	1	4.16	$572,700	N/A
160,000L Mixing Vessel	V305	$237,160	1	4.16	$986,600	N/A
Crystallization Unit	V306	$750,000	1	2.06	$1,545,000	Thermal Kinetics
Drying Unit	V307	$17,301	1	2.06	$35,600	N/A
Belt Conveyer	S320	$21,960	1	1.61	$35,400	N/A

Total Process 300 Equipment Cost = $6,293,000

21.1.2 Bare Module Factor Assumptions

Bare module factors were chosen for each type of equipment from Chapter 16 of *Product and Process Design Principles*[21-1], except for screw conveyors and agitators, which were suggested by the faculty advisors. Table 21-5 lists all the bare module factors used in the calculations in the previous section.

Table 21-5 Bare Module Factors

Equipment	Assumed Bare Module Factor
Reactor Vessels, Wash Vessels, Mixing Vessels, Flash Columns, Distillation Columns, Packed Bed Columns	4.16
Crystallization Units	2.06
Drying Units	2.06
Heat Exchangers (Shell and Tube)	3.17
Centrifugal Pumps	3.30
Belt Conveyors	1.61
Screw Conveyors	2.00
Vessel Agitators	1.50
Sprinklers	3.21

21.1.3 Other Material Costs

In addition to raw materials, several chemicals are purchased only once at the onset of production. Ethylene glycol, propane, and brine used as coolants, are refrigerated in-house after use. The quantities required for each material were calculated for one batch of production, and the utilities required to refrigerate each coolant to a pre-determined temperature are included in Section 22. Table 21-6 shows the quantities and costs for these material purchases. The total cost for single-purchase materials is $577,000.

Table 21-6 One-Time Material Purchase Costs

Material	Use	Amount Required (kg)	Price per kilogram	Price ($)	Vendor
Ethylene Glycol	V101 – Coolant	4,463	$2.50	$11,159	Jiangsu Yida Chemical Co.
Propane	V103 – Coolant	649,088	$0.40	$259,635	Infodrive India
Propane	V201 – Coolant	154,682	$0.40	$61,873	Infodrive India
Propane	V202 – Coolant	26,249	$0.40	$10,500	Infodrive India
Brine (WFI)	V203 – Coolant	13,800	$0.12	$1,656	N/A
Brine (Salt)	V203 – Coolant	3,450	$0.38	$1,311	N/A
Propane	V208 – Coolant	128,309	$0.40	$51,324	Infodrive India
Propane	V304 – Coolant	448,020	$0.40	$179,208	Infodrive India
Total One-Time Material Purchase Cost = $577,000					

21.2 Permanent Investment Costs

This section presents the plant investment costs relating to start-up, space requirements, and contractor fees. These costs, as indicated by the profitability spreadsheet, are derived from the Total Bare Module cost and are shown below in Table 21-7. The cost of site preparations is set at 5.0% of the Total Bare Module cost, the cost of service facilities is set at 5.0% of the Total Bare Module Cost, cost of contingencies and contractor fees is set at 18% of Bare Module Cost, the cost of land will be 2.0% of Bare Module Cost, and the cost of plant start-up is 2.0% of Bare Module Cost. These values were chosen in accordance with guidelines from *Product and Process Design Principles* (Seider, et al.).

Table 21-7 Total Permanent Investment Components

Total Permanent Investment

	% of Total Permanent Investment	
Year: **0**	100%	(default is first year of Construction, otherwise over-ride this year)
1	0%	
2	0%	
3	0%	

Cost of Site Preparations:	5.00% of Total Bare Module Costs
Cost of Service Facilities:	5.00% of Total Bare Module Costs
Allocated Costs for utility plants and related facilities:	$0
Cost of Contingencies and Contractor Fees:	18.00% of Direct Permanent Investment
Cost of Land:	2.00% of Total Depreciable Capital
Cost of Royalties:	$0
Cost of Plant Start-Up:	2.00% of Total Depreciable Capital

Endnotes

Seider, et al. (2016). Product and Process Design Principles.

Section 22 - Operating Costs

The manufacturing process incurs $4,117,000 of costs per batch produced. These are broken down into variable material costs and energy costs, and fixed labor costs and material costs. The vast majority of operating costs come from material costs, particularly methyluridine. As production ramps up in moderate and cautious estimations, the fixed costs per batch factor less into the overall cost of *sofosbuvir* production.

22.1 Variable Costs

22.1.1 Variable Material Costs

Due to the bulk quantities for raw materials required, raw material prices were obtained through Indian import/export data in 2016 (Appendix G). Assuming a batch size of 3,500 kg, the amount of each input was scaled up from the original patent. Calculations for each item can be found in Appendix L. These costs are summarized in Table 22-1 below in a per kilogram basis. Of the variable material costs, methyluridine is the most expensive, contributing $923 per kg of *sofosbuvir* produced. The variable raw material costs associated with the production of *sofosbuvir* also include consumed utilities water for injection (WFI) and anhydrous sodium sulfate. Water for injection, which is used for the washes, is purchased as a utility and purified on site. The cost for WFI includes both the cost of utility water and the costs incurred to purify it. Anhydrous sodium sulfate desiccant is considered a variable cost because the quantity is scaled according to the wash volumes. To maintain batch integrity, fresh anhydrous sodium sulfate is purchased for each batch.

Table 22-1 Variable Raw Material Costs per kilogram of Sofosbuvir

Raw Material	**$/kg Sofosbuvir**
2-Chloro-6-hydroxypyridine	$5.29
2'-Deoxy-2'-fluoro-2'-methyluridine	$923.41
Acetone	$0.95
Ammonium chloride	$0.76
Anhydrous Sodium sulfate	$0.14
DCM	$36.87
DIEA	$23.12
Ethyl acetate	$8.61
Hydrochloric Acid 0.5 M	$2.48
Isopropanol	$27.46
L-Alanine - HCl	$5.67
Phenyl Dichlorophosphate	$16.43
Ribavirin	$65.14
Sodium Bicarbonate	$0.14
Sodium Carbonate	$0.27
Sodium Chloride	$8.37
THF	$24.18
Thionyl Chloride	$1.58
Water for Injection	$12.65
Zinc Chloride	$0.74
Total	**$1,164.26**

22.1.2 Variable Energy Utility Costs

Compared to raw material costs, the cost of energy utilities is significantly smaller, totaling $6.85 per kilogram of *sofosbuvir* produced. The variable energy costs are summarized in Table 22-2 below. The majority of utility costs are incurred when regenerating refrigerants used to cool reactors and condensers. More detailed analysis of the utility costs can be found in Section 17.

Table 22-2 Variable Energy Costs per kilogram of Sofosbuvir

Utility	**$/kg Sofosbuvir**
Cooling Refrigerants	$4.89
Electricity	$1.96
Total	**$6.85**

22.2 Fixed Costs

22.2.1 Fixed Labor Costs

The day-to-day operations of the plant are managed by local chemical engineers, chemical operators, and experienced chemical plant workers. Two chemical engineers, working during the day shift, will oversee the entire operation and ensure that all units are operating properly. Each of the three shifts will have two chemical operators to oversee key transfer steps and ensure optimal reaction conditions. Experienced chemical plant workers will be employed to load raw materials, carry out the transfer steps, perform cleaning operations, and conduct routine maintenance. For the daytime process, 25 plant workers, 2 chemical operators, and 2 chemical engineers will be hired for a total of 29 employees in the day shift. Because only several reactions operate overnight, fewer employees are required during each of the two night shifts. In each shift, 20 plant workers will be overseen by 2 chemical operators for a total of 22 employees

per night-shift. Wages are obtained by considering the hourly wages of skilled chemical engineers[22-1], chemical operators[22-2], and plant workers[22-3] in the US. These wages were multiplied by a factor of 0.138, the ratio between the minimum wage in India[22-4] and the US, to account for the lower cost of living in India (Appendix D-1). Since the process is operated over a short period of time, employees would be expected to work overtime. The overtime rate is 25% more than the regular hourly rate. Night shift employees will earn 5% less than their daytime counterparts because they are less skilled. The total annual wages for employees of each position are calculated in Appendix D-2. Since these employees will only be working on this project for one third of the year, the 'Total pay' reflects the amount paid to employees of the position over the 4-month period. To evaluate the cost burden of wages, employee pay is calculated on a per batch basis. These figures are summarized in Table 22-3 below. For each batch of *sofosbuvir* produced, employees are paid $2,815.

Table 22-3 Summary of labor costs normalized per batch

Position	**Individual Pay ($/Batch)**	**Number of employees**	**Total Pay ($/Batch)**
Chemical Engineer	$82	2	$164
Chemical operator (day shift)	$67	2	$134
Plant worker (day)	$36	25	$900
Chemical operator (night shift)	$65	4	$259
Plant worker (night)	$34	40	$1,358
Total Wages			**$2,815**

22.2.2 Fixed Material Costs

Some raw materials are consumed on a per batch basis rather than proportionally with *sofosbuvir* produced. Sand, which is used to absorb and contain chemical spills, is purchased as a

safety precaution. Assuming a turnover for reused materials of once per 100 batches, the cost for replenishing sand amounts to $45 per batch. Nitrogen is used to clear out the tank and to prevent fires. For each batch, $16,427 of liquid nitrogen is needed to fill the head spaces of the reactors. The fixed costs of individual raw materials are tabulated below in Table 22-4.

Table 22-4 Summary of fixed material costs

Raw material Costs	**Total Cost ($)**	**Cost per Batch ($)**
Nitrogen	$1,642,672	$16,427
Sand	$4,547	$45
Total	**$1,647,219**	**$16,472**

Endnotes

22-1: PayScale Human Capital (2017). *Chemical Engineer Salary*. Retrieved from http://www.payscale.com/research/US/Job=Chemical_Engineer/Salary.

22-2: PayScale Human Capital (2017). *Chemical Operator Salary*. Retrieved from http://www.payscale.com/research/US/Job=Chemical_Operator/Hourly_Rate.

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Section 23 - Other Important Considerations

During the development of a commercial-scale synthesis design for *sofosbuvir*, the crucial considerations revolved around the chemical synthesis steps, the process development, equipment needs and overall costs and profitability. However, in order to justify most of the above considerations, various important considerations are also taken into account that must be satisfied for justifiable project development. Some important considerations include the project impact on the environment, the control systems required at the plant, the safety employees and the surrounding community and the work and shift schedule. These less obvious considerations all had an impact on some crucial consideration made in the process and, as such, were explored in much finer detail.

23.1 Environmental Considerations

Chemical processes produce a variety of chemicals and require a large amount of chemical inerts and unreacted chemicals; for the production of *sofosbuvir*, this was no exception. Each process previously discussed featured a significant amount of unreacted solvents, excess reactants and chemical inerts that had to be accounted for during and after the process. In order to limit and negate any impact the production had on the environment, various considerations were made to assure that the waste solvents and chemical inerts were safely handled and disposed.

Initial environmental considerations revolved around the selection of a safe metal catalyst for the reaction steps. Our team sought to avoid the use of heavy metal catalysts in any reaction step, which would have a significant positive impact on the environmental consciousness of the

process as a whole. In the end, a more organic, salt-like catalyst in zinc-chloride will be used in place of any toxic, heavy metals.

Perhaps the most prevalent issue in the process was the safe disposal of solvents and washing agents. Each process in the synthesis had waste considerations to be made in order to minimize impact on the environment. Process 100 required a significant volume of IPA, which was removed from the product stream after the reaction step. A distillation tower with a condenser was used for the solvent phase separation to minimize the escape of any gas phase solvent into the atmosphere. In order to minimize the amount of unreacted materials and chemical impurities in the outlet stream, multiple trays were added to the distillation column to increase the purity of the solvent waste stream, increasing the ability of the waste disposal services to re-use or re-purpose the IPA. Similar considerations were taken in Process 200, where solvent waste was flashed and condensed to remove a mostly pure solvent for proper disposal. Process 200 features two evaporation units, each of which condense their distillate streams to eliminate the potential for gas pollutant escaping to the atmosphere. These solvents will also be relatively pure, allowing for the purification and potential future re-use of those solvents rather than disposal. Furthermore, Process 200 will actively use and contaminate a large volume of both pure water and brine during wash processes. This wastewater will have to be disposed of through appropriate venues to avoid any possible water source contamination in the already contaminated waterways of India. Process 300 had waste considerations similar to Process 100, where the solvents, THF and ethyl acetate, were distilled to remove a nearly pure stream to increase the likelihood of reuse and minimize total waste. Furthermore, Process 300 will also feature a substantial use of water for wash cycles, which will result in significant wastewater disposal. Overall, major considerations were made with regards to the primary byproducts and waste

solvents the process would produce, aiming to minimize or eliminate their impact on the environment.

23.2 Process Control

For any chemical production process, control systems must be in place to ensure the efficacy of the synthesis, the safety of employees as well as the stability of the reaction conditions. Among the many requirements for a successful chemical plant operation, there are several that require process control. These include safety, production specifications, environmental regulation, operational constraints and economics.[23-1] The aforementioned requirements bring about the need for constant process monitoring, suppression of external disturbances on the process and assurance of process stability.

Each vessel involved in the entire production process requires a control system to manage the external disturbances that could affect the system. For example, the heat exchanger for thionyl chloride cooling in Process 100, V101, should feature a feedback control loop, where the set-point value is an outlet temperature of 0°C and a feedback PID controller could increase or decrease the flow rate of coolant into the heat exchanger to influence the exit temperature of thionyl chloride into the reactor, V102. Furthermore, a feedback controller is used on the distillation condensers in V103 and V304 to control the concentration of the outlet solvent waste. If a supplier specified that they required a certain purity in order to purchase the waste solvent, a PID control system could vary the set-point and adjust the tray conditions and inlet flow rate to control the overhead solvent purity. Control systems could be similarly used for the heat exchanger in Process 200 as well as the reaction vessels in Processes 200 and 300, where vessel temperature is relevant to the reaction. Overall, it is crucial to maintain a system of process

controls, such that the required reaction conditions are met and to maintain overall control on the outlet conditions of waste products and *sofosbuvir*.

23.3 Safety and Health Considerations

During the design of the process, various considerations were taken regarding the safety of both plant operators and the immediate community surrounding the plant. While the synthesis route was restrictive in terms of which chemicals could be used for the production of *sofosbuvir*, attention was still paid to the material safety of all the raw materials involved in the production process. Fire danger is associated with many of the solvents used in the process, namely acetone, EA, THF and IPA. In order to combat the risks of fire, our team projected the installation of a fire sprinklers in the entire facility. After reviewing the material safety data sheets, or MSDS, which can be seen in Appendix M, our team determined that water extinguishing of fires of all of the aforementioned solvents was appropriate. At a size of approximately 100,000 square feet, the cost of fire sprinkler installation for the entire facility is approximately $116,000.[23-2] Furthermore, various materials have a significant health hazard and caustic potential, namely HCl, NH_4Cl, ZnCl, sodium sulfate, DCM, DIEA, thionyl chloride and THF. In order to combat the risks of possible leaks, 45 metric tons of sand were included in capital costs, enough sand to absorb a massive chemical spill of a main solvent in the process. If the sand were to be used at any point, the same quantity could be purchased again. The cost of sand was relatively cheap: 45 metric tons totaling approximately $4500. Furthermore, it would be necessary to have strict oversight of any loading processes in which a hazardous material were being loaded or handled by operators.

During the process development, many safety considerations were made, especially with reaction vessels. For instance, the reactions taking place in Process 200 are all exothermic, which

could result in a runaway chemical reaction. Aside from the cooling coils in the tank that could be used to cool the vessels at any time with the constant volume of coolant, Process 200 also incorporates 2 runaway reaction vessels to quench a reaction if it becomes uncontrollable. Each of the 5 reaction vessels is connected to a runaway reaction vessel and the reactants could be re-routed and quenched with water in the event of a runaway reaction. Along those same lines, considerations were made with regards to the nitrogen protection of reactions in Processes 200 and 300. Our team made certain that reaction vessels would be sparged with nitrogen for any possible oxygen contamination, such as the introduction of new solvents during the process.

Aside from nitrogen protection of the reaction vessels, industrial consultants made safety recommendations regarding vessel transfers with nitrogen. Initially, our team considered nitrogen pumping between reaction vessels, but was advised by consultants that this type of pumping could have extreme hazards in situations where pressure was not constant in the process. In the event of a pressure difference between vessels, gaseous nitrogen could have an explosive blowback once the entire vessel were emptied, filling the contents of subsequent vessels rapidly and explosively. In order to avoid this hazard given the possible pressure variations from vessel to vessel before nitrogen caps and protection were in place, our team decided to simply use pumps to empty each vessel rather than using nitrogen. Furthermore, pressure release valves were accounted for on each reaction vessel and heat exchanger where any volatile solvent or coolant could be heated to its flash temperature and vaporize in the vessel. The emergency pressure release valve would release pressurized vapor in the event of an emergency pressure difference in the vessel.

A final safety consideration was made regarding the loading of solid powders into reaction vessels. In Process 300, two solid phase reactants, methyluridine and zinc chloride, are

loaded into the reactor as powder or fine particulates. Initially, the process was designed such that solid methyluridine powder was loaded into the vessel before THF solvent was added, but this raised concerns regarding the dust-up of the solid powder and its resulting flammability. In order to avoid this risk, our team revised the loading schedule, instead loading the liquid solvent THF before the solid powder methyluridine, reducing the risk of flammability by solid dust-up.

Overall, our team was able to take various safety and health hazards into consideration and work to mitigate risks. Installation of fire sprinklers, purchase of chemical spill absorbent, installation of runaway reactions vessels as well as changes made to process procedure should all noticeably reduce the risk of accidents.

23.4 Work Scheduling and Shift Considerations

The initial design project proposal made two important assumptions regarding the work scheduling: important staff worked a standard 40 hour week and that projects of this magnitude are typically completed with 3-4 months, with the product being stored for the remainder of the production year. With these two considerations in mind, our team sought to determine if it was possible to satisfy both conditions and, if so, under what circumstances. Initial project scheduling based on Processes 100 and 200 found that it was possible to operate the system with skilled workers during a day shift for the major changeover operations and with a small night staff for overseeing overnight reactions. However, full development of Process 300 significantly changed both the bottleneck equipment as well as the bottleneck time, making the day shift unable to consistently cover the same tasks in each batch. Development of the full process Gantt chart, Figure 23-1, allowed for a more exact analysis of the process scheduling.

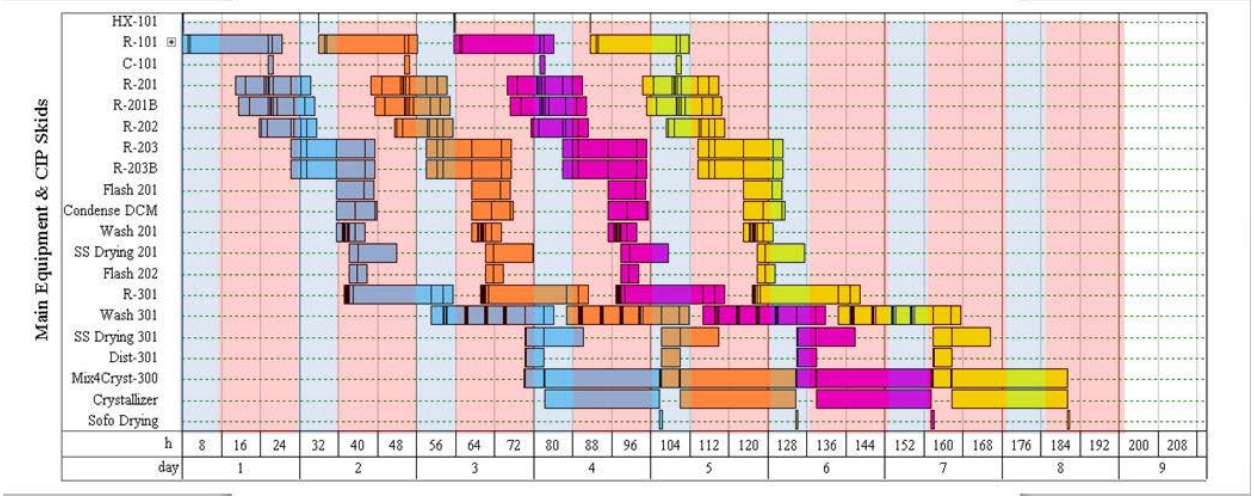

Figure 23-1 Gantt Chart with Shift Allocations. Four separate batches are shown along with independent day and night shifts in blue and red, respectively. Batch time is 4.1 days and cycle time is 1.16 days.

During discussions with industrial consultants, it became clear that highly skilled chemical engineers would work a day shift in a standard 40-hour week, and our team did its best to schedule the day shifts such that the skilled workers were present during important processes. For the purposes of the entire process, it was decided that the most important processes to oversee were the crystallization and distillation steps in Process 300, though many other processes could be overseen by a skilled chemical engineer. Furthermore, our team took into consideration which processes were the most labor intensive and would most significantly benefit from the skilled day workers being present. The wash steps in both Processes 200 and 300, each of which had the most moving parts, appeared to be the optimal candidates for day time shifts. Unfortunately, size constraints on the crystallization unit required a significant loading time and crystallization time, creating a bottleneck in the process that was an uneven multiple of the 8-hour day our team was attempting to plan. A brief sensitivity analysis as well as a discussion with industrial consultants revealed that scheduling a larger night staff was much more conducive to profitability than purchasing a larger crystallization unit. Furthermore, in

order to complete the drug production within the planned 4 month time window, it was necessary to schedule shifts during all 7 days of the week. With all these considerations taken into place, our team decided to move forward with the work schedule presented in Figure 23-1.

The work schedule will feature three 8-hour shifts. The 8-hour day shift is run with skilled workers and experienced chemical engineers. The two 8-hour night shifts, are run by two skilled chemical operators and less skilled plant workers. At any given time, the maximum number of processes occurring during a day shift will be 14, as seen on day 4 in Figure 23-1. Similarly, the night shift will operate up to 11 processes at once and 14 in a single shift. Using the advice of industrial consultants, it is wise to overestimate the amount of plant workers needed. With this advice in mind, our team determined that the work schedule would follow the following pattern: the day shift would employ 29 workers: 2 skilled chemical operators, 2 experienced chemical engineers and 25 skilled plant workers; similarly, the night shifts would each employ 22 workers: 2 skilled chemical operators and 20 plant workers. Using published information regarding average salary for chemical plant operators, workers and engineers, our team arrived at the average hourly wage for each type of employee; these calculations are available in Appendix D. For the entire 4-month production process, the total labor costs will be approximately $281,500. On a per batch basis, this labor cost is $2,815 per batch, which is a small fraction of total costs per batch compared to raw materials and utilities.

The original design goals were to orient the work shifts around a standard 40 hour work week, while completing the production of *sofosbuvir* in a 4-month production schedule. Our team determined that, given the reaction times involved in the process, it would be infeasible to complete the production of the drug in the 4 month window while also maintaining a standard 40 hour work week. Simple cost analysis determined that the cost of labor in India was sufficiently

low to justify working more hours per week to complete the production on schedule. The total labor costs even with overtime and around-the-clock wages considered is a small fraction of the total costs and sales for the project, which justified the labor schedule proposed.

Endnotes

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Section 24 - Profitability Analysis

Hepatitis C is a virus that affects 130 million people worldwide, predominantly in developing countries in Africa and East Asia. It claims 700,000 lives each year, and four million people are diagnosed with HCV each year.[24-1,24-2] To combat this global epidemic, this proposal set out to produce Gilead's highly successful *sofosbuvir* at an affordable price, while generating enough profit to sustain operation. The target customers of this facility are the 100 million people infected with HCV across the countries to which we may sell, per Gilead's low-cost production license.[24-3] As demonstrated in the following section, the project is highly successful, with room for production expansion to treat the entire affected population. The net present value (NPV) was calculated to be $1.22B, and the internal rate of return (IRR) was calculated to be 67.7%. As initial investment sums to below $100MM, accounting for working capital and ignoring tax benefits, the project shows promise to fully cure or drastically reduce the presence of HCV in the global population.

Various factors were analyzed for their effect on financial performance, such as prominent material costs. Additionally, the feasibility of increased production was assessed to 130 million affected globally, as well as those who are newly diagnosed each year. The Profitability Analysis-4.0.xls spreadsheet by Brian K. Downey was used to calculate economic performance of the plant. Data were gathered using Aspen, SuperPro, research, and suggestions from faculty advisors and industrial consultants.

24.1 Model Assumptions

The effective tax rate was assumed to be 34.61%, and the cost of capital, effectively the discount rate, was assumed to be 15% and remain constant for all years of interest.[24-4, 24-5] The

plant will occupy a space previously used for pharmaceutical manufacturing, thus start-up and construction costs were assumed to be relatively low. Leasing costs were based off the average rate for commercial property in Mumbai, a popular city for pharmaceutical manufacturing, at $1.64/ft^2.[24-6] Equipment costs were calculated via the procedure given by Seider, et al. rather than by the Aspen Process Economic Analyzer (APEA) methods.[24-7] Equipment was depreciated on a five-year schedule. All other factors were left at the default options as specified by the profitability spreadsheet.

As discussed in Section 16, *sofosbuvir* is administered in combination with RBV, in a ratio of 400 mg *sofosbuvir*/600 mg RBV. In addition to raw materials used in the synthesis process, RBV was purchased and combined with the produced *sofosbuvir* for formulation. The cost of tablet formulation and packaging was estimated at 20% of the cost to produce the drug, per data from Hill et al.[24-8] In the base assumption model, it was assumed that roughly 95% of the volume of organic solvents could be removed with minimal contamination via distillation, and the remaining impure 5% would be collected by a paid waste disposal service. Calculations shown in Appendix N show that the value from the resale of pure solvents was roughly enough to compensate for the cost to dispose of the impure 5%, for a net zero cost of organic material disposal. Water-based solvents, however, were fully contaminated and required paid disposal, also shown in Appendix N. Section 24.3.4 explores the case where the distillate streams are not pure enough for resale and thus 100% of the organic solvents must be disposed. Lastly, negative taxable income in Year 1 led to a positive tax bill; however, as we are operating as a component of a large pharmaceutical company, it is expected that this negative income would be used to offset income in another business division and provide a tax benefit.

24.2 Profitability Measures

The entire project has an 11-year schedule: ten years of operation, with all product from one year sold in the following year, and all construction and capital costs occurring in Year 1. The plant does not operate in Year 11, but the inventory generated in Year 10 is sold. During Years 1-10, the plant is run for 120 consecutive days to produce 100 batches/year of *sofosbuvir*, and labor and variable costs are limited to this period. The relative brevity of operation facilitates increased production or compensation for lost batches simply by running the plant for extra days. Sales are timed each year in line with production such that there is always a 50-batch stock reserve in the event of plant shutdown or lost product. If production is disrupted, as discussed in Section 24.3.5, operation can be extended past the 120-day mark to compensate for any lost product. The plant operation period of 10 years was assumed based on calculations performed in Appendix E, and various production schedules, as shown in Section 24.3.2, were created to model distribution. Given HCV's long latency period, producing 10 million batches of *sofosbuvir* over 10 years will avoid the deaths of many who are currently infected.

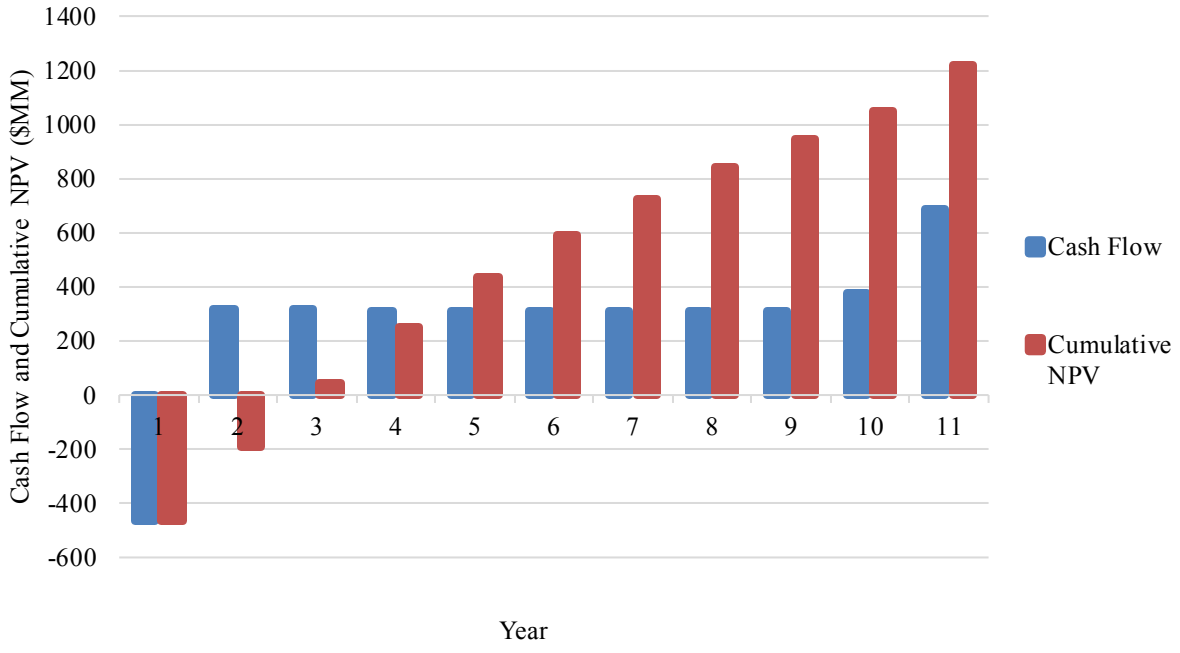

Figure 24-1: Cash Flows and Cumulative NPV vs. Year of Operation

In the base case scenario, IRR was calculated to be 67.7%, and NPV was calculated to be $1.22B, using a discount rate of 15%. The project NPV surpasses the revenue potential of $1.05B, demonstrating that *sofosbuvir* can be sold profitably at a much lower cost than originally marketed. Figure 24-1 shows the project cash flows, and Input and Cost Summary data are tabulated in Appendix L. The substantial profit margin causes the project to reach positive NPV in Year 3 and grow steadily through Year 11. Various internal cost benchmarks were set to ensure profitability; while variable costs were high, all individual costs fell at or well below these benchmarks. The target for total raw material costs and utilities was less than 50% of revenues to allocate enough of the budget to equipment and personnel costs. The intended limit for raw material costs was $1/g or $1,000/kg of *sofosbuvir* but was narrowly missed due to the high cost of methyluridine. The raw material costs were $1,170/kg of *sofosbuvir* or 39% of revenues, comprised primarily of methyluridine which cost $925/kg of *sofosbuvir*. The high cost associated with methyluridine is discussed in Section 24.3.3. Utility costs of $264/kg of *sofosbuvir*, composed primarily of the $239/kg formulation cost, brought the variable costs to 47.8% of revenues. Individual material costs can be found in Section 14. Capital investment costs were a concern in the early stages of the design due to the large vessel volumes required to produce such a large amount of *sofosbuvir*. Ultimately, these costs added up to less 10% of revenues. Despite the need for round-the-clock operators, personnel costs stayed below 1% of revenues, as hourly wages in India are relatively low. Low labor costs were countered by relatively high corporate taxes, comparable to those in the US, that accounted for 17.6% of revenues.[24-4] Although these high taxes cut into profits, they may encourage investment from the Indian government. As an investor, the government would realize returns through tax revenue, increased Indian gross domestic product, and particularly the humanitarian benefit of eradicating or reducing HCV.

24.3 Sensitivity Analysis

As *sofosbuvir* sales total $1.05B over ten years, an NPV of $1.22B is indicative of a very profitable operation. Despite this success, it is necessary to account for changes in various factors that contribute to the financial performance. The following were analyzed for sensitivity: the sale price of *sofosbuvir*, the production schedule for *sofosbuvir*, the purchase cost of methyluridine, the cost of solvent waste disposal, and plant shutdown. For each analysis, NPV is calculated using a 15% discount rate, and the base case is as discussed above: 350 metric tons of *sofosbuvir* produced per year for 10 years, sale price of $3,000/kg or $100/treatment, net zero organic waste disposal costs, and methyluridine purchase price of $888/kg. Tabulated data for all figures can be found in Appendix L.

24.3.1 Sofosbuvir Sale Price

The sale price of *sofosbuvir* is susceptible to change for many reasons, such as unforeseen costs, government regulations, patent expiry, or market competition. Additionally, if the sale price can be decreased while preserving profitability, it would be possible to eliminate or at least further reduce cost barriers for HCV patients. Figure 24-2 explores the effect of sale price on financial performance.

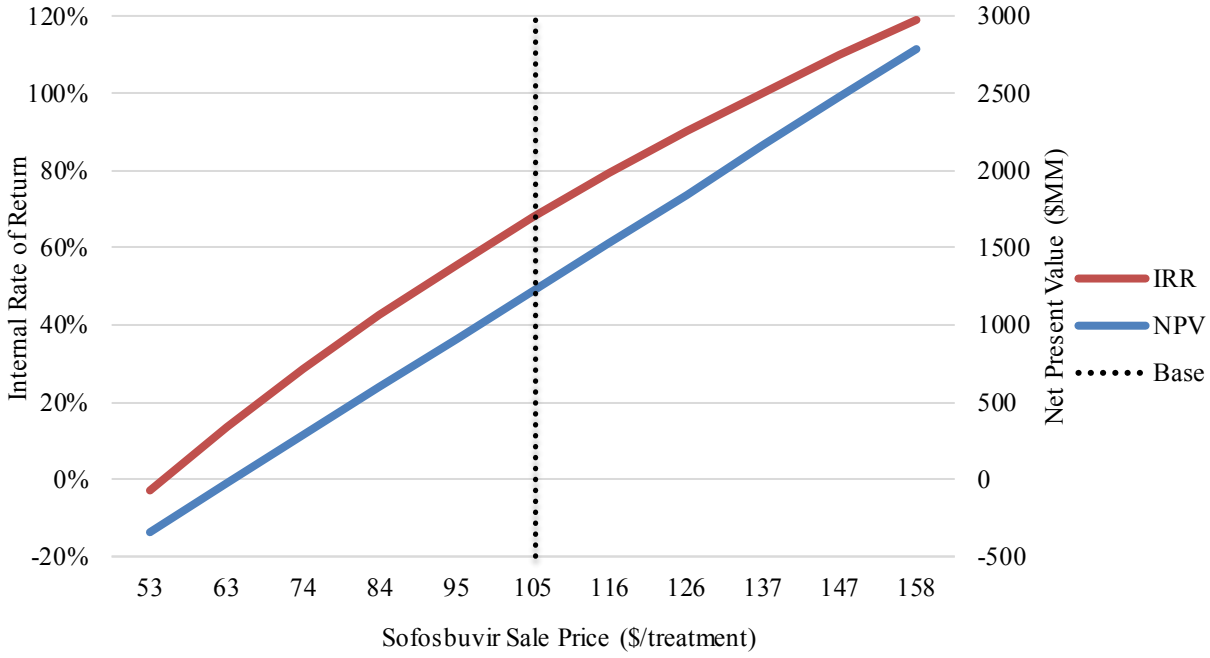

Figure 24-2: Sensitivity of IRR and NPV to change in sale price

The intended sale price of *sofosbuvir*, $3,000/kg or $100/treatment, was varied from 50% to 150% in increments of 10%. Break-even sale price, at which NPV is equal to zero, occurs at roughly $63/kg, indicating the opportunity for substantial decreases in price in countries of particular need or for price negotiation with national healthcare providers.

24.3.2 Sofosbuvir Production Schedule

The base production schedule was set to produce 10 million batches/year for 10 years to treat the 100 million patients in the countries included by the low-cost license. It is possible that Gilead decides to extend the license to countries currently excluded, such as China, to eliminate HCV on a global scale as well as to increase profits. If it can be shown that this facility has the capability to serve these additional markets, Gilead may be strongly encouraged to consider this option. The High-output case assumes unrestricted sales territory and production of enough *sofosbuvir* to treat all HCV patients through the end of operation. The current global population

affected by HCV is 130 million, and each year brings four million new diagnoses and 700,000 deaths, for a net increase of 3.3 million patients per year.[24-1, 24-2] Over the next ten years, the required amount of *sofosbuvir* rises to 163 million treatments, or 5,705 metric tons, a 63% increase from the base case. To account for this growth, production is ramped up linearly from standard capacity (350 metric tons/year) in Year 1 to 625 metric tons/year in Year 4 and maintained at this level through Year 10. The increase in production is accomplished by longer operating periods each year.

Another scenario, the Low-output case, was constructed to model slow plant startup. Entry into a new market may be hindered by government regulations, vendor delays, or other unforeseen circumstances. In this case, production begins at 50% of initial capacity and increases evenly to 100% through Year 6. In each case, all *sofosbuvir* is sold the year after it is produced. The yearly output schedules are shown for each case in Figure 24-3 as a percentage of the base 350 metric tons/year, and the IRR and NPV calculated for each case are shown in Table 24-1.

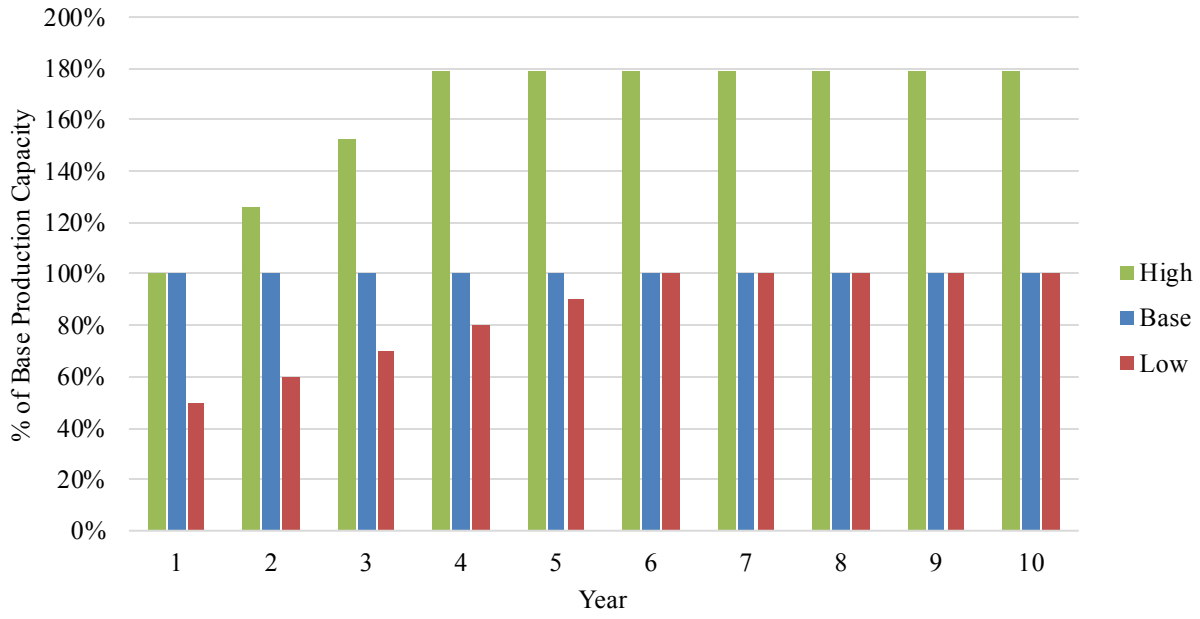

Figure 24-3: Production Capacity as % of Base vs. Year in three different scenarios, where base production is 350 metric tons/year

Table 24-1 IRR and NPV for all Production Schedule Models

Case	IRR	NPV
High	66.9%	$1,884 MM
Base	67.7%	$1,221 MM
Low	64.6%	$947 MM

All three scenarios are highly profitable, yielding large NPV and IRR significantly higher than the cost of capital. While shifting to the high-output case slightly decreases IRR, the NPV increases by 50%. These conflicting changes occur due to the one-year delay in sales; the higher variable costs to ramp up production are not fully offset by the previous years' stocks of *sofosbuvir*, and income is relatively lower in the first few years. However, the considerable increase in NPV from higher total sales outweighs the change in IRR, indicating the potential for this plant to treat the entire population of HCV patients. The low-output scenario displays both lower IRR and NPV but is still a highly profitable outcome.

24.3.3 Methyluridine Purchase Price

As discussed in Section 22, the highest individual cost incurred is the purchase price of the methyluridine. Synthesizing methyluridine was ruled out, as the cost of starting materials is only marginally lower and the requisite chemistry added an unnecessary amount of complexity to the operation. An increase in the price of methyluridine could drive the raw material costs further over the $1/g mark, cutting into the profit margin, while a decrease in price would greatly expand profit margin. Figure 24-4 shows how the purchase price of methyluridine affects IRR and NPV.

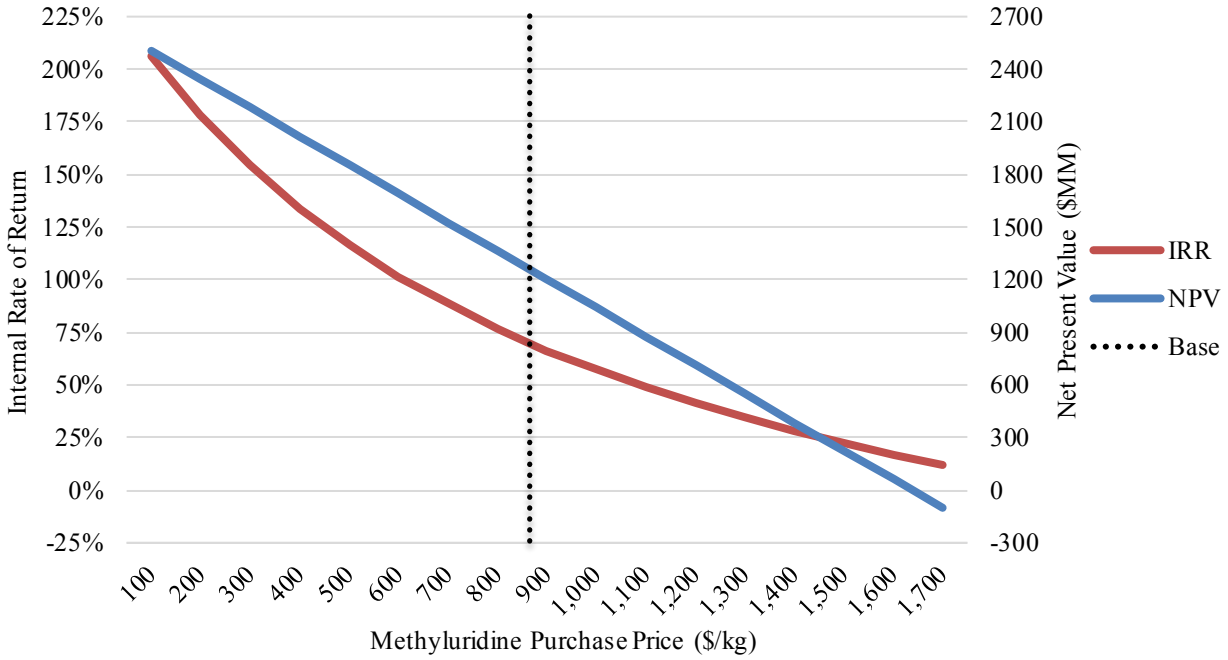

Figure 24-4: Sensitivity of IRR and NPV to Methyluridine Purchase Price

While the purchase price is not prohibitive, methyluridine comprises 79% of the raw material costs and 31% of revenues and thus would be a primary target for cost reduction to increase profit. The break-even cost of methyluridine is just below $1,640/kg, a highly unlikely increase of 85% from the current quoted cost. Online wholesale distributors sell methyluridine for as low as $100/kg, albeit for batch sizes on the order of kilograms. If a bulk order contract could be created with one of these vendors, it would triple the IRR and double the NPV; the drastic increase in profit margin could allow the sale price of *sofosbuvir* to decrease further to ensure affordability.

24.3.4 Solvent Waste Disposal Costs

Throughout the synthesis process, organic and aqueous outlet streams are generated, containing organic contaminants that must be properly handled. Solvents and starting materials are not recycled due to FDA regulations that dictate the need for batch integrity, the ability to separate discrete amounts of product for testing purposes and to track contamination. Any stream

that has contact with the active is considered contaminated. In all three parts of the process, roughly 95% of the organic solvent material is removed using distillation or flash. In the base scenario, it is assumed that these distillate streams are pure enough to be resold, and that the resale value and cost to dispose of the remaining 5% of the organic solvents sum to zero. The calculations for these costs and resale values, along with the amount of solvent waste generated, are shown in Appendix N.

Table 24-2 IRR and NPV With and Without Solvent Disposal Costs

Solvent Disposal	**IRR**	**NPV**
With Organic Solvent Resale	67.7%	$1,221 MM
Without Organic Solvent Resale	61.5%	$1,119 MM

The alternative is considered where the distillate streams are deemed too impure for resale and require paid collection. In both cases, the paid disposal of spent water-based streams is unavoidable for environmental purposes. Table 24-2 shows the impact on IRR and NPV of the waste disposal cost. The need for paid collection lowers IRR by over 6% and NPV by $102MM. These changes are by no means prohibitive, but waste management could be a future consideration to further reduce costs and boost profit.

24.3.5 Interruption of Batch Production

Despite various safety measures and constant supervision, there is always the possibility of a runaway reaction or other plant emergency. It is necessary to assess the financial impact of a production disturbance to determine if extra safety and damage control mechanisms need to be installed. A proposed disruption is a runaway reaction in Year 5 that causes the breakdown of units V203 and V209, duplicate 140,000 L reactors and duplicate 100,000 L runaway reaction vessels, respectively. It is assumed that no other equipment, materials, or staff are harmed, and that the vessels are replaced at their bare module costs as calculated in Section 21.

Table 24-3 IRR and NPV With and Without Runaway Reaction

Batch Interruption	IRR	NPV
Without	67.7%	$1,221 MM
With	67.5%	$1,216 MM

The disruption results in the use and repurchase of all stored sand, waste disposal of all materials from this batch, and a halt in production for three months awaiting the reinstallation of the broken vessels. Staff are paid continuously through the down time, as it is expected they would be reassigned to other tasks by the company. After the replacement equipment is installed, operations are resumed and extended to yield the target output for the year. The total expense in Year 5 is $12.8MM: $3MM to replace the vessels, $6MM for waste disposal and extra raw materials purchase, and $3MM for the additional staff wages and fixed costs. Table 24-3 shows the result of the runaway reaction on financial performance. The cost associated with this runaway reaction is more than compensated by the profit margin, as shown in the 0.2% decrease in IRR and $5MM decrease in NPV. Nevertheless, it is important to implement safeguards to prevent runaway reactions to limit dangers to the staff, equipment, and product.

24.4 Conclusion

Ultimately, the proposed design to produce *sofosbuvir* at a low cost has potential to make a tremendous impact on HCV and those affected. The $100MM total capital investment required to construct and prepare the facility can easily be financed by the company and will generate enough *sofosbuvir* to cure 75% of the global population suffering from HCV as well as an NPV of $1.22B and an IRR of 67.7%. Even in the more conservative cases discussed here, the project still meets low cost goals and stands to be highly lucrative. Profit can be used to streamline parts of the process previously unexplored, such as the purchase of methyluridine, and facilitate distribution to all target markets.

Endnotes

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Section 25 - Conclusions and Recommendations

This report describes a commercial-scale process design for the production of *sofosbuvir*, a much-needed treatment for Hepatitis C. HCV will kill or shorten the lifespan of nearly 150 million people worldwide over the next 25 years, assuming no intervention. The plant design is capable of producing enough drugs to treat all current global cases at a cost that can be readily afforded by patients out-of-pocket or with assistance from their local governments.

The proposed facility requires full operation for 120 days/year, with each batch producing 3,500 kg of *sofosbuvir*. The process, with an overall yield of 41%, consists of three processes: 100, 200 and 300. Abiding by the timing and scheduling presented in Section 23 and Appendix D, 100 batches per year is projected to produce 350,000 kg per year, meeting the demand for 10 million patients.

From a financial standpoint, it is highly recommended that this project be carried out. The internal rate of return is greater than 67%, and the net present value is in excess of $1.2 billion. To compute these financial measures, we assumed a ten-year operation period. These numbers motivate further investigation and investment as a financially feasible design to produce a Hepatitis C therapeutic at an affordable price in India. The demand for this drug is very high in India and low-income developing countries, and this venture provides a valuable medication at an affordable price to patients. This financial analysis does not consider the distribution costs of the drug product. It is recommended that this project is conducted at an existing pharmaceutical facility to save on land costs and general equipment costs.

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During the course of this design project, our team received considerable assistance, support, guidance and overall dedication from a variety of advisors, professors, consultants and external industry experts regarding the development and refining of the project as a whole. First and foremost, our team would like to extend our sincerest gratitude to our project author and advisor Dr. John Crocker. Dr. Crocker was paramount in advising our team with regards to standard industrial practice, reasonable assumptions and was helpful with each step of our process, from patent interpretation to the most banal of process details. Furthermore, our team would like to thank Professor Bruce Vrana for his continuous support throughout the project, both as senior design project professor as well as industrial consultant. Professor Vrana made himself available at all times, providing extremely helpful insight when needed. Our team would also like to thank Professors Len Fabiano and Warren Seider for their assistance throughout the project as well; Professor Fabiano's dedication to making himself available outside of weekly meeting times was paramount for the refining of finer details of the project.

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Given the complex nature of our project, our team often reached out to consultants and experts outside of the industrial consultants available in weekly meetings. Our team would like to specifically thank Dr. Andrew Hill of the Department of Pharmacology and Therapeutics at Liverpool University for his assistant early in the project regarding synthesis route determination and project cost potentials. Furthermore, our team must acknowledge the unparalleled pharmaceutical, organic chemistry and general production knowledge provided by Dr. Joseph M. Fortunak, professor of Chemistry and Pharmaceutical Sciences at Howard University. Dr. Fortunak was crucial in our team's understanding of the chemistry behind *sofosbuvir* synthesis as well as the standard method of production currently employed in Southeast Asia. Additionally, our team would like to thank Natalie Eyke at Merck Process Development for her advice in small molecule separations, Daniel Wu at the University of Pennsylvania for his assistance with analyzing patent literature, and Dr. Igor Dubovyk of the Pharmacylics Medicicinal Chemistry Department for his insights on the purification process.

Finally, our team would like to take the opportunity to acknowledge the impact others outside of the design project had on our work. We would like to specifically acknowledge the CBE Department as a whole for providing our team with the knowledge necessary to complete the project as well as assisting with minor questions throughout the semester. Moreover, our team would like to express our sincerest thanks to our parents for their support during our entire careers at the University of Pennsylvania, which has culminated in this design project. Our team is very fortunate to have been assisted by all of those involved in this project and would like to, again, expressly thank those listed above for their guidance, support and wisdom.

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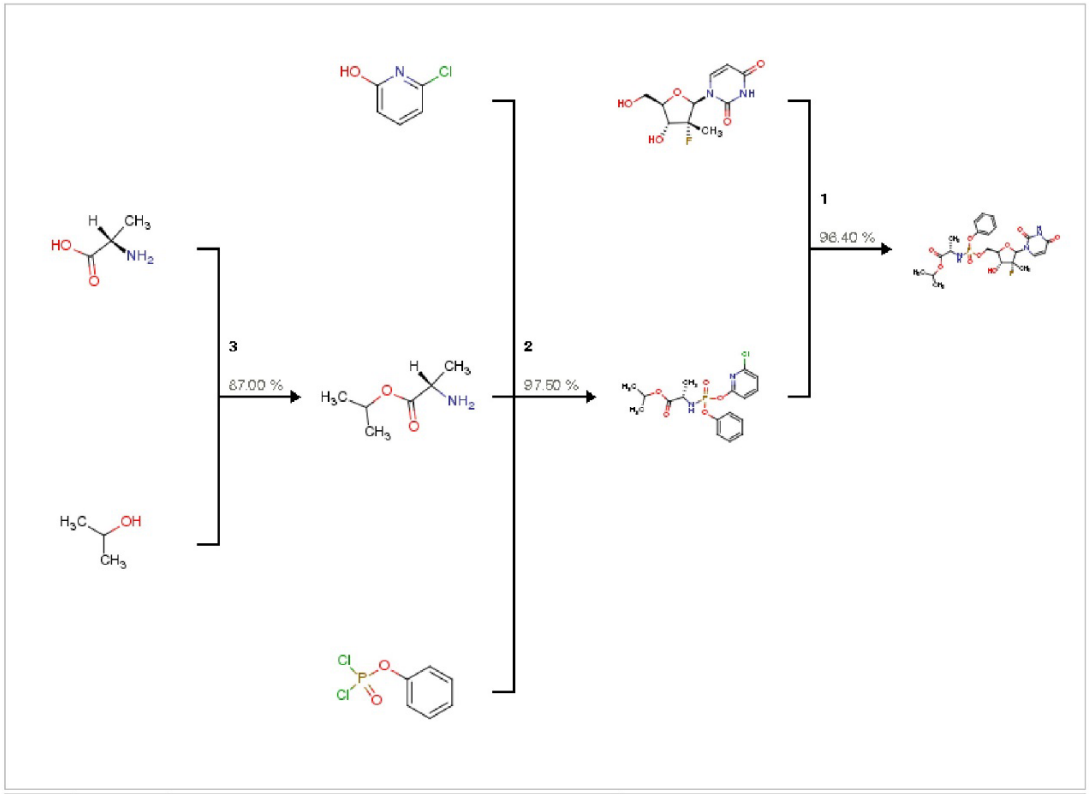
Appendix A – Patent Search

Appendix A-1 Reaxys Synthesis

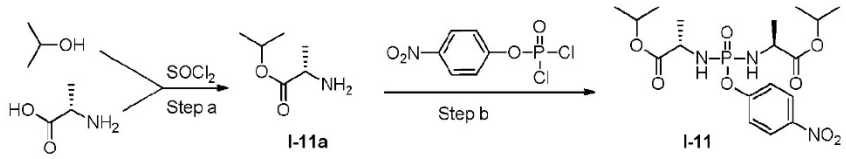


Step	Yield	Conditions	References
1 Reaxys	96.4%	**With** N-ethyl-N,N-diisopropylamine; zinc(II) chloride **in** tetrahydrofuran T=55 - 60°C; Inert atmosphere;	**Jiangsu Hanson Pharma Group Co., Ltd.; Zhu, Qiang; Liu, Zhaopeng; Li, Bin; Li, Yunfei; Yang, Baohai** **Patent:** CN105461773 A,**2016** ; **Location in patent:** Paragraph 0097; 0098; 0099; 0100;
	7.1:1, to intermediate A1 as the starting material The 2 the the [...] -deoxy-2-fluoro -2 the [...][...] -C D-methyl uridine (2.6g, 10 . 0mmol, 1 . 0equiv.), intermediate A1 (7.96g, 20 . 0mmol, 2 . 0equiv.), N, N-diisopropyl ethylamine (DIEA, 1.95g, 15 . 0mmol, 1 . 5equiv.), zinc chloride (2.06g, 15 . 0mmol, 1 . 5equiv.) adding flask R $_1$ in, to 40 ml tetrahydrofuran as solvent. N $_2$ under the protection of the, heating to 55-60°C, stirring 15-40h. After the reaction, by adding 80 ml ethyl acetate, saturated ammonium chloride washing (40mLx1), 0.5M hydrochloric acid washing (40mLx1), Na $_2$ CO $_3$/NaHCO $_3$ buffer solution (40mLx1), saturated salt water washing (40mLx1), anhydrous sodium sulfate for drying. Remove the solvent to obtain oil turns on lathe does, using acetone/dichloromethane (1/8, V/V) beating crystallization. Product 2.5g, quality yield of 96.4percent.	
2 Reaxys	97.5%	Stage #1: isopropyl L-alanine; O-phenyl phosphorodichloridate **With** N-ethyl-N,N-diisopropylamine **in** dichloromethane T=-50 - -5°C; Inert atmosphere; Stage #2: 6-chloro-2-hydroxypyridine **With** N-ethyl-N,N-diisopropylamine **in** dichloromethane T=-10 - 0°C; Inert atmosphere;	**Jiangsu Hanson Pharma Group Co., Ltd.; Zhu, Qiang; Liu, Zhaopeng; Li, Bin; Li, Yunfei; Yang, Baohai** **Patent:** CN105461773 A,**2016** ; **Location in patent:** Paragraph 0065; 0066; 0067; 0068; 0069;
	1:Embodiment 1, type A1 preparation of compounds The 40 ml dichloromethane to join flask R $_1$ in, N $_2$ protection, stirring cooling to -50 °C. Adding dichloroborane phosphoric acid phenyl ester (2.31g, 11 . 0mmol, 1 . 1equiv.), stirring 10-20min; disposable adding L-c amino acid isopropyl ester (1.85g, 11 . 0mmol, 1 . 1equiv.), slowly dropping N, N-diisopropyl ethylamine (2.8g, 22 . 0mmol, 2 . 2equiv.); the drop finishes, 3-4h to the temperature in the -10 - - 5°C. The other flask R $_2$, by adding 2-hydroxy-6-chloro-pyridine (1.29g, 10 . 0mmol, 1 . 0equiv.) and 20 ml dichloromethane, N $_2$ protection, stirring cooling to -10 ° C; slowly dropping N, N-diisopropyl ethylamine (1.4g, 11 . 0mmol, 1 . 1equiv.); the drop finishes, 1-2h to the temperature in the-5-0°C. To be R $_1$ temperature to -10 - - 5°C mixed in, will R $_2$instillment to in slowly mixed solution of R $_1$ in, temperature control 0 °C left and right; the drop finishes, to room temperature, stirring 6h. After the reaction, the organic phase washed 2 times, saturated salt water to wash 1 time, drying by anhydrous sodium sulfate, removal of solvent to obtain colorless oily turns on lathe does 3.88g, molar yield 97.5percent.	

3 Reaxys	87%	**With** hydrochlorid acid; thionyl chloride T=0 - 20°C;	**MEDIVIR AB; KALAYANOV, Genadiy; PINHO, Pedro; WESTERLIND, Hans; WIKTELIUS, Daniel; WÄHLING, Horst** **Patent:** WO2015/56213 A1,**2015** ; **Location in patent:** Page/Page column 66;
	11.a:(S)-isopropyl 2-aminopropanoate (I-11a) SOCl2 (29 mL, 400 mmcl) was added dropwise at 0 °C to a suspension of the HCl salt of L-alanine (17.8 g, 200 mmcl) in isopropanol (700 mL). The suspension was stirred at roomtemperature over night, then concentrated, which gave the title compound (29.2 g, 87percent).		
	74%	**With** alumina methanesulfonic acid T=120°C; 0.333333 h; Microwave irradiation;	**Fabian, Lucas; Gomez, Matias; Kuran, Juan A. Caturelli; Moltrasio, Graciela; Moglioni, Albertina** Synthetic Communications, **2014** , vol. 44, # 16 p. 2386 - 2392
	Representative Procedure for Preparation of a-Amino Acids Esters(Table 2) General procedure: In a typical reaction, AMA 2:3 (498 g, 1 mol), the corresponding aminoacid(1 mol) and alcohol (1.5–2 mol) were mixed in the provided reaction glass tubeequipped with a screw cap and magnetic agitation until a wet mixture was achieved.The reaction mixture was irradiated with microwaves (Anton Parr Monowave 300reactor) at 120 C for 20 min. On cooling, the mixture was diluted with chloroform(41 mL), filtered with glass frit over celite under vacuum, and washed with chloroform;then the filtrate was washed with Na2CO3 (ss) and water. The organic layerwas dried over Na2SO4, filtered, and concentrated under reduced pressure to givethe ester.		
	69%	**With** sulfuric acid 12 h; Reflux;	**Quevedo, Rodolfo; Pabon, Laura; Quevedo-Acosta, Yovanny** Journal of Molecular Structure, **2013** , vol. 1041, p. 68 - 72
	Synthesis of L-amino acid isopropyl esters General procedure: Synthesis of L-amino acid isopropyl esters Concentrated sulfuric acid was added to a suspension of the respective L-amino acid (1 g, amino acid:sulfuric acid ratio 1:1.2) in isopropanol (10 mL). The resulting solution was refluxed for 12 h. After this time, the solution was cooled to 0 °C and neutralized with concentrated NH_4OH. The ammonium sulfate formed was filtered and washed with isopropanol (3 * 5 mL). The filtrate was concentrated under reduced pressure (50 mm Hg, 50 °C) to a third of its volume. The ester was extracted with chloroform (3 * 5 mL), the organic phase was dried with anhydrous sodium sulfate, and chloroform was removed under reduced pressure (50 mm Hg, room temperature). L-Alanine isopropyl ester ($C_6H_{13}NO_2 \cdot HOC_3H_7$) b.p.125-127 °C , yield 69percent. ^1H NMR ($CDCl_3$) δ: 1.27 (d,6H, J = 6.8 Hz), 1.29 (d,6H, J = 6.4 Hz), 1.61 (d,3H, J = 7.2 Hz), 4.11 (q,1H, J = 7.2 Hz), 4.62 (heptet,1H, J = 6.4 Hz), 5.10 (heptet,1H, J = 6.4 Hz), ESI-MS: m/z 131.90 $[M + H]^+$.		

Appendix A-2 Process 100 Patent

Intermediate 11



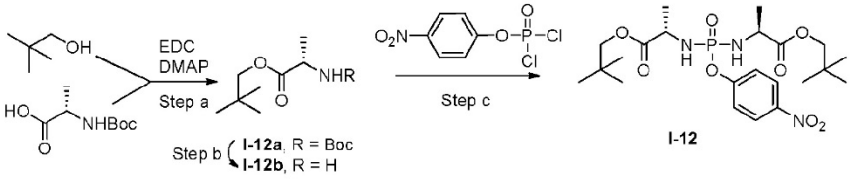
Step a) (S)-isopropyl 2-aminopropanoate (I-11a)

$SOCl_2$ (29 mL, 400 mmol) was added dropwise at 0 °C to a suspension of the HCl salt of L-alanine (17.8 g, 200 mmol) in isopropanol (700 mL). The suspension was stirred at room temperature over night, then concentrated, which gave the title compound (29.2 g, 87%).

Step b) (2S)-Isopropyl 2-(((((S)-1-isopropoxy-1-oxopropan-2-yl)amino)(4-nitrophenoxy)phosphoryl)-amino)propanoate (I-11)

A solution of 4-nitrophenyl dichlorophosphate (1.8 g 7 mmol) in DCM was added dropwise at -60 °C to a solution of the amine I-11a (2.35 g, 14 mmol) and triethylamine (7.7 mL, 56 mmol) in DCM. The reaction mixture was allowed to attain room temperature, stirred over night, concentrated and then diluted with ethyl acetate and ether and left at room temperature overnight. The triethylamine-HCl salt was filtered of, the filtrate was concentrated under reduced pressure and the afforded residue was purified by chromatography on silica gel eluted with iso-hexane-ethyl acetate, which gave the title compound (1.6 g, 50%).

Intermediate 12



Step a) (S)-Neopentyl 2-((tert-butoxycarbonyl)amino)propanoate (I-12a)

EDAC and DMAP was added in portions at -5 °C to a solution of Boc-alanine (18.9 g, 100 mmol) and neopentylalcohol (13.0 mL, 120 mmol) in DCM (200 mL). The reaction mixture was allowed to attain room temperature and stirred for 72 h. EtOAc (700 mL) was added and the organic phase was washed three times with a saturated solution of $NaHCO_3$ and once with brine, then concentrated. The afforded residue was purified by column chromatography eluted with hexane-EtOAc 90/10 to 80/20, which gave the title compound (21 g, 81%).

Step b) (S)-Neopentyl 2-aminopropanoate (I-12b)

p-Toluene sulfonic acid (15.6 g, 82.0 mmol) was added at -65 °C to a solution of the Boc protected amine I-12a (21.1 g, 82.0 mmol) in EtOAc (330 mL). The reaction mixture was stirred

Appendix A-3 Process 200 Patent

Jiangsu Hanson Pharma Group Co., Ltd.; Zhu, Qiang; Liu,

Zhaopeng; Li, Bin; Li, Yunfei; Yang, Baohai

Patent: CN105461773 A,2016 ;

Location in patent: Paragraph 0065; 0066; 0067; 0068; 0069;

[0065] 实施例1、式A1化合物的制备

[0066] 将40ml二氯甲烷加入烧瓶R_1中，N_2保护下，搅拌冷却至-50℃。加入二氯磷酸苯酯(2.31g,11.0mmol,1.1equiv.)，搅拌10-20min；一次性加入L-丙氨基酸异丙酯(1.85g,11.0mmol,1.1equiv.)，缓慢滴加N,N-二异丙基乙胺(2.8g,22.0mmol,2.2equiv.)；滴毕，3-4h内升温至-10～-5℃。

[0067] 另取一烧瓶R_2，加入2-羟基-6-氯吡啶(1.29g,10.0mmol,1.0equiv.)和20mL二氯甲烷，N_2保护下，搅拌冷却至-10℃；缓慢滴加N,N-二异丙基乙胺(1.4g,11.0mmol,1.1equiv.)；滴毕，1-2h内升温至-5～0℃。

[0068] 待R_1中混合液升温至-10～-5℃，将R_2中的混合液缓慢滴加至R_1中，控温0℃左右；滴毕，升至室温，搅拌6h。

[0069] 反应完毕后，有机相水洗2次，饱和食盐水洗涤1次，无水硫酸钠干燥，旋干除去溶剂得无色油状物3.88g，摩尔收率97.5%。^{1}H-NMR(400MHz,$CDCl_3$,δ,ppm)：7.95(t,1H),7.30-7.20(m,5H),6.85(d,1H),6.50(d,1H),4.95(m,1H),3.65(m,1H),1.35-1.25(m,9H)。

Translation: Example 1, Preparation of Intermediate A1

40mL of dichloromethane was added into flask R1. Under N_2 protection, the solvent was cooled to -50°C with constant stirring. Phenyl dichlorophosphate (2.31g, 11.0 mmol, 1.1 equiv.) was added and the mixture was stirred for 10-20 min; (S)-Isopropyl 2-aminopropanoate hydrochloride (1.85g, 11.0 mmol, 1.1 equiv.) was added, and N, N-diisopropyl ethylamine (2.8g, 22.0 mmol, 2.2 equiv.) was added dropwise; once N, N-diisopropyl ethylamine was completely added, the temperature was raised to -10～-5°C over 3-4 hours.

In another flask R2, 2-Chloro-6-hydroxypyridine (1.29g, 10.0mmol, 1.0equiv.) and 20 ml dichloromethane were added. Under N_2 protection, the mixture was cooled to -10 ° C with constant stirring. N, N-diisopropyl ethylamine (1.4g, 11.0mmol, 1.1equiv.) was added dropwise;

Once N,N-diisopropyl ethylamine was completely added, the temperature in R2 was gradually increased between -5 and 0°C over 1-2 hours.

Once R1 reached a temperature between -10 and -5°C, the mixture in R2 was added dropwise to R1. While mixing, the temperature was controlled at around 0°C. Once finished, the mixture equilibrated to room temperature with constant stirring for 6h.

After completion of the reaction, the organic phase was washed twice, then washed with saturated salt water once and dried over anhydrous sodium sulfate. The resulting substance was Rotor-evaporated to obtain 3.88g of a colorless oily substance, the molar yield was 97.5%.

Appendix A-4 Process 300 Patent

Jiangsu Hanson Pharma Group Co., Ltd.; Zhu, Qiang; Liu,

Zhaopeng; Li, Bin; Li, Yunfei; Yang, Baohai

Patent: CN105461773 A,2016 ;

Location in patent: Paragraph 0097; 0098; 0099; 0100;

[0097] 1、以中间体A1为起始原料

[0098] 将2'-脱氧-2'-氟-2'-C-甲基尿苷D(2.6g,10.0mmol,1.0equiv.),中间体A1(7.96g,20.0mmol,2.0equiv.),N,N-二异丙基乙胺(DIEA,1.95g,15.0mmol,1.5equiv.),氯化锌(2.06g,15.0mmol,1.5equiv.)加入烧瓶R_1中,以40mL四氢呋喃为溶剂。N_2保护下,加热至55-60℃,搅拌15-40h。

[0099] 反应完毕后,加入80mL乙酸乙酯,饱和氯化铵洗涤(40mL x 1),0.5M盐酸洗涤(40mL x 1),Na_2CO_3/$NaHCO_3$缓冲溶液洗涤(40mL x 1),饱和食盐水洗涤(40mL x 1),无水硫酸钠干燥。

[0100] 旋干除去溶剂得油状物,采用丙酮/二氯甲烷(1/8,V/V)打浆析晶。得产品2.5g,质量收率96.4%。^{1}H-NMR(400MHz,DMSO-d^6,δ,ppm):11.53(s,1H),7.57(d,J=3.8Hz,1H),7.40-7.36(m,2H),7.24-7.17(m,3H),6.06(t,J=6.4Hz,2H),5.86(d,J=3.2Hz,1H),5.55(d,J=4.2Hz,1H),4.89-4.83(m,1H),4.36-4.22(m,1H),4.03-4.00(m,1H),3.87-3.83(m,1H),3.82-3.35(m,2H),1.32-1.23(m,6H),1.15(d,J=3.2Hz,6H)。

1, Using Intermediate A1 as the Starting Material

In flask R1 containing 40 ml tetrahydrofuran, 2'-deoxy-2'-fluoro-2'-methyluridine (2.6g, 10.0mmol, 1.0equiv.), intermediate A1 (7.96g, 20.0mmol, 2.0equiv.), N, N-diisopropyl ethylamine (DIEA, 1.95g, 15.0mmol, 1.5equiv.), and zinc chloride (2.06g, 15.0mmol, 1.5equiv.) were added. Under N_2 protection, the mixture was heated to 55-60°C while stirring for 15-40h. After the reaction, the solution was washed once with 80 ml ethyl acetate and saturated ammonium chloride solution (40mLx1), washed once with 0.5M hydrochloric acid (40mLx1), washed once with Na_2CO_3/$NaHCO_3$ buffer solution (40mLx1), washed once with saturated salt water (40mLx1), and dried over anhydrous sodium sulfate.

The remaining solution was rotor-evaporated leaving an oily substance, crystallize using acetone/dichloromethane (1/8, V/V). Yields 2.5g of Sofosbuvir product, quality yield of 96.4%.

Appendix B - Equipment Costing Sheets

Appendix B-1 Pressure Vessel Calculations

Note: if carbon steel, S = 13750
For 304 Stainless, S = 11200
Potential Values for S (low alloy steel):

Temperature (°F)	Maximum Allowable Stress (psi)
−20 to 650	15,000
700	15,000
750	15,000
800	14,750
850	14,200
900	13,100

Table 22.26 Materials-of-Construction Factors, F_M, for Pressure Vessels

Material of Construction	Material Factor [F_M, in Eq. (22.52)]
Carbon steel	1.0
Low-alloy steel	1.2
Stainless steel 304	1.7
Stainless steel 316	2.1
Carpenter 20CB-3	3.2
Nickel-200	5.4
Monel-400	3.6
Inconel-600	3.9
Incoloy-825	3.7
Titanium	7.7

Reactor Vessel V102, V209

Distillation, Absorption, Stripping Column — Summary page

FBM = 4.16 CE = 565

	Type	Di	L	Pressure	Pd	E	S	tp	Wind/Quake?
		ft	ft	psig	psig		psi (see below)	ft	Include=Y
1	Vertical	15	20	10	15	1	11200	0.01021	Y

tw	taverage	Corrosion tc	ts	tsrounded	tsrounded	Density	Weight	Cv	Cpl	Fm	Cp	CP
ft	ft	inch	inch	inch	ft	lb/ft^3	lb	$ (CE=567)	$ (CE=567)	Table 22.26	$(CE=567)	$ (Given CE)
0.00058	0.01050	0.125	0.25101	0.50000	0.0417	490	30873	96845	25240	1.7	189877	189207

Reaction Vessel V201, V202

Distillation, Absorption, Stripping Column — Summary page

FBM = 4.16 CE = 565

	Type	Di	L	Pressure	Pd	E	S	tp	Wind/Quake?
		ft	ft	psig	psig		psi (see below)	ft	Include=Y
1	Vertical	14	20	10	15	1	11200	0.00953	Y

tw	taverage	Corrosion tc	ts	tsrounded	tsrounded	Density	Weight	Cv	Cpl	Fm	Cp	CP
ft	ft	inch	inch	inch	ft	lb/ft^3	lb	$ (CE=567)	$ (CE=567)	Table 22.26	$(CE=567)	$ (Given CE)
0.00062	0.00984	0.125	0.24311	0.50000	0.0417	490	28100	91053	23984	1.7	178774	178144

Reaction Vessel V203

Distillation, Absorption, Stripping Column — Summary page

FBM = 4.16 CE = 565

	Type	Di (ft)	L (ft)	Pressure (psig)	Pd (psig)	E	S (psi (see below))	tp (ft)	Wind/Quake? (Include=Y)
1	Vertical	16	25	10	15	1	11200	0.01089	Y

tw (ft)	taverage (ft)	Corrosion tc (inch)	ts (inch)	tsrounded (inch)	tsrounded (ft)	Density (lb/ft^3)	Weight (lb)	Cv ($ (CE=567))	Cpl ($ (CE=567))	Fm (Table 22.26)	Cp ($(CE=567))	CP ($ (Given CE))
0.00084	0.01131	0.125	0.26076	0.50000	0.0417	490	38893	112863	30995	1.7	222861	222075

Reaction Vessel V301

Distillation, Absorption, Stripping Column — Summary page

FBM = 4.16 CE = 565

	Type	Di (ft)	L (ft)	Pressure (psig)	Pd (psig)	E	S (psi (see below))	tp (ft)	Wind/Quake? (Include=Y)
1	Vertical	15	21	10	15	1	11200	0.01021	Y

tw (ft)	taverage (ft)	Corrosion tc (inch)	ts (inch)	tsrounded (inch)	tsrounded (ft)	Density (lb/ft^3)	Weight (lb)	Cv ($ (CE=567))	Cpl ($ (CE=567))	Fm (Table 22.26)	Cp ($(CE=567))	CP ($ (Given CE))
0.00063	0.01053	0.125	0.25137	0.50000	0.0417	490	31838	98826	26125	1.7	194130	193445

Wash Vessel V205

Distillation, Absorption, Stripping Column — Summary page

FBM = 4.16 CE = 565

	Type	Di (ft)	L (ft)	Pressure (psig)	Pd (psig)	E	S (psi (see below))	tp (ft)	Wind/Quake? (Include=Y)
1	Vertical	27	25	10	15	1	11200	0.01838	Y

tw (ft)	taverage (ft)	Corrosion tc (inch)	ts (inch)	tsrounded (inch)	tsrounded (ft)	Density (lb/ft^3)	Weight (lb)	Cv ($ (CE=567))	Cpl ($ (CE=567))	Fm (Table 22.26)	Cp ($(CE=567))	CP ($ (Given CE))
0.00048	0.01862	0.125	0.34848	0.50000	0.0417	490	80827	186260	45641	1.7	362282	361004

Wash Vessel V302

Distillation, Absorption, Stripping Column — Summary page

FBM = 4.16 CE = 565

	Type	Di (ft)	L (ft)	Pressure (psig)	Pd (psig)	E	S (psi (see below))	tp (ft)	Wind/Quake? (Include=Y)
1	Vertical	19	24	10	15	1	11200	0.01294	Y

tw (ft)	taverage (ft)	Corrosion tc (inch)	ts (inch)	tsrounded (inch)	tsrounded (ft)	Density (lb/ft^3)	Weight (lb)	Cv ($ (CE=567))	Cpl ($ (CE=567))	Fm (Table 22.26)	Cp ($(CE=567))	CP ($ (Given CE))
0.00064	0.01326	0.125	0.28409	0.50000	0.0417	490	47877	129800	34195	1.7	254854	253955

Mixing Vessel V305

Distillation, Absorption, Stripping Column — Summary page

FBM = 4.16 CE = 565

	Type	Di (ft)	L (ft)	Pressure (psig)	Pd (psig)	E	S (psi (see below))	tp (ft)	Wind/Quake? (Include=Y)
1	Vertical	18	23	10	15	1	11200	0.01226	Y

tw (ft)	taverage (ft)	Corrosion tc (inch)	ts (inch)	tsrounded (inch)	tsrounded (ft)	Density (lb/ft^3)	Weight (lb)	Cv ($ (CE=567))	Cpl ($ (CE=567))	Fm (Table 22.26)	Cp ($(CE=567))	CP ($ (Given CE))
0.00062	0.01257	0.125	0.27582	0.50000	0.0417	490	43280	121246	31881	1.7	237999	237160

Appendix B-2 Distillation Column and Packed Column Calculations

Distillation Columns

Distillation, Absorption, Stripping Column — Summary page

FBM = 4.16 CE = 565

	Di	L	Pressure	Pd	E	Stress (S)	tp	Wind/Quake?	tw	taverage	Corrosion tc	ts	tsrounded	tsrounded
	ft	ft	psig	psig		psi (see below)	ft	Include=Y	ft	ft	inch	inch	inch	ft
1	15	31	10	15	1	11200	0.01021	Y	0.00138	0.01090	0.125	0.2559	0.5000	0.0417

Density	Weight	Cv	Cpl	Fm	Cp	CP	Nt	Fnt	Ftt	Material Type	Ftm	Cbt	Ct (only trays)	Ct (only trays)	Cbm
lb/ft^3	lb	$ (CE=567)	$ (CE=567)	Table 22.26	$(CE=567)	$ (Given CE)			see below			$ (CE=567)	$ (CE=567)	$ (Given CE)	$ (Given CE)
490	41486	129991	29722	1.7	250708	249823	3	1.99	1	304 Stainless Steel	2.7355	4322	70659	70410	1332171

Distillation, Absorption, Stripping Column — Summary page

FBM = 4.16 CE = 565

	Di	L	Pressure	Pd	E	Stress (S)	tp	Wind/Quake?	tw	taverage	Corrosion tc	ts	tsrounded	tsrounded
	ft	ft	psig	psig		psi (see below)	ft	Include=Y	ft	ft	inch	inch	inch	ft
1	8	29	10	15	1	11200	0.00545	Y	0.00245	0.00667	0.125	0.2051	0.4375	0.0365

Density	Weight	Cv	Cpl	Fm	Cp	CP	Nt	Fnt	Ftt	Material Type	Ftm	Cbt	Ct (only trays)	Ct (only trays)	Cbm
lb/ft^3	lb	$ (CE=567)	$ (CE=567)	Table 22.26	$(CE=567)	$ (Given CE)			see below			$ (CE=567)	$ (CE=567)	$ (Given CE)	$ (Given CE)
490	15967	70132	18922	1.7	138146	137659	3	1.99	1	304 Stainless Steel	2.3316	1532	21343	21267	661133

Packed Columns

Distillation, Absorption, Stripping Column — Summary page

FBM = 4.16 CE = 565

	Di	L	Pressure	Pd	E	Stress (S)	tp	Wind/Quake?	tw	taverage	Corrosion tc	ts	tsrounded	tsrounded
	ft	ft	psig	psig		psi (see below)	ft	Include=Y	ft	ft	inch	inch	inch	ft
1	3.4	13.6	10	15	1	11200	0.00232	Y	0.00154	0.00308	0.125	0.1620	0.2500	0.0208

Density	Weight	Cv	Cpl	Fm	Cp	CP	Vp	Packing Classification	Cpk structured	Cpk dumped	A	Cdr	Cp (only packing)	Cp (only packing)	Cbm
lb/ft^3	lb	$ (CE=567)	$ (CE=567)	Table 22.26	$(CE=567)	$ (Given CE)	ft^3	(dumped or structured)	$ (CE=567)	Table 22.27 $ (CE=567)	ft^2	$ (CE=567)	$ (CE=567)	$ (Given CE)	$ (Given CE)
490	1790	24861	5998	1.7	48262	48091			285		9.08	1271	1271	1267	205329

Distillation, Absorption, Stripping Column — Summary page

FBM = 4.16 CE = 565

	Di	L	Pressure	Pd	E	Stress (S)	tp	Wind/Quake?	tw	taverage	Corrosion tc	ts	tsrounded	tsrounded	Density
	ft	ft	psig	psig		psi (see below)	ft	Include=Y	ft	ft	inch	inch	inch	ft	lb/ft^3
1	6	12.4	10	15	1	11200	0.00409	Y	0.00063	0.00440	0.125	0.1778	0.3750	0.0313	490

Density	Weight	Cv	Cpl	Fm	Cp	CP	Vp	Packing Classification	Cpk structured	Cpk dumped	A	Cdr	Cp (only packing)	Cp (only packing)	Cbm
lb/ft^3	lb	$ (CE=567)	$ (CE=567)	Table 22.26	$(CE=567)	$ (Given CE)	ft^3	(dumped or structured)	$ (CE=567)	Table 22.27 $ (CE=567)	ft^2	$ (CE=567)	$ (CE=567)	$ (Given CE)	$ (Given CE)
490	4990	37856	7981	1.7	72337	72082			285		28.27	3958	3958	3944	316269

Appendix B-3 Condensers and Head Exchangers

Table 22.25 Materials of Construction Factors, F_M, for Shell-and-Tube Heat Exchangers

Materials of Construction Shell/Tube	a in Eq. (22.44)	b in Eq. (22.44)
Carbon steel/carbon steel	0.00	0.00
Carbon steel/brass	1.08	0.05
Carbon steel/stainless steel	1.75	0.13
Carbon steel/Monel	2.1	0.13
Carbon steel/titanium	5.2	0.16
Carbon steel/Cr–Mo steel	1.55	0.05
Cr–Mo steel/Cr–Mo steel	1.70	0.07
Stainless steel/stainless steel	2.70	0.07
Monel/Monel	3.3	0.08
Titanium/titanium	9.6	0.06

Tube Length (ft)	F_L
8	1.25
12	1.12
16	1.05
20	1.00

Tube Heat Exchangers Summary page

FBM = 3.17 CE = 565

	Heat Exchanger Design	Surface Area *ft^2*	CB *$ (CE=567)*	a *Table 22.25*	b *Table 22.25*	FM	Pressure *psig*	Fp	FL *See below*	Cp *$ (CE=567)*	Cp *$(Given CE)*	CBM *$ (Given CE)*
1	Fixed Head	269	11410	1.75	0.13	2.88728103	10	0.982117	1.12	36238	36110	114470

Tube Heat Exchangers Summary page

FBM = 3.17 CE = 565

	Heat Exchanger Design	Surface Area *ft^2*	CB *$ (CE=567)*	a *Table 22.25*	b *Table 22.25*	FM	Pressure *psig*	Fp	FL *See below*	Cp *$ (CE=567)*	Cp *$(Given CE)*	CBM *$ (Given CE)*
1	Fixed Head	1614	21643	1.75	0.13	3.1855802	10	0.982117	1	67711	67473	213888

Appendix C- Calculations

Appendix C-1 Equipment Cost Calculations

Screw Conveyer

$Cp = 80DL^{0.59}$ where D is diameter in inches and L is length in feet

D = 20 inches, L = 30 feet. Cp = $11,902

Agitator

Turbine closed vessel

$Cp = 4105\ S^{0.57}$ where S = power in horsepower

S = 15 hp Cp = $19,216

Dryer

Batch Tray

$Cp = 4400\ A^{0.35}$

Area = 50 ft2

Cp = $17,301

Belt Conveyer

Cp = 24.4 WL where W = width in inches, L = length in feet

W = 30 inches, L = 30 feet

Cp = $21,960

Appendix C-2 Distillation Column Sizing

Process 100

24 inch spacing between plates

f = 0.85

G = 111 kg/sec vapor

L = 119 kg/sec liquid

Uf = C*[(rhoL-rhoG] / RhoG)^0.5 = 10.307 ft/s = 3.1 meters/s

Rho G = 2.5 kg/m3

Rho L = 1000 kg/m3

C =Csb Fst Ff Fha

Csb = 0.4 ft/s

Flg = (L/G) (rhog/rhoL)^0.5 = (112/119)*(2.5/1000) ^0.5 = 0.047

Fst = [(sigma)/20] ^ 0.2 = (72/20)^0.2 = 1.29

Ff = 1

Fha = 1

C = 0.516

Ad/At = 0.1

Dt = [4G/(fUf * PI* (1-ad/at) * rhoG)] ^0.5= 4.613 meters = **15 feet**

H = 2 feet * 3 stages + 25 feet = **31 feet**

Process 300

24 inch spacing between plates

f = 0.85

G = 18 kg/s

L = 26 kg/s

Uf = C*[(rhoL-rhoG] / RhoG)^0.5 = 9.29 ft/s = 2.83 meter/s

Rho G = 1.911 kg/m3

Rho L = 689 kg/m3

C =Csb Fst Ff Fha

Csb = 0.38 ft/s

Flg = (L/G) (rhog/rhoL)^0.5 = 0.076

Fst = [(sigma)/20] ^ 0.2 = (72/20)^0.2 = 1.29

Ff = 1

Fha = 1

C = 0.49

Ad/At = 0.1

Dt = [4G/(fUf * PI* (1-ad/at) * rhoG)] ^0.5 = 2.35 meter = **7.7 feet**

H = 2 stages * 2 feet + 25 feet = **29 feet**

Chiller Sizing

1 ton = 3.517 kW

Propane total cooling:

79496 kwh

24 hour turnaround: 3312 kw = 946 tons

Ethylene Glycol total Cooling:

61 kwh

18 hour turnaround: 3.3 kw = 1 tons. Round to 10, to be reasonable

Brine total cooling: 230 kwh = 65 tons

Cost = $400/ton for chiller[C-1]

Propane chiller = $378,500

Ethylene Glycol Chiller = $4000

Brine Chiller = $26,158

Endnotes

C-1: Florida Power and Light Company (2010). *Water-Cooled Chillers*. Retrieved from https://www.fpl.com/business/pdf/water-cooled-chillers-primer.pdf

Appendix D - Project Labor and Salary Considerations

The minimum wage in the United States is: $7.25 [D-1]
The 'minimum wage' in India is: ~$1.00 [D-2]
Therefore, the multiple for $ in US to $ in India is **0.138**.

Appendix D-1 Labor Costs in India by position on a per hour basis

Position	Average Pay in US ($/hr)	Calculated Pay in India ($/hr)
Highly trained chemical engineer	$56 [D-4]	$8.00
Skilled chemical operator	$46 [D-5]	$6.50
Skilled plant worker	$24 [D-3]	$3.50

Appendix D-2 Labor Costs for the Entire Project+

Position	$/hr	Regular Days worked	$/hr OT^	OT days	Hours per day	Number of employees	Total pay ($)
Chemical Engineer	$8.00	86	$10.00	34	8	2	$16,448
Chemical operator (day shift)	$6.50	86	$8.13	34	8	2	$13,367
Plant worker (day)	$3.50	86	$4.38	34	8	25	$89,984
Chemical operator (night shift)	$6.30*	86	$7.88	34	8	4	$25,911
Plant worker (night)	$3.30*	86	$4.13	34	8	40	$135,750

*Slightly lowered the salary for night-time workers, as they will be less highly skilled, yet will still do similar work.
^Calculation assumes an OT rate of 25% above baseline pay.
+Total pay = ($/hr * Regular days worked*hours per day + OT $/hr * OT days worked*hours per day)*# employees

Total labor costs are: $281,460 or $2,815 per batch.

Endnotes

D-1: United States Department of Labor Wage and Hour Division (WHD) (2017): *History of Federal Minimum Wage Rates Under the Fair Labor Standards Act*, 1938 - 2009

D-2: Einhorn, Bloomberg (2014): *India vs. China: The Battle for Global Manufacturing*

D-3: Salary.com (2017): US Salary Information for chemical operators

D-4: Salary.com (2017): *US Salary Information for Chemical Engineers IV* (Senior Chemical Engineer)

D-5: Salary.com (2017): *US Salary Information for Chemical Plant Superintendents and Highly Skilled Plant Operators*

Appendix E - Annual Sales Projections

Annual US Sales of *sofosbuvir* name brand *Sovaldi* are $10.3 billion. At approximately $84,000 per treatment, the total number of treatment sales in the United States is 0.12 million, accounting for significant figures to remain conservative.[E-1]

In the United States, 3.2 million people are infected with Hepatitis C, which indicates a sale of 0.0375 treatments per person infected with Hepatitis C.[E-2]

A key assumption made was that the new, lower price point of *sofosbuvir* would allow for a sales rate similar to that seen in the United States in the target market. At the previously determined multiplier, it was possible to determine the approximate annual sales.

Approximately 100 million people in the developing world are infected with Hepatitis C in countries covered by Gilead's low-cost license, which would reflect 5.25 million annual sales of the affordable treatment.[E-5] At 33.6 g per treatment, annual sales would be 176,400 kg, or 176 metric tons. The project plans to synthesize 350 metric tons of *sofosbuvir* each year for 10 years. However, our team has reasoned that the United States has a significant market saturation, with 4-5 competitive Hepatitis C treatments on the market. Furthermore, the treatment has been on the market for a significant amount of time, meaning that it has acquired most of its majority customer share, as seen in Figure E-1, the sales adoption curve.

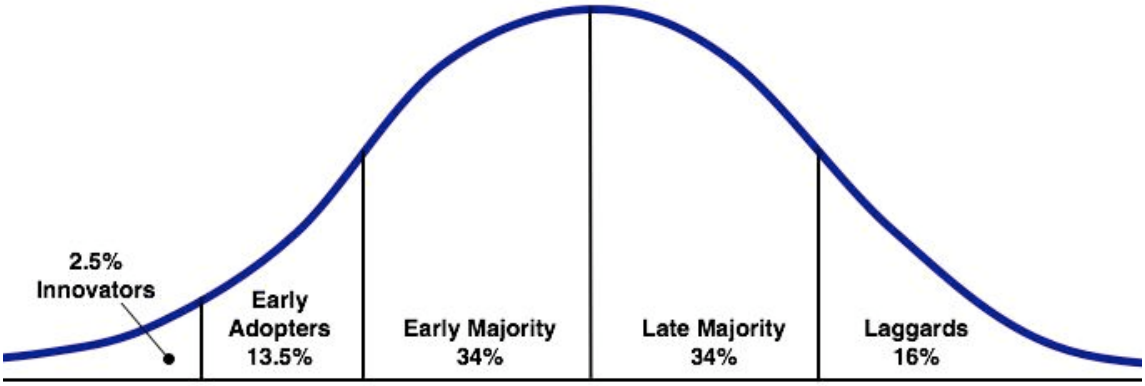


Figure E-1: Sales Adoption Curve[E-4]

Justifiably, it is possible that the US Hepatitis C drug market is in the latter stages of sales and is also affected by significant market saturation. Since Hepatitis C drugs are currently sold in India, albeit at a much more prohibitive price, our team determined that the sales curve had already progressed significantly in the developing world. Therefore, our team felt confident to make optimistic sales projections for *sofosbuvir* rather than over a 20-year sales cycle. Overall, we have projected the following sales by year, shown in Table E-1. Our team projects early and

rapid sales of the generic, affordable *sofosbuvir*, allowing for rapid and extensive market expansion.

Appendix E-1 Production Schedules by Year[+]

Year	High Output *Production (metric tons)*	Base Case *Production (metric tons)*	Low Output *Production (metric tons)*
1	350	350	175
2	442	350	210
3	534	350	245
4	626	350	280
5	626	350	315
6	626	350	350
7	626	350	350
8	626	350	350
9	626	350	350
10	626	350	350
11	0	0	0

[+]350 metric tons is 100 batches.

Endnotes

E-1: Pollack, New York Times (2015): Sales of Sovaldi, New Gilead Hepatitis C Drug, Soar to $10.3 Billion.

E-2: Viral Hepatitis Action Coalition (2017): *Hepatitis C*.

E-3: The Hindu (2016): India may soon get treatment for Hepatitis C.

E-4: Rogers, Everett M. (1995): *Diffusion of Innovations*. Free Press, New York City.

E-5: World Health Organization (2016): *Hepatitis C*

Appendix F - Energy Utilities

Appendix F-1 Costing of Energy Utilities [F-1]

Cost Factor	Typical Factor in American Engineering Units	Typical Factor in SI Units
Feedstocks (raw materials)		
Utilities		
Steam, 450 psig[b]	$8.00/1,000 lb	$17.60/1,000 kg
Steam, 150 psig[b]	$7.00/1,000 lb	$15.30/1,000 kg
Steam, 50 psig[b]	$6.00/1,000 lb	$13.20/1,000 kg
Electricity[b]	$0.070/kW-hr	$0.070/kW-hr
Cooling water (cw)[b]	$0.10/1,000 gal	$0.027/$m^3$
Process water[b]	$0.80/1,000 gal	$0.27/$m^3$
Boiler-feed water (bfw)[b]	$2.00/1,000 gal	$0.56/$m^3$
Refrigeration, – 150°F[b]	$10.00/ton-day	$33.20/GJ
Refrigeration, – 90°F[b]	$7.00/ton-day	$23.30/GJ
Refrigeration, –30°F[b]	$4.00/ton-day	$13.17/GJ
Refrigeration, 10°F[b]	$2.00/ton-day	$6.47/GJ
Chilled water, 40°F[b]	$1.50/ton-day	$5.00/GJ
Natural gas	$5.00/1,000 SCF	$0.213/SCM
Fuel oil	$3.50/gal	$933/$m^3$
Coal—Appalacia, 12,500–13,000 Btu/lb	$60/ton	$66/1,000 kg
Coal—Powder River Basin, 8,800 Btu/lb	$13/ton	$14.34/1,000 kg
Wastewater treatment[c]	$0.15/lb organic removed	$0.33/kg organic removed
Landfill	$0.08/dry lb	$0.17/drykg
Operations (labor-related) (O) (See Table 17.3)		
Direct wages and benefits (DW&B)	$40/operator-hr	$40/operator-hr
Direct salaries and benefits	15% of DW&B	15% of DW&B
Operating supplies and services	6% of DW&B	6% of DW&B
Technical assistance to manufacturing	$60,000/(operator/shift)-yr	$60,000/(operator/shift)-yr
Control laboratory	$65,000/(operator/shift)-yr	$65,000/(operator/shift)-yr
Maintenance (M)		
Wages and benefits (MW&B)		
Fluid handling process	3.5% of C_{TDC}	3.5% of C_{TDC}
Solids–fluids handling process	4.5% of C_{TDC}	4.5% of C_{TDC}
Solids-handling process	5.0% of C_{TDC}	5.0% of C_{TDC}
Salaries and benefits	25% of MW&B	25% of MW&B
Materials and services	100% of MW&B	100% of MW&B
Maintenance overhead	5% of MW&B	5% of MW&B
Operating overhead		
General plant overhead	7.1% of M&O-SW&B	7.1% of M&O-SW&B
Mechanical department services	2.4% of M&O-SW&B	2.4% of M&O-SW&B
Employee relations department	5.9% of M&O-SW&B	5.9% of M&O-SW&B
Business services	7.4% of M&O-SW&B	7.4% of M&O-SW&B
Property taxes and insurance	2% of C_{TDC}	2% of C_{TDC}
Depreciation (see also Section 17.6)		
Direct plant	8% of (C_{TDC} – 1.18 C_{alloc})	8% of (C_{TDC} – 1.18C_{alloc})
Allocated plant	6% of 1.18C_{alloc}	6% of 1.18C_{alloc}
Rental fees (office and lab space)	(no guideline)	(no guideline)
Licensing fees	(no guideline)	(no guideline)
COST OF MANUFACTURE (COM)	Sum of above	Sum of above
General Expenses		
Selling (or transfer) expense	3% (1%) of sales	3% (1%) of sales
Direct research	4.8% of sales	4.8% of sales
Allocated research	0.5% of sales	0.5% of sales
Administrative expense	2.0% of sales	2.0% of sales
Management incentive compensation	1.25% of sales	1.25% of sales
TOTAL GENERAL EXPENSES (GE)		
TOTAL PRODUCTION COST (C)	COM + GE	COM + GE

[a] DW&B = direct wages and benefits; MW&B = maintenance wages and benefits; M&O-SW&B = maintenance and operations salary, wages, and benefits. See Table 16.9 for C_{TDC} and C_{alloc}. 1 ton of refrigeration = 12,000 Btu/hr.
[b] assumes natural gas is the energy source.
[c] normal wastewater and organics – amenable to aerobic and anaerobic digestion.
Source: Busche, 1995 with modifications.

Appendix F-2 Parameters for Coolant Selection

Table 12.1 Heat-Transfer Media

Medium	Typical Temperature Range (°F)	Mode
Coolants		
Ethylene	–150 to –100	Vaporizing
Propylene	–50 to 10	Vaporizing
Propane	–40 to 20	Vaporizing
Ammonia	–30 to 30	Vaporizing
Tetrafluoroethane	–15 to 60	Vaporizing
Chilled brine	0 to 60	Sensible
Chilled water	45 to 90	Sensible
Cooling water	90 to 120	Sensible
Air	90 to 140	Sensible
Boiler feed water	220 to 450	Vaporizing
Heat Sources		
Hot water	100 to 200	Sensible
Steam	220 to 450	Condensing
Heating oils	30 to 600	Sensible
Dowtherm A	450 to 750	Condensing
Molten salts	300 to 1,100	Sensible
Molten metals	100 to 1,400	Sensible
Combustion gases	30 to 2,000	Sensible

Appendix F-3 Pump Energy Utility Calculations

```
BLOCK:  PUMP     MODEL: PUMP
------------------------------
  INLET STREAM:          1 PUMP_IN
  OUTLET STREAM:         2 PUMP_OUT
  PROPERTY OPTION SET:   NRTL      RENON (NRTL) / IDEAL GAS

                     ***  MASS AND ENERGY BALANCE  ***
                                  IN                OUT         RELATIVE DIFF.
   TOTAL BALANCE
      MOLE(KMOL/HR )            1655.19          1655.19          0.00000
      MASS(KG/HR   )            29818.7          29818.7          0.00000
      ENTHALPY(CAL/SEC )     -0.313852E+08    -0.313851E+08    -0.328300E-05

                           ***  RESULTS  ***
   VOLUMETRIC FLOW RATE  L/MIN                              500.000
   PRESSURE CHANGE  BAR                                    0.30000
   NPSH AVAILABLE   M-KGF/KG                               9.93390
   FLUID POWER  KW                                         0.24617
   BRAKE POWER  KW                                         0.43140
   ELECTRICITY  KW                                         0.43140
   HEAD DEVELOPED M-KGF/KG                                 3.03056
```

Pump Stream Calculations

Unit	Time (hr)	Flow rate (L/min)	kW	kWh
Pump (Isopropanol to 101)	1	2200	1.514	1.514
Pump (Thionyl Chloride to 101)	0.18	500	0.438	0.08
Pump (101 to flash vessel)	1	2200	1.514	1.514
Pump (Storage to 200)	1	250	0.143	0.143
				3.251

Unit	Time (hr)	Flow rate (L/min)	kW	kWh
Pump (DCM to 201)	3.8	500	0.438	1.664
Pump (DIEA to 201)	1.1	100	0.143	0.157
Pump (DCM to 202)	1.9	500	0.438	0.832
Pump (DIEA to 202)	0.66	100	0.143	0.094
Pump (201 to 203)	3.8	500	0.438	1.664
Pump (202 Storage to 203)	1.9	500	0.438	0.832
Pump (203 to Flash)	5.7	250	0.143	0.815
Pump (Flash to wash	1.15	500	0.438	0.504
Pump (water to Wash)	4.98	500	0.438	2.181
Pump (wash effluent)	4.98	500	0.438	2.181
Pump (Sodium Sulfate drying)	1.75	500	2.19	3.833
Pump (Wash to evaporator)	1.75	500	0.438	0.767
Pump (Evaporator to 300)	0.48	500	0.438	0.21
				15.735

Unit	Time (hr)	Flow rate (L/min)	kW	kWh
Pump (THF to 301)	1.17	500	0.438	0.511
Pump (DIEA to 301)	0.12	500	0.438	0.054
Pump (301 to wash vessel)	1.25	500	0.438	0.548
Pump (Ethyl Acetate to Wash)	1.87	1000	0.769	1.435
Pump (NH4Cl to Wash)	0.93	1000	0.769	0.718
Pump (0.5M HCl to Wash)	0.93	1000	0.769	0.718
Pump (Buffer to Wash)	0.93	1000	0.769	0.718
Pump (Salt to Wash)	0.93	1000	0.769	0.718
Pump (Sodium sulfate drying)	2.45	1000	3.33	8.159
Pump (Wash to waste)	4.32	1000	0.769	3.32
Pump (Acetone to Crystallizer)	0.37	500	0.438	0.163
Pump (DCM to crystallizer)	1.49	1000	0.769	1.147
Pump Crystallizer Out	23.52	100	0.143	3.363
				21.569
				40.555

Appendix F-4 Screw Conveyor Power Requirements [F-2]

Table 4. Mean values of power requirements for the evaluated screw conveyors at different screw clearances and screw rotational speeds

Auger diameter, cm	Screw speed, rpm	Power requirements, W Screw clearance, mm			
		6	9	12	15
20	200	130.47 (4.55)*	128.58 (8.09)	124.86 (7.71)	121.13 (8.36)
	300	196.25 (5.02)	192.18 (6.58)	190.73 (8.19)	186.69 (8.18)
	400	263.17 (4.05)	261.82 (6.06)	259.66 (7.33)	255.74 (4.01)
	500	327.49 (8.58)	324.77 (8.62)	321.82 (4.58)	317.41 (9.63)
	600	373.36 (9.17)	369.14 (4.41)	365.78 (4.80)	361.59 (6.57)
25	200	186.47 (5.27)	184.93 (4.82)	182.72 (5.33)	178.26 (4.55)
	300	264.19 (7.81)	260.44 (6.21)	255.38 (6.52)	247.83 (7.59)
	400	317.52 (6.56)	314.49 (6.81)	308.65 (4.81)	300.25 (5.09)
	500	387.58 (4.81)	384.26 (3.56)	381.66 (6.91)	375.36 (4.83)
	600	461.49 (5.46)	458.64 (5.23)	456.93 (8.66)	450.77 (7.01)

*Values in parentheses are standard deviation

Endnotes

F-1: Seider, W. D., Lewin, D. R., Seader, J. D., Widagdo, S., Gani, R., & Ng, K. M. (2017). *Product and process design principles: Synthesis, analysis and evaluation. Hoboken*, NJ: Wiley.

F-2: Zareiforoush H, Komarizadeh MH, Alizadeh MR, Masoomi M. *Screw conveyors power and throughput analysis during horizontal handling of paddy grains*. J Agric Sci 2010; 2:147–57.

Appendix G - Import/Export

Date	HS Code	Description	Origin Country	Port of Discharge	Unit	Quantity	Value (INR)	Per Unit (INR)	USD/KG
21-Jul-16	28289090	L-ALANINE (ISOPROPYL ESTER HYDROCHLORIDE)	China	Nhava Sheva Sea	KGS	2,000	481,114	241	3.615
22-Nov-16	29215990	L-ALANINE ISOPROPYL ESTER HYDROCHLORIDE	China	Bombay Air Cargo	KGS	787	2,256,795	2,868	43.02
21-Jul-16	28289090	L-ALANINE (ISOPROPYL ESTER HYDROCHLORIDE)	China	Nhava Sheva Sea	KGS	500	120,278	241	3.615
20-Jul-16	29224990	L-ALANINE ISOPROPYL ESTER HYDROCHLORIDE (INTERI	China	Delhi Air Cargo	KGS	400	1,432,746	3,582	53.73
3-Oct-15	29224990	L-ALANINE ISOPROPYL ESTER HYDROCHLORIDE (INTERI	China	Delhi Air Cargo	KGS	400	1,760,733	4,402	66.03
27-Apr-16	29420090	L-ALANINE ISOPROPYL ESTER HYDROCHLORIDE	China	Bombay Air Cargo	KGS	375	1,646,994	4,392	65.88
17-Nov-16	29339900	L-ALANINE ISOPROPYL ESTER HYDROCHLORIDE (INTERI	China	Delhi Air Cargo	KGS	275	976,347	3,550	53.25
9-Dec-15	29224990	L-ALANINE ISOPROPYL ESTER HYDROCHLORIDE	China	Bombay Air Cargo	KGS	220	941,406	4,279	64.185
									44.165625

Date	HS Code	Description	Origin Country	Port of Discharge	Unit	Quantity	Value (INR)	Per Unit (INR)	USD/KG
6-Oct-16	29051220	ISOPROPYL ALCOHOL 99.8 PCT	Taiwan	Kolkata Sea	KGS	12,800	867,113	68	1.02
18-May-16	29051220	ISOPROPYL ALCOHOL 99.8 PCT	Taiwan	Kolkata Sea	KGS	12,800	720,536	56	0.84
17-May-16	29051220	ISOPROPYL ALCOHOL 99.8PCT	Taiwan	Kolkata Sea	KGS	12,800	722,178	56	0.84
25-Feb-16	29051220	ISOPROPYL ALCOHOL 99.8 PCT	Taiwan	Kolkata Sea	KGS	12,800	738,910	58	0.87
13-Jan-16	29051220	ISOPROPYL ALCOHOL 99.8 PCT MIN	Taiwan	Kolkata Sea	KGS	12,800	763,641	60	0.9
30-Dec-15	29051220	ISOPROPYL ALCOHOL 99.8 PCT	Taiwan	Kolkata Sea	KGS	12,800	816,636	64	0.96
21-Nov-15	29051220	ISOPROPYL ALCOHOL 99.8 PCT	Taiwan	Kolkata Sea	KGS	12,800	855,834	67	1.005
27-Aug-15	29051220	ISOPROPYL ALCOHOL 99.8 PCT	Taiwan	Kolkata Sea	KGS	12,800	989,981	77	1.155
16-Jul-15	29051220	ISO PROPYL ALCOHOL (INDUSTRIAL GRADE) IPA (ISOPR	South Korea	Nhava Sheva Sea	KGS	25,600	1,902,129	74	1.11
									0.966666667

Date	HS Code	Description	Origin Country	Port of Discharge	Unit	Quantity	Value (INR)	Per Unit (INR)	USD/KG
Nov192016	28121047	INORGANIC CHEMICAL THIONYL CHLORIDE 99.6%	South Korea	Nhava Sheva Sea	KGS	16,200	767,665	47	0.701492537
Nov132016	28121047	INORGANIC CHEMICAL THIONYL CHLORIDE 99.6%	South Korea	Nhava Sheva Sea	KGS	16,200	810,364	50	0.746268656
19-Nov-17	28121047	THIONYL CHLORIDE	Japan	Mundra	KGS	24000	796000	33	0.492537313
									0.646766169

Date	HS Code	Description	Origin Country	Port of Discharge	Unit	Quantity	Value (INR)	Per Unit (INR)	USD/KG
27-Apr-16	29420090	PHENYL DICHLOROPHOSPHATE	China	Chennai Sea	KGS	1,860	701,285	377	5.655
31-May-16	29199090	PHENYL DICHLOROPHOSPHATE	China	Chennai Sea	KGS	1,250	429,566	344	5.16
19-Nov-16	29199090	PHENYL DICHLOROPHOSPHATE	China	Bombay Air Cargo	KGS	901	602,863	669	10.035
24-Feb-16	29209099	PHENYL DICHLOROPHOSPHATE, 99% MIN	China	Chennai Sea	KGS	762	307,779	404	6.06
5-Nov-15	29224990	PHENYL DICHLOROPHOSPHATE	China	Hyderabad Air Cargo	KGS	300	322,757	1,076	16.14
3-Oct-15	29199090	PHENYL DICHLOROPHOSPHATE,99% MIN CAS NO:770-	China	Bombay Air Cargo	KGS	300	325,058	1,084	16.26
26-Sep-15	29224990	PHENYL DICHLOROPHOSPHATE	China	Hyderabad Air Cargo	KGS	300	331,153	1,104	16.56
22-Apr-16	29159090	PHENYL DICHLOROPHOSPHATE	China	Bombay Air Cargo	KGS	118	152,848	1,295	19.425
									8.675

Date	HS Code	Description	Origin Country	Port of Discharge	Unit	Quantity	Value (INR)	Per Unit (INR)	USD/KG
12-Apr-16	29420090	2-DEOXY-2-FLUORO-2 METHYL-URIDINE	China	Chennai Air Cargo	KGS	380	23,315,850	61,358	920.37
21-Apr-16	29420090	(2 R)-2-DEOXY-2-FLUORO-2 METHYL-URIDINE	China	Chennai Air Cargo	KGS	360	22,072,338	61,312	919.68
8-Apr-16	29420090	(2 R)-2-DEOXY-2-FLUORO-2 METHYL-URIDINE	China	Chennai Air Cargo	KGS	360	22,072,338	61,312	919.68
7-Apr-16	29420090	2-DEOXY-2-FLUORO-2 METHYL-URIDINE	China	Chennai Air Cargo	KGS	360	22,072,338	61,312	919.68
23-May-16	29339900	(2R)-2-DEOXY-2-FLUORO-2-METHYL-URIDINE	China	Hyderabad Air Cargo	KGS	350	20,535,574	58,673	880.095
22-Jul-16	29339900	2R)-2-DEOXY-2-FLUORO-2-METHYL-URIDINE	China	Hyderabad Air Cargo	KGS	300	17,640,750	58,803	882.045
15-Jul-16	29339900	(2R)-2-DEOXY-2-FLUORO-2-METHYL-URIDINE	China	Hyderabad Air Cargo	KGS	300	17,640,750	58,803	882.045
17-Aug-16	29339900	(2R)-2-DEOXY-2-FLUORO-2-METHYL-URIDINE	China	Hyderabad Air Cargo	KGS	300	17,654,296	58,848	882.72
10-May-16	29339900	(2R)-2-DEOXY-2-FLUORO-2-METHYL-URIDINE	China	Hyderabad Air Cargo	KGS	250	14,474,261	57,897	868.455
17-Jun-16	29339900	(2R)-2-DEOXY-2-FLUORO-2-METHYL-URIDINE	China	Hyderabad Air Cargo	KGS	250	14,722,145	58,889	883.335
2-May-16	29420090	2-DEOXY-2-FLUORO-2-C-METHYL URIDINE	China	Hyderabad Air Cargo	KGS	200	11,216,454	56,082	841.23
25-Apr-16	29420090	2-DEOXY-2-FLUORO-2-C-METHYL URIDINE	China	Hyderabad Air Cargo	KGS	200	11,216,454	56,082	841.23
25-Apr-16	29420090	2-DEOXY-2-FLUORO-2-C-METHYL URIDINE	China	Hyderabad Air Cargo	KGS	200	11,317,050	56,585	848.775
12-Jul-16	29339900	(2R)-2-DEOXY-2-FLUORO-2-METHYL-URIDINE	China	Hyderabad Air Cargo	KGS	200	11,760,499	58,802	882.03
25-Aug-16	29339900	(2R)-2-DEOXY-2-FLUORO-2-METHYL-URIDINE	China	Hyderabad Air Cargo	KGS	200	11,769,530	58,848	882.72
18-May-16	29420090	2R-2-DEOXY-2-FLUORO-2-METHYL-URIDINE	China	Hyderabad Air Cargo	KGS	200	11,967,782	59,839	897.585
16-Apr-16	29420090	2-DEOXY-2-FLUORO-2-C-METHYL URIDINE	China	Hyderabad Air Cargo	KGS	155	9,404,741	60,676	910.14
21-Jun-16	29339900	(2R)-2-DEOXY-2-FLUORO-2-METHYL-URIDINE	China	Hyderabad Air Cargo	KGS	150	8,800,941	58,673	880.095
12-Apr-16	29420090	2-DEOXY-2-FLUORO-2-C-METHYL URIDINE	China	Hyderabad Air Cargo	KGS	150	9,101,362	60,676	910.14
12-Apr-16	29420090	2-DEOXY-2-FLUORO-2-C-METHYL URIDINE	China	Hyderabad Air Cargo	KGS	150	9,101,362	60,676	910.14
									888.1095

Date	HS Code	Description	Origin Country	Port of Discharge	Unit	Quantity	Value (INR)	Per Unit (INR)	USD/KG
26-Sep-16	28289090	L-ALANINE	China	Nhava Sheva Sea	KGS	5,000	992,199	198	2.97
2-Sep-16	29225090	L-ALANINE	China	Chennai Sea	KGS	3,500	694,539	198	2.97
28-Sep-16	29225090	L-ALANINE	China	Nhava Sheva Sea	KGS	2,000	390,998	195	2.925
19-Sep-16	29222990	L-ALANINE (NOT FOR MEDICINAL USE)	China	Chennai Sea	KGS	2,000	377,185	189	2.835
22-Nov-16	29339900	L-ALANINE	China	Hyderabad Air Cargo	KGS	1,250	418,191	335	5.025
3-Oct-16	29224990	L-ALANINE	China	Nhava Sheva Sea	KGS	1,000	232,654	233	3.495
21-Nov-16	29224990	L-ALANINE	China	Chennai Sea	KGS	800	205,684	257	3.855
29-Oct-16	28289090	L-ALANINE	China	Bombay Air Cargo	KGS	250	107,455	430	6.45
27-Oct-16	21069099	A11310 L-ALANINE (WIDELY USED IN FOOD ADDITIVES)	China	Delhi Air Cargo	KGS	125	71,125	569	8.535
									4.34

Date	HS Code	Description	Origin Country	Port of Discharge	Unit	Quantity	Value (INR)	Per Unit (INR)	USD/KG
22-Nov-16	29031200	METHYLENE CHLORIDE IN BULK (MANUFACTURER : SH	China	Kandla	KGS	13,000	313,974	24	0.36
9-Nov-16	29031200	DICHLOROMETHANE (METHYLENE CHLORIDE)	China	Nhava Sheva Sea	KGS	7,830	218,862	28	0.42
9-Nov-16	29031200	DICHLOROMETHANE (METHYLENE CHLORIDE)	China	Nhava Sheva Sea	KGS	5,940	166,648	28	0.42
22-Nov-16	29031200	METHYLENE CHLORIDE (ADC LIST SL NO: 1018)	China	Chennai Sea	KGS	3,750	116,498	31	0.465
10-Nov-16	29031200	METHYLENE CHLORIDE (ADC LIST SL NO.1018)	Taiwan	Chennai Sea	KGS	2,966	102,336	35	0.525
22-Nov-16	29031200	METHYLENE CHLORIDE	Taiwan	Nhava Sheva Sea	KGS	1,012	37,974	38	0.57
									0.412173913

Date	HS Code	Description	Origin Country	Port of Discharge	Unit	Quantity	Value (INR)	Per Unit (INR)	USD/KG
6-Sep-16	29211990	N-ETHYLDIISOPROPYLAMINE	Germany	Nhava Sheva Sea	KGS	1,800	652,798	363	5.445
6-Sep-16	29211990	N-ETHYLDIISOPROPYLAMINE	Germany	Nhava Sheva Sea	KGS	4,200	1,523,196	363	5.445
6-Sep-16	29211990	N-ETHYLDIISOPROPYLAMINE	Germany	Nhava Sheva Sea	KGS	6,000	2,175,995	363	5.445
2-Aug-16	29211990	N-ETHYLDIISOPROPYLAMINE	Japan	Nhava Sheva Sea	KGS	11,200	4,008,747	358	5.37
14-Mar-16	29211990	N-ETHYLDIISOPROPYLAMINE	Germany	Nhava Sheva Sea	KGS	6,000	2,184,024	364	5.46
14-Dec-15	29211990	N-ETHYLDIISOPROPYLAMINE	Japan	Nhava Sheva Sea	KGS	6,300	2,396,306	380	5.7
									5.4775

Date	HS Code	Description	Origin Country	Port of Discharge	Unit	Quantity	Value (INR)	Per Unit (INR)	USD/KG
22-Nov-16	29321100	TETRAHYDROFURAN (THF)	Malaysia	Nhava Sheva Sea	KGS	14,400	1,661,565	115	1.725
22-Nov-16	29321100	TETRAHYDROFURAN	Germany	Vizac Sea	KGS	14,400	1,581,698	110	1.65
22-Nov-16	29321100	TETRAHYDROFURAN	Germany	Vizac Sea	KGS	14,400	1,581,698	110	1.65
22-Nov-16	29321100	TETRAHYDROFURAN (THF)	Malaysia	Vizac Sea	KGS	14,400	1,651,733	115	1.725
									1.695

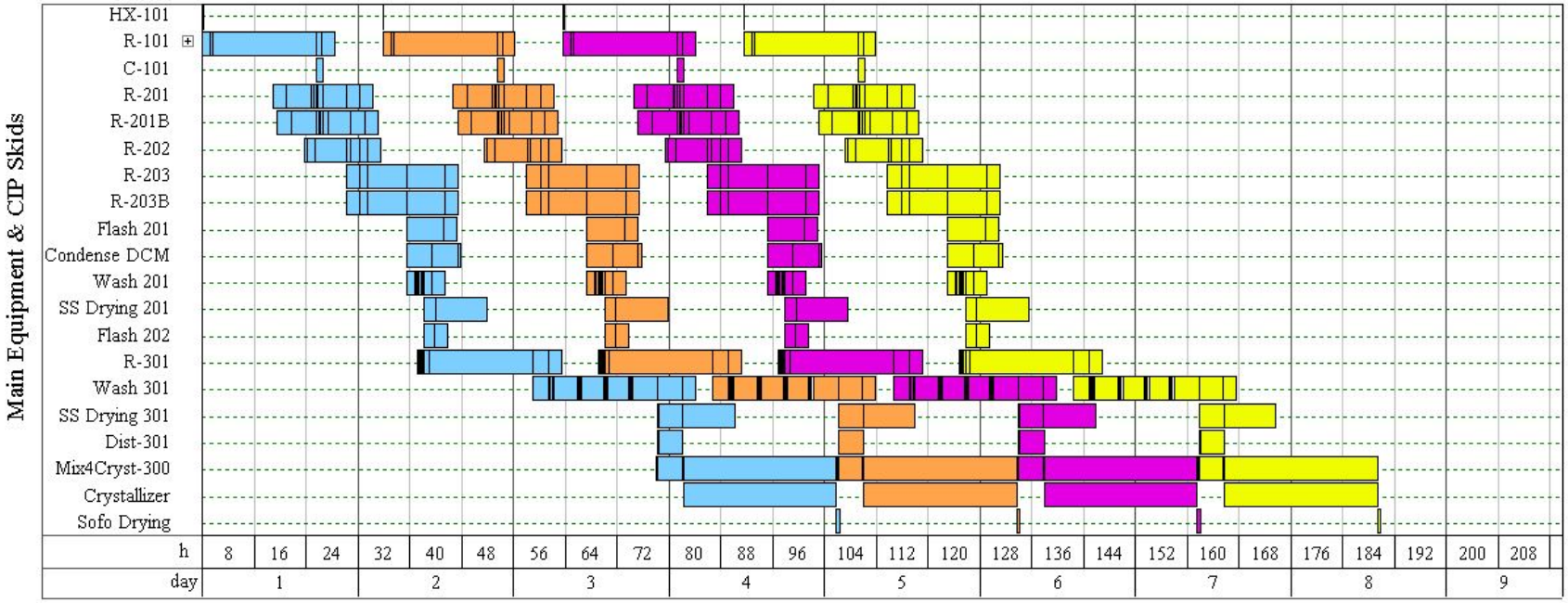
31-Aug-15	29420090	RIBAVIRIN USP/IP	China	Nhava Sheva Sea	KGS	300	839,988	2,800	42
14-Oct-16	29420090	RIBAVIRIN USP37/IP2014	China	Nhava Sheva Sea	KGS	500	1,433,989	2,868	43.02
9-Dec-15	29420090	RIBAVIRIN USP37/IP2014	China	Nhava Sheva Sea	KGS	500	1,433,848	2,868	43.02
1-May-15	29420090	RIBAVIRIN USP/IP	China	Bombay Air Cargo	KGS	200	610,363	3,052	45.78
15-Jun-15	29420090	RIBAVIRIN USP/IP	China	Bombay Air Cargo	KGS	300	941,724	3,139	47.09
									44.182

25-Oct-16	28331100	SODIUM SULPHATE ANHYDROUS .	China	Nhava Sheva Sea	KGS	108,000	604,205	6	0.09
17-Oct-16	28331100	SODIUM SULPHATE ANHYDROUS PH 6-8 - INDUSTRIAL	China	Bangalore	KGS	216,000	1,325,322	6	0.09
8-Oct-16	28331100	SODIUM SULPHATE ANHYDROUS	China	Tiruvallur-ILP ICD	KGS	216,000	1,295,870	6	0.09
6-Oct-16	28331100	(DISODIUM SULPHATE) SODIUM SULPHATE ANHYDROU	China	Tuticorin Sea	KGS	216,000	1,345,011	6	0.09
									0.09

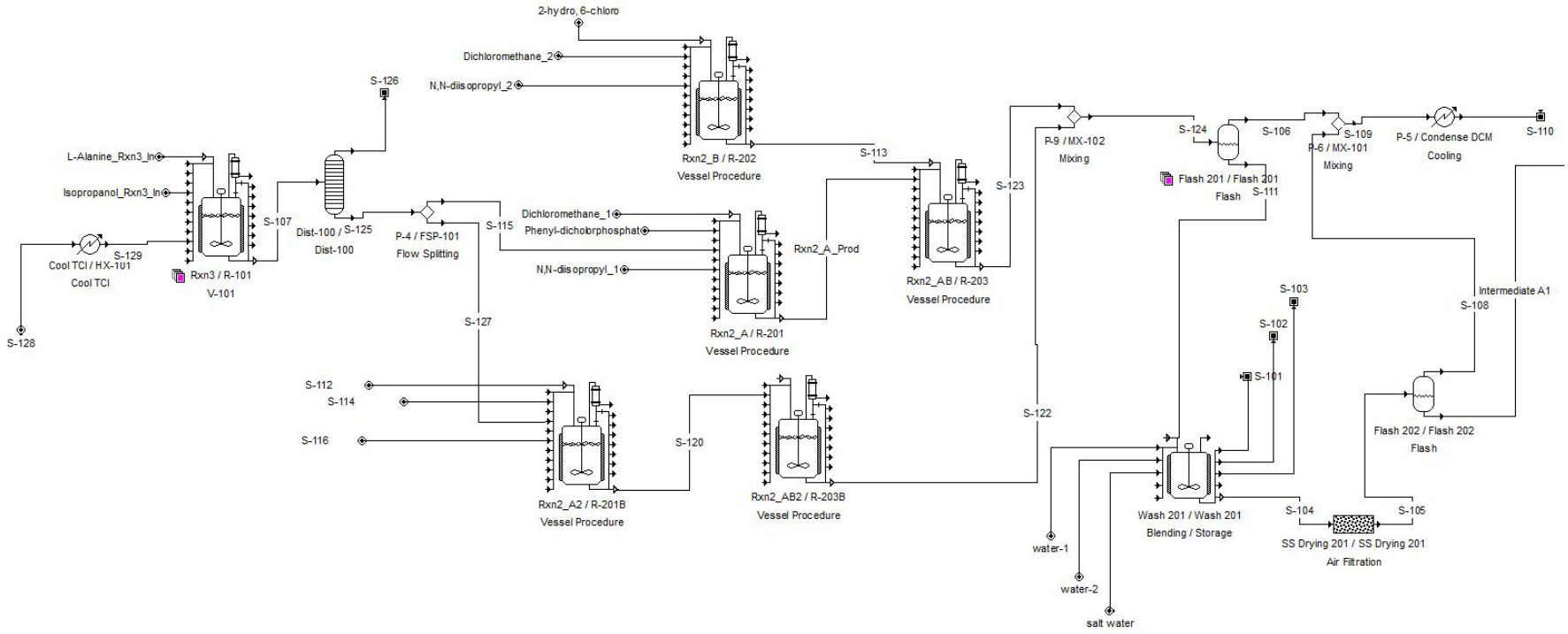
Appendix H - SuperPro and Gantt Charts

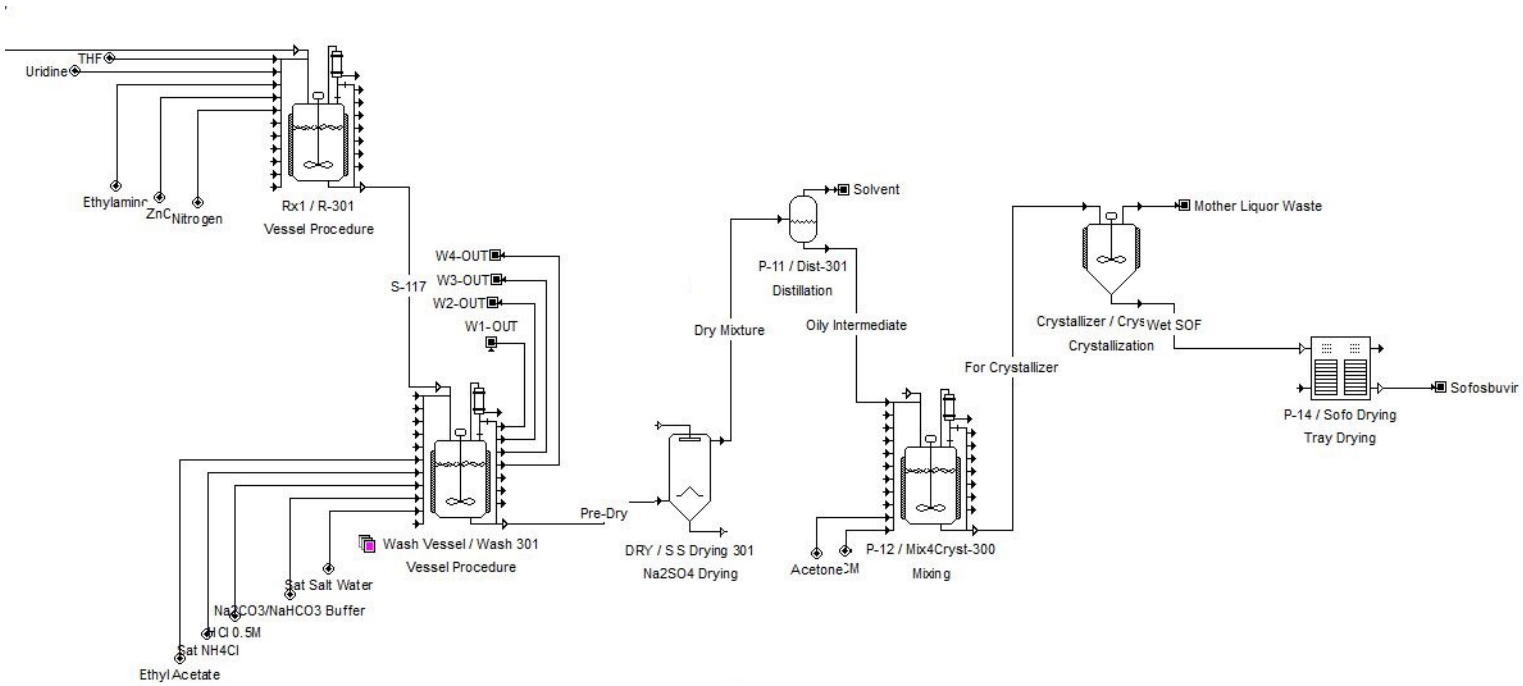
Appendix H-1 Overall Gantt Chart

s

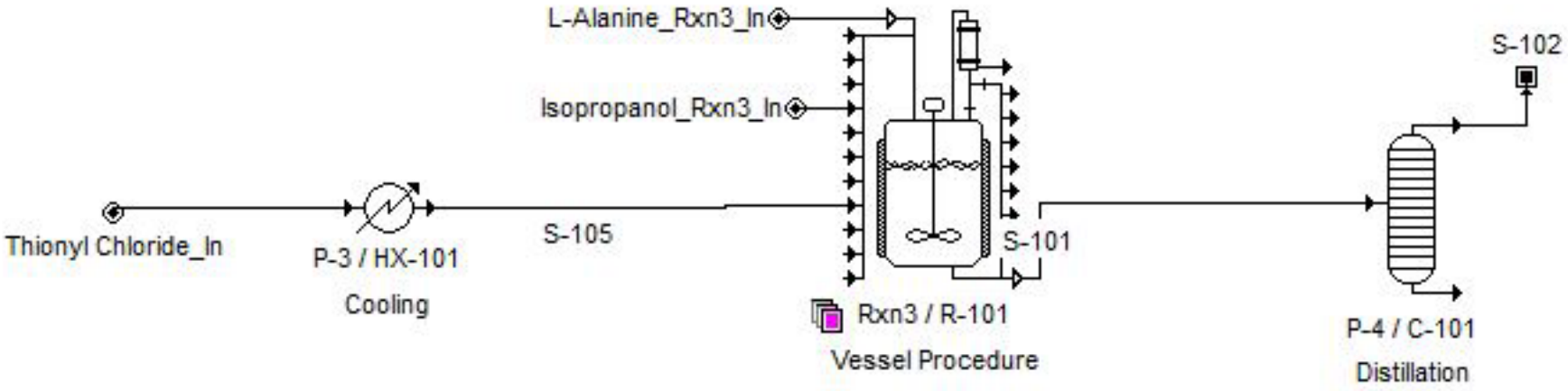


Appendix H-2 Overall Process Super Pro

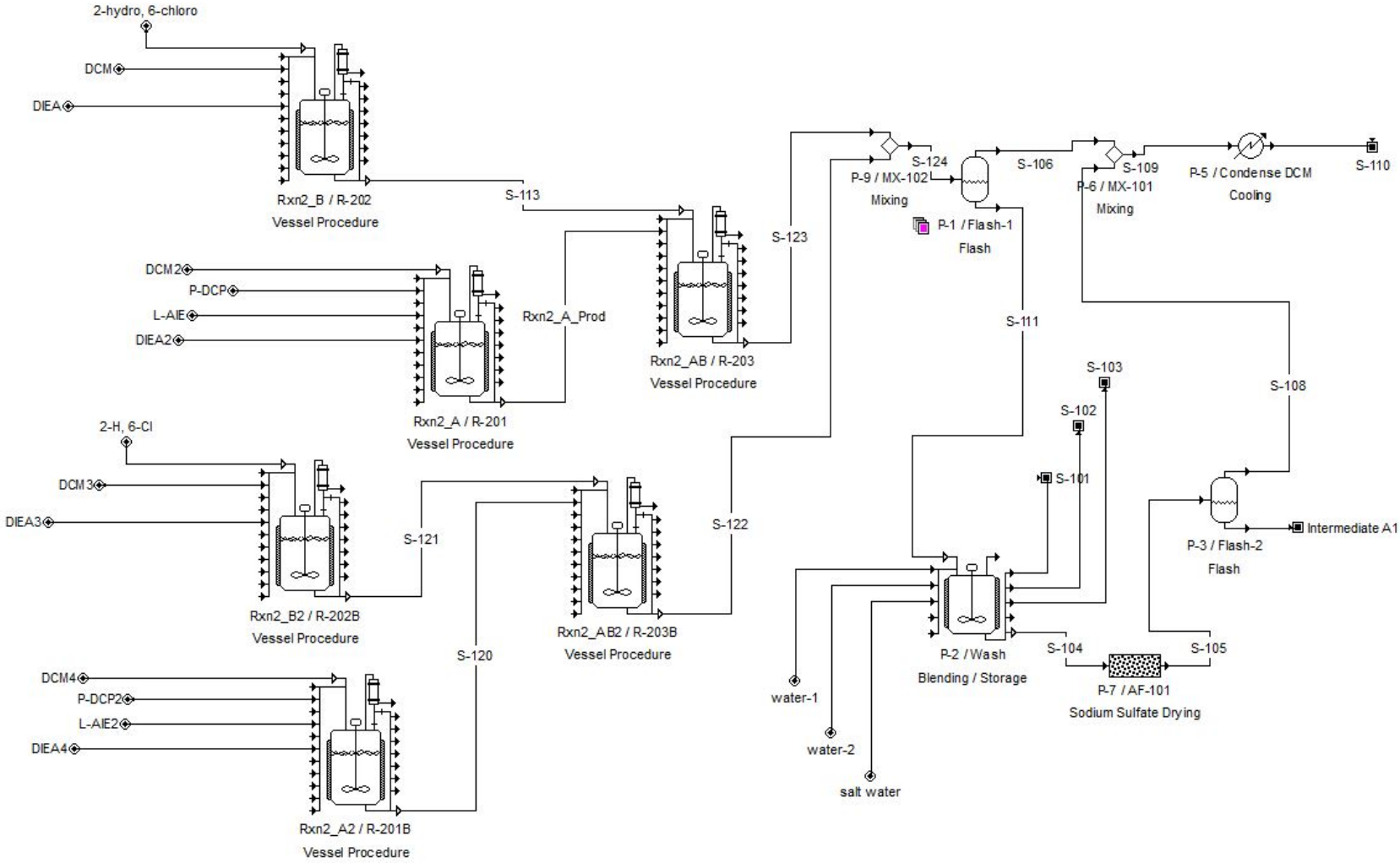



THF
Uridine
Ethylamine
ZnCl
Nitrogen
Rx1 / R-301
Vessel Procedure
S-117
W4-OUT
W3-OUT
W2-OUT
W1-OUT
Wash Vessel / Wash 301
Vessel Procedure
Sat Salt Water
Na2CO3/NaHCO3 Buffer
HCl 0.5M
Sat NH4Cl
Ethyl Acetate
Pre-Dry
DRY / S S Drying 301
Na2SO4 Drying
Solvent
P-11 / Dist-301
Distillation
Dry Mixture
Oily Intermediate
Acetone
P-12 / Mix4Cryst-300
Mixing
For Crystallizer
Mother Liquor Waste
Crystallizer / Crys
Crystallization
Wet SOF
P-14 / Sofo Drying
Tray Drying
Sofosbuvir

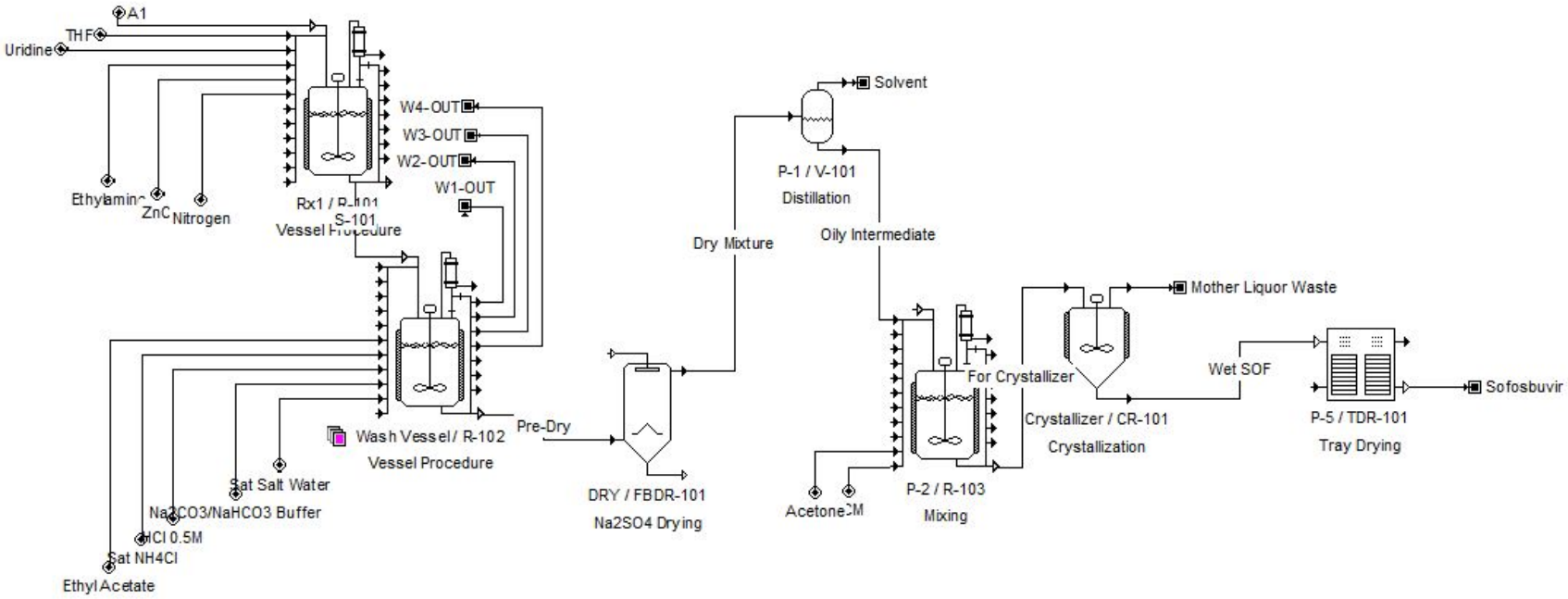
Appendix H-3 Process 100 Super Pro



Appendix H-4 Process 200 Super Pro



Appendix H-5 Process 300 Super Pro



Appendix I - ASPEN Block and Stream Reports

Appendix I-1 Thionyl Chloride Cooling - HeatEx Block Report (V101)

```
BLOCK: B1        MODEL: HEATX
------------------------------
 HOT SIDE:
 ---------
 INLET STREAM:             3
 OUTLET STREAM:            4
 PROPERTY OPTION SET:   IDEAL      IDEAL LIQUID / IDEAL GAS
 COLD SIDE:
 ----------
 INLET STREAM:             1
 OUTLET STREAM:            2
 PROPERTY OPTION SET:   IDEAL      IDEAL LIQUID / IDEAL GAS
                  ***   MASS AND ENERGY BALANCE      ***
                                  IN                   OUT          RELATIVE DIFF.
 TOTAL BALANCE
    MOLE(KMOL/HR )              945.008            945.008          0.00000
    MASS(KG/HR   )              81900.0            81900.0          0.00000
    ENTHALPY(CAL/SEC )       -0.230949E+08      -0.230949E+08       0.00000
                  *** CO2 EQUIVALENT SUMMARY ***
 FEED STREAMS CO2E           0.00000      KG/HR
 PRODUCT STREAMS CO2E        0.00000      KG/HR
 NET STREAMS CO2E PRODUCTION 0.00000      KG/HR
 UTILITIES CO2E PRODUCTION   0.00000      KG/HR
 TOTAL CO2E PRODUCTION       0.00000      KG/HR

                        ***   INPUT DATA   ***

FLASH SPECS FOR HOT SIDE:
TWO    PHASE      FLASH
MAXIMUM NO. ITERATIONS                                      30
CONVERGENCE TOLERANCE                                        0.000100000

FLASH SPECS FOR COLD SIDE:
TWO    PHASE      FLASH
MAXIMUM NO. ITERATIONS                                      30
CONVERGENCE TOLERANCE                                        0.000100000
FLOW DIRECTION AND SPECIFICATION:
  COUNTERCURRENT   HEAT EXCHANGER
  SPECIFIED HOT OUTLET TEMP
  SPECIFIED VALUE               C                            0.0000
  LMTD CORRECTION FACTOR                                     1.00000
PRESSURE SPECIFICATION:
  HOT SIDE PRESSURE DROP          BAR                        0.0000
  COLD SIDE PRESSURE DROP         BAR                        0.0000
HEAT TRANSFER COEFFICIENT SPECIFICATION:
  HOT LIQUID    COLD LIQUID     CAL/SEC-SQCM-K               0.0203
  HOT 2-PHASE   COLD LIQUID     CAL/SEC-SQCM-K               0.0203
  HOT VAPOR     COLD LIQUID     CAL/SEC-SQCM-K               0.0203
  HOT LIQUID    COLD 2-PHASE    CAL/SEC-SQCM-K               0.0203
  HOT 2-PHASE   COLD 2-PHASE    CAL/SEC-SQCM-K               0.0203
  HOT VAPOR     COLD 2-PHASE    CAL/SEC-SQCM-K               0.0203
  HOT LIQUID    COLD VAPOR      CAL/SEC-SQCM-K               0.0203
  HOT 2-PHASE   COLD VAPOR      CAL/SEC-SQCM-K               0.0203
```

```
  HOT VAPOR     COLD VAPOR       CAL/SEC-SQCM-K                    0.0203

                     ***    OVERALL RESULTS    ***

STREAMS:
                   ---------------------------------------
                   |                                     |
3           ------>|                HOT                  |----->     4
T=    2.5000D+01   |                                     |           T=    0.0000D+00
P=    1.0000D+00   |                                     |           P=    1.0000D+00
V=    0.0000D+00   |                                     |           V=    0.0000D+00
                   |                                     |
2           <------|                COLD                 |<-----     1
T=    4.8660D+00   |                                     |           T= -1.0000D+01
P=    1.0000D+00   |                                     |           P= 1.0000D+00
V=    0.0000D+00   |                                     |           V= 0.0000D+00
                   ---------------------------------------
DUTY AND AREA:
  CALCULATED HEAT DUTY               CAL/SEC                73571.3464
  CALCULATED (REQUIRED) AREA         SQM                       25.0254
  ACTUAL EXCHANGER AREA              SQM                       25.0254
  PER CENT OVER-DESIGN                                          0.0000

HEAT TRANSFER COEFFICIENT:
  AVERAGE COEFFICIENT (DIRTY)        CAL/SEC-SQCM-K             0.0203
  UA (DIRTY)                         CAL/SEC-K               5080.6220
LOG-MEAN TEMPERATURE DIFFERENCE:
  LMTD CORRECTION FACTOR                                        1.0000
  LMTD (CORRECTED)              C                              14.4808
  NUMBER OF SHELLS IN SERIES                                     1

PRESSURE DROP:
  HOTSIDE, TOTAL                     BAR                       0.0000
  COLDSIDE, TOTAL                    BAR                       0.0000

                          ***   ZONE RESULTS    ***

TEMPERATURE LEAVING EACH ZONE:
                                  HOT
       ------------------------------------------------------------
       |                                                          |
HOT IN |                            LIQ                           | HOT OUT
------>|                                                          |------>
 25.0  |                                                          |    0.0
       |                                                          |
COLDOUT|                            LIQ                           | COLDIN
<------|                                                          |<------
  4.9  |                                                          | -10.0
       |                                                          |
       ------------------------------------------------------------
                                  COLD
ZONE HEAT TRANSFER AND AREA:
ZONE         HEAT DUTY          AREA         LMTD       AVERAGE U        UA
             CAL/SEC            SQM           C         CAL/SEC-SQCM-K   CAL/SEC-K
  1        73571.346           25.0254        14.4808     0.0203         5080.6220

HEATX COLD-TQCU B1       TQCURV INLET
-------------------------------------
 PRESSURE PROFILE:      CONSTANT2
 PRESSURE DROP:         0.0         BAR
 PROPERTY OPTION SET:   IDEAL     IDEAL LIQUID / IDEAL GAS
```

DUTY	PRES	TEMP	VFRAC
CAL/SEC	BAR	C	
0.0	1.0000	4.8660	0.0
3503.3974	1.0000	4.1632	0.0
7006.7949	1.0000	3.4598	0.0
1.0510+04	1.0000	2.7560	0.0
1.4014+04	1.0000	2.0516	0.0
1.7517+04	1.0000	1.3467	0.0
2.1020+04	1.0000	0.6413	0.0
2.4524+04	1.0000	-6.4647-02	0.0
2.8027+04	1.0000	-0.7711	0.0
3.1531+04	1.0000	-1.4780	0.0
3.5034+04	1.0000	-2.1855	0.0
3.8537+04	1.0000	-2.8935	0.0
4.2041+04	1.0000	-3.6019	0.0
4.5544+04	1.0000	-4.3109	0.0
4.9048+04	1.0000	-5.0203	0.0
5.2551+04	1.0000	-5.7303	0.0
5.6054+04	1.0000	-6.4407	0.0
5.9558+04	1.0000	-7.1516	0.0
6.3061+04	1.0000	-7.8630	0.0
6.6565+04	1.0000	-8.5749	0.0
7.0068+04	1.0000	-9.2872	0.0
7.3571+04	1.0000	-10.0000	0.0

HEATX HOT-TQCUR B1 TQCURV INLET

PRESSURE PROFILE:	CONSTANT2	
PRESSURE DROP:	0.0	BAR
PROPERTY OPTION SET:	IDEAL	IDEAL LIQUID / IDEAL GAS

DUTY	PRES	TEMP	VFRAC
CAL/SEC	BAR	C	
0.0	1.0000	25.0000	0.0
3503.3974	1.0000	23.8308	0.0
7006.7949	1.0000	22.6595	0.0
1.0510+04	1.0000	21.4862	0.0
1.4014+04	1.0000	20.3107	0.0
1.7517+04	1.0000	19.1331	0.0
2.1020+04	1.0000	17.9534	0.0
2.4524+04	1.0000	16.7716	0.0
2.8027+04	1.0000	15.5876	0.0
3.1531+04	1.0000	14.4015	0.0
3.5034+04	1.0000	13.2133	0.0
3.8537+04	1.0000	12.0229	0.0
4.2041+04	1.0000	10.8304	0.0
4.5544+04	1.0000	9.6357	0.0
4.9048+04	1.0000	8.4389	0.0

```
!------------+------------+------------+------------!
! 5.2551+04 !      1.0000 !     7.2399 !     0.0    !
! 5.6054+04 !      1.0000 !     6.0387 !     0.0    !
! 5.9558+04 !      1.0000 !     4.8353 !     0.0    !
! 6.3061+04 !      1.0000 !     3.6298 !     0.0    !
! 6.6565+04 !      1.0000 !     2.4221 !     0.0    !
!------------+------------+------------+------------!
! 7.0068+04 !      1.0000 !     1.2121 !     0.0    !
! 7.3571+04 !      1.0000 ! 3.9530-07 !     0.0    !
-------------------------------------------------------
```

Appendix I-2 Distillation Column - Radfrac Stream and Block Reports (V103)

```
S1 S2 S3
-------------

STREAM
ID                S1          S2          S3
FROM :                      ----        B1          B1
TO   :                      B1          ----        ----

SUBSTREAM: MIXED
PHASE:                      LIQUID      LIQUID      LIQUID
COMPONENTS: KMOL/SEC
  ISOPR-01             0.4709      1.1491-03   0.4697
  L-ALA-01             1.3614-03   1.3614-03   7.7991-13
  THION-01             1.1772-02   5.6213-07   1.1771-02
  HYDRO-01             9.1103-03   4.9487-17   9.1103-03
  SULFU-01             9.1103-03   9.6251-13   9.1103-03
TOTAL FLOW:
  KMOL/SEC             0.5022      2.5111-03   0.4997
  KG/SEC               30.7349     0.1904      30.5445
  CUM/SEC              3.8083-02   5.0377-04   3.3599-02
STATE VARIABLES:
  TEMP   K             298.1500    309.7911    208.7851
  PRES   N/SQM         1.0000+05   5332.8947   5332.8947
  VFRAC                0.0         0.0         0.0
  LFRAC                1.0000      1.0000      1.0000
  SFRAC                0.0         0.0         0.0
ENTHALPY:
  J/KMOL              -3.1302+08  -4.1217+08  -3.2731+08
  J/KG                -5.1149+06  -5.4354+06  -5.3549+06
  WATT                -1.5720+08  -1.0350+06  -1.6356+08
ENTROPY:
  J/KMOL-K            -4.3383+05  -8.8447+05  -4.9042+05
  J/KG-K              -7088.9766  -1.1664+04  -8023.2898
DENSITY:
  KMOL/CUM             13.1876      4.9847     14.8729
  KG/CUM               807.0488    377.9916    909.0958
AVG MW                 61.1978     75.8308     61.1242
```

```
BLOCK: B1        MODEL: RADFRAC
------------------------------
  INLETS   - S1       STAGE   2
  OUTLETS  - S3       STAGE   1
             S2       STAGE   3
 PROPERTY OPTION SET:   IDEAL         IDEAL LIQUID / IDEAL GAS
                      ***    MASS AND ENERGY BALANCE   ***
                                     IN               OUT          RELATIVE DIFF.
 TOTAL BALANCE
    MOLE(KMOL/SEC)                 0.502222         0.502222          0.00000
    MASS(KG/SEC )                   31.5055          31.5055         0.234953E-09
    ENTHALPY(WATT       )         -0.161346E+09    -0.161454E+09     0.673947E-03
                  *** CO2 EQUIVALENT SUMMARY ***
 FEED STREAMS CO2E            0.00000      KG/SEC
 PRODUCT STREAMS CO2E         0.00000      KG/SEC
```

```
 NET STREAMS CO2E PRODUCTION  0.00000      KG/SEC
 UTILITIES CO2E PRODUCTION    0.00000      KG/SEC
 TOTAL CO2E PRODUCTION        0.00000      KG/SEC



                        **********************
                        **** INPUT DATA ****
                        **********************



****   INPUT PARAMETERS        ****



 NUMBER OF STAGES                                                    3
 ALGORITHM OPTION                                                 STANDARD
 ABSORBER OPTION                                                  NO
 INITIALIZATION OPTION                                            STANDARD
 HYDRAULIC PARAMETER CALCULATIONS                                 NO
 INSIDE LOOP CONVERGENCE METHOD                                   BROYDEN
 DESIGN SPECIFICATION METHOD                                      NESTED
 MAXIMUM NO. OF OUTSIDE LOOP ITERATIONS                            25
 MAXIMUM NO. OF INSIDE LOOP ITERATIONS                             10
 MAXIMUM NUMBER OF FLASH ITERATIONS                                30
 FLASH TOLERANCE                                                    0.000100000
 OUTSIDE LOOP CONVERGENCE TOLERANCE                                 0.000100000
****   COL-SPECS      ****
 MOLAR VAPOR DIST / TOTAL DIST                                         0.0
 MOLAR REFLUX RATIO                                                    3.00000
 BOTTOMS TO FEED RATIO                                                 0.040000



****      PROFILES    ****
 P-SPEC              STAGE    1   PRES, N/SQM              5,332.89
                             *******************
                             **** RESULTS ****
                             *******************



***    COMPONENT SPLIT FRACTIONS       ***



                               OUTLET STREAMS
                               --------------
               S3                S2
 COMPONENT:
```

```
 ISOPR-01       .98943        .10574E-01
 L-ALA-01       .68188E-09    1.0000
 THION-01       .99798        .20220E-02



***      SUMMARY OF KEY RESULTS        ***
 TOP STAGE TEMPERATURE                 K                          295.867
 BOTTOM STAGE TEMPERATURE              K                          320.862
 TOP STAGE LIQUID FLOW                 KMOL/SEC                     1.44640
 BOTTOM STAGE LIQUID FLOW              KMOL/SEC                     0.020089
 TOP STAGE VAPOR FLOW                  KMOL/SEC                     0.0
 BOILUP VAPOR FLOW                     KMOL/SEC                     1.82840
 MOLAR REFLUX RATIO                                                 3.00000
 MOLAR BOILUP RATIO                                                91.0157
 CONDENSER DUTY (W/O SUBCOOL)          WATT                        -0.884715+08
 REBOILER DUTY                         WATT                         0.883627+08



****     MAXIMUM FINAL RELATIVE ERRORS        ****
 DEW POINT                             0.46351E-06     STAGE=   3
 BUBBLE POINT                          0.28072E-06     STAGE=   3
 COMPONENT MASS BALANCE                0.32587E-07     STAGE=   2 COMP=L-ALA-01
 ENERGY BALANCE                        0.71674E-07     STAGE=   2



****      PROFILES     ****



**NOTE** REPORTED VALUES FOR STAGE LIQUID AND VAPOR RATES ARE THE FLOWS
         FROM THE STAGE INCLUDING ANY SIDE PRODUCT.



                                              ENTHALPY
STAGE TEMPERATURE     PRESSURE                  J/KMOL                  HEAT DUTY
     K                N/SQM              LIQUID       VAPOR           WATT



1      295.87        5332.9       -0.31626E+09 -0.26727E+09       -.88471+08
2      296.57        5332.9       -0.31908E+09 -0.27039E+09
3      320.86        5332.9       -0.44683E+09 -0.26935E+09        .88363+08



STAGE    FLOW RATE                          FEED RATE                 PRODUCT RATE
```

```
         KMOL/SEC                          KMOL/SEC                    KMOL/SEC
    LIQUID     VAPOR            LIQUID      VAPOR      MIXED       LIQUID    VAPOR
1 1.929       0.000                        .34912-02                 0.4821
2 1.848       1.925            0.4987
3 0.2009E-01 1.828                                                 .20089-01



 ****    MASS FLOW PROFILES     ****



STAGE     FLOW RATE                         FEED RATE                  PRODUCT RATE
          KG/SEC                            KG/SEC                      KG/SEC
     LIQUID     VAPOR            LIQUID      VAPOR      MIXED       LIQUID    VAPOR
1   119.4      0.000                          0.2266                 29.8595
2   112.7      119.2            31.2788
3   1.646      111.1                                                  1.6459
                    ****   MOLE-X-PROFILE    ****
STAGE       ISOPR-01       L-ALA-01      THION-01
   1      0.96881        0.21309E-10   0.31187E-01
   2      0.98070        0.81508E-02   0.11150E-01
   3      0.24848        0.75000       0.15165E-02
                   ****    MOLE-Y-PROFILE    ****



STAGE     ISOPR-01     L-ALA-01         THION-01
  1    0.91567      0.55216E-19      0.84332E-01
  2    0.96891      0.21205E-10      0.31095E-01
  3    0.98874      0.22169E-08      0.11256E-01
                    ****   K-VALUES    ****
STAGE     ISOPR-01     L-ALA-01      THION-01
  1    0.94514      0.25913E-08    2.7041
  2    0.98797      0.26016E-08    2.7887
  3     3.9791      0.29559E-08    7.4225
                    ****   MASS-X-PROFILE   ****
STAGE     ISOPR-01     L-ALA-01      THION-01
  1    0.94009      0.30654E-10   0.59910E-01
  2    0.96634      0.11907E-01   0.21751E-01
  3    0.18225      0.81554       0.22020E-02
                    ****   MASS-Y-PROFILE     ****
STAGE     ISOPR-01     L-ALA-01      THION-01
  1    0.84579      0.75613E-19   0.15421
  2    0.94026      0.30508E-10   0.59738E-01
  3    0.97796      0.32508E-08   0.22041E-01
```

Appendix I-3 Flash Separation - Flash2 Stream and Block Reports (V204)

```
BLOCK:  B1       MODEL: FLASH2
------------------------------
  INLET STREAM:          1
  OUTLET VAPOR STREAM:   2
  OUTLET LIQUID STREAM:  3
  PROPERTY OPTION SET:   IDEAL     IDEAL LIQUID / IDEAL GAS



                    ***  MASS AND ENERGY BALANCE  ***
                                  IN              OUT        RELATIVE DIFF.
   TOTAL BALANCE
      MOLE(KMOL/HR )            440.425         440.425         0.00000
      MASS(KG/HR   )            39413.0         39413.0         0.00000
      ENTHALPY(CAL/SEC )     -0.361206E+07   -0.303710E+07   -0.159178



                    ***  CO2 EQUIVALENT SUMMARY ***
   FEED STREAMS CO2E             310347.      KG/HR
   PRODUCT STREAMS CO2E          310347.      KG/HR
   NET STREAMS CO2E PRODUCTION   0.00000      KG/HR
   UTILITIES CO2E PRODUCTION     0.00000      KG/HR
   TOTAL CO2E PRODUCTION         0.00000      KG/HR



                        ***  INPUT DATA  ***
  TWO    PHASE  TP  FLASH
  SPECIFIED TEMPERATURE C                                  25.0000
  SPECIFIED PRESSURE    BAR                                 0.50000
  MAXIMUM NO. ITERATIONS                                   30
  CONVERGENCE TOLERANCE                                    0.000100000



                          ***  RESULTS  ***
  OUTLET TEMPERATURE    C                                   25.000
  OUTLET PRESSURE       BAR                                0.50000
  HEAT DUTY             CAL/SEC                            0.57496E+06
  VAPOR FRACTION                                           0.67805



  V-L PHASE EQUILIBRIUM :



     COMP             F(I)          X(I)          Y(I)          K(I)
     DICHL-01        0.95364       0.85600       1.0000        1.1682
```

PHENY-01	0.46362E-01	0.14400	0.23158E-08	0.16082E-07

1 2 3

STREAM ID	1	2	3
FROM :	----	B1	B1
TO :	B1	----	----
SUBSTREAM: MIXED			
PHASE:	LIQUID	VAPOR	LIQUID
COMPONENTS: KMOL/HR			
DICHL-01	420.0057	298.6291	121.3766
PHENY-01	20.4189	6.9157-07	20.4189
TOTAL FLOW:			
KMOL/HR	440.4246	298.6291	141.7955
KG/HR	3.9413+04	2.5363+04	1.4050+04
L/MIN	500.0000	2.4676+05	181.0709
STATE VARIABLES:			
TEMP C	25.0000	25.0000	25.0000
PRES BAR	1.0100	0.5000	0.5000
VFRAC	0.0	1.0000	0.0
LFRAC	1.0000	0.0	1.0000
SFRAC	0.0	0.0	0.0
ENTHALPY:			
CAL/MOL	-2.9525+04	-2.2815+04	-2.9059+04
CAL/GM	-329.9270	-268.6206	-293.2771
CAL/SEC	-3.6121+06	-1.8925+06	-1.1446+06
ENTROPY:			
CAL/MOL-K	-43.2111	-19.8744	-43.0882
CAL/GM-K	-0.4829	-0.2340	-0.4349
DENSITY:			
MOL/CC	1.4681-02	2.0170-05	1.3052-02
GM/CC	1.3138	1.7131-03	1.2932
AVG MW	89.4886	84.9323	99.0845

Appendix I-4 Intermediate A1 Wash - Decanter Block Report (V205)

```
BLOCK:  B1       MODEL: DECANTER
------------------------------
  INLET STREAM:          S1
  FIRST LIQUID OUTLET:   S3
  SECOND LIQUID OUTLET:  S2
  PROPERTY OPTION SET:   NRTL      RENON (NRTL) / IDEAL GAS

                    ***  MASS AND ENERGY BALANCE  ***
                                 IN              OUT        RELATIVE DIFF.
   TOTAL BALANCE
      MOLE(KMOL/HR )          1089.50         1089.50        0.00000
      MASS(KG/HR   )          35627.9         35627.9        0.782301E-08
      ENTHALPY(CAL/SEC )      -0.180794E+08   -0.180973E+08  0.987702E-03

                    ***  CO2 EQUIVALENT SUMMARY ***
   FEED STREAMS CO2E             176679.      KG/HR
   PRODUCT STREAMS CO2E          176679.      KG/HR
   NET STREAMS CO2E PRODUCTION -0.307765E-02  KG/HR
   UTILITIES CO2E PRODUCTION     0.00000      KG/HR
   TOTAL CO2E PRODUCTION       -0.307765E-02  KG/HR

                         ***  INPUT DATA  ***

  LIQUID-LIQUID SPLIT, TP SPECIFICATION
  SPECIFIED TEMPERATURE              C                        25.0000
  SPECIFIED PRESSURE                 BAR                     1.00000
  CONVERGENCE TOLERANCE ON EQUILIBRIUM                      0.10000E-03
  MAXIMUM NO ITERATIONS ON EQUILIBRIUM                      30
  EQUILIBRIUM METHOD                          EQUATION-SOLVING
  KLL COEFFICIENTS FROM                       OPTION SET OR EOS
  KLL BASIS                                                MOLE
  KEY COMPONENT(S):       DICHL-01  WATER

                         ***  RESULTS  ***

  OUTLET TEMPERATURE      C                                  25.000
  OUTLET PRESSURE         BAR                                1.0000
  CALCULATED HEAT DUTY    CAL/SEC                           -17875.
  MOLAR RATIO 1ST LIQUID / TOTAL LIQUID                     0.22190

  L1-L2 PHASE EQUILIBRIUM :
     COMP          F            X1           X2            K
     DICHL-01   0.21947       0.98131      0.0022004     0.0022423
     WATER      0.78053       0.018690     0.99780       53.3855
```

Appendix I-5 Flash Distillate Condenser - HeatEx Block Report (V208)

```
BLOCK:  CONDENSE MODEL: HEATX
------------------------------
  HOT SIDE:
  ---------
  INLET STREAM:             DCM-IN
  OUTLET STREAM:            DCM-OUT
  PROPERTY OPTION SET:   UNIF-LL   UNIFAC / REDLICH-KWONG
  COLD SIDE:
  ----------
  INLET STREAM:             CW-IN
  OUTLET STREAM:            CW-OUT
  PROPERTY OPTION SET:   UNIF-LL   UNIFAC / REDLICH-KWONG

                    ***  MASS AND ENERGY BALANCE  ***
                                 IN              OUT        RELATIVE DIFF.
   TOTAL BALANCE
      MOLE(KMOL/HR )            891.207         891.207         0.00000
      MASS(KG/HR   )            62229.2         62229.2         0.00000
      ENTHALPY(CAL/SEC )     -0.204374E+08   -0.204374E+08     0.00000

                    ***  CO2 EQUIVALENT SUMMARY ***
   FEED STREAMS CO2E             223424.      KG/HR
   PRODUCT STREAMS CO2E          223424.      KG/HR
   NET STREAMS CO2E PRODUCTION   0.00000      KG/HR
   UTILITIES CO2E PRODUCTION     0.00000      KG/HR
   TOTAL CO2E PRODUCTION         0.00000      KG/HR

                        ***  INPUT DATA  ***

  FLASH SPECS FOR HOT SIDE:
  TWO    PHASE      FLASH
  MAXIMUM NO. ITERATIONS                                  30
  CONVERGENCE TOLERANCE                                    0.000100000

  FLASH SPECS FOR COLD SIDE:
  TWO    PHASE      FLASH
  MAXIMUM NO. ITERATIONS                                  30
  CONVERGENCE TOLERANCE                                    0.000100000

  FLOW DIRECTION AND SPECIFICATION:
    COUNTERCURRENT   HEAT EXCHANGER
    SPECIFIED HOT VAPOR FRACTION
    SPECIFIED VALUE                                        0.0000
    LMTD CORRECTION FACTOR                                 1.00000

  PRESSURE SPECIFICATION:
    HOT  SIDE PRESSURE DROP        BAR                     0.0000
    COLD SIDE PRESSURE DROP        BAR                     0.0000

  HEAT TRANSFER COEFFICIENT SPECIFICATION:
    HOT LIQUID    COLD LIQUID      CAL/SEC-SQCM-K          0.0203
    HOT 2-PHASE   COLD LIQUID      CAL/SEC-SQCM-K          0.0203
    HOT VAPOR     COLD LIQUID      CAL/SEC-SQCM-K          0.0203
    HOT LIQUID    COLD 2-PHASE     CAL/SEC-SQCM-K          0.0203
    HOT 2-PHASE   COLD 2-PHASE     CAL/SEC-SQCM-K          0.0203
    HOT VAPOR     COLD 2-PHASE     CAL/SEC-SQCM-K          0.0203
```

```
    HOT LIQUID    COLD VAPOR       CAL/SEC-SQCM-K           0.0203
    HOT 2-PHASE   COLD VAPOR       CAL/SEC-SQCM-K           0.0203
    HOT VAPOR     COLD VAPOR       CAL/SEC-SQCM-K           0.0203

                        ***  OVERALL RESULTS  ***

  STREAMS:
                    ---------------------------------------
                    |                                     |
  DCM-IN    ----->  |               HOT                   | -----> DCM-OUT
  T=  2.5000D+01    |                                     |        T=  2.1161D+01
  P=  5.0000D-01    |                                     |        P=  5.0000D-01
  V=  1.0000D+00    |                                     |        V=  0.0000D+00
                    |                                     |
  CW-OUT    <-----  |               COLD                  | <----- CW-IN
  T=  2.1609D+01    |                                     |        T= -9.0000D+01
  P=  1.0132D+00    |                                     |        P=  1.0132D+00
  V=  0.0000D+00    |                                     |        V=  0.0000D+00
                    ---------------------------------------

  DUTY AND AREA:
    CALCULATED HEAT DUTY           CAL/SEC             590551.3185
    CALCULATED (REQUIRED) AREA     SQM                    149.8232
    ACTUAL EXCHANGER AREA          SQM                    149.8232
    PER CENT OVER-DESIGN                                    0.0000

  HEAT TRANSFER COEFFICIENT:
    AVERAGE COEFFICIENT (DIRTY)    CAL/SEC-SQCM-K           0.0203
    UA (DIRTY)                     CAL/SEC-K            30416.9486

  LOG-MEAN TEMPERATURE DIFFERENCE:
    LMTD CORRECTION FACTOR                                  1.0000
    LMTD (CORRECTED)               C                       19.4152
    NUMBER OF SHELLS IN SERIES                               1

  PRESSURE DROP:
    HOTSIDE, TOTAL                 BAR                      0.0000
    COLDSIDE, TOTAL                BAR                      0.0000

                       ***  ZONE RESULTS  ***

  TEMPERATURE LEAVING EACH ZONE:

                                  HOT
          ------------------------------------------------------------
          |                           |                              |
HOT IN    |             VAP           |             COND             | HOT OUT
------>   |                           |                              |------>
  25.0    |                      21.2 |                              |   21.2
          |                           |                              |
COLDOUT   |             LIQ           |             LIQ              | COLDIN
<------   |                           |                              |<------
  21.6    |                      20.9 |                              |  -90.0
          |                           |                              |
          ------------------------------------------------------------
                                  COLD

  ZONE HEAT TRANSFER AND AREA:

  ZONE       HEAT DUTY       AREA       LMTD       AVERAGE U       UA
             CAL/SEC         SQM         C         CAL/SEC-SQCM-K  CAL/SEC-K
    1       3967.806        12.3106      1.5876     0.0203        2499.2784
```

```
    2     586583.512       137.5126      21.0112     0.0203       27917.6703

HEATX COLD-TQCU CONDENSE TQCURV INLET
-------------------------------------
  PRESSURE PROFILE:      CONSTANT2
  PRESSURE DROP:         0.0         BAR
  PROPERTY OPTION SET:   UNIF-LL   UNIFAC / REDLICH-KWONG

-----------------------------------------------------
!  DUTY      !  PRES      !  TEMP      !  VFRAC     !
!            !            !            !            !
!            !            !            !            !
!            !            !            !            !
!  CAL/SEC   !  BAR       !  C         !            !
!            !            !            !            !
!============!============!============!============!
!     0.0    !     1.0133 !    21.6091 !     0.0    !
!  3967.8059 !     1.0133 !    20.8978 !     0.0    !
!  2.8121+04 !     1.0133 !    16.5543 !     0.0    !
!  5.6243+04 !     1.0133 !    11.4688 !     0.0    !
!  8.4364+04 !     1.0133 !     6.3536 !     0.0    !
!------------+------------+------------+------------!
!  1.1249+05 !     1.0133 !     1.2095 !     0.0    !
!  1.4061+05 !     1.0133 !    -3.9621 !     0.0    !
!  1.6873+05 !     1.0133 !    -9.1602 !     0.0    !
!  1.9685+05 !     1.0133 !   -14.3835 !     0.0    !
!  2.2497+05 !     1.0133 !   -19.6331 !     0.0    !
!------------+------------+------------+------------!
!  2.5309+05 !     1.0133 !   -24.9093 !     0.0    !
!  2.8121+05 !     1.0133 !   -30.2117 !     0.0    !
!  3.0934+05 !     1.0133 !   -35.5395 !     0.0    !
!  3.3746+05 !     1.0133 !   -40.8920 !     0.0    !
!  3.6558+05 !     1.0133 !   -46.2682 !     0.0    !
!------------+------------+------------+------------!
!  3.9370+05 !     1.0133 !   -51.6674 !     0.0    !
!  4.2182+05 !     1.0133 !   -57.0882 !     0.0    !
!  4.4994+05 !     1.0133 !   -62.5297 !     0.0    !
!  4.7807+05 !     1.0133 !   -67.9905 !     0.0    !
!  5.0619+05 !     1.0133 !   -73.4693 !     0.0    !
!------------+------------+------------+------------!
!  5.3431+05 !     1.0133 !   -78.9648 !     0.0    !
!  5.6243+05 !     1.0133 !   -84.4755 !     0.0    !
!  5.9055+05 !     1.0133 !   -90.0000 !     0.0    !
-----------------------------------------------------

HEATX HOT-TQCUR CONDENSE TQCURV INLET
-------------------------------------
  PRESSURE PROFILE:      CONSTANT2
  PRESSURE DROP:         0.0         BAR
  PROPERTY OPTION SET:   UNIF-LL   UNIFAC / REDLICH-KWONG

-----------------------------------------------------
!  DUTY      !  PRES      !  TEMP      !  VFRAC     !
!            !            !            !            !
!            !            !            !            !
!            !            !            !            !
!  CAL/SEC   !  BAR       !  C         !            !
!            !            !            !            !
!============!============!============!============!
!     0.0    !     0.5000 !    25.0000 !     1.0000 !
!  3967.8059 !     0.5000 !    21.1608 ! DEW>1.0000 !
!  2.8121+04 !     0.5000 !    21.1608 !     0.9588 !
```

```
!  5.6243+04 !     0.5000 !    21.1608 !     0.9109 !
!  8.4364+04 !     0.5000 !    21.1608 !     0.8629 !
!------------+------------+------------+------------!
!  1.1249+05 !     0.5000 !    21.1608 !     0.8150 !
!  1.4061+05 !     0.5000 !    21.1608 !     0.7671 !
!  1.6873+05 !     0.5000 !    21.1608 !     0.7191 !
!  1.9685+05 !     0.5000 !    21.1608 !     0.6712 !
!  2.2497+05 !     0.5000 !    21.1608 !     0.6232 !
!------------+------------+------------+------------!
!  2.5309+05 !     0.5000 !    21.1608 !     0.5753 !
!  2.8121+05 !     0.5000 !    21.1608 !     0.5274 !
!  3.0934+05 !     0.5000 !    21.1608 !     0.4794 !
!  3.3746+05 !     0.5000 !    21.1608 !     0.4315 !
!  3.6558+05 !     0.5000 !    21.1608 !     0.3835 !
!------------+------------+------------+------------!
!  3.9370+05 !     0.5000 !    21.1608 !     0.3356 !
!  4.2182+05 !     0.5000 !    21.1608 !     0.2876 !
!  4.4994+05 !     0.5000 !    21.1608 !     0.2397 !
!  4.7807+05 !     0.5000 !    21.1608 !     0.1918 !
!  5.0619+05 !     0.5000 !    21.1608 !     0.1438 !
!------------+------------+------------+------------!
!  5.3431+05 !     0.5000 !    21.1608 !  9.5882-02 !
!  5.6243+05 !     0.5000 !    21.1608 !  4.7941-02 !
!  5.9055+05 !     0.5000 !    21.1608 !     0.0    !
-------------------------------------------------------
```

Appendix I-6 Solvent Removal Distillation Column - Radfrac Block Report (V304)

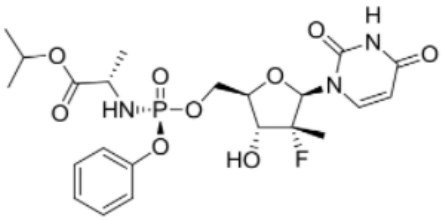
```
BLOCK:  VOLRED   MODEL: RADFRAC
------------------------------
   INLETS   - DRYWASH  STAGE   1
   OUTLETS  - SOLV     STAGE   1
              CONC     STAGE   2
  PROPERTY OPTION SET:   IDEAL     IDEAL LIQUID / IDEAL
GAS

                     ***  MASS AND ENERGY BALANCE  ***
                                  IN              OUT        RELATIVE DIFF.
   TOTAL BALANCE
      MOLE(KMOL/HR )            302.660         302.660        0.187812E-15
      MASS(KG/HR   )            25633.6         25633.6        0.152100E-06
      ENTHALPY(CAL/SEC )     -0.786110E+07   -0.786975E+07    0.109857E-02

                     ***  CO2 EQUIVALENT SUMMARY ***
   FEED STREAMS CO2E             23853.1      KG/HR
   PRODUCT STREAMS CO2E          23853.2      KG/HR
   NET STREAMS CO2E PRODUCTION  0.108865      KG/HR
   UTILITIES CO2E PRODUCTION     0.00000      KG/HR
   TOTAL CO2E PRODUCTION        0.108865      KG/HR



                        **********************
                        ****  INPUT DATA  ****
                        **********************

  ****   INPUT PARAMETERS   ****

   NUMBER OF STAGES                                          2
   ALGORITHM OPTION                                      STANDARD
   ABSORBER OPTION                                       NO
   INITIALIZATION OPTION                                 STANDARD
   HYDRAULIC PARAMETER CALCULATIONS                      NO
   INSIDE LOOP CONVERGENCE METHOD                        BROYDEN
   DESIGN SPECIFICATION METHOD                           NESTED
   MAXIMUM NO. OF OUTSIDE LOOP ITERATIONS                 25
   MAXIMUM NO. OF INSIDE LOOP ITERATIONS                  10
   MAXIMUM NUMBER OF FLASH ITERATIONS                     30
   FLASH TOLERANCE                                         0.000100000
   OUTSIDE LOOP CONVERGENCE TOLERANCE                      0.000100000

  ****   COL-SPECS   ****

   MOLAR VAPOR DIST / TOTAL DIST                           0.0
   MOLAR REFLUX RATIO                                      3.00000
   MASS BOTTOMS TO FEED RATIO                              0.085000

  ****    PROFILES   ****

   P-SPEC          STAGE   1  PRES, ATM                    0.15791

                        ******************
                        ****  RESULTS  ****
                        ******************


  ***   COMPONENT SPLIT FRACTIONS   ***
```

```
                          OUTLET STREAMS
                          --------------
                SOLV         CONC
  COMPONENT:
  L-ALA-01    .25001       .74999
  ETHYL-01    .93884       .61157E-01
  TETRA-01    .96139       .38613E-01
  DICHL-01    .98454       .15460E-01


 ***    SUMMARY OF KEY RESULTS    ***

  TOP STAGE TEMPERATURE          K                        293.902
  BOTTOM STAGE TEMPERATURE       K                        310.795
  TOP STAGE LIQUID FLOW          KMOL/HR                  832.839
  BOTTOM STAGE LIQUID FLOW       KMOL/HR                   25.0473
  TOP STAGE VAPOR FLOW           KMOL/HR                    0.0
  BOILUP VAPOR FLOW              KMOL/HR                  807.792
  MOLAR REFLUX RATIO                                        3.00000
  MOLAR BOILUP RATIO                                       32.2506
  CONDENSER DUTY (W/O SUBCOOL)   CAL/SEC          -1,946,020.
  REBOILER DUTY                  CAL/SEC           1,937,370.

 ****   MAXIMUM FINAL RELATIVE ERRORS   ****

  DEW POINT                       0.71594E-04  STAGE=  2
  BUBBLE POINT                    0.31367E-05  STAGE=  2
  COMPONENT MASS BALANCE          0.67813E-04  STAGE=  2 COMP=L-ALA-01
  ENERGY BALANCE                  0.79773E-05  STAGE=  2


 ****    PROFILES   ****

 **NOTE** REPORTED VALUES FOR STAGE LIQUID AND VAPOR RATES ARE THE FLOWS
          FROM THE STAGE INCLUDING ANY SIDE PRODUCT.

                                          ENTHALPY
STAGE TEMPERATURE   PRESSURE              CAL/MOL             HEAT DUTY
      K             ATM            LIQUID       VAPOR        CAL/SEC

  1   293.90       0.15791       -92288.      -62787.      -.19460+07
  2   310.80       0.15791     -0.10822E+06   -83160.       .19374+07

STAGE     FLOW RATE                  FEED RATE                PRODUCT RATE
           KMOL/HR                    KMOL/HR                   KMOL/HR
      LIQUID     VAPOR       LIQUID    VAPOR    MIXED      LIQUID    VAPOR
  1  1110.      0.000       298.1608    4.4996             277.6131
  2  25.05      807.8                                       25.0473

  ****  MASS FLOW PROFILES  ****

STAGE     FLOW RATE                  FEED RATE                PRODUCT RATE
           KG/HR                      KG/HR                    KG/HR
      LIQUID     VAPOR       LIQUID    VAPOR    MIXED      LIQUID    VAPOR
  1 0.9382E+05  0.000      .25258+05  375.2479            .23455+05
  2  2179.     0.6819E+05                                 2178.8540

                        ****   MOLE-X-PROFILE     ****
  STAGE     L-ALA-01      ETHYL-01      TETRA-01      DICHL-01
     1    0.12214E-01   0.66905       0.20425       0.11448
     2    0.40610       0.48305       0.90923E-01   0.19925E-01
```

```
                        ****   MOLE-Y-PROFILE     ****
STAGE     L-ALA-01      ETHYL-01      TETRA-01      DICHL-01
   1    0.10430E-10   0.42076       0.22746       0.35178
   2    0.38046E-09   0.67482       0.20776       0.11742

                        ****   K-VALUES           ****
STAGE     L-ALA-01      ETHYL-01      TETRA-01      DICHL-01
   1    0.85397E-09   0.62889        1.1137        3.0727
   2    0.93671E-09    1.3970        2.2850        5.8927

                        ****   MASS-X-PROFILE     ****
STAGE     L-ALA-01      ETHYL-01      TETRA-01      DICHL-01
   1    0.12880E-01   0.69771       0.17432       0.11509
   2    0.41592       0.48925       0.75368E-01   0.19454E-01

                        ****   MASS-Y-PROFILE     ****
STAGE     L-ALA-01      ETHYL-01      TETRA-01      DICHL-01
   1    0.11148E-10   0.44477       0.19678       0.35845
   2    0.40158E-09   0.70437       0.17748       0.11814
```

Appendix J - Solubility from EMA[J-1]

Sofosbuvir

Structure of the active substance	
Molecular weight.	529.45 g/mol
Solubility in water (mg/mL @ 37 °C)	pH 2 (HCl) 2.0 pH 4.5 (Acetate buffer) 2.1 pH 6.8 (Phosphate buffer) 1.9 pH 7.7 (Unbuffered) 2.2
Pka.	9.3
Distribution coefficient.	log P = 1.62 (in n-octanol/0.15M KCl)
Solubility in other solvents (mg/mL @ ambient temp.)	Methanol 675 Acetone 313 Acetonitrile 235 Ethanol 204 2-Propanol 45 Ethyl acetate 23
Stability.	Sofosbuvir is stable at both long-term and accelerated conditions.
Possible chirality and its consequences.	Sofosbuvir has six stereocenters and is chirally pure.
Polymorphism.	Eight solid forms of sofosbuvir have been isolated in laboratory studies. Sofosbuvir Form II is a unsolvated polymorph and the designated commercial drug substance.

Endnotes

J-1: European Medicines Agency (2016). *Committee for Medicinal Products for Human Use (CHMP) Assessment report: Epclusa EMA/399285/2016*. Retrieved from http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004210/WC500211152.pdf.

Appendix K - Molecule Costing Spreadsheet

Chemical Name	Category	State	MW	Density (kg/m3)	Price ($/kg)	Target Amt		Price	
L-Alanine - HCl	Limiting Reactant	Aq	89.09	--	4.34	4,568.72	kg	19,828.22	$/batch
Isopropanol	Reactant	Liquid	60.1	786	0.96	127,363.63	L	96,103.50	$/batch
Thionyl Chloride	Solvent	Liquid	118.97	1640	0.64	5,276.49	L	5,538.21	$/batch
L-Alanine Isopropyl Ester - HCl	Product	Solid	167.8	--	--	5,312.88	kg	121,469.93	$/batch
								22.86	$/kg product
								34.71	$/kg sofos

Reaction 2a									
Chemical Name	**Category**	**State**	**MW**	**Density (kg/m3)**	**Price ($/kg)**	**Target Amt**		**Price**	
Phenyl Dichlorophosphate	Reactant	Solid	210.98	--	8.67	6,633.92	kg	57,516.12	$/batch
L-Alanine Isopropyl Ester	Reactant	Solid	167.8	--	22.86	5,312.88	kg	121,469.93	$/batch
DCM	Solvent	Liquid	84.93	1330	0.425	114,873.14	L	64,932.04	$/batch
DIEA	Solvent	Liquid	129.25	742	5.47	8,041.12	kg	43,984.93	$/batch

Reaction 2b									
2-Chloro-6-hydroxypyridine	Limiting Reactant	Solid	129.54	--	5	3,704.66	kg	18,523.29	$/batch
DCM	Solvent	Liquid	84.93	1330	0.425	57,436.57	L	32,466.02	$/batch
DIEA	Solvent	Liquid	129.25	742	5.47	4,020.56	kg	21,992.46	$/batch

Reaction 2d (Wash)									
Water for Injection (Salt wash)	Solvent	Liquid		1000	0.12	201,027.99	L	24,123.36	$/batch
Sodium Chloride					0.38	60,308.40	kg	22,917.19	$/batch
Anhydrous Sodium sulfate	Dessicant	Solid	142.036	--	0.1	2,371.00	kg	237.10	$/batch
A1 (Product)	Product	Solid	398.8	--	--	11,142.69	kg	408,162.44	$/batch
								36.63	$/kg prod
								116.62	$/kg sofos

Reaction 3a									
Chemical Name	**Category**	**State**	**MW**	**Density (kg/m3)**	**Price ($/kg)**	**Target Amt**		**Price**	
2'-deoxy-2'-fluoro-2'-methyluridine	Limiting Reactant	Solid	260	--	**888**	3,639.57	kg	3,231,941.36	$/batch
Intermediate A1	Reactant	Solid	398.8	--	36.63	11,142.69	kg	408,162.44	$/batch
DIEA	Solvent	Liquid	129.25	742	5.47	2,729.68	kg	14,931.35	$/batch
Zinc Chloride	Catalyst	Solid		--	0.9	2,883.66	kg	2,595.30	$/batch
THF	Solvent	Liquid		889	1.7	55,993.44	L	84,622.89	$/batch

Reaction 3b (Wash steps)									
Ethyl acetate	Solvent	Liquid		897	0.3	111,986.88	L	30,135.67	$/batch
Water for Injection	Solvent	Liquid		1000	0.12	55,993.44	L	6,719.21	$/batch
Ammonium chloride	Salt	Solid	53.489		0.135	19,597.70	kg	2,645.69	$/batch
Hydrochloric Acid 0.5 M	Solvent	Liquid		1000	0.155	55,993.44	L	8,678.98	$/batch
Water for Injection (for buffer)	Solvent	Liquid			0.12	55,993.44	L	6,719.21	$/batch
Sodium Carbonate	Salt	Solid	105.988		0.2	4,759.44	kg	951.89	$/batch
Sodium Bicarbonate	Salt	Solid	84.006	--	0.22	2,239.74	kg	492.74	$/batch
Water for Injection (for salt water)	Solvent	Liquid			0.12	55,993.44	L	6,719.21	$/batch
Sodium Chloride	Salt	Solid	58.44		0.38	16,798.03	kg	6,383.25	$/batch
Anhydrous Sodium Sulfate	Dessicant	Solid	142.036	--	0.1	2,500.00	kg	250.00	$/batch

Reaction 3c (Crystallization step)									
Acetone	Solvent	Liquid		791	0.6	6,999.18	L	3,321.81	$/batch
DCM	Solvent	Liquid	84.93	1330	0.425	55,993.44	L	31,650.29	$/batch
Sofosbuvir (Product)	Product	Solid	530	--	--	3,499.59	kg	3,846,921.30	$/batch
								1,099.12	$/kg sof

Raw material Costs	Category	State	MW	Density (kg/m3)	Price ($/kg)	Target Amt		Price ($)	
Nitrogen		Gas		1.2506	--	100,000,000.00	L		
Nitrogen		Liquid		807	0.106	154,969.02	L	16,426.72	$/batch
Ribavirin		Solid			44.182	5,160.00	kg	227,979.12	$/batch
Ethylene Glycol (101)		Liquid			0.75	4,463	kg	3,347.56	1-time cost
Propane (103)					0.4	649,088	kg	259,635.02	1-time cost
Propane (201)		Liquid	44.0956	490	0.4	154,682	kg	61,872.71	1 time cost
Propane (202)		Liquid	44.0956	490	0.4	26,249	kg	10,499.61	1 time cost
Brine (203) - 20%						17,250	kg		
Brine -Salt					0.38	3,450.00	kg	1,311.00	1 time cost
Brine -WFI					0.12	13,800.00	kg	1,656.00	1 time cost
Propane (Condense DCM - 208)		Liquid	44.0956	490	0.4	128,308.85	kg	51,323.54	1 time cost
Propane (304)		Liquid			0.4	448,020	kg	179,208.08	1-time cost
Sand		Solid			0.02976	152,781.28	kg	4,546.77	per year

Appendix L - Tabulated Data for Profitability Analysis

Appendix L-1 Input Summary

General Information

Process Title:	**Sofosbuvir Production**
Product:	**Sofosbuvir**
Plant Site Location:	**India**
Site Factor:	**1.00**
Operating Hours per Year:	**2880**
Operating Days Per Year:	**120**
Operating Factor:	**0.3288**

Product Information

This Process will Yield

	122	kg of Sofosbuvir per hour
	2,917	kg of Sofosbuvir per day
	350,000	kg of Sofosbuvir per year
Price	**$3,000.00**	**/kg**

Chronology

Year	Action	Distribution of Permanent Investment	Production Capacity	Sale Capacity	Depreciation 5 year MACRS	Product Price
0	Production	100%	100.0%	0.0%	20.00%	$3,000.00
1	Production	0%	100.0%	100.0%	32.00%	$3,000.00
2	Production	0%	100.0%	100.0%	19.20%	$3,000.00
3	Production	0%	100.0%	100.0%	11.52%	$3,000.00
4	Production	0%	100.0%	100.0%	11.52%	$3,000.00
5	Production	6%	100.0%	100.0%	5.76%	$3,000.00
6	Production	0%	100.0%	100.0%		$3,000.00
7	Production	0%	100.0%	100.0%		$3,000.00

8	Production	0%	100.0%	100.0%	$3,000.00
9	Production	0%	100.0%	100.0%	$3,000.00
10	Production	0%	0.0%	100.0%	$3,000.00

Equipment Costs

Equipment Description		Bare Module Cost
Agitator	Process Machinery	$345,600
Centrifugal Pumps	Process Machinery	$693,000
Ethylene Glycol Chiller	Process Machinery	$12,840
Heat Exchanger	Process Machinery	$114,437
100,000L Reaction Vessel	Process Machinery	$1,574,144
Distillation Column	Process Machinery	$1,039,168
85,000 L Reaction Vessel	Process Machinery	$1,482,624
85,000L Reaction Vessel	Process Machinery	$741,312
140,000L Reaction Vessel	Process Machinery	$1,847,872
Flash Vessel	Process Machinery	$457,600
400,000 L Wash Vessel	Process Machinery	$1,501,760
Packed Bed Drying Vessel	Process Machinery	$299,936
Condenser (Heat Exchanger)	Process Machinery	$213,975
100,000L Runaway Reaction Vessel	Process Machinery	$1,574,144
Brine Chiller	Process Machinery	$83,054
Propane Chiller	Process Machinery	$100,172
120,000L Reactor	Process Machinery	$804,960
192,000L Wash Vessel	Process Machinery	$2,113,280
Packed Bed Drying Vessel	Process Machinery	$200,096
Distillation Column	Process Machinery	$572,832
160,000L Mixing Vessel	Process Machinery	$986,752
Crystallization Unit	Process Machinery	$1,545,000
Drying Unit	Process Machinery	$35,638
Belt Conveyer	Process Machinery	$35,420
Screw Conveyer	Process Machinery	$94,800
Sprinkler s	Other Equipment	$516,810

Coolants	Other Equipment	$577,000
Total		***$19,564,226***

Raw Materials

	Raw Material:	Unit:	Required Ratio:		Cost of Raw Material:	
1	Materials 100	kg	1	kg per kg of Sofosbuvir	$34.710	per kg
2	Materials 200	kg	1	kg per kg of Sofosbuvir	$81.91	per kg
3	Materials 300	kg	1	kg per kg of Sofosbuvir	$982.50	per kg
4	Sand	kg	1	kg per kg of Sofosbuvir	$1.30	per kg
5	Nitrogen	kg	1	kg per kg of Sofosbuvir	$4.69	per kg
6	Ribavirin	kg	1	kg per kg of Sofosbuvir	$65.14	per kg
	Total Weighted Average:				$1170.250	per kg of Sofosbuvir

Byproducts

	Byproduct:	Unit:	Ratio to Product	Byproduct Selling Price	
	Total Weighted Average:			$0.00	per kg of Sofosbuvir

Utilities

	Utility:	Unit:	Required Ratio		Utility Cost	
1	Heating	unit	1	unit per kg of Sofosbuvir	$1.950	per unit
2	Cooling	unit	1	unit per kg of Sofosbuvir	$4.890	per unit
3	Transport	unit	1	unit per kg of Sofosbuvir	$9.000E-04	per unit
4	Stirring	unit	1	unit per kg of Sofosbuvir	$0.020	per unit
5	Waste Disposal	unit	1	unit per kg of Sofosbuvir	$17.640	per unit
6	Leasing Costs	unit	1	unit per kg of Sofosbuvir	$0.456	per unit
7	Formulation	unit	1	unit per kg of Sofosbuvir	$239.04	per unit
	Total Weighted Average:				$263.999	per kg of Sofosbuvir

Variable Costs

General Expenses:

Selling / Transfer Expenses:	**3.00%**	**of Sales**
Direct Research:	**0.00%**	**of Sales**
Allocated Research:	**0.00%**	**of Sales**

Administrative Expense:	**2.00%**	**of Sales**
Management Incentive Compensation:	**1.25%**	**of Sales**

Working Capital

Accounts Receivable	⇨	**30**	**Days**
Cash Reserves (excluding Raw Materials)	⇨	**30**	**Days**
Accounts Payable	⇨	**30**	**Days**
Sofosbuvir Inventory	⇨	**4**	**Days**
Raw Materials	⇨	**2**	**Days**

Total Permanent Investment

Cost of Site Preparations:	**5.00%**	**of Total Bare Module Costs**
Cost of Service Facilities:	**5.00%**	**of Total Bare Module Costs**
Allocated Costs for utility plants and related facilities:	**$0**	
Cost of Contingencies and Contractor Fees:	**18.00%**	**of Direct Permanent Investment**
Cost of Land:	**2.00%**	**of Total Depreciable Capital**
Cost of Royalties:	**$0**	
Cost of Plant Start-Up:	**2.00%**	**of Total Depreciable Capital**

Fixed Costs

Operations

Operators per Shift:	**4**	**(assuming 1 shifts)**
Direct Wages and Benefits:	**$34**	**/operator hour**

Direct Salaries and Benefits:	**15%**	**of Direct Wages and Benefits**
Operating Supplies and Services:	**6%**	**of Direct Wages and Benefits**
Technical Assistance to Manufacturing:	**$0.00**	**per year, for each Operator per Shift**
Control Laboratory:	**$0.00**	**per year, for each Operator per Shift**

Maintenance

Wages and Benefits:	**4.50%**	**of Total Depreciable Capital**
Salaries and Benefits:	**25%**	**of Maintenance Wages and Benefits**
Materials and Services:	**100%**	**of Maintenance Wages and Benefits**
Maintenance Overhead:	**5%**	**of Maintenance Wages and Benefits**

Operating Overhead

General Plant Overhead:	**7.10%**	**of Maintenance and Operations Wages and Benefits**
Mechanical Department Services:	**2.40%**	**of Maintenance and Operations Wages and Benefits**
Employee Relations Department:	**5.90%**	**of Maintenance and Operations Wages and Benefits**
Business Services:	**7.40%**	**of Maintenance and Operations Wages and Benefits**

Property Taxes and Insurance

Property Taxes and Insurance:	**2%**	**of Total Depreciable Capital**

Straight Line Depreciation

Direct Plant:	8.00%	**of Total Depreciable Capital, less 1.18 times the Allocated Costs for Utility Plants and Related Facilities**
Allocated Plant:	6.00%	**of 1.18 times the Allocated Costs for Utility Plants and Related Facilities**

Other Annual Expenses

Rental Fees (Office and Laboratory Space):	**$0**

Licensing Fees:	**$0**
Miscellaneous:	**$0**

Depletion Allowance

Annual Depletion Allowance:	**$0**

Appendix L-2 Cost Summary

Variable Cost Summary

Variable Costs at 100% Capacity:

General Expenses

	Selling / Transfer Expenses:		$31,500,000
	Direct Research:		$-
	Allocated Research:		$-
	Administrative Expense:		$21,000,000
	Management Incentive Compensation:		$13,125,000
Total General Expenses			$65,625,000
Raw Materials	$1,170.25	per kg of Sofosbuvir	$409,587,493
Byproducts	$0.00	per kg of Sofosbuvir	$0
Utilities	$264.00	per kg of Sofosbuvir	$92,399,577
Total Variable Costs			**$567,612,070**

Fixed Cost Summary

Operations

Direct Wages and Benefits	$281,500
Direct Salaries and Benefits	$42,225
Operating Supplies and Services	$16,890
Technical Assistance to Manufacturing	$-
Control Laboratory	$-
Total Operations	**$340,615**

Maintenance

	Wages and Benefits	$1,142,746
	Salaries and Benefits	$285,687
	Materials and Services	$1,142,746
	Maintenance Overhead	$57,137
	Total Maintenance	**$2,628,317**
Operating Overhead		
	General Plant Overhead:	$124,403
	Mechanical Department Services:	$42,052
	Employee Relations Department:	$103,377
	Business Services:	$129,660
	Total Operating Overhead	**$399,492**
Property Taxes and Insurance		
	Property Taxes and Insurance:	$507,887
Other Annual Expenses		
	Rental Fees (Office and Laboratory Space):	$-
	Licensing Fees:	$-
	Miscellaneous:	$-
	Total Other Annual Expenses	**$-**
Total Fixed Costs		**$3,876,311**

Investment Summary	
Total Bare Module Costs:	
Fabricated Equipment	$-
Process Machinery	$18,470,416
Spares	$-
Storage	$-
Other Equipment	$1,093,810

Catalysts	$-	
Computers, Software, Etc.	$-	
Total Bare Module Costs:		**$19,564,226**

Direct Permanent Investment

Cost of Site Preparations:	$978,211	
Cost of Service Facilities:	$978,211	
Allocated Costs for utility plants and related facilities:	$-	
Direct Permanent Investment		**$21,520,649**

Total Depreciable Capital

Cost of Contingencies & Contractor Fees	$3,873,717	
Total Depreciable Capital		**$25,394,365**

Total Permanent Investment

Cost of Land:	$507,887	
Cost of Royalties:	$-	
Cost of Plant Start-Up:	$507,887	
Total Permanent Investment - Unadjusted		$26,410,140
Site Factor		1.00
Total Permanent Investment		**$26,410,140**

Working Capital

	-1	**0**	**1**
Accounts Receivable	$86,301,370	$-	$-
Cash Reserves	$7,913,087	$-	$-
Accounts Payable	$(41,259,211)	$-	$-
Sofosbuvir Inventory	$11,506,849	$-	$-

	Raw Materials	$2,244,315	$-	$-
	Total	**$66,706,410**	**$-**	**$-**
	Present Value at 15%	*$76,712,371*	*$-*	*$-*

Total Capital Investment **$103,122,511**

Appendix L-3 Sensitivity Tables

Table L-1 Sensitivity of IRR and NPV to Sofosbuvir Sale Price

***Sofosbuvir* price/kg**	**IRR**	**NPV**
$1,500	-2.90%	($343MM)
$1,800	13.5%	($30MM)
$2,100	28.5%	$283MM
$2,400	42.5%	$596MM
$2,700	55.5%	$908MM
$3,000	**67.7%**	**$1,221MM**
$3,300	79.2%	$1,534MM
$3,600	90.0%	$1,847MM
$3,900	100%	$2,160MM
$4,200	110%	$2,473MM
$4,500	119%	$2,785MM

Table L-2 Sensitivity of IRR and NPV to Sofosbuvir Production Schedule

***Sofosbuvir* Production Schedule**	**IRR**	**NPV**
High	66.9%	$1,884MM
Base	**67.7%**	**$1,222MM**
Low	64.6%	$947MM

Table L-3 Sensitivity of IRR and NPV to Methyluridine Purchase Price

Methyluridine price/kg	**IRR**	**NPV**
$100	206%	$2,505MM

$200	178%	$2,342MM
$300	154%	$2,179MM
$400	134%	$2,016MM
$500	117%	$1,853MM
$600	102%	$1,690MM
$700	88.5%	$1,527MM
$800	76.9%	$1,365MM
$888	**67.7%**	**$1,222MM**
$900	66.5%	$1,202MM
$1,000	57.2%	$1,039MM
$1,100	48.9%	$877MM
$1,200	41.3%	$714MM
$1,300	34.4%	$551MM
$1,400	28.1%	$388MM
$1,500	22.3%	$225MM
$1,600	16.9%	$62MM
$1,700	12.0%	($100MM)

Table L-4 Sensitivity of IRR and NPV to Solvent Waste Disposal Cost

Solvent Disposal	IRR	NPV
With Organic Solvent Resale	67.7%	$1,221
Without Organic Solvent Resale	61.5%	$1,118

Table L-5 IRR and NPV with and without Runaway Reaction

Batch Interruption	IRR	NPV
Without	67.7%	$1,221 MM
With	67.5%	$1,216 MM

Appendix M - MSDS Sheets

Appendix M-1 MSDS of Starting Materials

SIGMA-ALDRICH sigma-aldrich.com

SAFETY DATA SHEET

Version 3.8
Revision Date 09/18/2015
Print Date 01/23/2017

1. PRODUCT AND COMPANY IDENTIFICATION

1.1 Product identifiers

Product name : L-Alanine

Product Number : A7627
Brand : Sigma

CAS-No. : 56-41-7

1.2 Relevant identified uses of the substance or mixture and uses advised against

Identified uses : Laboratory chemicals, Synthesis of substances

1.3 Details of the supplier of the safety data sheet

Company : Sigma-Aldrich
3050 Spruce Street
SAINT LOUIS MO 63103
USA

Telephone : +1 800-325-5832
Fax : +1 800-325-5052

1.4 Emergency telephone number

Emergency Phone # : +1-703-527-3887 (CHEMTREC)

2. HAZARDS IDENTIFICATION

2.1 Classification of the substance or mixture

Not a hazardous substance or mixture.

2.2 GHS Label elements, including precautionary statements

Not a hazardous substance or mixture.

2.3 Hazards not otherwise classified (HNOC) or not covered by GHS - none

3. COMPOSITION/INFORMATION ON INGREDIENTS

3.1 Substances

Synonyms : (S)-2-Aminopropionic acid
L-α-Aminopropionic acid

Formula : $C_3H_7NO_2$
Molecular weight : 89.09 g/mol
CAS-No. : 56-41-7
EC-No. : 200-273-8

No components need to be disclosed according to the applicable regulations.

4. FIRST AID MEASURES

4.1 Description of first aid measures

If inhaled
If breathed in, move person into fresh air. If not breathing, give artificial respiration.

In case of skin contact
Wash off with soap and plenty of water.

In case of eye contact
Flush eyes with water as a precaution.

If swallowed
Never give anything by mouth to an unconscious person. Rinse mouth with water.

4.2 Most important symptoms and effects, both acute and delayed
The most important known symptoms and effects are described in the labelling (see section 2.2) and/or in section 11

4.3 Indication of any immediate medical attention and special treatment needed
No data available

5. FIREFIGHTING MEASURES

5.1 Extinguishing media

Suitable extinguishing media
Use water spray, alcohol-resistant foam, dry chemical or carbon dioxide.

5.2 Special hazards arising from the substance or mixture
Carbon oxides, Nitrogen oxides (NOx)

5.3 Advice for firefighters
Wear self-contained breathing apparatus for firefighting if necessary.

5.4 Further information
No data available

6. ACCIDENTAL RELEASE MEASURES

6.1 Personal precautions, protective equipment and emergency procedures
Avoid dust formation. Avoid breathing vapours, mist or gas.
For personal protection see section 8.

6.2 Environmental precautions
No special environmental precautions required.

6.3 Methods and materials for containment and cleaning up
Sweep up and shovel. Keep in suitable, closed containers for disposal.

6.4 Reference to other sections
For disposal see section 13.

7. HANDLING AND STORAGE

7.1 Precautions for safe handling
Further processing of solid materials may result in the formation of combustible dusts. The potential for combustible dust formation should be taken into consideration before additional processing occurs.
Provide appropriate exhaust ventilation at places where dust is formed.
For precautions see section 2.2.

7.2 Conditions for safe storage, including any incompatibilities
Keep container tightly closed in a dry and well-ventilated place.
Storage class (TRGS 510): Non Combustible Solids

7.3 Specific end use(s)
Apart from the uses mentioned in section 1.2 no other specific uses are stipulated

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

8.1 Control parameters

Components with workplace control parameters
Contains no substances with occupational exposure limit values.

8.2 Exposure controls

Appropriate engineering controls
General industrial hygiene practice.

Personal protective equipment

Eye/face protection
Use equipment for eye protection tested and approved under appropriate government standards such as NIOSH (US) or EN 166(EU).

Skin protection
Handle with gloves. Gloves must be inspected prior to use. Use proper glove removal technique (without touching glove's outer surface) to avoid skin contact with this product. Dispose of contaminated gloves after use in accordance with applicable laws and good laboratory practices. Wash and dry hands.

Full contact
Material: Nitrile rubber
Minimum layer thickness: 0.11 mm
Break through time: 480 min
Material tested:Dermatril® (KCL 740 / Aldrich Z677272, Size M)

Splash contact
Material: Nitrile rubber
Minimum layer thickness: 0.11 mm
Break through time: 480 min
Material tested:Dermatril® (KCL 740 / Aldrich Z677272, Size M)

data source: KCL GmbH, D-36124 Eichenzell, phone +49 (0)6659 87300, e-mail sales@kcl.de, test method: EN374
If used in solution, or mixed with other substances, and under conditions which differ from EN 374, contact the supplier of the CE approved gloves. This recommendation is advisory only and must be evaluated by an industrial hygienist and safety officer familiar with the specific situation of anticipated use by our customers. It should not be construed as offering an approval for any specific use scenario.

Body Protection
Choose body protection in relation to its type, to the concentration and amount of dangerous substances, and to the specific work-place., The type of protective equipment must be selected according to the concentration and amount of the dangerous substance at the specific workplace.

Respiratory protection
Respiratory protection is not required. Where protection from nuisance levels of dusts are desired, use type N95 (US) or type P1 (EN 143) dust masks. Use respirators and components tested and approved under appropriate government standards such as NIOSH (US) or CEN (EU).

Control of environmental exposure
No special environmental precautions required.

9. PHYSICAL AND CHEMICAL PROPERTIES

9.1 Information on basic physical and chemical properties

a)	Appearance	Form: crystalline Colour: white
b)	Odour	odourless
c)	Odour Threshold	No data available
d)	pH	5.5 - 7 at 89.1 g/l at 25 °C (77 °F)
e)	Melting point/freezing point	314.5 °C (598.1 °F)
f)	Initial boiling point and boiling range	No data available
g)	Flash point	No data available
h)	Evaporation rate	No data available

i)	Flammability (solid, gas)	No data available
j)	Upper/lower flammability or explosive limits	No data available
k)	Vapour pressure	No data available
l)	Vapour density	No data available
m)	Relative density	1.432 g/cm3 at 20 °C (68 °F)
n)	Water solubility	89.1 g/l at 20 °C (68 °F) - completely soluble
o)	Partition coefficient: n-octanol/water	log Pow: -2.74 at 20 °C (68 °F)
p)	Auto-ignition temperature	No data available
q)	Decomposition temperature	No data available
r)	Viscosity	No data available
s)	Explosive properties	No data available
t)	Oxidizing properties	No data available

9.2 Other safety information
No data available

10. STABILITY AND REACTIVITY

10.1 Reactivity
No data available

10.2 Chemical stability
Stable under recommended storage conditions.

10.3 Possibility of hazardous reactions
No data available

10.4 Conditions to avoid
No data available

10.5 Incompatible materials
Strong oxidizing agents

10.6 Hazardous decomposition products
Other decomposition products - No data available
In the event of fire: see section 5

11. TOXICOLOGICAL INFORMATION

11.1 Information on toxicological effects

Acute toxicity
LD50 Oral - Rat - male and female - > 5,110 mg/kg

Inhalation: No data available

Dermal: No data available

No data available

Skin corrosion/irritation
No data available

Serious eye damage/eye irritation
No data available

Respiratory or skin sensitisation
No data available

Germ cell mutagenicity
No data available

reverse mutation assay
Escherichia coli
Result: negative

Carcinogenicity

IARC: No component of this product present at levels greater than or equal to 0.1% is identified as probable, possible or confirmed human carcinogen by IARC.

ACGIH: No component of this product present at levels greater than or equal to 0.1% is identified as a carcinogen or potential carcinogen by ACGIH.

NTP: No component of this product present at levels greater than or equal to 0.1% is identified as a known or anticipated carcinogen by NTP.

OSHA: No component of this product present at levels greater than or equal to 0.1% is identified as a carcinogen or potential carcinogen by OSHA.

Reproductive toxicity
No data available

No data available

Specific target organ toxicity - single exposure
No data available

Specific target organ toxicity - repeated exposure
No data available

Aspiration hazard
No data available

Additional Information
RTECS: Not available

To the best of our knowledge, the chemical, physical, and toxicological properties have not been thoroughly investigated.

12. ECOLOGICAL INFORMATION

12.1 Toxicity
No data available

Toxicity to daphnia and other aquatic invertebrates	static test EC50 - Daphnia magna (Water flea) - > 100 mg/l - 48 h (OECD Test Guideline 202)

12.2 Persistence and degradability
No data available

12.3 Bioaccumulative potential
No data available

12.4 Mobility in soil
No data available

12.5 Results of PBT and vPvB assessment
PBT/vPvB assessment not available as chemical safety assessment not required/not conducted

12.6 Other adverse effects

No data available

13. DISPOSAL CONSIDERATIONS

13.1 Waste treatment methods

Product
Offer surplus and non-recyclable solutions to a licensed disposal company.

Contaminated packaging
Dispose of as unused product.

14. TRANSPORT INFORMATION

DOT (US)
Not dangerous goods

IMDG
Not dangerous goods

IATA
Not dangerous goods

15. REGULATORY INFORMATION

SARA 302 Components
No chemicals in this material are subject to the reporting requirements of SARA Title III, Section 302.

SARA 313 Components
This material does not contain any chemical components with known CAS numbers that exceed the threshold (De Minimis) reporting levels established by SARA Title III, Section 313.

SARA 311/312 Hazards
No SARA Hazards

Massachusetts Right To Know Components
No components are subject to the Massachusetts Right to Know Act.

Pennsylvania Right To Know Components

	CAS-No.	Revision Date
L-Alanine	56-41-7	

New Jersey Right To Know Components

	CAS-No.	Revision Date
L-Alanine	56-41-7	

California Prop. 65 Components
This product does not contain any chemicals known to State of California to cause cancer, birth defects, or any other reproductive harm.

16. OTHER INFORMATION

HMIS Rating

Health hazard:	0
Chronic Health Hazard:	
Flammability:	0
Physical Hazard	0

NFPA Rating

Health hazard:	0
Fire Hazard:	0
Reactivity Hazard:	0

Further information

The above information is believed to be correct but does not purport to be all inclusive and shall be used only as a guide. The information in this document is based on the present state of our knowledge and is applicable to the product with regard to appropriate safety precautions. It does not represent any guarantee of the properties of the product. Sigma-Aldrich Corporation and its Affiliates shall not be held liable for any damage resulting from handling or from contact with the above product. See www.sigma-aldrich.com and/or the reverse side of invoice or packing slip for additional terms and conditions of sale.

Preparation Information

Sigma-Aldrich Corporation
Product Safety – Americas Region
1-800-521-8956

Version: 3.6 Revision Date: 09/18/2015 Print Date: 01/23/2017

SAFETY DATA SHEET

Version 4.3
Revision Date 07/01/2014
Print Date 02/14/2017

1. PRODUCT AND COMPANY IDENTIFICATION

1.1 Product identifiers

Product name	:	6-Chloro-2-hydroxypyridine
Product Number	:	136786
Brand	:	Aldrich
CAS-No.	:	16879-02-0

1.2 Relevant identified uses of the substance or mixture and uses advised against

Identified uses	:	Laboratory chemicals, Manufacture of substances

1.3 Details of the supplier of the safety data sheet

Company	:	Sigma-Aldrich 3050 Spruce Street SAINT LOUIS MO 63103 USA
Telephone	:	+1 800-325-5832
Fax	:	+1 800-325-5052

1.4 Emergency telephone number

Emergency Phone #	:	+1-703-527-3887 (CHEMTREC)

2. HAZARDS IDENTIFICATION

2.1 Classification of the substance or mixture

GHS Classification in accordance with 29 CFR 1910 (OSHA HCS)
Skin irritation (Category 2), H315
Eye irritation (Category 2A), H319
Specific target organ toxicity - single exposure (Category 3), Respiratory system, H335

For the full text of the H-Statements mentioned in this Section, see Section 16.

2.2 GHS Label elements, including precautionary statements

Pictogram

Signal word: Warning

Hazard statement(s)

H315	Causes skin irritation.
H319	Causes serious eye irritation.
H335	May cause respiratory irritation.

Precautionary statement(s)

P261	Avoid breathing dust/ fume/ gas/ mist/ vapours/ spray.
P264	Wash skin thoroughly after handling.
P271	Use only outdoors or in a well-ventilated area.
P280	Wear protective gloves/ eye protection/ face protection.
P302 + P352	IF ON SKIN: Wash with plenty of soap and water.
P304 + P340	IF INHALED: Remove victim to fresh air and keep at rest in a position comfortable for breathing.
P305 + P351 + P338	IF IN EYES: Rinse cautiously with water for several minutes. Remove

	contact lenses, if present and easy to do. Continue rinsing.
P312	Call a POISON CENTER or doctor/ physician if you feel unwell.
P321	Specific treatment (see supplemental first aid instructions on this label).
P332 + P313	If skin irritation occurs: Get medical advice/ attention.
P337 + P313	If eye irritation persists: Get medical advice/ attention.
P362	Take off contaminated clothing and wash before reuse.
P403 + P233	Store in a well-ventilated place. Keep container tightly closed.
P405	Store locked up.
P501	Dispose of contents/ container to an approved waste disposal plant.

2.3 Hazards not otherwise classified (HNOC) or not covered by GHS - none

3. COMPOSITION/INFORMATION ON INGREDIENTS

3.1 Substances

Synonyms : 6-Chloro-2-pyridinol

Formula : C_5H_4ClNO

Molecular Weight : 129.54 g/mol

CAS-No. : 16879-02-0

EC-No. : 240-909-1

Hazardous components

Component	Classification	Concentration
6-Chloropyridin-2-ol		
	Skin Irrit. 2; Eye Irrit. 2A; STOT SE 3; H315, H319, H335	-

For the full text of the H-Statements mentioned in this Section, see Section 16.

4. FIRST AID MEASURES

4.1 Description of first aid measures

General advice
Consult a physician. Show this safety data sheet to the doctor in attendance.Move out of dangerous area.

If inhaled
If breathed in, move person into fresh air. If not breathing, give artificial respiration. Consult a physician.

In case of skin contact
Wash off with soap and plenty of water. Consult a physician.

In case of eye contact
Rinse thoroughly with plenty of water for at least 15 minutes and consult a physician.

If swallowed
Never give anything by mouth to an unconscious person. Rinse mouth with water. Consult a physician.

4.2 Most important symptoms and effects, both acute and delayed
The most important known symptoms and effects are described in the labelling (see section 2.2) and/or in section 11

4.3 Indication of any immediate medical attention and special treatment needed
no data available

5. FIREFIGHTING MEASURES

5.1 Extinguishing media

Suitable extinguishing media
Use water spray, alcohol-resistant foam, dry chemical or carbon dioxide.

5.2 Special hazards arising from the substance or mixture
Carbon oxides, nitrogen oxides (NOx), Hydrogen chloride gas

5.3 Advice for firefighters
Wear self contained breathing apparatus for fire fighting if necessary.

5.4 Further information
no data available

6. ACCIDENTAL RELEASE MEASURES

6.1 Personal precautions, protective equipment and emergency procedures
Use personal protective equipment. Avoid dust formation. Avoid breathing vapours, mist or gas. Ensure adequate ventilation. Evacuate personnel to safe areas. Avoid breathing dust.
For personal protection see section 8.

6.2 Environmental precautions
Do not let product enter drains.

6.3 Methods and materials for containment and cleaning up
Pick up and arrange disposal without creating dust. Sweep up and shovel. Keep in suitable, closed containers for disposal.

6.4 Reference to other sections
For disposal see section 13.

7. HANDLING AND STORAGE

7.1 Precautions for safe handling
Avoid contact with skin and eyes. Avoid formation of dust and aerosols.
Provide appropriate exhaust ventilation at places where dust is formed. Normal measures for preventive fire protection.
For precautions see section 2.2.

7.2 Conditions for safe storage, including any incompatibilities
Keep container tightly closed in a dry and well-ventilated place.

Keep in a dry place.

7.3 Specific end use(s)
Apart from the uses mentioned in section 1.2 no other specific uses are stipulated

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

8.1 Control parameters

Components with workplace control parameters
Contains no substances with occupational exposure limit values.

8.2 Exposure controls

Appropriate engineering controls
Handle in accordance with good industrial hygiene and safety practice. Wash hands before breaks and at the end of workday.

Personal protective equipment

Eye/face protection
Safety glasses with side-shields conforming to EN166 Use equipment for eye protection tested and approved under appropriate government standards such as NIOSH (US) or EN 166(EU).

Skin protection
Handle with gloves. Gloves must be inspected prior to use. Use proper glove removal technique (without touching glove's outer surface) to avoid skin contact with this product. Dispose of contaminated gloves after use in accordance with applicable laws and good laboratory practices. Wash and dry hands.

Body Protection
impervious clothing, The type of protective equipment must be selected according to the concentration and amount of the dangerous substance at the specific workplace.

Respiratory protection
For nuisance exposures use type P95 (US) or type P1 (EU EN 143) particle respirator.For higher level protection use type OV/AG/P99 (US) or type ABEK-P2 (EU EN 143) respirator cartridges. Use respirators and components tested and approved under appropriate government standards such as NIOSH (US) or CEN (EU).

Control of environmental exposure
Do not let product enter drains.

9. PHYSICAL AND CHEMICAL PROPERTIES

9.1 Information on basic physical and chemical properties

a)	Appearance	Form: powder
b)	Odour	no data available
c)	Odour Threshold	no data available
d)	pH	no data available
e)	Melting point/freezing point	Melting point/range: 128 - 130 °C (262 - 266 °F) - lit.
f)	Initial boiling point and boiling range	no data available
g)	Flash point	no data available
h)	Evapouration rate	no data available
i)	Flammability (solid, gas)	no data available
j)	Upper/lower flammability or explosive limits	no data available
k)	Vapour pressure	no data available
l)	Vapour density	no data available
m)	Relative density	no data available
n)	Water solubility	no data available
o)	Partition coefficient: n-octanol/water	no data available
p)	Auto-ignition temperature	no data available
q)	Decomposition temperature	no data available
r)	Viscosity	no data available
s)	Explosive properties	no data available
t)	Oxidizing properties	no data available

9.2 Other safety information
no data available

10. STABILITY AND REACTIVITY

10.1 Reactivity
no data available

10.2 Chemical stability
Stable under recommended storage conditions.

10.3 Possibility of hazardous reactions
no data available

10.4 Conditions to avoid
no data available

10.5 Incompatible materials
Strong oxidizing agents, Strong acids

10.6 Hazardous decomposition products
Other decomposition products - no data available
In the event of fire: see section 5

11. TOXICOLOGICAL INFORMATION

11.1 Information on toxicological effects

Acute toxicity
no data available

Dermal: no data available

no data available

Skin corrosion/irritation
no data available

Serious eye damage/eye irritation
no data available

Respiratory or skin sensitisation
no data available

Germ cell mutagenicity
no data available

Carcinogenicity

IARC: No component of this product present at levels greater than or equal to 0.1% is identified as probable, possible or confirmed human carcinogen by IARC.

ACGIH: No component of this product present at levels greater than or equal to 0.1% is identified as a carcinogen or potential carcinogen by ACGIH.

NTP: No component of this product present at levels greater than or equal to 0.1% is identified as a known or anticipated carcinogen by NTP.

OSHA: No component of this product present at levels greater than or equal to 0.1% is identified as a carcinogen or potential carcinogen by OSHA.

Reproductive toxicity
no data available

no data available

Specific target organ toxicity - single exposure
Inhalation - May cause respiratory irritation.

Specific target organ toxicity - repeated exposure
no data available

Aspiration hazard
no data available

Additional Information
RTECS: Not available

To the best of our knowledge, the chemical, physical, and toxicological properties have not been thoroughly investigated.

12. ECOLOGICAL INFORMATION

12.1 Toxicity

Toxicity to fish	LC50 - Pimephales promelas (fathead minnow) - 214 mg/l - 96 h

12.2 Persistence and degradability
no data available

12.3 Bioaccumulative potential
no data available

12.4 Mobility in soil
no data available

12.5 Results of PBT and vPvB assessment
PBT/vPvB assessment not available as chemical safety assessment not required/not conducted

12.6 Other adverse effects

no data available

13. DISPOSAL CONSIDERATIONS

13.1 Waste treatment methods

Product
Offer surplus and non-recyclable solutions to a licensed disposal company. Contact a licensed professional waste disposal service to dispose of this material. Dissolve or mix the material with a combustible solvent and burn in a chemical incinerator equipped with an afterburner and scrubber.

Contaminated packaging
Dispose of as unused product.

14. TRANSPORT INFORMATION

DOT (US)
Not dangerous goods

IMDG
Not dangerous goods

IATA
Not dangerous goods

15. REGULATORY INFORMATION

SARA 302 Components
SARA 302: No chemicals in this material are subject to the reporting requirements of SARA Title III, Section 302.

SARA 313 Components
SARA 313: This material does not contain any chemical components with known CAS numbers that exceed the threshold (De Minimis) reporting levels established by SARA Title III, Section 313.

SARA 311/312 Hazards
Acute Health Hazard

Massachusetts Right To Know Components
No components are subject to the Massachusetts Right to Know Act.

Pennsylvania Right To Know Components

	CAS-No.	Revision Date
6-Chloropyridin-2-ol	16879-02-0	

New Jersey Right To Know Components

	CAS-No.	Revision Date
6-Chloropyridin-2-ol	16879-02-0	

California Prop. 65 Components
This product does not contain any chemicals known to State of California to cause cancer, birth defects, or any other reproductive harm.

16. OTHER INFORMATION

Full text of H-Statements referred to under sections 2 and 3.

Eye Irrit.	Eye irritation
H315	Causes skin irritation.
H319	Causes serious eye irritation.
H335	May cause respiratory irritation.
Skin Irrit.	Skin irritation
STOT SE	Specific target organ toxicity - single exposure

HMIS Rating

Health hazard:	2
Chronic Health Hazard:	
Flammability:	0
Physical Hazard	0

NFPA Rating

Health hazard:	2
Fire Hazard:	0
Reactivity Hazard:	0

Further information

The above information is believed to be correct but does not purport to be all inclusive and shall be used only as a guide. The information in this document is based on the present state of our knowledge and is applicable to the product with regard to appropriate safety precautions. It does not represent any guarantee of the properties of the product. Sigma-Aldrich Corporation and its Affiliates shall not be held liable for any damage resulting from handling or from contact with the above product. See www.sigma-aldrich.com and/or the reverse side of invoice or packing slip for additional terms and conditions of sale.

Preparation Information

Sigma-Aldrich Corporation
Product Safety – Americas Region
1-800-521-8956

Version: 4.3 Revision Date: 07/01/2014 Print Date: 02/14/2017

SAFETY DATA SHEET

Version 4.3
Revision Date 07/09/2014
Print Date 01/23/2017

1. PRODUCT AND COMPANY IDENTIFICATION

1.1 Product identifiers

Product name	:	Phenyl dichlorophosphate
Product Number	:	P22389
Brand	:	Aldrich
CAS-No.	:	770-12-7

1.2 Relevant identified uses of the substance or mixture and uses advised against

Identified uses	:	Laboratory chemicals, Manufacture of substances

1.3 Details of the supplier of the safety data sheet

Company	:	Sigma-Aldrich 3050 Spruce Street SAINT LOUIS MO 63103 USA
Telephone	:	+1 800-325-5832
Fax	:	+1 800-325-5052

1.4 Emergency telephone number

Emergency Phone #	:	+1-703-527-3887 (CHEMTREC)

2. HAZARDS IDENTIFICATION

2.1 Classification of the substance or mixture

GHS Classification in accordance with 29 CFR 1910 (OSHA HCS)
Skin corrosion (Category 1B), H314
Serious eye damage (Category 1), H318

For the full text of the H-Statements mentioned in this Section, see Section 16.

2.2 GHS Label elements, including precautionary statements

Pictogram

Signal word: Danger

Hazard statement(s)

H314	Causes severe skin burns and eye damage.

Precautionary statement(s)

P264	Wash skin thoroughly after handling.
P280	Wear protective gloves/ protective clothing/ eye protection/ face protection.
P301 + P330 + P331	IF SWALLOWED: rinse mouth. Do NOT induce vomiting.
P303 + P361 + P353	IF ON SKIN (or hair): Remove/ Take off immediately all contaminated clothing. Rinse skin with water/ shower.
P304 + P340	IF INHALED: Remove victim to fresh air and keep at rest in a position comfortable for breathing.
P305 + P351 + P338	IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
P310	Immediately call a POISON CENTER or doctor/ physician.

P321	Specific treatment (see supplemental first aid instructions on this label).
P363	Wash contaminated clothing before reuse.
P405	Store locked up.
P501	Dispose of contents/container to an approved waste disposal plant.

2.3 Hazards not otherwise classified (HNOC) or not covered by GHS - none

3. COMPOSITION/INFORMATION ON INGREDIENTS

3.1 Substances

Synonyms : Phenyl phosphodichloridate
Phenyl phosphoryl dichloride
Phenyl phosphorodichloridate

Formula : $C_6H_5Cl_2O_2P$
Molecular Weight : 210.98 g/mol
CAS-No. : 770-12-7
EC-No. : 212-220-6

Hazardous components

Component	Classification	Concentration
Phenyl phosphorodichloridate		
	Skin Corr. 1B; Eye Dam. 1; H314	-

For the full text of the H-Statements mentioned in this Section, see Section 16.

4. FIRST AID MEASURES

4.1 Description of first aid measures

General advice
Consult a physician. Show this safety data sheet to the doctor in attendance. Move out of dangerous area.

If inhaled
If breathed in, move person into fresh air. If not breathing, give artificial respiration. Consult a physician.

In case of skin contact
Take off contaminated clothing and shoes immediately. Wash off with soap and plenty of water. Consult a physician.

In case of eye contact
Rinse thoroughly with plenty of water for at least 15 minutes and consult a physician. Continue rinsing eyes during transport to hospital.

If swallowed
Do NOT induce vomiting. Never give anything by mouth to an unconscious person. Rinse mouth with water. Consult a physician.

4.2 Most important symptoms and effects, both acute and delayed
The most important known symptoms and effects are described in the labelling (see section 2.2) and/or in section 11

4.3 Indication of any immediate medical attention and special treatment needed
no data available

5. FIREFIGHTING MEASURES

5.1 Extinguishing media

Suitable extinguishing media
Use water spray, alcohol-resistant foam, dry chemical or carbon dioxide.

5.2 Special hazards arising from the substance or mixture
Carbon oxides, Oxides of phosphorus, Hydrogen chloride gas

5.3 Advice for firefighters
Wear self contained breathing apparatus for fire fighting if necessary.

5.4 Further information
no data available

6. ACCIDENTAL RELEASE MEASURES

6.1 Personal precautions, protective equipment and emergency procedures
Use personal protective equipment. Avoid breathing vapours, mist or gas. Ensure adequate ventilation. Evacuate personnel to safe areas.
For personal protection see section 8.

6.2 Environmental precautions
Do not let product enter drains.

6.3 Methods and materials for containment and cleaning up
Soak up with inert absorbent material and dispose of as hazardous waste. Keep in suitable, closed containers for disposal.

6.4 Reference to other sections
For disposal see section 13.

7. HANDLING AND STORAGE

7.1 Precautions for safe handling
Avoid inhalation of vapour or mist.
Normal measures for preventive fire protection.
For precautions see section 2.2.

7.2 Conditions for safe storage, including any incompatibilities
Keep container tightly closed in a dry and well-ventilated place. Containers which are opened must be carefully resealed and kept upright to prevent leakage.

Moisture sensitive.

7.3 Specific end use(s)
Apart from the uses mentioned in section 1.2 no other specific uses are stipulated

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

8.1 Control parameters

Components with workplace control parameters
Contains no substances with occupational exposure limit values.

8.2 Exposure controls

Appropriate engineering controls
Handle in accordance with good industrial hygiene and safety practice. Wash hands before breaks and at the end of workday.

Personal protective equipment

Eye/face protection
Tightly fitting safety goggles. Faceshield (8-inch minimum). Use equipment for eye protection tested and approved under appropriate government standards such as NIOSH (US) or EN 166(EU).

Skin protection
Handle with gloves. Gloves must be inspected prior to use. Use proper glove removal technique (without touching glove's outer surface) to avoid skin contact with this product. Dispose of contaminated gloves after use in accordance with applicable laws and good laboratory practices. Wash and dry hands.

Body Protection
Complete suit protecting against chemicals, The type of protective equipment must be selected according to the concentration and amount of the dangerous substance at the specific workplace.

Respiratory protection
Where risk assessment shows air-purifying respirators are appropriate use a full-face respirator with multi-purpose combination (US) or type ABEK (EN 14387) respirator cartridges as a backup to engineering controls. If the respirator is the sole means of protection, use a full-face supplied air respirator. Use respirators and components tested and approved under appropriate government standards such as NIOSH (US) or CEN (EU).

Control of environmental exposure
Do not let product enter drains.

9. PHYSICAL AND CHEMICAL PROPERTIES

9.1 Information on basic physical and chemical properties

a)	Appearance	Form: clear, liquid Colour: colourless
b)	Odour	no data available
c)	Odour Threshold	no data available
d)	pH	no data available
e)	Melting point/freezing point	no data available
f)	Initial boiling point and boiling range	241 - 243 °C (466 - 469 °F) - lit.
g)	Flash point	113 °C (235 °F) - closed cup
h)	Evapouration rate	no data available
i)	Flammability (solid, gas)	no data available
j)	Upper/lower flammability or explosive limits	no data available
k)	Vapour pressure	no data available
l)	Vapour density	no data available
m)	Relative density	1.412 g/cm3 at 25 °C (77 °F)
n)	Water solubility	no data available
o)	Partition coefficient: n-octanol/water	no data available
p)	Auto-ignition temperature	no data available
q)	Decomposition temperature	no data available
r)	Viscosity	no data available
s)	Explosive properties	no data available
t)	Oxidizing properties	no data available

9.2 Other safety information
no data available

10. STABILITY AND REACTIVITY

10.1 Reactivity
no data available

10.2 Chemical stability
Stable under recommended storage conditions.

10.3 Possibility of hazardous reactions
no data available

10.4 Conditions to avoid
no data available

10.5 Incompatible materials
Strong bases, Strong oxidizing agents, Alcohols

10.6 Hazardous decomposition products
Other decomposition products - no data available
In the event of fire: see section 5

11. TOXICOLOGICAL INFORMATION

11.1 Information on toxicological effects

Acute toxicity
no data available

Dermal: no data available

no data available

Skin corrosion/irritation
no data available

Serious eye damage/eye irritation
no data available

Respiratory or skin sensitisation
no data available

Germ cell mutagenicity
no data available

Carcinogenicity

IARC: No component of this product present at levels greater than or equal to 0.1% is identified as probable, possible or confirmed human carcinogen by IARC.

ACGIH: No component of this product present at levels greater than or equal to 0.1% is identified as a carcinogen or potential carcinogen by ACGIH.

NTP: No component of this product present at levels greater than or equal to 0.1% is identified as a known or anticipated carcinogen by NTP.

OSHA: No component of this product present at levels greater than or equal to 0.1% is identified as a carcinogen or potential carcinogen by OSHA.

Reproductive toxicity
no data available

no data available

Specific target organ toxicity - single exposure
no data available

Specific target organ toxicity - repeated exposure
no data available

Aspiration hazard
no data available

Additional Information
RTECS: TD4393000

Material is extremely destructive to tissue of the mucous membranes and upper respiratory tract, eyes, and skin., Cough, Shortness of breath, Headache, Nausea

12. ECOLOGICAL INFORMATION

12.1 Toxicity
no data available

12.2 Persistence and degradability
no data available

12.3 Bioaccumulative potential
no data available

12.4 Mobility in soil
no data available

12.5 Results of PBT and vPvB assessment
PBT/vPvB assessment not available as chemical safety assessment not required/not conducted

12.6 Other adverse effects

no data available

13. DISPOSAL CONSIDERATIONS

13.1 Waste treatment methods

Product
Offer surplus and non-recyclable solutions to a licensed disposal company. Contact a licensed professional waste disposal service to dispose of this material. Dissolve or mix the material with a combustible solvent and burn in a chemical incinerator equipped with an afterburner and scrubber.

Contaminated packaging
Dispose of as unused product.

14. TRANSPORT INFORMATION

DOT (US)
UN number: 3265 Class: 8 Packing group: II
Proper shipping name: Corrosive liquid, acidic, organic, n.o.s. (Phenyl phosphorodichloridate)
Marine pollutant: No
Poison Inhalation Hazard: No

IMDG
UN number: 3265 Class: 8 Packing group: II EMS-No: F-A, S-B
Proper shipping name: CORROSIVE LIQUID, ACIDIC, ORGANIC, N.O.S. (Phenyl phosphorodichloridate)
Marine pollutant: No

IATA
UN number: 3265 Class: 8 Packing group: II
Proper shipping name: Corrosive liquid, acidic, organic, n.o.s. (Phenyl phosphorodichloridate)

15. REGULATORY INFORMATION

SARA 302 Components
SARA 302: No chemicals in this material are subject to the reporting requirements of SARA Title III, Section 302.

SARA 313 Components
SARA 313: This material does not contain any chemical components with known CAS numbers that exceed the threshold (De Minimis) reporting levels established by SARA Title III, Section 313.

SARA 311/312 Hazards
Acute Health Hazard

Massachusetts Right To Know Components
No components are subject to the Massachusetts Right to Know Act.

Pennsylvania Right To Know Components

	CAS-No.	Revision Date
Phenyl phosphorodichloridate	770-12-7	

New Jersey Right To Know Components

	CAS-No.	Revision Date
Phenyl phosphorodichloridate	770-12-7	

California Prop. 65 Components
This product does not contain any chemicals known to State of California to cause cancer, birth defects, or any other reproductive harm.

16. OTHER INFORMATION

Full text of H-Statements referred to under sections 2 and 3.

Eye Dam.	Serious eye damage
H314	Causes severe skin burns and eye damage.
H318	Causes serious eye damage.
Skin Corr.	Skin corrosion

HMIS Rating

Health hazard:	3
Chronic Health Hazard:	
Flammability:	1
Physical Hazard	0

NFPA Rating

Health hazard:	3
Fire Hazard:	1
Reactivity Hazard:	0

Further information

The above information is believed to be correct but does not purport to be all inclusive and shall be used only as a guide. The information in this document is based on the present state of our knowledge and is applicable to the product with regard to appropriate safety precautions. It does not represent any guarantee of the properties of the product. Sigma-Aldrich Corporation and its Affiliates shall not be held liable for any damage resulting from handling or from contact with the above product. See www.sigma-aldrich.com and/or the reverse side of invoice or packing slip for additional terms and conditions of sale.

Preparation Information
Sigma-Aldrich Corporation
Product Safety – Americas Region
1-800-521-8956

Version: 4.3 Revision Date: 07/09/2014 Print Date: 01/23/2017

Material Safety Data Sheet
Acetone MSDS

Section 1: Chemical Product and Company Identification

Product Name: Acetone

Catalog Codes: SLA3502, SLA1645, SLA3151, SLA3808

CAS#: 67-64-1

RTECS: AL3150000

TSCA: TSCA 8(b) inventory: Acetone

CI#: Not applicable.

Synonym: 2-propanone; Dimethyl Ketone; Dimethylformaldehyde; Pyroacetic Acid

Chemical Name: Acetone

Chemical Formula: C3-H6-O

Contact Information:

Sciencelab.com, Inc.
14025 Smith Rd.
Houston, Texas 77396

US Sales: **1-800-901-7247**
International Sales: **1-281-441-4400**

Order Online: ScienceLab.com

CHEMTREC (24HR Emergency Telephone), call: 1-800-424-9300

International CHEMTREC, call: 1-703-527-3887

For non-emergency assistance, call: 1-281-441-4400

Section 2: Composition and Information on Ingredients

Composition:

Name	CAS #	% by Weight
Acetone	67-64-1	100

Toxicological Data on Ingredients: Acetone: ORAL (LD50): Acute: 5800 mg/kg [Rat]. 3000 mg/kg [Mouse]. 5340 mg/kg [Rabbit]. VAPOR (LC50): Acute: 50100 mg/m 8 hours [Rat]. 44000 mg/m 4 hours [Mouse].

Section 3: Hazards Identification

Potential Acute Health Effects:
Hazardous in case of skin contact (irritant), of eye contact (irritant), of ingestion, of inhalation. Slightly hazardous in case of skin contact (permeator).

Potential Chronic Health Effects:
CARCINOGENIC EFFECTS: A4 (Not classifiable for human or animal.) by ACGIH. MUTAGENIC EFFECTS: Not available. TERATOGENIC EFFECTS: Not available. DEVELOPMENTAL TOXICITY: Classified Reproductive system/toxin/female, Reproductive system/toxin/male [SUSPECTED]. The substance is toxic to central nervous system (CNS). The substance may be toxic to kidneys, the reproductive system, liver, skin. Repeated or prolonged exposure to the substance can produce target organs damage.

Section 4: First Aid Measures

Eye Contact:
Check for and remove any contact lenses. Immediately flush eyes with running water for at least 15 minutes, keeping eyelids open. Cold water may be used. Get medical attention.

Skin Contact:
In case of contact, immediately flush skin with plenty of water. Cover the irritated skin with an emollient. Remove contaminated clothing and shoes. Cold water may be used.Wash clothing before reuse. Thoroughly clean shoes before reuse. Get medical attention.

Serious Skin Contact:
Wash with a disinfectant soap and cover the contaminated skin with an anti-bacterial cream. Seek medical attention.

Inhalation:
If inhaled, remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Get medical attention if symptoms appear.

Serious Inhalation:
Evacuate the victim to a safe area as soon as possible. Loosen tight clothing such as a collar, tie, belt or waistband. If breathing is difficult, administer oxygen. If the victim is not breathing, perform mouth-to-mouth resuscitation. Seek medical attention.

Ingestion:
Do NOT induce vomiting unless directed to do so by medical personnel. Never give anything by mouth to an unconscious person. Loosen tight clothing such as a collar, tie, belt or waistband. Get medical attention if symptoms appear.

Serious Ingestion: Not available.

Section 5: Fire and Explosion Data

Flammability of the Product: Flammable.

Auto-Ignition Temperature: 465°C (869°F)

Flash Points: CLOSED CUP: -20°C (-4°F). OPEN CUP: -9°C (15.8°F) (Cleveland).

Flammable Limits: LOWER: 2.6% UPPER: 12.8%

Products of Combustion: These products are carbon oxides (CO, CO2).

Fire Hazards in Presence of Various Substances: Highly flammable in presence of open flames and sparks, of heat.

Explosion Hazards in Presence of Various Substances:
Risks of explosion of the product in presence of mechanical impact: Not available. Slightly explosive in presence of open flames and sparks, of oxidizing materials, of acids.

Fire Fighting Media and Instructions:
Flammable liquid, soluble or dispersed in water. SMALL FIRE: Use DRY chemical powder. LARGE FIRE: Use alcohol foam, water spray or fog.

Special Remarks on Fire Hazards: Vapor may travel considerable distance to source of ignition and flash back.

Special Remarks on Explosion Hazards:
Forms explosive mixtures with hydrogen peroxide, acetic acid, nitric acid, nitric acid + sulfuric acid, chromic anydride, chromyl chloride, nitrosyl chloride, hexachloromelamine, nitrosyl perchlorate, nitryl perchlorate, permonosulfuric acid, thiodiglycol + hydrogen peroxide, potassium ter-butoxide, sulfur dichloride, 1-methyl-1,3-butadiene, bromoform, carbon, air, chloroform, thitriazylperchlorate.

Section 6: Accidental Release Measures

Small Spill:
Dilute with water and mop up, or absorb with an inert dry material and place in an appropriate waste disposal container.

Large Spill:
Flammable liquid. Keep away from heat. Keep away from sources of ignition. Stop leak if without risk. Absorb with DRY earth, sand or other non-combustible material. Do not touch spilled material. Prevent entry into sewers, basements or confined areas; dike if needed. Be careful that the product is not present at a concentration level above TLV. Check TLV on the MSDS and with local authorities.

Section 7: Handling and Storage

Precautions:
Keep locked up.. Keep away from heat. Keep away from sources of ignition. Ground all equipment containing material. Do not ingest. Do not breathe gas/fumes/ vapor/spray. Wear suitable protective clothing. In case of insufficient ventilation, wear suitable respiratory equipment. If ingested, seek medical advice immediately and show the container or the label. Avoid contact with skin and eyes. Keep away from incompatibles such as oxidizing agents, reducing agents, acids, alkalis.

Storage:
Store in a segregated and approved area (flammables area) . Keep container in a cool, well-ventilated area. Keep container tightly closed and sealed until ready for use. Keep away from direct sunlight and heat and avoid all possible sources of ignition (spark or flame).

Section 8: Exposure Controls/Personal Protection

Engineering Controls:
Provide exhaust ventilation or other engineering controls to keep the airborne concentrations of vapors below their respective threshold limit value. Ensure that eyewash stations and safety showers are proximal to the work-station location.

Personal Protection:
Splash goggles. Lab coat. Vapor respirator. Be sure to use an approved/certified respirator or equivalent. Gloves.

Personal Protection in Case of a Large Spill:
Splash goggles. Full suit. Vapor respirator. Boots. Gloves. A self contained breathing apparatus should be used to avoid inhalation of the product. Suggested protective clothing might not be sufficient; consult a specialist BEFORE handling this product.

Exposure Limits:
TWA: 500 STEL: 750 (ppm) from ACGIH (TLV) [United States] TWA: 750 STEL: 1000 (ppm) from OSHA (PEL) [United States] TWA: 500 STEL: 1000 [Austalia] TWA: 1185 STEL: 2375 (mg/m3) [Australia] TWA: 750 STEL: 1500 (ppm) [United Kingdom (UK)] TWA: 1810 STEL: 3620 (mg/m3) [United Kingdom (UK)] TWA: 1800 STEL: 2400 from OSHA (PEL) [United States]Consult local authorities for acceptable exposure limits.

Section 9: Physical and Chemical Properties

Physical state and appearance: Liquid.

Odor: Fruity. Mint-like. Fragrant. Ethereal

Taste: Pungent, Sweetish

Molecular Weight: 58.08 g/mole

Color: Colorless. Clear

pH (1% soln/water): Not available.

Boiling Point: 56.2°C (133.2°F)

Melting Point: -95.35 (-139.6°F)

Critical Temperature: 235°C (455°F)

Specific Gravity: 0.79 (Water = 1)

Vapor Pressure: 24 kPa (@ 20°C)

Vapor Density: 2 (Air = 1)

Volatility: Not available.

Odor Threshold: 62 ppm

Water/Oil Dist. Coeff.: The product is more soluble in water; log(oil/water) = -0.2

Ionicity (in Water): Not available.

Dispersion Properties: See solubility in water.

Solubility: Easily soluble in cold water, hot water.

Section 10: Stability and Reactivity Data

Stability: The product is stable.

Instability Temperature: Not available.

Conditions of Instability: Excess heat, ignition sources, exposure to moisture, air, or water, incompatible materials.

Incompatibility with various substances: Reactive with oxidizing agents, reducing agents, acids, alkalis.

Corrosivity: Non-corrosive in presence of glass.

Special Remarks on Reactivity: Not available.

Special Remarks on Corrosivity: Not available.

Polymerization: Will not occur.

Section 11: Toxicological Information

Routes of Entry: Absorbed through skin. Dermal contact. Eye contact. Inhalation.

Toxicity to Animals:
WARNING: THE LC50 VALUES HEREUNDER ARE ESTIMATED ON THE BASIS OF A 4-HOUR EXPOSURE. Acute oral toxicity (LD50): 3000 mg/kg [Mouse]. Acute toxicity of the vapor (LC50): 44000 mg/m3 4 hours [Mouse].

Chronic Effects on Humans:
CARCINOGENIC EFFECTS: A4 (Not classifiable for human or animal.) by ACGIH. DEVELOPMENTAL TOXICITY: Classified Reproductive system/toxin/female, Reproductive system/toxin/male [SUSPECTED]. Causes damage to the following organs: central nervous system (CNS). May cause damage to the following organs: kidneys, the reproductive system, liver, skin.

Other Toxic Effects on Humans:
Hazardous in case of skin contact (irritant), of ingestion, of inhalation. Slightly hazardous in case of skin contact (permeator).

Special Remarks on Toxicity to Animals: Not available.

Special Remarks on Chronic Effects on Humans:
May affect genetic material (mutagenicity) based on studies with yeast (S. cerevisiae), bacteria, and hamster fibroblast cells. May cause reproductive effects (fertility) based upon animal studies. May contain trace amounts of benzene and formaldehyde which may cancer and birth defects. Human: passes the placental barrier.

Special Remarks on other Toxic Effects on Humans:
Acute Potential Health Effects: Skin: May cause skin irritation. May be harmful if absorbed through the skin. Eyes: Causes eye irritation, characterized by a burning sensation, redness, tearing, inflammation, and possible corneal injury. Inhalation: Inhalation at high concentrations affects the sense organs, brain and causes respiratory tract irritation. It also may affect the Central Nervous System (behavior) characterized by dizzness, drowsiness, confusion, headache, muscle weakeness, and possibly motor incoordination, speech abnormalities, narcotic effects and coma. Inhalation may also affect the gastrointestinal tract (nausea, vomiting). Ingestion: May cause irritation of the digestive (gastrointestinal) tract (nausea, vomiting). It may also

affect the Central Nevous System (behavior), characterized by depression, fatigue, excitement, stupor, coma, headache, altered sleep time, ataxia, tremors as well at the blood, liver, and urinary system (kidney, bladder, ureter) and endocrine system. May also have musculoskeletal effects. Chronic Potential Health Effects: Skin: May cause dermatitis. Eyes: Eye irritation.

Section 12: Ecological Information

Ecotoxicity:
Ecotoxicity in water (LC50): 5540 mg/l 96 hours [Trout]. 8300 mg/l 96 hours [Bluegill]. 7500 mg/l 96 hours [Fatthead Minnow]. 0.1 ppm any hours [Water flea].

BOD5 and COD: Not available.

Products of Biodegradation:
Possibly hazardous short term degradation products are not likely. However, long term degradation products may arise.

Toxicity of the Products of Biodegradation: The product itself and its products of degradation are not toxic.

Special Remarks on the Products of Biodegradation: Not available.

Section 13: Disposal Considerations

Waste Disposal:
Waste must be disposed of in accordance with federal, state and local environmental control regulations.

Section 14: Transport Information

DOT Classification: CLASS 3: Flammable liquid.

Identification: : Acetone UNNA: 1090 PG: II

Special Provisions for Transport: Not available.

Section 15: Other Regulatory Information

Federal and State Regulations:
California prop. 65: This product contains the following ingredients for which the State of California has found to cause reproductive harm (male) which would require a warning under the statute: Benzene California prop. 65: This product contains the following ingredients for which the State of California has found to cause birth defects which would require a warning under the statute: Benzene California prop. 65: This product contains the following ingredients for which the State of California has found to cause cancer which would require a warning under the statute: Benzene, Formaldehyde Connecticut hazardous material survey.: Acetone Illinois toxic substances disclosure to employee act: Acetone Illinois chemical safety act: Acetone New York release reporting list: Acetone Rhode Island RTK hazardous substances: Acetone Pennsylvania RTK: Acetone Florida: Acetone Minnesota: Acetone Massachusetts RTK: Acetone Massachusetts spill list: Acetone New Jersey: Acetone New Jersey spill list: Acetone Louisiana spill reporting: Acetone California List of Hazardous Substances (8 CCR 339): Acetone TSCA 8(b) inventory: Acetone TSCA 4(a) final test rules: Acetone TSCA 8(a) IUR: Acetone

Other Regulations:
OSHA: Hazardous by definition of Hazard Communication Standard (29 CFR 1910.1200). EINECS: This product is on the European Inventory of Existing Commercial Chemical Substances.

Other Classifications:

WHMIS (Canada):
CLASS B-2: Flammable liquid with a flash point lower than 37.8°C (100°F). CLASS D-2B: Material causing other toxic effects (TOXIC).

DSCL (EEC):
R11- Highly flammable. R36- Irritating to eyes. S9- Keep container in a well-ventilated place. S16- Keep away from sources of ignition - No smoking. S26- In case of contact with eyes, rinse immediately with plenty of water and seek medical advice.

HMIS (U.S.A.):

Health Hazard: 2

Fire Hazard: 3

Reactivity: 0

Personal Protection: h

National Fire Protection Association (U.S.A.):

Health: 1

Flammability: 3

Reactivity: 0

Specific hazard:

Protective Equipment:
Gloves. Lab coat. Vapor respirator. Be sure to use an approved/certified respirator or equivalent. Wear appropriate respirator when ventilation is inadequate. Splash goggles.

Section 16: Other Information

References:
-Material safety data sheet issued by: la Commission de la SantÃ© et de la SÃ©curitÃ© du Travail du QuÃ©bec. -The Sigma-Aldrich Library of Chemical Safety Data, Edition II. -Hawley, G.G.. The Condensed Chemical Dictionary, 11e ed., New York N.Y., Van Nostrand Reinold, 1987. LOLI, RTECS, HSDB databases. Other MSDSs

Other Special Considerations: Not available.

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Material Safety Data Sheet
Ammonium chloride MSDS

Section 1: Chemical Product and Company Identification

Product Name: Ammonium chloride

Catalog Codes: SLA3415, SLA1069, SLA2575, SLA4078, SLA1732, SLS3118

CAS#: 12125-02-9

RTECS: BP4550000

TSCA: TSCA 8(b) inventory: Ammonium chloride

CI#: Not applicable.

Synonym: Ammonium Chloratum; Ammonium Chloridum; Ammonium Muriate; Sal Ammonia; Salmiac

Chemical Name: Ammonium Chloride

Chemical Formula: NH4Cl

Contact Information:

Sciencelab.com, Inc.
14025 Smith Rd.
Houston, Texas 77396

US Sales: **1-800-901-7247**
International Sales: **1-281-441-4400**

Order Online: ScienceLab.com

CHEMTREC (24HR Emergency Telephone), call: 1-800-424-9300

International CHEMTREC, call: 1-703-527-3887

For non-emergency assistance, call: 1-281-441-4400

Section 2: Composition and Information on Ingredients

Composition:

Name	CAS #	% by Weight
Ammonium chloride	12125-02-9	100

Toxicological Data on Ingredients: Ammonium chloride: ORAL (LD50): Acute: 1650 mg/kg [Rat.]. 1300 mg/kg [Mouse].

Section 3: Hazards Identification

Potential Acute Health Effects:
Hazardous in case of eye contact (irritant). Slightly hazardous in case of skin contact (irritant, sensitizer), of ingestion, of inhalation.

Potential Chronic Health Effects:
CARCINOGENIC EFFECTS: Not available. MUTAGENIC EFFECTS: Not available. TERATOGENIC EFFECTS: Not available. DEVELOPMENTAL TOXICITY: Not available. Repeated or prolonged exposure is not known to aggravate medical condition.

Section 4: First Aid Measures

Eye Contact:

Check for and remove any contact lenses. In case of contact, immediately flush eyes with plenty of water for at least 15 minutes. Cold water may be used. Get medical attention.

Skin Contact:
In case of contact, immediately flush skin with plenty of water. Cover the irritated skin with an emollient. Remove contaminated clothing and shoes. Cold water may be used.Wash clothing before reuse. Thoroughly clean shoes before reuse. Get medical attention.

Serious Skin Contact:
Wash with a disinfectant soap and cover the contaminated skin with an anti-bacterial cream. Seek immediate medical attention.

Inhalation:
If inhaled, remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Get medical attention.

Serious Inhalation: Not available.

Ingestion:
Do NOT induce vomiting unless directed to do so by medical personnel. Never give anything by mouth to an unconscious person. If large quantities of this material are swallowed, call a physician immediately. Loosen tight clothing such as a collar, tie, belt or waistband.

Serious Ingestion: Not available.

Section 5: Fire and Explosion Data

Flammability of the Product: Non-flammable.

Auto-Ignition Temperature: Not applicable.

Flash Points: Not applicable.

Flammable Limits: Not applicable.

Products of Combustion: Not available.

Fire Hazards in Presence of Various Substances: Not applicable.

Explosion Hazards in Presence of Various Substances:
Risks of explosion of the product in presence of mechanical impact: Not available. Risks of explosion of the product in presence of static discharge: Not available.

Fire Fighting Media and Instructions: Not applicable.

Special Remarks on Fire Hazards:
Reaction between Ammonium Chloride and Bromine pentafluoride at ambient or slightly elevated temperature is violent, and ignition often occurs.

Special Remarks on Explosion Hazards: Explosive reaction between bromine trifluoride and ammonium halides.

Section 6: Accidental Release Measures

Small Spill:
Use appropriate tools to put the spilled solid in a convenient waste disposal container. Finish cleaning by spreading water on the contaminated surface and dispose of according to local and regional authority requirements.

Large Spill:
Use a shovel to put the material into a convenient waste disposal container. Be careful that the product is not present at a concentration level above TLV. Check TLV on the MSDS and with local authorities.

Section 7: Handling and Storage

Precautions:
Do not ingest. Do not breathe dust. Wear suitable protective clothing. In case of insufficient ventilation, wear suitable respiratory equipment. If ingested, seek medical advice immediately and show the container or the label. Avoid contact with skin and eyes. Keep away from incompatibles such as oxidizing agents, acids, alkalis.

Storage: Keep container tightly closed. Keep container in a cool, well-ventilated area.

Section 8: Exposure Controls/Personal Protection

Engineering Controls:
Use process enclosures, local exhaust ventilation, or other engineering controls to keep airborne levels below recommended exposure limits. If user operations generate dust, fume or mist, use ventilation to keep exposure to airborne contaminants below the exposure limit.

Personal Protection:
Splash goggles. Lab coat. Dust respirator. Be sure to use an approved/certified respirator or equivalent. Gloves.

Personal Protection in Case of a Large Spill:
Splash goggles. Full suit. Dust respirator. Boots. Gloves. A self contained breathing apparatus should be used to avoid inhalation of the product. Suggested protective clothing might not be sufficient; consult a specialist BEFORE handling this product.

Exposure Limits:
TWA: 10 STEL: 20 (mg/m3) from ACGIH (TLV) [United States] Inhalation TWA: 10 STEL: 20 (mg/m3) [United Kingdom (UK)] Inhalation TWA: 10 STEL: 20 (mg/m3) from NIOSH [United States] Inhalation TWA: 10 STEL: 20 (mg/m3) from OSHA (PEL) [United States]Consult local authorities for acceptable exposure limits.

Section 9: Physical and Chemical Properties

Physical state and appearance: Solid. (Solid crystalline powder.)

Odor: Odorless. (Slight.)

Taste: Cooling, Saline.

Molecular Weight: 53.49 g/mole

Color: White.

pH (1% soln/water): 5.5 [Acidic.]

Boiling Point: 520°C (968°F)

Melting Point: Decomposition temperature: 338°C (640.4°F)

Critical Temperature: Not available.

Specific Gravity: 1.53 (Water = 1)

Vapor Pressure: Not applicable.

Vapor Density: Not available.

Volatility: Not available.

Odor Threshold: Not available.

Water/Oil Dist. Coeff.: Not available.

Ionicity (in Water): Not available.

Dispersion Properties: See solubility in water, methanol.

Solubility:

Soluble in cold water, hot water, methanol. Insoluble in diethyl ether, acetone. Almost insoluble in ethyl acetate. Very slightly soluble in Ethanol; Solubility in Ethanol: 0.6 g/100 ml water at 19 deg. C. Solubility in Water: 29.7 g/100ml water at O deg. C 75.8 g/100 ml water at 100 deg. C 37.8 lbs./100 lbs. water at 70 deg. F 28.3% (w/w) in water at 25 deg. C Soluble in liquid ammonia.

Section 10: Stability and Reactivity Data

Stability: The product is stable.

Instability Temperature: Not available.

Conditions of Instability: Incompatible materials, moisture.

Incompatibility with various substances: Reactive with oxidizing agents, acids, alkalis.

Corrosivity:
Extremely corrosive in presence of copper. Corrosive in presence of steel, of stainless steel(304). Slightly corrosive in presence of aluminum, of stainless steel(316).

Special Remarks on Reactivity:
Incompatible with lead and silver salts. It can react violently with ammonium nitrate and potassium chlorate. Also incompatible with bromine trifluoride, ammonium halides, bromine pentafluoride, alkalis and their carbonates. At fire temperature, ammonium chloride may dissociate into ammonia and hydrogen chloride. Hygroscopic; keep container tightly closed.

Special Remarks on Corrosivity: Severe corrosive effect on brass and bronze.

Polymerization: Will not occur.

Section 11: Toxicological Information

Routes of Entry: Inhalation. Ingestion.

Toxicity to Animals: Acute oral toxicity (LD50): 1300 mg/kg [Mouse].

Chronic Effects on Humans: Not available.

Other Toxic Effects on Humans: Slightly hazardous in case of skin contact (irritant, sensitizer), of ingestion, of inhalation.

Special Remarks on Toxicity to Animals:
Lowest Published Lethal Dose: LDL [Human Infant] - Route: Oral; Dose: 2000 mg/kg

Special Remarks on Chronic Effects on Humans: May affect genetic material (mutagenic) Animal: passes through the placental barrier.

Special Remarks on other Toxic Effects on Humans:
Acute Potential Health Effects: Skin: It can cause skin irritation which is usually mild. Eyes: Causes moderate eye irritation. It may cause Salt Cataract, increased ocular pressure, and degeneration of the retina Inhalation: It can cause respiratory tract and mucous membrane irritation which is usually mild. Ingestion: May be harmful if swallowed. May cause digestive tract irritation with nausea and vomiting, and thirst. May affect behavior/central nervous system (headache, somnolence, confusion, drowsiness, tremor, convulsions, coma), eyes (Mydriasis), cardiovascular system (bradycardia), respiration (respiratory stimulation, apnea, hyperventilation, pulmonary edema). May cause serious metabolic acidosis with h y p o k a l e m i a . T r a n s i e n t hyperglycemia and glycosuria may also occur. Chronic Potential Health Effects: Skin: Prologned or repeated contact may cause dermatitis, an allergic reaction. Inhalation: Prolonged or repeated inhalation may affect the kidneys. Ingestion: Prolonged or repeated ingestion may affect metabolism (anorexia, metabolic acidosis) and urinary system (enlargement of kidneys). Inhalation: Prolonged or repeated inhalation may cause bronchospasm (asthma)

Section 12: Ecological Information

Ecotoxicity: Not available.

BOD5 and COD: Not available.

Products of Biodegradation:
Possibly hazardous short term degradation products are not likely. However, long term degradation products may arise.

Toxicity of the Products of Biodegradation: The products of degradation are less toxic than the product itself.

Special Remarks on the Products of Biodegradation: Not available.

Section 13: Disposal Considerations

Waste Disposal:
Waste must be disposed of in accordance with federal, state and local environmental control regulations.

Section 14: Transport Information

DOT Classification: Not a DOT controlled material (United States).

Identification: : Not available. UNNA: 9085 PG: III

Special Provisions for Transport: Not applicable.

Section 15: Other Regulatory Information

Federal and State Regulations:
Illinois toxic substances disclosure to employee act: Ammonium chloride Illinois chemical safety act: Ammonium chloride New York release reporting list: Ammonium chloride Rhode Island RTK hazardous substances: Ammonium chloride Pennsylvania RTK: Ammonium chloride Minnesota: Ammonium chloride Massachusetts RTK: Ammonium chloride Massachusetts spill list: Ammonium chloride New Jersey: Ammonium chloride New Jersey spill list: Ammonium chloride Louisiana spill reporting: Ammonium chloride California Director's List of Hazardous Substances: Ammonium chloride TSCA 8(b) inventory: Ammonium chloride CERCLA: Hazardous substances.: Ammonium chloride: 5000 lbs. (2268 kg)

Other Regulations: EINECS: This product is on the European Inventory of Existing Commercial Chemical Substances.

Other Classifications:

WHMIS (Canada): Not controlled under WHMIS (Canada).

DSCL (EEC):

HMIS (U.S.A.):

Health Hazard: 2

Fire Hazard: 0

Reactivity: 0

Personal Protection: E

National Fire Protection Association (U.S.A.):

Health: 2

Flammability: 0

Reactivity: 0

Specific hazard:

Protective Equipment:
Gloves. Lab coat. Dust respirator. Be sure to use an approved/certified respirator or equivalent. Splash goggles.

Section 16: Other Information

References:
-Material safety data sheet emitted by: la Commission de la SantÃ© et de la SÃ©curitÃ© du Travail du QuÃ©bec. -The Sigma-Aldrich Library of Chemical Safety Data, Edition II. -Hawley, G.G.. The Condensed Chemical Dictionary, 11e ed., New York N.Y., Van Nostrand Reinold, 1987. -Manufacturer's Material Safety Data Sheet.

Other Special Considerations: Not available.

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Material Safety Data Sheet
Dichloromethane MSDS

Section 1: Chemical Product and Company Identification

Product Name: Dichloromethane

Catalog Codes:

Synonyms: Methylene chloride; Methane dichloride; Methylene bichloride; Methylene dichloride; Dichloromethane; DCM.

Contact Information:

Sciencelab.com, Inc.
14025 Smith Rd.
Houston, Texas 77396

US Sales: **1-800-901-7247**
International Sales: **1-281-441-4400**

Order Online: ScienceLab.com

CHEMTREC (24HR Emergency Telephone), call: 1-800-424-9300

International CHEMTREC, call: 1-703-527-3887

For non-emergency assistance, call: 1-281-441-4400

Section 2: Composition and Information on Ingredients

CAS#	Chemical Name	Percent	EINECS/ELINCS
75-09-2	Methylene chloride	>99.5	200-838-9

Hazard Symbols: XN

Risk Phrases: 40

Section 3: Hazards Identification

EMERGENCY OVERVIEW: Appearance: colorless liquid. This substance has caused adverse reproductive and fetal effects in animals. Potential cancer hazard.

Warning!: Causes eye and skin irritation. Causes respiratory tract irritation. Harmful if swallowed. May be harmful if inhaled. May cause central nervous system effects. Methylene chloride is metabolically converted to carbon monoxide after systemic absorption, which yields increased concentrations of carboxyhemoglobin in the blood. May cause kidney damage.

Target Organs: Blood, kidneys, heart, central nervous system, liver, lungs, pancreas.

Potential Health Effects:

Eye: Contact with eyes may cause severe irritation, and possible eye burns.

Skin: May be absorbed through the skin. Causes irritation with burning pain, itching, and redness. Prolonged exposure may result in skin burns.

Ingestion: Causes gastrointestinal irritation with nausea, vomiting and diarrhea. May cause kidney damage. May cause central nervous system depression, characterized by excitement, followed by headache, dizziness, drowsiness, and nausea.

Advanced stages may cause collapse, unconsciousness, coma and possible death due to respiratory failure. May cause carboxyhemoglobinemia.

Inhalation: Inhalation of high concentrations may cause central nervous system effects characterized by nausea, headache, dizziness, unconsciousness and coma. Causes respiratory tract irritation. May cause narcotic effects in high concentration. Vapors may cause dizziness or suffocation. May cause blood changes. Overexposure may cause an increase in carboxyhemoglobin levels in the blood. Can produce delayed pulmonary edema. Because of its high volatility, airborne concentrations of methylene c hloride can accumulate in poorly ventilated areas. Odor is a poor indi cator of possibly dangerous air concentrations of methylene chloride.

Chronic: Possible cancer hazard based on tests with laboratory animals. Prolonged or repeated skin contact may cause dermatitis. May cause reproductive and fetal effects. Laboratory experiments have resulted in mutagenic effects. Chronic exposure may cause lung, liver, and pancreatic tumors. May cause conjunctivitis and/or corneal burns.

Section 4: First Aid Measures

Eyes: In case of contact, immediately flush eyes with plenty of water for at least 15 minutes. Get medical aid.

Skin: In case of contact, flush skin with plenty of water. Remove contaminated clothing and shoes. Get medical aid if irritation develops and persists. Wash clothing before reuse.

Ingestion: If swallowed, do not induce vomiting unless directed to do so by medical personnel. Never give anything by mouth to an unconscious person. Get medical aid.

Inhalation: If inhaled, remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Get medical aid.

Notes to Physician: Treat symptomatically and supportively.

Section 5: Fire and Explosion Data

General Information: As in any fire, wear a self-contained breathing apparatus in pressure-demand, MSHA/NIOSH (approved or equivalent), and full protective gear. Use water spray to keep fire-exposed containers cool. No flash point in conventional closed tester, but forms flammable vapor-air mixtures in larger volumes and may be an explosion hazard in a confined space.

Extinguishing Media: Use water spray, dry chemical, carbon dioxide, or appropriate foam.

Flash Point: Not applicable.

Autoignition Temperature: 556 deg C (1,032.80 deg F)

Explosion Limits, Lower: 13 vol %

Upper: 23 vol %

NFPA Rating: (estimated) Health: 2; Flammability: 1; Instability: 0

Section 6: Accidental Release Measures

General Information: Use proper personal protective equipment as indicated in Section 8.

Spills/Leaks: Absorb spill with inert material (e.g. vermiculite, sand or earth), then place in suitable container. Avoid runoff into storm sewers and ditches which lead to waterways. Clean up spills immediately, observing precautions in the Protective Equipment section. Remove all sources of ignition. Provide ventilation.

Section 7: Handling and Storage

Handling: Wash thoroughly after handling. Remove contaminated clothing and wash before reuse. Avoid contact with eyes, skin, and clothing. Keep container tightly closed. Keep away from heat, sparks and flame. Use only with adequate ventilation. Avoid breathing vapor or mist.

Storage: Store in a tightly closed container. Keep from contact with oxidizing materials. Store in a cool, dry, well-ventilated area away from incompatible substances. Store below 40#C. Keep away from active metals.

Section 8: Exposure Controls/Personal Protection

Engineering Controls: Facilities storing or utilizing this material should be equipped with an eyewash facility and a safety shower. Use adequate general or local exhaust ventilation to keep airborne concentrations below the permissible exposure limits.

Exposure Limits:

Chemical Name	ACGIH	NIOSH	OSHA - Final PELs
Methylene chloride	50 ppm TWA	2300 ppm IDLH	25 ppm TWA (8 hr); 125 ppm STEL (15 min); 12.5 ppm Action Level (See 29 CFR 1910 .1052)

OSHA Vacated PELs: Methylene chloride: 500 ppm TWA

Personal Protective Equipment:

Eyes: Wear chemical goggles.

Skin: Wear appropriate protective gloves to prevent skin exposure.

Clothing: Wear appropriate protective clothing to prevent skin exposure.

Respirators: A respiratory protection program that meets OSHA's 29 CFR 1910.134 and ANSI Z88.2 requirements or European Standard EN 149 must be followed whenever workplace conditions warrant a respirator's use.

Section 9: Physical and Chemical Properties

Physical State: Liquid

Appearance: colorless

Odor: ethereal odor - chloroform-like

pH: Not available.

Vapor Pressure: 350 mm Hg @ 20 deg C

Vapor Density: 2.93 (Air=1)

Evaporation Rate: Not available.

Viscosity: Not available.

Boiling Point: 40 deg C

Freezing/Melting Point: -97 deg C

Decomposition Temperature: Not available.

Solubility: Slightly soluble.

Specific Gravity/Density: 1.33 (Water=1)

Molecular Formula: CH2Cl2

Molecular Weight: 84.92

Section 10: Stability and Reactivity Data

Chemical Stability: Stable at room temperature in closed containers under normal storage and handling conditions. May form explosive mixtures in atmospheres having high oxygen content.

Conditions to Avoid: Excess heat, attacks some plastics, rubber, and coatings, confined spaces, When no water is present, dichloromethane is not corrosive to metals. At high temperatures and in the presence of water (causing slow decomposition forming HCl), corrosion of iron, some stainless steels, copper and aluminum can occur..

Incompatibilities with Other Materials: Strong oxidizing agents, strong bases, chemically active metals.

Hazardous Decomposition Products: Hydrogen chloride, phosgene, carbon monoxide, carbon dioxide.

Hazardous Polymerization: Will not occur.

Section 11: Toxicological Information

RTECS#:

CAS#: 75-09-2: PA8050000

LD50/LC50: CAS# 75-09-2: Draize test, rabbit, eye: 162 mg Moderate; Draize test, rabbit, eye: 10 mg Mild; Draize test, rabbit, eye: 500 mg/24H Mild; Draize test, rabbit, skin: 810 mg/24H Severe; Draize test, rabbit, skin: 100 mg/24H Moderate; Inhalation, mouse: LC50 = 14400 ppm/7H; Inhalation, rat: LC50 = 52 gm/m3; Oral, mouse: LD50 = 873 mg/kg; Oral, rat: LD50 = 1600 mg/kg;

Carcinogenicity: CAS# 75-09-2:

ACGIH: A3 - Confirmed animal carcinogen with unknown relevance to humans

California: carcinogen, initial date 4/1/88

NIOSH: potential occupational carcinogen

NTP: Suspect carcinogen

OSHA: Possible Select carcinogen

IARC: Group 2B carcinogen

Epidemiology: There are few reports of injury despite widespread use of dichloromethane (ACGIH, 1991). Solvent abuse has led to death (Harbison, 1998).

Teratogenicity: Inhalation, rat: TCLo = 4500 ppm/24H (female 1-17 day(s) after conception) Effects on Newborn - behavioral.; Inhalation, rat: TCLo = 1250 ppm/7H (female 6-15 day(s) after conception) Specific Developmental Abnormalities - musculoskeletal system and urogenital system.

Reproductive Effects: Reproductive effects have occurred in experimental animals.

Neurotoxicity: No information available.

Mutagenicity: DNA inhibition: Human, Fibroblast = 5000 ppm/1H (Continuous).; Morphological transformation: Rat, Embryo = 160 umol/L.; DNA damage: Oral, rat = 1275 mg/kg.; Inhalation, mouse: TCLo = 2000 ppm/5H/2Y-C (Tumorigenic - Carcinogenic by RTECS criteria--Lungs, Thorax, or Respiration - Tumors).

Other Studies: See actual entry in RTECS for complete information.

Section 12: Ecological Information

Ecotoxicity: Fish: Bluegill/Sunfish: 230mg/L; 24H; StaticFish: Fathead Minnow: 196mg/L; 96H; This chemical has a moderate potential to affect some aquatic organisms. It is resistant to biodegradation, and has a low potential to persist in the aquatic environment. 96-hr. EC50 (loss of equilibrium); Fathead minnow: 99mg/L; 96-hr. EC10: 66.3 mg/L. Bluegill sunfish: 96-hr. LC50=220 mg/L; Water flea: 24-hr. LC50=2270 mg/L; No observed effect level:1550 mg/L.

Environmental: Terrestrial: Expected to evaporate from near surface soil into the atmosphere; expected to leach. Aquatic: Primarily lost by evaporation to the atmosphere which should take several hours depending on wind and mixing conditions.

Atmospheric: Will degrade by reaction with hydroxyl radicals with a half life of several months. . Dichloromethane is reported to completely biodegrade under aerobic conditions with sewage seed or activated sludge between 6 hours to 7 days. Not expected to bioconcentrate due to its low octanol/water coefficient.

Physical: No information available.

Other: No information available.

Section 13: Disposal Considerations

RCRA P-Series: None listed.

RCRA U-Series: CAS# 75-09-2: waste number U080.

Section 14: Transport Information

	US DOT	IATA	RID/ADR	IMO	Canada TDG
Shipping Name:	DICHLOROMETHANE				METHYLENE CHLORIDE
Hazard Class:	6.1				6.1
UN Number:	UN1593				UN1593
Packing Group:	III				III

Section 15: Other Regulatory Information

US FEDERAL:

TSCA: CAS# 75-09-2 is listed on the TSCA inventory.

Health & Safety Reporting List: CAS# 75-09-2: Effective 10/4/82; Sunset 10/4/92

Chemical Test Rules: None of the chemicals in this product are under a Chemical Test Rule.

Section 12b: None of the chemicals are listed under TSCA Section 12b.

TSCA Significant New Use Rule: None of the chemicals in this material have a SNUR under TSCA.

SARA:

CERCLA Hazardous Substances and corresponding RQs: CAS# 75-09-2: 1000 lb final RQ; 454 kg final RQ

SARA Section 302 Extremely Hazardous Substances: None of the chemicals in this product have a TPQ.

SARA Codes: CAS # 75-09-2: acute, chronic.

Section 313: This material contains Methylene chloride (CAS# 75-09-2, 99 5%),which is subject to the reporting requirements of Section 313 of SARA Title III and 40 CFR Part 373.

Clean Air Act: CAS# 75-09-2 is listed as a hazardous air pollutant (HAP). This material does not contain any Class 1 Ozone depletors. This material does not contain any Class 2 Ozone depletors.

Clean Water Act: None of the chemicals in this product are listed as Hazardous Substances under the CWA. CAS# 75-09-2 is listed as a Priority Pollutant under the Clean Water Act. CAS# 75-09-2 is listed as a Toxic Pollutant under the Clean Water Act.

OSHA: None of the chemicals in this product are considered highly hazardous by OSHA.

STATE: CAS# 75-09-2 can be found on the following state right to know lists: California, New Jersey, Pennsylvania, Minnesota, Massachusetts.

The following statement(s) is(are) made in order to comply with the California Safe Drinking Water Act: WARNING: This product contains Methylene chloride, a chemical known to the state of California to cause cancer. California No Significant Risk Level: CAS# 75-09-2: 200 #g/day NSRL (inhalation); 50 #g/day NSRL (except inhalation)

European/International Regulations:

European Labeling in Accordance with EC Directives:

Hazard Symbols: XN

Risk Phrases: R 40 Limited evidence of a carcinogenic effect.

Safety Phrases: S 23 Do not inhale gas/fumes/vapour/spray. S 24/25 Avoid contact with skin and eyes. S 36/37 Wear suitable protective clothing and gloves.

WGK (Water Danger/Protection): CAS# 75-09-2: 2

Canada - DSL/NDSL: CAS# 75-09-2 is listed on Canada's DSL List.

Canada - WHMIS: This product has a WHMIS classification of D1B, D2A.

Canadian Ingredient Disclosure List: CAS# 75-09-2 is listed on the Canadian Ingredient Disclosure List.

Exposure Limits: CAS# 75-09-2: OEL-AUSTRALIA:TWA 100 ppm (350 mg/m3);Carcinogen OEL- AUSTRIA:TWA 100 ppm (360 mg/m3) OEL-BELGIUM:TWA 50 ppm (174 mg/m3);Ca rcinogen OEL-CZECHOSLOVAKIA:TWA 500 mg/m3;STEL 2500 mg/m3 OEL-DENMAR K:TWA 50 ppm (175 mg/m3);Skin;Carcinoge OEL-FINLAND:TWA 100 ppm (350 mg/m3);STEL 250 ppm (870 mg/m3) OEL-FRANCE:TWA 100 ppm (360 mg/m3);ST EL 500 ppm (1800 mg/m3) OEL-GERMANY:TWA 100 ppm (360 mg/m3);Carcinoge n OEL-HUNGARY:STEL 10 mg/m3;Carcinogen OEL-JAPAN:TWA 100 ppm (350 mg /m3) OEL-THE NETHERLANDS:TWA 100 ppm (350 mg/m3);STEL 500 ppm OEL-TH E PHILIPINES:TWA 500 ppm (1740 mg/ m3) OEL-POLAND:TWA 50 mg/m3 OEL-RU SSIA:TWA 100 ppm;STEL 50 mg/m3 OEL-SWEDEN:TWA 35 ppm (120 mg/ m3);STEL 70 ppm (25 mg/m3);Skin OEL-SWITZERLAND:TWA 100 ppm (360 mg/m3);STEL 500 ppm OEL-THAILAND:TWA 500 mg/m3;STEL 1000 mg/m3 OEL-TURKEY:TWA 50 0 ppm (1740 mg/m3) OEL-UNITED KINGDOM:TWA 100 ppm (350 mg/m3);STEL 25 0 ppm OEL IN BULGARIA, COLOMBIA, JORDAN, KOREA check ACGIH TLV OEL I N NEW ZEALAND, SINGAPORE, VIETNAM check ACGI TLV

Section 16: Other Information

Created: 04/19/2005 12:24 PM

Last Updated: 05/21/2013 12:00 PM

The information above is believed to be accurate and represents the best information currently available to us. However, we make no warranty of merchantability or any other warranty, express or implied, with respect to such information, and we assume no liability resulting from its use. Users should make their own investigations to determine the suitability of the information for their particular purposes. In no event shall ScienceLab.com be liable for any claims, losses, or damages of any third party or for lost profits or any special, indirect, incidental, consequential or exemplary damages, howsoever arising, even if ScienceLab.com has been advised of the possibility of such damages.

Material Safety Data Sheet
N,N-Diisopropylethylamine MSDS

Section 1: Chemical Product and Company Identification

Product Name: N,N-Diisopropylethylamine

Catalog Codes: SLD1771

CAS#: 7087-68-5

RTECS: Not available.

TSCA: TSCA 8(b) inventory: N,N-Diisopropylethylamine

CI#: Not available.

Synonym: N-Ethyldiisopropylamine; Hunigs's Base

Chemical Name: N,N-Diisopropylethylamine

Chemical Formula: C8-H19-N

Contact Information:

Sciencelab.com, Inc.
14025 Smith Rd.
Houston, Texas 77396

US Sales: **1-800-901-7247**
International Sales: **1-281-441-4400**

Order Online: ScienceLab.com

CHEMTREC (24HR Emergency Telephone), call: 1-800-424-9300

International CHEMTREC, call: 1-703-527-3887

For non-emergency assistance, call: 1-281-441-4400

Section 2: Composition and Information on Ingredients

Composition:

Name	CAS #	% by Weight
{N,N-}Diisopropylethylamine	7087-68-5	100

Toxicological Data on Ingredients: N,N-Diisopropylethylamine LD50: Not available. LC50: Not available.

Section 3: Hazards Identification

Potential Acute Health Effects:
Hazardous in case of skin contact (irritant), of eye contact (irritant), of ingestion, of inhalation. Slightly hazardous in case of skin contact (corrosive, permeator), of eye contact (corrosive).

Potential Chronic Health Effects:
CARCINOGENIC EFFECTS: Not available. MUTAGENIC EFFECTS: Not available. TERATOGENIC EFFECTS: Not available. DEVELOPMENTAL TOXICITY: Not available. Repeated or prolonged exposure is not known to aggravate medical condition.

Section 4: First Aid Measures

Eye Contact:
Check for and remove any contact lenses. In case of contact, immediately flush eyes with plenty of water for at least 15 minutes. Get medical attention immediately.

Skin Contact:
In case of contact, immediately flush skin with plenty of water for at least 15 minutes while removing contaminated clothing and shoes. Cover the irritated skin with an emollient. Wash clothing before reuse. Thoroughly clean shoes before reuse. Get medical attention immediately.

Serious Skin Contact:
Wash with a disinfectant soap and cover the contaminated skin with an anti-bacterial cream. Seek medical attention.

Inhalation:
If inhaled, remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Get medical attention.

Serious Inhalation:
Evacuate the victim to a safe area as soon as possible. Loosen tight clothing such as a collar, tie, belt or waistband. Seek medical attention.

Ingestion:
Do NOT induce vomiting unless directed to do so by medical personnel. Never give anything by mouth to an unconscious person. If large quantities of this material are swallowed, call a physician immediately. Loosen tight clothing such as a collar, tie, belt or waistband.

Serious Ingestion: Not available.

Section 5: Fire and Explosion Data

Flammability of the Product: Flammable.

Auto-Ignition Temperature: Not available.

Flash Points: CLOSED CUP: 10°C (50°F).

Flammable Limits: Not available.

Products of Combustion: These products are carbon oxides (CO, CO2).

Fire Hazards in Presence of Various Substances:
Highly flammable in presence of open flames and sparks, of heat. Non-flammable in presence of shocks.

Explosion Hazards in Presence of Various Substances:
Risks of explosion of the product in presence of mechanical impact: Not available. Risks of explosion of the product in presence of static discharge: Not available.

Fire Fighting Media and Instructions:
Flammable liquid. SMALL FIRE: Use DRY chemical powder. LARGE FIRE: Use alcohol foam, water spray or fog.

Special Remarks on Fire Hazards: Not available.

Special Remarks on Explosion Hazards: Not available.

Section 6: Accidental Release Measures

Small Spill: Absorb with an inert material and put the spilled material in an appropriate waste disposal.

Large Spill:
Flammable liquid. Keep away from heat. Keep away from sources of ignition. Stop leak if without risk. Absorb with DRY earth, sand or other non-combustible material. Do not touch spilled material. Prevent entry into sewers, basements or confined areas; dike if needed.

Section 7: Handling and Storage

Precautions:

Keep container dry. Keep away from heat. Keep away from sources of ignition. Ground all equipment containing material. Do not breathe gas/fumes/ vapor/spray. Never add water to this product. In case of insufficient ventilation, wear suitable respiratory equipment. If you feel unwell, seek medical attention and show the label when possible. Avoid contact with skin and eyes. Keep away from incompatibles such as oxidizing agents, acids.

Storage:
Store in a segregated and approved area. Keep container in a cool, well-ventilated area. Keep container tightly closed and sealed until ready for use. Avoid all possible sources of ignition (spark or flame).

Section 8: Exposure Controls/Personal Protection

Engineering Controls:
Provide exhaust ventilation or other engineering controls to keep the airborne concentrations of vapors below their respective threshold limit value. Ensure that eyewash stations and safety showers are proximal to the work-station location.

Personal Protection:
Splash goggles. Lab coat. Vapor respirator. Be sure to use an approved/certified respirator or equivalent. Gloves.

Personal Protection in Case of a Large Spill:
Splash goggles. Full suit. Vapor respirator. Boots. Gloves. A self contained breathing apparatus should be used to avoid inhalation of the product. Suggested protective clothing might not be sufficient; consult a specialist BEFORE handling this product.

Exposure Limits: Not available.

Section 9: Physical and Chemical Properties

Physical state and appearance: Liquid.

Odor: Ammoniacal.

Taste: Not available.

Molecular Weight: 129.25 g/mole

Color: Colorless to light yellow. Clear

pH (1% soln/water): Not available.

Boiling Point: 127°C (260.6°F)

Melting Point: <-50°C (-58°F)

Critical Temperature: Not available.

Specific Gravity: 0.742 (Water = 1)

Vapor Pressure: Not available.

Vapor Density: Not available.

Volatility: Not available.

Odor Threshold: Not available.

Water/Oil Dist. Coeff.: Not available.

Ionicity (in Water): Not available.

Dispersion Properties: Not available.

Solubility: Not available.

Section 10: Stability and Reactivity Data

Stability: The product is stable.

Instability Temperature: Not available.

Conditions of Instability: Not available.

Incompatibility with various substances: Reactive with oxidizing agents, acids.

Corrosivity: Not available.

Special Remarks on Reactivity: Incompatible with acid chlorides, acid anhydrides, carbon dioxide, copper, brass, rubber.

Special Remarks on Corrosivity: Not available.

Polymerization: Will not occur.

Section 11: Toxicological Information

Routes of Entry: Absorbed through skin. Eye contact.

Toxicity to Animals:
LD50: Not available. LC50: Not available.

Chronic Effects on Humans: Not available.

Other Toxic Effects on Humans:
Hazardous in case of skin contact (irritant), of ingestion, of inhalation. Slightly hazardous in case of skin contact (corrosive, permeator), of eye contact (corrosive).

Special Remarks on Toxicity to Animals: Not available.

Special Remarks on Chronic Effects on Humans: Not available.

Special Remarks on other Toxic Effects on Humans:
Acute Potential Health Effects: Skin: Causes skin irritation and possible burns. Eyes: Causes eye irritation and possible burns. Inhalation: May cause respiratory tracts and possible burns. Ingestion: May cause digestive tract irritation and possible burns. The toxicological properties of this substance have not been fully investigated.

Section 12: Ecological Information

Ecotoxicity: Not available.

BOD5 and COD: Not available.

Products of Biodegradation:
Possibly hazardous short term degradation products are not likely. However, long term degradation products may arise.

Toxicity of the Products of Biodegradation: The product itself and its products of degradation are not toxic.

Special Remarks on the Products of Biodegradation: Not available.

Section 13: Disposal Considerations

Waste Disposal:
Waste must be disposed of in accordance with federal, state and local environmental control regulations.

Section 14: Transport Information

DOT Classification:

CLASS 3: Flammable liquid. Class 8: Corrosive material

Identification: : Amines, Flammable, Corrosive, n.o.s. UNNA: 2733 PG: II

Special Provisions for Transport: Not available.

Section 15: Other Regulatory Information

Federal and State Regulations: TSCA 8(b) inventory: N,N-Diisopropylethylamine

Other Regulations: OSHA: Hazardous by definition of Hazard Communication Standard (29 CFR 1910.1200).

Other Classifications:

WHMIS (Canada): Not controlled under WHMIS (Canada).

DSCL (EEC):
R11- Highly flammable. R34- Causes burns. S2- Keep out of the reach of children. S16- Keep away from sources of ignition - No smoking. S26- In case of contact with eyes, rinse immediately with plenty of water and seek medical advice. S36/37/39- Wear suitable protective clothing, gloves and eye/face protection. S45- In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible). S46- If swallowed, seek medical advice immediately and show this container or label.

HMIS (U.S.A.):

Health Hazard: 2

Fire Hazard: 3

Reactivity: 0

Personal Protection: h

National Fire Protection Association (U.S.A.):

Health: 2

Flammability: 3

Reactivity: 0

Specific hazard:

Protective Equipment:
Gloves. Lab coat. Vapor respirator. Be sure to use an approved/certified respirator or equivalent. Splash goggles.

Section 16: Other Information

References: Not available.

Other Special Considerations: Not available.

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Last Updated: 05/21/2013 12:00 PM

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Material Safety Data Sheet
Ethyl acetate MSDS

Section 1: Chemical Product and Company Identification

Product Name: Ethyl acetate

Catalog Codes: SLE2452, SLE2317

CAS#: 141-78-6

RTECS: AH5425000

TSCA: TSCA 8(b) inventory: Ethyl acetate

CI#: Not available.

Synonym: Acetic Acid, Ethyl Ester Acetic Ether

Chemical Name: Ethyl Acetate

Chemical Formula: C4-H8-O2

Contact Information:

Sciencelab.com, Inc.
14025 Smith Rd.
Houston, Texas 77396

US Sales: **1-800-901-7247**
International Sales: **1-281-441-4400**

Order Online: ScienceLab.com

CHEMTREC (24HR Emergency Telephone), call: 1-800-424-9300

International CHEMTREC, call: 1-703-527-3887

For non-emergency assistance, call: 1-281-441-4400

Section 2: Composition and Information on Ingredients

Composition:

Name	CAS #	% by Weight
Ethyl acetate	141-78-6	100

Toxicological Data on Ingredients: Ethyl acetate: ORAL (LD50): Acute: 5620 mg/kg [Rat]. 4100 mg/kg [Mouse]. 4935 mg/kg [Rabbit]. VAPOR (LC50): Acute: 45000 mg/m 3 hours [Mouse]. 16000 ppm 6 hours [Rat].

Section 3: Hazards Identification

Potential Acute Health Effects:
Hazardous in case of ingestion, of inhalation. Slightly hazardous in case of skin contact (irritant, permeator), of eye contact (irritant).

Potential Chronic Health Effects:
CARCINOGENIC EFFECTS: A4 (Not classifiable for human or animal.) by ACGIH. MUTAGENIC EFFECTS: Not available. TERATOGENIC EFFECTS: Not available. DEVELOPMENTAL TOXICITY: Not available. The substance is toxic to mucous membranes, upper respiratory tract. The substance may be toxic to blood, kidneys, liver, central nervous system (CNS). Repeated or prolonged exposure to the substance can produce target organs damage.

Section 4: First Aid Measures

Eye Contact:
Check for and remove any contact lenses. In case of contact, immediately flush eyes with plenty of water for at least 15 minutes. Cold water may be used. Get medical attention.

Skin Contact:
Wash with soap and water. Cover the irritated skin with an emollient. Get medical attention if irritation develops. Cold water may be used.

Serious Skin Contact: Not available.

Inhalation:
If inhaled, remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Get medical attention if symptoms appear.

Serious Inhalation:
Evacuate the victim to a safe area as soon as possible. Loosen tight clothing such as a collar, tie, belt or waistband. If breathing is difficult, administer oxygen. If the victim is not breathing, perform mouth-to-mouth resuscitation. Seek medical attention.

Ingestion:
Do NOT induce vomiting unless directed to do so by medical personnel. Never give anything by mouth to an unconscious person. Loosen tight clothing such as a collar, tie, belt or waistband. Get medical attention if symptoms appear.

Serious Ingestion: Not available.

Section 5: Fire and Explosion Data

Flammability of the Product: Flammable.

Auto-Ignition Temperature: 426.67°C (800°F)

Flash Points: CLOSED CUP: -4.4°C (24.1°F). (TAG) OPEN CUP: 7.2°C (45°F) (Cleveland).

Flammable Limits: LOWER: 2.2% UPPER: 9%

Products of Combustion: These products are carbon oxides (CO, CO2).

Fire Hazards in Presence of Various Substances:
Highly flammable in presence of open flames and sparks, of heat. Slightly flammable to flammable in presence of oxidizing materials, of acids, of alkalis. Non-flammable in presence of shocks.

Explosion Hazards in Presence of Various Substances:
Risks of explosion of the product in presence of static discharge: Not available. Slightly explosive in presence of heat. Non-explosive in presence of shocks.

Fire Fighting Media and Instructions:
Flammable liquid, soluble or dispersed in water. SMALL FIRE: Use DRY chemical powder. LARGE FIRE: Use alcohol foam, water spray or fog.

Special Remarks on Fire Hazards:
Vapor may travel considerable distance to source of ignition and flash back. When heated to decomposition it emits acrid smoke and irritating fumes.

Special Remarks on Explosion Hazards:
The liquid produces a vapor that forms explosive mixtures with air at normal temperatures. Explosive reaction with lithium tetrahydroaluminate.

Section 6: Accidental Release Measures

Small Spill:
Dilute with water and mop up, or absorb with an inert dry material and place in an appropriate waste disposal container.

Large Spill:
Flammable liquid. Keep away from heat. Keep away from sources of ignition. Stop leak if without risk. Absorb with DRY earth, sand or other non-combustible material. Do not touch spilled material. Prevent entry into sewers, basements or confined areas; dike if needed. Be careful that the product is not present at a concentration level above TLV. Check TLV on the MSDS and with local authorities.

Section 7: Handling and Storage

Precautions:
Keep away from heat. Keep away from sources of ignition. Ground all equipment containing material. Do not ingest. Do not breathe gas/fumes/ vapor/spray. Wear suitable protective clothing. In case of insufficient ventilation, wear suitable respiratory equipment. If ingested, seek medical advice immediately and show the container or the label. Keep away from incompatibles such as oxidizing agents, acids, alkalis.

Storage:
Store in a segregated and approved area. Keep container in a cool, well-ventilated area. Keep container tightly closed and sealed until ready for use. Avoid all possible sources of ignition (spark or flame). Moisture sensitive.

Section 8: Exposure Controls/Personal Protection

Engineering Controls:
Provide exhaust ventilation or other engineering controls to keep the airborne concentrations of vapors below their respective threshold limit value. Ensure that eyewash stations and safety showers are proximal to the work-station location.

Personal Protection:
Safety glasses. Lab coat. Vapor respirator. Be sure to use an approved/certified respirator or equivalent. Gloves.

Personal Protection in Case of a Large Spill:
Splash goggles. Full suit. Vapor respirator. Boots. Gloves. A self contained breathing apparatus should be used to avoid inhalation of the product. Suggested protective clothing might not be sufficient; consult a specialist BEFORE handling this product.

Exposure Limits:
TWA: 400 (ppm) from OSHA (PEL) [United States] TWA: 400 from ACGIH (TLV) [United States] TWA: 1400 (mg/m3) from NIOSH [United States] TWA: 400 (ppm) from NIOSH [United States] TWA: 400 (ppm) [Canada] TWA: 1440 (mg/m3) [Canada] TWA: 1400 (mg/m3) from OSHA (PEL) [United States]3 Consult local authorities for acceptable exposure limits.

Section 9: Physical and Chemical Properties

Physical state and appearance: Liquid.

Odor: Ethereal. Fruity. (Slight.)

Taste: Bittersweet, wine-like burning taste

Molecular Weight: 88.11 g/mole

Color: Colorless.

pH (1% soln/water): Not available.

Boiling Point: 77°C (170.6°F)

Melting Point: -83°C (-117.4°F)

Critical Temperature: 250°C (482°F)

Specific Gravity: 0.902 (Water = 1)

Vapor Pressure: 12.4 kPa (@ 20°C)

Vapor Density: 3.04 (Air = 1)

Volatility: Not available.

Odor Threshold: 3.9 ppm

Water/Oil Dist. Coeff.: The product is more soluble in oil; log(oil/water) = 0.7

Ionicity (in Water): Not available.

Dispersion Properties: See solubility in water, diethyl ether, acetone.

Solubility: Soluble in cold water, hot water, diethyl ether, acetone, alcohol, benzene.

Section 10: Stability and Reactivity Data

Stability: The product is stable.

Instability Temperature: Not available.

Conditions of Instability: Heat, ignition sources (flames, sparks, static), incompatible materials

Incompatibility with various substances: Reactive with oxidizing agents, acids, alkalis.

Corrosivity: Non-corrosive in presence of glass.

Special Remarks on Reactivity:
Also incompatible with nitrates, chlorosulfonic acid, oleum, potassium-tert-butoxide, and lithium tetrahydroaluminate. Moisture sensitive. On storage, it is slowly decomposed by water.

Special Remarks on Corrosivity: Not available.

Polymerization: Will not occur.

Section 11: Toxicological Information

Routes of Entry: Absorbed through skin. Eye contact. Inhalation. Ingestion.

Toxicity to Animals:
WARNING: THE LC50 VALUES HEREUNDER ARE ESTIMATED ON THE BASIS OF A 4-HOUR EXPOSURE. Acute oral toxicity (LD50): 4100 mg/kg [Mouse]. Acute toxicity of the vapor (LC50): 45000 mg/m3 3 hours [Mouse].

Chronic Effects on Humans:
CARCINOGENIC EFFECTS: A4 (Not classifiable for human or animal.) by ACGIH. Causes damage to the following organs: mucous membranes, upper respiratory tract. May cause damage to the following organs: blood, kidneys, liver, central nervous system (CNS).

Other Toxic Effects on Humans:
Hazardous in case of ingestion, of inhalation. Slightly hazardous in case of skin contact (irritant, permeator).

Special Remarks on Toxicity to Animals: LD50 [Rabbit] - Route: skin; Dose >20,000 ml/kg

Special Remarks on Chronic Effects on Humans:
May affect genetic material (mutagenic). May cause adverse reproductive effects. based on animal test data. No human data found at this time.

Special Remarks on other Toxic Effects on Humans:
Acute Potential Health Effects: Skin: May cause skin irritation. Eyes: Causes eye irritation. May cause irritation of the conjunctivia. Inhalation: May cause respiratory tract and mucous membrane irritation. May affect respiration and may cause acute pulmonary edema. May affect gastrointestinal tract (nausea, vomiting). May affect behavior/central nervous system (mild central nervous system depression - exhilaration, talkativeness, boastfulness, belligerancy, vertigo, diplopia, drowsiness, slurred speech, slowed reaction time, dizziness, lightheadedness, somnolence, ataxia, unconciousness, irritability, fatigue, sleep disturbances, reduced memory and concentration, stupor, coma), cardiovascular system (peripheral vascular collapse (shock) - rapid pulse, hypotension, cold pale skin, hypothermia). Other symptoms may include: flushing of face and sweating.

Ingestion: May cause gastrointestinal tract irritation with nausea and vomiting. May affect blood, behavior/central nervous system (CNS depression - effects may be similar to that of inhalation). Chronic Potential Health Effects: Skin: Repeated or prolonged skin contact may cause drying and cracking of the skin. Ingestlon: Prolonged or repeated ingestion may affect the liver. Inhalation: Prolonged inhalation may affect behavior/central nervous system (symptoms similar to those of acute inhalation), and cause liver, kidney, lung, and heart damage. It may also affect metabolism, and blood (anemia, leukocytosis).

Section 12: Ecological Information

Ecotoxicity:
Ecotoxicity in water (LC50): 220 mg/l 96 hours [Fish (Fathead minnow)]. 212.5 ppm 96 hours [Fish (Indian catfish)].

BOD5 and COD: Not available.

Products of Biodegradation:
Possibly hazardous short term degradation products are not likely. However, long term degradation products may arise.

Toxicity of the Products of Biodegradation: The product itself and its products of degradation are not toxic.

Special Remarks on the Products of Biodegradation: Not available.

Section 13: Disposal Considerations

Waste Disposal:
Waste must be disposed of in accordance with federal, state and local environmental control regulations.

Section 14: Transport Information

DOT Classification: CLASS 3: Flammable liquid.

Identification: : Ethyl Acetate UNNA: 1173 PG: II

Special Provisions for Transport: Not available.

Section 15: Other Regulatory Information

Federal and State Regulations:
Connecticut hazardous material survey.: Ethyl acetate Illinois toxic substances disclosure to employee act: Ethyl acetate Illinois chemical safety act: Ethyl acetate New York release reporting list: Ethyl acetate Rhode Island RTK hazardous substances: Ethyl acetate Pennsylvania RTK: Ethyl acetate Florida: Ethyl acetate Minnesota: Ethyl acetate Massachusetts RTK: Ethyl acetate Massachusetts spill list: Ethyl acetate New Jersey: Ethyl acetate New Jersey spill list: Ethyl acetate Louisiana spill reporting: Ethyl acetate California Director's list of Hazardous Substances: Ethyl acetate TSCA 8(b) inventory: Ethyl acetate TSCA 4(a) final test rules: Ethyl acetate TSCA 8(a) IUR: Ethyl acetate TSCA 12(b) annual export notification: Ethyl acetate CERCLA: Hazardous substances.: Ethyl acetate: 5000 lbs. (2268 kg)

Other Regulations:
OSHA: Hazardous by definition of Hazard Communication Standard (29 CFR 1910.1200). EINECS: This product is on the European Inventory of Existing Commercial Chemical Substances.

Other Classifications:

WHMIS (Canada): CLASS B-2: Flammable liquid with a flash point lower than 37.8°C (100°F).

DSCL (EEC):
R11- Highly flammable. R36- Irritating to eyes. S2- Keep out of the reach of children. S16- Keep away from sources of ignition - No smoking. S26- In case of contact with eyes, rinse immediately with plenty of water and seek medical advice. S33- Take precautionary measures against static discharges. S46- If swallowed, seek medical advice immediately and show this container or label.

HMIS (U.S.A.):

Health Hazard: 2

Fire Hazard: 3

Reactivity: 0

Personal Protection: g

National Fire Protection Association (U.S.A.):

Health: 1

Flammability: 3

Reactivity: 0

Specific hazard:

Protective Equipment:
Gloves. Lab coat. Vapor respirator. Be sure to use an approved/certified respirator or equivalent. Wear appropriate respirator when ventilation is inadequate. Safety glasses.

Section 16: Other Information

References: Not available.

Other Special Considerations: Not available.

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Last Updated: 05/21/2013 12:00 PM

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Material Safety Data Sheet
Hydrochloric acid MSDS

Section 1: Chemical Product and Company Identification

Product Name: Hydrochloric acid

Catalog Codes: SLH1462, SLH3154

CAS#: Mixture.

RTECS: MW4025000

TSCA: TSCA 8(b) inventory: Hydrochloric acid

CI#: Not applicable.

Synonym: Hydrochloric Acid; Muriatic Acid

Chemical Name: Not applicable.

Chemical Formula: Not applicable.

Contact Information:

Sciencelab.com, Inc.
14025 Smith Rd.
Houston, Texas 77396

US Sales: **1-800-901-7247**
International Sales: **1-281-441-4400**

Order Online: ScienceLab.com

CHEMTREC (24HR Emergency Telephone), call:
1-800-424-9300

International CHEMTREC, call: 1-703-527-3887

For non-emergency assistance, call: 1-281-441-4400

Section 2: Composition and Information on Ingredients

Composition:

Name	CAS #	% by Weight
Hydrogen chloride	7647-01-0	20-38
Water	7732-18-5	62-80

Toxicological Data on Ingredients: Hydrogen chloride: GAS (LC50): Acute: 4701 ppm 0.5 hours [Rat].

Section 3: Hazards Identification

Potential Acute Health Effects:
Very hazardous in case of skin contact (corrosive, irritant, permeator), of eye contact (irritant, corrosive), of ingestion, . Slightly hazardous in case of inhalation (lung sensitizer). Non-corrosive for lungs. Liquid or spray mist may produce tissue damage particularly on mucous membranes of eyes, mouth and respiratory tract. Skin contact may produce burns. Inhalation of the spray mist may produce severe irritation of respiratory tract, characterized by coughing, choking, or shortness of breath. Severe over-exposure can result in death. Inflammation of the eye is characterized by redness, watering, and itching. Skin inflammation is characterized by itching, scaling, reddening, or, occasionally, blistering.

Potential Chronic Health Effects:
Slightly hazardous in case of skin contact (sensitizer). CARCINOGENIC EFFECTS: Classified 3 (Not classifiable for human.) by IARC [Hydrochloric acid]. MUTAGENIC EFFECTS: Not available. TERATOGENIC EFFECTS: Not available. DEVELOPMENTAL TOXICITY: Not available. The substance may be toxic to kidneys, liver, mucous membranes, upper respiratory tract, skin, eyes, Circulatory System, teeth. Repeated or prolonged exposure to the substance can produce target

organs damage. Repeated or prolonged contact with spray mist may produce chronic eye irritation and severe skin irritation. Repeated or prolonged exposure to spray mist may produce respiratory tract irritation leading to frequent attacks of bronchial infection. Repeated exposure to a highly toxic material may produce general deterioration of health by an accumulation in one or many human organs.

Section 4: First Aid Measures

Eye Contact:
Check for and remove any contact lenses. In case of contact, immediately flush eyes with plenty of water for at least 15 minutes. Cold water may be used. Get medical attention immediately.

Skin Contact:
In case of contact, immediately flush skin with plenty of water for at least 15 minutes while removing contaminated clothing and shoes. Cover the irritated skin with an emollient. Cold water may be used.Wash clothing before reuse. Thoroughly clean shoes before reuse. Get medical attention immediately.

Serious Skin Contact:
Wash with a disinfectant soap and cover the contaminated skin with an anti-bacterial cream. Seek immediate medical attention.

Inhalation:
If inhaled, remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Get medical attention immediately.

Serious Inhalation:
Evacuate the victim to a safe area as soon as possible. Loosen tight clothing such as a collar, tie, belt or waistband. If breathing is difficult, administer oxygen. If the victim is not breathing, perform mouth-to-mouth resuscitation. WARNING: It may be hazardous to the person providing aid to give mouth-to-mouth resuscitation when the inhaled material is toxic, infectious or corrosive. Seek immediate medical attention.

Ingestion:
If swallowed, do not induce vomiting unless directed to do so by medical personnel. Never give anything by mouth to an unconscious person. Loosen tight clothing such as a collar, tie, belt or waistband. Get medical attention immediately.

Serious Ingestion: Not available.

Section 5: Fire and Explosion Data

Flammability of the Product: Non-flammable.

Auto-Ignition Temperature: Not applicable.

Flash Points: Not applicable.

Flammable Limits: Not applicable.

Products of Combustion: Not available.

Fire Hazards in Presence of Various Substances: of metals

Explosion Hazards in Presence of Various Substances: Non-explosive in presence of open flames and sparks, of shocks.

Fire Fighting Media and Instructions: Not applicable.

Special Remarks on Fire Hazards:
Non combustible. Calcium carbide reacts with hydrogen chloride gas with incandescence. Uranium phosphide reacts with hydrochloric acid to release spontaneously flammable phosphine. Rubidium acetylene carbides burns with slightly warm hydrochloric acid. Lithium silicide in contact with hydrogen chloride becomes incandescent. When dilute hydrochloric acid is used, gas spontaneously flammable in air is evolved. Magnesium boride treated with concentrated hydrochloric acid produces spontaneously flammble gas. Cesium acetylene carbide burns hydrogen chloride gas. Cesium carbide ignites in contact with hydrochloric acid unless acid is dilute. Reacts with most metals to produce flammable Hydrodgen gas.

Special Remarks on Explosion Hazards:

Hydrogen chloride in contact with the following can cause an explosion, ignition on contact, or other violent/vigorous reaction: Acetic anhydride AgClO + CCl4 Alcohols + hydrogen cyanide, Aluminum Aluminum-titanium alloys (with HCl vapor), 2-Amino ethanol, Ammonium hydroxide, Calcium carbide Ca3P2 Chlorine + dinitroanilines (evolves gas), Chlorosulfonic acid Cesium carbide Cesium acetylene carbide, 1,1-Difluoroethylene Ethylene diamine Ethylene imine, Fluorine, HClO4 Hexalithium disilicide H2SO4 Metal acetylides or carbides, Magnesium boride, Mercuric sulfate, Oleum, Potassium permanganate, beta-Propiolactone Propylene oxide Rubidium carbide, Rubidium, acetylene carbide Sodium (with aqueous HCl), Sodium hydroxide Sodium tetraselenium, Sulfonic acid, Tetraselenium tetranitride, U3P4 , Vinyl acetate. Silver perchlorate with carbon tetrachloride in the presence of hydrochloric acid produces trichloromethyl perchlorate which detonates at 40 deg. C.

Section 6: Accidental Release Measures

Small Spill:
Dilute with water and mop up, or absorb with an inert dry material and place in an appropriate waste disposal container. If necessary: Neutralize the residue with a dilute solution of sodium carbonate.

Large Spill:
Corrosive liquid. Poisonous liquid. Stop leak if without risk. Absorb with DRY earth, sand or other non-combustible material. Do not get water inside container. Do not touch spilled material. Use water spray curtain to divert vapor drift. Use water spray to reduce vapors. Prevent entry into sewers, basements or confined areas; dike if needed. Call for assistance on disposal. Neutralize the residue with a dilute solution of sodium carbonate. Be careful that the product is not present at a concentration level above TLV. Check TLV on the MSDS and with local authorities.

Section 7: Handling and Storage

Precautions:
Keep locked up.. Keep container dry. Do not ingest. Do not breathe gas/fumes/ vapor/spray. Never add water to this product. In case of insufficient ventilation, wear suitable respiratory equipment. If ingested, seek medical advice immediately and show the container or the label. Avoid contact with skin and eyes. Keep away from incompatibles such as oxidizing agents, organic materials, metals, alkalis, moisture. May corrode metallic surfaces. Store in a metallic or coated fiberboard drum using a strong polyethylene inner package.

Storage: Keep container tightly closed. Keep container in a cool, well-ventilated area.

Section 8: Exposure Controls/Personal Protection

Engineering Controls:
Provide exhaust ventilation or other engineering controls to keep the airborne concentrations of vapors below their respective threshold limit value. Ensure that eyewash stations and safety showers are proximal to the work-station location.

Personal Protection:
Face shield. Full suit. Vapor respirator. Be sure to use an approved/certified respirator or equivalent. Gloves. Boots.

Personal Protection in Case of a Large Spill:
Splash goggles. Full suit. Vapor respirator. Boots. Gloves. A self contained breathing apparatus should be used to avoid inhalation of the product. Suggested protective clothing might not be sufficient; consult a specialist BEFORE handling this product.

Exposure Limits:
CEIL: 5 (ppm) from OSHA (PEL) [United States] CEIL: 7 (mg/m3) from OSHA (PEL) [United States] CEIL: 5 from NIOSH CEIL: 7 (mg/m3) from NIOSH TWA: 1 STEL: 5 (ppm) [United Kingdom (UK)] TWA: 2 STEL: 8 (mg/m3) [United Kingdom (UK)]Consult local authorities for acceptable exposure limits.

Section 9: Physical and Chemical Properties

Physical state and appearance: Liquid.

Odor: Pungent. Irritating (Strong.)

Taste: Not available.

Molecular Weight: Not applicable.

Color: Colorless to light yellow.

pH (1% soln/water): Acidic.

Boiling Point:
108.58 C @ 760 mm Hg (for 20.22% HCl in water) 83 C @ 760 mm Hg (for 31% HCl in water) 50.5 C (for 37% HCl in water)

Melting Point:
-62.25°C (-80°F) (20.69% HCl in water) -46.2 C (31.24% HCl in water) -25.4 C (39.17% HCl in water)

Critical Temperature: Not available.

Specific Gravity:
1.1- 1.19 (Water = 1) 1.10 (20%and 22% HCl solutions) 1.12 (24% HCl solution) 1.15 (29.57% HCl solution) 1.16 (32% HCl solution) 1.19 (37% and 38%HCl solutions)

Vapor Pressure: 16 kPa (@ 20°C) average

Vapor Density: 1.267 (Air = 1)

Volatility: Not available.

Odor Threshold: 0.25 to 10 ppm

Water/Oil Dist. Coeff.: Not available.

Ionicity (in Water): Not available.

Dispersion Properties: See solubility in water, diethyl ether.

Solubility: Soluble in cold water, hot water, diethyl ether.

Section 10: Stability and Reactivity Data

Stability: The product is stable.

Instability Temperature: Not available.

Conditions of Instability: Incompatible materials, water

Incompatibility with various substances:
Highly reactive with metals. Reactive with oxidizing agents, organic materials, alkalis, water.

Corrosivity:
Extremely corrosive in presence of aluminum, of copper, of stainless steel(304), of stainless steel(316). Non-corrosive in presence of glass.

Special Remarks on Reactivity:
Reacts with water especially when water is added to the product. Absorption of gaseous hydrogen chloride on mercuric sulfate becomes violent @ 125 deg. C. Sodium reacts very violently with gaseous hydrogen chloride. Calcium phosphide and hydrochloric acid undergo very energetic reaction. It reacts with oxidizers releasing chlorine gas. Incompatible with, alkali metals, carbides, borides, metal oxides, vinyl acetate, acetylides, sulphides, phosphides, cyanides, carbonates. Reacts with most metals to produce flammable Hydrogen gas. Reacts violently (moderate reaction with heat of evolution) with water especially when water is added to the product. Isolate hydrogen chloride from heat, direct sunlight, alkalies (reacts vigorously), organic materials, and oxidizers (especially nitric acid and chlorates), amines, metals, copper and alloys (e.g. brass), hydroxides, zinc (galvanized materials), lithium silicide (incandescence), sulfuric acid(increase in temperature and pressure) Hydrogen chloride gas is emitted when this product is in contact with sulfuric acid. Adsorption of Hydrochloric Acid onto silicon dioxide results in exothmeric reaction. Hydrogen chloride causes aldehydes and epoxides to violently polymerize. Hydrogen chloride or Hydrochloric Acid in contact with the folloiwng can cause explosion or ignition on contact or

Special Remarks on Corrosivity:

Highly corrosive. Incompatible with copper and copper alloys. It attacks nearly all metals (mercury, gold, platinium, tantalum, silver, and certain alloys are exceptions). It is one of the most corrosive of the nonoxidizing acids in contact with copper alloys. No corrosivity data on zinc, steel. Severe Corrosive effect on brass and bronze

Polymerization: Will not occur.

Section 11: Toxicological Information

Routes of Entry: Absorbed through skin. Dermal contact. Eye contact. Inhalation.

Toxicity to Animals:
Acute oral toxicity (LD50): 900 mg/kg [Rabbit]. Acute toxicity of the vapor (LC50): 1108 ppm, 1 hours [Mouse]. Acute toxicity of the vapor (LC50): 3124 ppm, 1 hours [Rat].

Chronic Effects on Humans:
CARCINOGENIC EFFECTS: Classified 3 (Not classifiable for human.) by IARC [Hydrochloric acid]. May cause damage to the following organs: kidneys, liver, mucous membranes, upper respiratory tract, skin, eyes, Circulatory System, teeth.

Other Toxic Effects on Humans:
Very hazardous in case of skin contact (corrosive, irritant, permeator), of ingestion, . Hazardous in case of eye contact (corrosive), of inhalation (lung corrosive).

Special Remarks on Toxicity to Animals:
Lowest Published Lethal Doses (LDL/LCL) LDL [Man] -Route: Oral; 2857 ug/kg LCL [Human] - Route: Inhalation; Dose: 1300 ppm/30M LCL [Rabbit] - Route: Inhalation; Dose: 4413 ppm/30M

Special Remarks on Chronic Effects on Humans:
May cause adverse reproductive effects (fetoxicity). May affect genetic material.

Special Remarks on other Toxic Effects on Humans:
Acute Potential Health Effects: Skin: Corrosive. Causes severe skin irritation and burns. Eyes: Corrosive. Causes severe eye irritation/conjuntivitis, burns, corneal necrosis. Inhalation: May be fatal if inhaled. Material is extremely destructive to tissue of the mucous membranes and upper respiratory tract. Inhalation of hydrochloric acid fumes produces nose, throat, and larryngeal burning, and irritation, pain and inflammation, coughing, sneezing, choking sensation, hoarseness, laryngeal spasms, upper respiratory tract edema, chest pains, as well has headache, and palpitations. Inhalation of high concentrations can result in corrosive burns, necrosis of bronchial epithelium, constriction of the larynx and bronchi, nasospetal perforation, glottal closure, occur, particularly if exposure is prolonged. May affect the liver. Ingestion: May be fatal if swallowed. Causes irritation and burning, ulceration, or perforation of the gastrointestinal tract and resultant peritonitis, gastric hemorrhage and infection. Can also cause nausea, vomitting (with "coffee ground" emesis), diarrhea, thirst, difficulty swallowing, salivation, chills, fever, uneasiness, shock, strictures and stenosis (esophogeal, gastric, pyloric). May affect behavior (excitement), the cardiovascular system (weak rapid pulse, tachycardia), respiration (shallow respiration), and urinary system (kidneys- renal failure, nephritis). Acute exposure via inhalation or ingestion can also cause erosion of tooth enamel. Chronic Potential Health Effects: dyspnea, bronchitis. Chemical pneumonitis and pulmonary edema can also

Section 12: Ecological Information

Ecotoxicity: Not available.

BOD5 and COD: Not available.

Products of Biodegradation:
Possibly hazardous short term degradation products are not likely. However, long term degradation products may arise.

Toxicity of the Products of Biodegradation: The products of degradation are less toxic than the product itself.

Special Remarks on the Products of Biodegradation: Not available.

Section 13: Disposal Considerations

Waste Disposal:

Waste must be disposed of in accordance with federal, state and local environmental control regulations.

Section 14: Transport Information

DOT Classification: Class 8: Corrosive material

Identification: : Hydrochloric acid, solution UNNA: 1789 PG: II

Special Provisions for Transport: Not available.

Section 15: Other Regulatory Information

Federal and State Regulations:
Connecticut hazardous material survey.: Hydrochloric acid Illinois toxic substances disclosure to employee act: Hydrochloric acid Illinois chemical safety act: Hydrochloric acid New York release reporting list: Hydrochloric acid Rhode Island RTK hazardous substances: Hydrochloric acid Pennsylvania RTK: Hydrochloric acid Minnesota: Hydrochloric acid Massachusetts RTK: Hydrochloric acid Massachusetts spill list: Hydrochloric acid New Jersey: Hydrochloric acid New Jersey spill list: Hydrochloric acid Louisiana RTK reporting list: Hydrochloric acid Louisiana spill reporting: Hydrochloric acid California Director's List of Hazardous Substances: Hydrochloric acid TSCA 8(b) inventory: Hydrochloric acid TSCA 4(a) proposed test rules: Hydrochloric acid SARA 302/304/311/312 extremely hazardous substances: Hydrochloric acid SARA 313 toxic chemical notification and release reporting: Hydrochloric acid CERCLA: Hazardous substances.: Hydrochloric acid: 5000 lbs. (2268 kg)

Other Regulations:
OSHA: Hazardous by definition of Hazard Communication Standard (29 CFR 1910.1200). EINECS: This product is on the European Inventory of Existing Commercial Chemical Substances.

Other Classifications:

WHMIS (Canada):
CLASS D-2A: Material causing other toxic effects (VERY TOXIC). CLASS E: Corrosive liquid.

DSCL (EEC):
R34- Causes burns. R37- Irritating to respiratory system. S26- In case of contact with eyes, rinse immediately with plenty of water and seek medical advice. S45- In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible).

HMIS (U.S.A.):

Health Hazard: 3

Fire Hazard: 0

Reactivity: 1

Personal Protection:

National Fire Protection Association (U.S.A.):

Health: 3

Flammability: 0

Reactivity: 1

Specific hazard:

Protective Equipment:
Gloves. Full suit. Vapor respirator. Be sure to use an approved/certified respirator or equivalent. Wear appropriate respirator when ventilation is inadequate. Face shield.

Section 16: Other Information

References:
-Hawley, G.G.. The Condensed Chemical Dictionary, 11e ed., New York N.Y., Van Nostrand Reinold, 1987. -SAX, N.I. Dangerous Properties of Indutrial Materials. Toronto, Van Nostrand Reinold, 6e ed. 1984. -The Sigma-Aldrich Library of Chemical Safety Data, Edition II. -Guide de la loi et du règlement sur le transport des marchandises dangeureuses au canada. Centre de conformité internatinal Ltée. 1986.

Other Special Considerations: Not available.

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Last Updated: 05/21/2013 12:00 PM

Material Safety Data Sheet
Isopropyl alcohol MSDS

Section 1: Chemical Product and Company Identification

Product Name: Isopropyl alcohol

Catalog Codes: SLI1153, SLI1579, SLI1906, SLI1246, SLI1432

CAS#: 67-63-0

RTECS: NT8050000

TSCA: TSCA 8(b) inventory: Isopropyl alcohol

CI#: Not available.

Synonym: 2-Propanol

Chemical Name: isopropanol

Chemical Formula: C3-H8-O

Contact Information:

Sciencelab.com, Inc.
14025 Smith Rd.
Houston, Texas 77396

US Sales: **1-800-901-7247**
International Sales: **1-281-441-4400**

Order Online: ScienceLab.com

CHEMTREC (24HR Emergency Telephone), call: 1-800-424-9300

International CHEMTREC, call: 1-703-527-3887

For non-emergency assistance, call: 1-281-441-4400

Section 2: Composition and Information on Ingredients

Composition:

Name	CAS #	% by Weight
Isopropyl alcohol	67-63-0	100

Toxicological Data on Ingredients: Isopropyl alcohol: ORAL (LD50): Acute: 5045 mg/kg [Rat]. 3600 mg/kg [Mouse]. 6410 mg/kg [Rabbit]. DERMAL (LD50): Acute: 12800 mg/kg [Rabbit].

Section 3: Hazards Identification

Potential Acute Health Effects:
Hazardous in case of eye contact (irritant), of ingestion, of inhalation. Slightly hazardous in case of skin contact (irritant, sensitizer, permeator).

Potential Chronic Health Effects:
Slightly hazardous in case of skin contact (sensitizer). CARCINOGENIC EFFECTS: A4 (Not classifiable for human or animal.) by ACGIH, 3 (Not classifiable for human.) by IARC. MUTAGENIC EFFECTS: Not available. TERATOGENIC EFFECTS: Not available. DEVELOPMENTAL TOXICITY: Classified Reproductive system/toxin/female, Development toxin [POSSIBLE]. The substance may be toxic to kidneys, liver, skin, central nervous system (CNS). Repeated or prolonged exposure to the substance can produce target organs damage.

Section 4: First Aid Measures

Eye Contact:
Check for and remove any contact lenses. In case of contact, immediately flush eyes with plenty of water for at least 15 minutes. Cold water may be used. Get medical attention.

Skin Contact:
Wash with soap and water. Cover the irritated skin with an emollient. Get medical attention if irritation develops. Cold water may be used.

Serious Skin Contact: Not available.

Inhalation:
If inhaled, remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Get medical attention if symptoms appear.

Serious Inhalation:
Evacuate the victim to a safe area as soon as possible. Loosen tight clothing such as a collar, tie, belt or waistband. If breathing is difficult, administer oxygen. If the victim is not breathing, perform mouth-to-mouth resuscitation. Seek medical attention.

Ingestion:
Do NOT induce vomiting unless directed to do so by medical personnel. Never give anything by mouth to an unconscious person. Loosen tight clothing such as a collar, tie, belt or waistband. Get medical attention if symptoms appear.

Serious Ingestion: Not available.

Section 5: Fire and Explosion Data

Flammability of the Product: Flammable.

Auto-Ignition Temperature: 399°C (750.2°F)

Flash Points: CLOSED CUP: 11.667°C (53°F) - 12.778 deg. C (55 deg. F) (TAG)

Flammable Limits: LOWER: 2% UPPER: 12.7%

Products of Combustion: These products are carbon oxides (CO, CO2).

Fire Hazards in Presence of Various Substances:
Highly flammable in presence of open flames and sparks, of heat. Flammable in presence of oxidizing materials. Non-flammable in presence of shocks.

Explosion Hazards in Presence of Various Substances:
Risks of explosion of the product in presence of mechanical impact: Not available. Explosive in presence of open flames and sparks, of heat.

Fire Fighting Media and Instructions:
Flammable liquid, soluble or dispersed in water. SMALL FIRE: Use DRY chemical powder. LARGE FIRE: Use alcohol foam, water spray or fog.

Special Remarks on Fire Hazards:
Vapor may travel considerable distance to source of ignition and flash back. CAUTION: MAY BURN WITH NEAR INVISIBLE FLAME. Hydrogen peroxide sharply reduces the autoignition temperature of Isopropyl alcohol. After a delay, Isopropyl alcohol ignites on contact with dioxgenyl tetrafluorborate, chromium trioxide, and potassium tert-butoxide. When heated to decomposition it emits acrid smoke and fumes.

Special Remarks on Explosion Hazards:
Secondary alcohols are readily autooxidized in contact with oxygen or air, forming ketones and hydrogen peroxide. It can become potentially explosive. It reacts with oxygen to form dangerously unstable peroxides which can concentrate and explode during distillation or evaporation. The presence of 2-butanone increases the reaction rate for peroxide formation. Explosive in the form of vapor when exposed to heat or flame. May form explosive mixtures with air. Isopropyl alcohol + phosgene forms isopropyl chloroformate and hydrogen chloride. In the presence of iron salts, thermal decompositon can occur, whicn in some cases can become explosive. A homogeneous mixture of concentrated peroxides + isopropyl alcohol are capable of detonation by shock or heat. Barium perchlorate + isopropyl alcohol gives the highly explosive alkyl perchlorates.

It forms explosive mixtures with trinitormethane and hydrogen peroxide. It produces a violent explosive reaction when heated with aluminum isopropoxide + crotonaldehyde. Mixtures of isopropyl alcohol + nitroform are explosive.

Section 6: Accidental Release Measures

Small Spill:
Dilute with water and mop up, or absorb with an inert dry material and place in an appropriate waste disposal container.

Large Spill:
Flammable liquid. Keep away from heat. Keep away from sources of ignition. Stop leak if without risk. Absorb with DRY earth, sand or other non-combustible material. Do not touch spilled material. Prevent entry into sewers, basements or confined areas; dike if needed. Be careful that the product is not present at a concentration level above TLV. Check TLV on the MSDS and with local authorities.

Section 7: Handling and Storage

Precautions:
Keep away from heat. Keep away from sources of ignition. Ground all equipment containing material. Do not ingest. Do not breathe gas/fumes/ vapor/spray. Avoid contact with eyes. Wear suitable protective clothing. In case of insufficient ventilation, wear suitable respiratory equipment. If ingested, seek medical advice immediately and show the container or the label. Keep away from incompatibles such as oxidizing agents, acids.

Storage:
Store in a segregated and approved area. Keep container in a cool, well-ventilated area. Keep container tightly closed and sealed until ready for use. Avoid all possible sources of ignition (spark or flame).

Section 8: Exposure Controls/Personal Protection

Engineering Controls:
Provide exhaust ventilation or other engineering controls to keep the airborne concentrations of vapors below their respective threshold limit value. Ensure that eyewash stations and safety showers are proximal to the work-station location.

Personal Protection:
Splash goggles. Lab coat. Vapor respirator. Be sure to use an approved/certified respirator or equivalent. Gloves.

Personal Protection in Case of a Large Spill:
Splash goggles. Full suit. Vapor respirator. Boots. Gloves. A self contained breathing apparatus should be used to avoid inhalation of the product. Suggested protective clothing might not be sufficient; consult a specialist BEFORE handling this product.

Exposure Limits:
TWA: 983 STEL: 1230 (mg/m3) [Australia] TWA: 200 STEL: 400 (ppm) from ACGIH (TLV) [United States] [1999] TWA: 980 STEL: 1225 (mg/m3) from NIOSH TWA: 400 STEL: 500 (ppm) from NIOSH TWA: 400 STEL: 500 (ppm) [United Kingdom (UK)] TWA: 999 STEL: 1259 (mg/m3) [United Kingdom (UK)] TWA: 400 STEL: 500 (ppm) from OSHA (PEL) [United States] TWA: 980 STEL: 1225 (mg/m3) from OSHA (PEL) [United States]Consult local authorities for acceptable exposure limits.

Section 9: Physical and Chemical Properties

Physical state and appearance: Liquid.

Odor:
Pleasant. Odor resembling that of a mixture of ethanol and acetone.

Taste: Bitter. (Slight.)

Molecular Weight: 60.1 g/mole

Color: Colorless.

pH (1% soln/water): Not available.

Boiling Point: 82.5°C (180.5°F)

Melting Point: -88.5°C (-127.3°F)

Critical Temperature: 235°C (455°F)

Specific Gravity: 0.78505 (Water = 1)

Vapor Pressure: 4.4 kPa (@ 20°C)

Vapor Density: 2.07 (Air = 1)

Volatility: Not available.

Odor Threshold:
22 ppm (Sittig, 1991) 700 ppm for unadapted panelists (Verschuren, 1983).

Water/Oil Dist. Coeff.: The product is equally soluble in oil and water; log(oil/water) = 0.1

Ionicity (in Water): Not available.

Dispersion Properties: See solubility in water, methanol, diethyl ether, n-octanol, acetone.

Solubility:
Easily soluble in cold water, hot water, methanol, diethyl ether, n-octanol, acetone. Insoluble in salt solution. Soluble in benzene. Miscible with most organic solvents including alcohol, ethyl alcohol, chloroform.

Section 10: Stability and Reactivity Data

Stability: The product is stable.

Instability Temperature: Not available.

Conditions of Instability: Heat, Ignition sources, incompatible materials

Incompatibility with various substances: Reactive with oxidizing agents, acids, alkalis.

Corrosivity: Non-corrosive in presence of glass.

Special Remarks on Reactivity:
Reacts violently with hydrogen + palladium combination, nitroform, oleum, $COCl_2$, aluminum triisopropoxide, oxidants Incompatible with acetaldehyde, chlorine, ethylene oxide, isocyanates, acids, alkaline earth, alkali metals, caustics, amines, crotonaldehyde, phosgene, ammonia. Isopropyl alcohol reacts with metallic aluminum at high temperatures. Isopropyl alcohol attacks some plastics, rubber, and coatings. Vigorous reaction with sodium dichromate + sulfuric acid.

Special Remarks on Corrosivity: May attack some forms of plastic, rubber and coating

Polymerization: Will not occur.

Section 11: Toxicological Information

Routes of Entry: Absorbed through skin. Dermal contact. Eye contact. Inhalation.

Toxicity to Animals:
WARNING: THE LC50 VALUES HEREUNDER ARE ESTIMATED ON THE BASIS OF A 4-HOUR EXPOSURE. Acute oral toxicity (LD50): 3600 mg/kg [Mouse]. Acute dermal toxicity (LD50): 12800 mg/kg [Rabbit]. Acute toxicity of the vapor (LC50): 16000 8 hours [Rat].

Chronic Effects on Humans:
CARCINOGENIC EFFECTS: A4 (Not classifiable for human or animal.) by ACGIH, 3 (Not classifiable for human.) by IARC. DEVELOPMENTAL TOXICITY: Classified Reproductive system/toxin/female, Development toxin [POSSIBLE]. May cause damage to the following organs: kidneys, liver, skin, central nervous system (CNS).

Other Toxic Effects on Humans:
Hazardous in case of ingestion, of inhalation. Slightly hazardous in case of skin contact (irritant, sensitizer, permeator).

Special Remarks on Toxicity to Animals: Not available.

Special Remarks on Chronic Effects on Humans:
May cause adverse reproductive/teratogenic effects (fertility, fetoxicity, developmental abnormalities(developmental toxin)) based on animal studies. Detected in maternal milk in human.

Special Remarks on other Toxic Effects on Humans:
Acute Potential Health Effects: Skin: May cause mild skin irritation, and sensitization. Eyes: Can cause eye irritation. Inhalation: Breathing in small amounts of this material during normal handling is not likely to cause harmful effects. However, breathing large amounts may be harmful and may affect the respiratory system and mucous membranes (irritation), behavior and brain (Central nervous system depression - headache, dizziness, drowsiness, stupor, incoordination, unconciousness, coma and possible death), peripheral nerve and senstation, blood, urinary system, and liver. Ingestion: Swallowing small amouts during normal handling is not likely to cause harmful effects. Swallowing large amounts may be harmful. Swallowing large amounts may cause gastrointestinal tract irritation with nausea, vomiting and diarrhea, abdominal pain. It also may affect the urinary system, cardiovascular system, sense organs, behavior or central nervous system (somnolence, generally depressed activity, irritability, headache, dizziness, drowsiness), liver, and respiratory system (breathing difficulty). Chronic Potential Health Effects: May cause defatting of the skin and dermatitis and allergic reaction. May cause adverse reproductive effects based on animal data (studies).

Section 12: Ecological Information

Ecotoxicity: Ecotoxicity in water (LC50): 100000 mg/l 96 hours [Fathead Minnow]. 64000 mg/l 96 hours [Fathead Minnow].

BOD5 and COD: Not available.

Products of Biodegradation:
Possibly hazardous short term degradation products are not likely. However, long term degradation products may arise.

Toxicity of the Products of Biodegradation: The product itself and its products of degradation are not toxic.

Special Remarks on the Products of Biodegradation: Not available.

Section 13: Disposal Considerations

Waste Disposal:
Waste must be disposed of in accordance with federal, state and local environmental control regulations.

Section 14: Transport Information

DOT Classification: CLASS 3: Flammable liquid.

Identification: : Isopropyl Alcohol UNNA: 1219 PG: II

Special Provisions for Transport: Not available.

Section 15: Other Regulatory Information

Federal and State Regulations:
Connecticut hazardous material survey.: Isopropyl alcohol Illinois toxic substances disclosure to employee act: Isopropyl alcohol Rhode Island RTK hazardous substances: Isopropyl alcohol Pennsylvania RTK: Isopropyl alcohol Florida: Isopropyl alcohol Minnesota: Isopropyl alcohol Massachusetts RTK: Isopropyl alcohol New Jersey: Isopropyl alcohol New Jersey spill list: Isopropyl alcohol Director's list of Hazardous Substances: Isopropyl alcohol Tennesee: Isopropyl alcohol TSCA 8(b) inventory: Isopropyl alcohol TSCA 4(a) final testing order: Isopropyl alcohol TSCA 8(a) IUR: Isopropyl alcohol TSCA 8(d) H

and S data reporting: Isopropyl alcohol: Effective date: 12/15/86 Sunset Date: 12/15/96 TSCA 12(b) one time export: Isopropyl alcohol SARA 313 toxic chemical notification and release reporting: Isopropyl alcohol

Other Regulations:
OSHA: Hazardous by definition of Hazard Communication Standard (29 CFR 1910.1200). EINECS: This product is on the European Inventory of Existing Commercial Chemical Substances.

Other Classifications:

WHMIS (Canada):
CLASS B-2: Flammable liquid with a flash point lower than 37.8°C (100°F). CLASS D-2B: Material causing other toxic effects (TOXIC).

DSCL (EEC):
R11- Highly flammable. R36- Irritating to eyes. S7- Keep container tightly closed. S16- Keep away from sources of ignition - No smoking. S24/25- Avoid contact with skin and eyes. S26- In case of contact with eyes, rinse immediately with plenty of water and seek medical advice.

HMIS (U.S.A.):

Health Hazard: 2

Fire Hazard: 3

Reactivity: 0

Personal Protection: h

National Fire Protection Association (U.S.A.):

Health: 1

Flammability: 3

Reactivity: 0

Specific hazard:

Protective Equipment:
Gloves. Lab coat. Vapor respirator. Be sure to use an approved/certified respirator or equivalent. Wear appropriate respirator when ventilation is inadequate. Splash goggles.

Section 16: Other Information

References: Not available.

Other Special Considerations: Not available.

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Last Updated: 05/21/2013 12:00 PM

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Material Safety Data Sheet
Sodium bicarbonate MSDS

Section 1: Chemical Product and Company Identification

Product Name: Sodium bicarbonate

Catalog Codes: SLS3241, SLS2446, SLS3868

CAS#: 144-55-8

RTECS: VZ0950000

TSCA: TSCA 8(b) inventory: Sodium bicarbonate

CI#: Not available.

Synonym: Baking Soda; Bicarbonate of soda; Sodium acid carbonate; Monosodium carbonate; Sodium hydrogen carbonate; Carbonic acid monosodium salt

Chemical Name: Sodium Bicarbonate

Chemical Formula: NaHCO3

Contact Information:

Sciencelab.com, Inc.
14025 Smith Rd.
Houston, Texas 77396

US Sales: **1-800-901-7247**
International Sales: **1-281-441-4400**

Order Online: ScienceLab.com

CHEMTREC (24HR Emergency Telephone), call: 1-800-424-9300

International CHEMTREC, call: 1-703-527-3887

For non-emergency assistance, call: 1-281-441-4400

Section 2: Composition and Information on Ingredients

Composition:

Name	CAS #	% by Weight
Sodium bicarbonate	144-55-8	100

Toxicological Data on Ingredients: Not applicable.

Section 3: Hazards Identification

Potential Acute Health Effects: Slightly hazardous in case of skin contact (irritant), of eye contact (irritant), of ingestion, of inhalation.

Potential Chronic Health Effects:
CARCINOGENIC EFFECTS: Not available. MUTAGENIC EFFECTS: Not available. TERATOGENIC EFFECTS: Not available. DEVELOPMENTAL TOXICITY: Not available. Repeated or prolonged exposure is not known to aggravate medical condition.

Section 4: First Aid Measures

Eye Contact:
Check for and remove any contact lenses. In case of contact, immediately flush eyes with plenty of water for at least 15 minutes. Cold water may be used. Get medical attention if irritation occurs.

Skin Contact:
Wash with soap and water. Cover the irritated skin with an emollient. Get medical attention if irritation develops. Cold water may be used.

Serious Skin Contact: Not available.

Inhalation:
If inhaled, remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Get medical attention.

Serious Inhalation: Not available.

Ingestion:
Do NOT induce vomiting unless directed to do so by medical personnel. Never give anything by mouth to an unconscious person. Loosen tight clothing such as a collar, tie, belt or waistband. Get medical attention if symptoms appear.

Serious Ingestion: Not available.

Section 5: Fire and Explosion Data

Flammability of the Product: Non-flammable.

Auto-Ignition Temperature: Not applicable.

Flash Points: Not applicable.

Flammable Limits: Not applicable.

Products of Combustion: Not available.

Fire Hazards in Presence of Various Substances: Not applicable.

Explosion Hazards in Presence of Various Substances:
Risks of explosion of the product in presence of mechanical impact: Not available. Risks of explosion of the product in presence of static discharge: Not available.

Fire Fighting Media and Instructions: Not applicable.

Special Remarks on Fire Hazards: When heated to decomposition it emits acrid smoke and irritating fumes.

Special Remarks on Explosion Hazards: Not available.

Section 6: Accidental Release Measures

Small Spill:
Use appropriate tools to put the spilled solid in a convenient waste disposal container. Finish cleaning by spreading water on the contaminated surface and dispose of according to local and regional authority requirements.

Large Spill:
Use a shovel to put the material into a convenient waste disposal container. Finish cleaning by spreading water on the contaminated surface and allow to evacuate through the sanitary system.

Section 7: Handling and Storage

Precautions:
Do not ingest. Do not breathe dust. If ingested, seek medical advice immediately and show the container or the label. Keep away from incompatibles such as acids.

Storage: Keep container tightly closed. Keep container in a cool, well-ventilated area.

Section 8: Exposure Controls/Personal Protection

Engineering Controls:
Use process enclosures, local exhaust ventilation, or other engineering controls to keep airborne levels below recommended exposure limits. If user operations generate dust, fume or mist, use ventilation to keep exposure to airborne contaminants below the exposure limit.

Personal Protection: Safety glasses. Lab coat. Dust respirator. Be sure to use an approved/certified respirator or equivalent. Gloves.

Personal Protection in Case of a Large Spill:
Splash goggles. Full suit. Dust respirator. Boots. Gloves. A self contained breathing apparatus should be used to avoid inhalation of the product. Suggested protective clothing might not be sufficient; consult a specialist BEFORE handling this product.

Exposure Limits: Not available.

Section 9: Physical and Chemical Properties

Physical state and appearance: Solid.

Odor: Odorless.

Taste: Saline. Alkaline.

Molecular Weight: 84.01g/mole

Color: White.

pH (1% soln/water): Not available.

Boiling Point: Not available.

Melting Point: Not available.

Critical Temperature: Not available.

Specific Gravity: Density: 2.159 (Water = 1)

Vapor Pressure: Not applicable.

Vapor Density: Not available.

Volatility: Not available.

Odor Threshold: Not available.

Water/Oil Dist. Coeff.: Not available.

Ionicity (in Water): Not available.

Dispersion Properties: See solubility in water.

Solubility:
Soluble in cold water. Slightly soluble in alcohol. Solubility in Water: 6.4, 7.6, 8.7, 10.0, 11.3, 12.7, 14.2, 16.5, 19.1 g/100 solution at 0, 10, 20, 30, 40, 50, 60, 80, adn 100 deg. C, respectively. Solubility in Water: 6.9, 8,2, 9.6, 11.1, 12.7, 14.5, 16.5, 19.7, and 23.6 g/100g water at 0, 10, 20, 30, 40, 50, 60, 80, 100 deg. C, respectively.

Section 10: Stability and Reactivity Data

Stability: The product is stable.

Instability Temperature: Not available.

Conditions of Instability: Incompatible materials, Moisture. Stable in dry air, but slowly decomposes in moist air.

Incompatibility with various substances: Reactive with acids.

Corrosivity: Non-corrosive in presence of glass.

Special Remarks on Reactivity:
Reacts with acids to form carbon dioxide. Dangerous reaction with monoammonium phosphate or a sodium-potassium alloy.

Special Remarks on Corrosivity: Not available.

Polymerization: Will not occur.

Section 11: Toxicological Information

Routes of Entry: Inhalation. Ingestion.

Toxicity to Animals: Acute oral toxicity (LD50): 3360 mg/kg [Mouse].

Chronic Effects on Humans: Not available.

Other Toxic Effects on Humans: Slightly hazardous in case of skin contact (irritant), of ingestion, of inhalation.

Special Remarks on Toxicity to Animals: Not available.

Special Remarks on Chronic Effects on Humans:
Sodium Bicarbonate as produced genetic effects in rats (unscheduled DNA synthesis). However, no affects have been found in humans.

Special Remarks on other Toxic Effects on Humans:
Acute Potential Health Effects: Skin: May cause mild skin irritation. Eyes: May cause mild eye irritation. Inhalation: May cause respiratory tract irritation. Symptoms may include coughing and sneezing. Ingestion: Symptoms of overexposure to Sodium Bicarbonate include thirst, abdominal pain, gastroenteritis, and inflammation of the digestive tract. Chronic Potential Health Effects: Skin: Repeated or prolonged skin contact may cause irritation, drying or cracking of the skin. Ingestion and Inhalation: Chronic toxicity usually occurs within 4 to 10 days following ingestion of very large amounts. Repeated or prolonged ingestion or inhalation of large amounts may cause metabolic abnormalities, and sodium retention. Metabolic abnormalities such as acidosis, hypernatremia, hypochloremia, alkalosis, hypocalcemia, or sodium retention may affect the blood, kidneys, respiration (cyanosis, apnea secondary to metabolic acidosis or pulmonary edema), and cardiovascular system (tachycardia, hypotension). Severe toxicity may also affect behavior/central nervous system/nervous system. Neurological changes may result from metabolic abnormalities. These may include fatigue, irritability, dizziness, mental confusion, paresthesia, seizures, tetany, cerebral edema Medical Conditions Aggravated by Exposure: Persons with pre-existing skin conditions might have increased sensitivity. Predisposing conditions that contribute to a mild alkali syndrome include, renal disease, dehydration, adn electrolyte imbalance, hypertension, sarcoidosis, congestive heart failure, edema, or other sodium retaining conditions.

Section 12: Ecological Information

Ecotoxicity: Not available.

BOD5 and COD: Not available.

Products of Biodegradation:
Possibly hazardous short term degradation products are not likely. However, long term degradation products may arise.

Toxicity of the Products of Biodegradation: The product itself and its products of degradation are not toxic.

Special Remarks on the Products of Biodegradation: Not available.

Section 13: Disposal Considerations

Waste Disposal:
Waste must be disposed of in accordance with federal, state and local environmental control regulations.

Section 14: Transport Information

DOT Classification: Not a DOT controlled material (United States).

Identification: Not applicable.

Special Provisions for Transport: Not applicable.

Section 15: Other Regulatory Information

Federal and State Regulations: TSCA 8(b) inventory: Sodium bicarbonate

Other Regulations: Not available.

Other Classifications:

WHMIS (Canada): Not controlled under WHMIS (Canada).

DSCL (EEC):
This product is not classified according to the EU regulations. Not applicable.

HMIS (U.S.A.):

Health Hazard: 1

Fire Hazard: 0

Reactivity: 0

Personal Protection: E

National Fire Protection Association (U.S.A.):

Health: 1

Flammability: 0

Reactivity: 0

Specific hazard:

Protective Equipment:
Gloves. Lab coat. Dust respirator. Be sure to use an approved/certified respirator or equivalent. Safety glasses.

Section 16: Other Information

References: Not available.

Other Special Considerations: Not available.

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Material Safety Data Sheet
Sodium carbonate MSDS

Section 1: Chemical Product and Company Identification

Product Name: Sodium carbonate

Catalog Codes: SLS3481, SLS1264, SLS4105, SLS1894, SLS3316

CAS#: 497-19-8

RTECS: VZ4050000

TSCA: TSCA 8(b) inventory: Sodium carbonate

CI#: Not available.

Synonym: Crystal Carbonate, Disodium Carbonate, Sal Soda, Soda Asha, Washing Soda

Chemical Name: Sodium Carbonate, Anhydrous

Chemical Formula: Na2-C-O3

Contact Information:

Sciencelab.com, Inc.
14025 Smith Rd.
Houston, Texas 77396

US Sales: **1-800-901-7247**
International Sales: **1-281-441-4400**

Order Online: ScienceLab.com

CHEMTREC (24HR Emergency Telephone), call: 1-800-424-9300

International CHEMTREC, call: 1-703-527-3887

For non-emergency assistance, call: 1-281-441-4400

Section 2: Composition and Information on Ingredients

Composition:

Name	CAS #	% by Weight
Sodium carbonate	497-19-8	100

Toxicological Data on Ingredients: Sodium carbonate: ORAL (LD50): Acute: 4090 mg/kg [Rat]. 6600 mg/kg [Mouse]. DUST (LC50): Acute: 2300 mg/m 2 hours [Rat]. 1200 mg/m 2 hours [Mouse].

Section 3: Hazards Identification

Potential Acute Health Effects: Hazardous in case of skin contact (irritant), of eye contact (irritant), of ingestion, of inhalation (lung irritant).

Potential Chronic Health Effects:
Slightly hazardous in case of skin contact (sensitizer). CARCINOGENIC EFFECTS: Not available. MUTAGENIC EFFECTS: Not available. TERATOGENIC EFFECTS: Not available. DEVELOPMENTAL TOXICITY: Not available. The substance may be toxic to upper respiratory tract, skin, eyes. Repeated or prolonged exposure to the substance can produce target organs damage.

Section 4: First Aid Measures

Eye Contact:
Check for and remove any contact lenses. In case of contact, immediately flush eyes with plenty of water for at least 15 minutes. Cold water may be used. Get medical attention.

Skin Contact:
In case of contact, immediately flush skin with plenty of water. Cover the irritated skin with an emollient. Remove contaminated clothing and shoes. Cold water may be used.Wash clothing before reuse. Thoroughly clean shoes before reuse. Get medical attention.

Serious Skin Contact:
Wash with a disinfectant soap and cover the contaminated skin with an anti-bacterial cream. Seek immediate medical attention.

Inhalation:
If inhaled, remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Get medical attention.

Serious Inhalation: Not available.

Ingestion:
Do NOT induce vomiting unless directed to do so by medical personnel. Never give anything by mouth to an unconscious person. Loosen tight clothing such as a collar, tie, belt or waistband. Get medical attention if symptoms appear.

Serious Ingestion: Not available.

Section 5: Fire and Explosion Data

Flammability of the Product: Non-flammable.

Auto-Ignition Temperature: Not applicable.

Flash Points: Not applicable.

Flammable Limits: Not applicable.

Products of Combustion: Emits Na2O fumes when heated to decompositon.

Fire Hazards in Presence of Various Substances: Not applicable.

Explosion Hazards in Presence of Various Substances:
Risks of explosion of the product in presence of mechanical impact: Not available. Risks of explosion of the product in presence of static discharge: Not available.

Fire Fighting Media and Instructions: Not applicable.

Special Remarks on Fire Hazards:
Sodium carbonate can ignite and burn fiercely in contact with fluoride. Sodium Carbonate in contact with fluorine decomposed at ordinary temperature with incandescence.

Special Remarks on Explosion Hazards:
Reacts explosively with red-hot aluminum metal. Sodium carbonate + ammonia in arabic gum solution will explode.

Section 6: Accidental Release Measures

Small Spill:
Use appropriate tools to put the spilled solid in a convenient waste disposal container. If necessary: Neutralize the residue with a dilute solution of acetic acid. Finish cleaning by spreading water on the contaminated surface and dispose of according to local and regional authority requirements.

Large Spill:
Use a shovel to put the material into a convenient waste disposal container. Neutralize the residue with a dilute solution of acetic acid. Finish cleaning by spreading water on the contaminated surface and allow to evacuate through the sanitary system.

Section 7: Handling and Storage

Precautions:
Do not ingest. Do not breathe dust. Wear suitable protective clothing. In case of insufficient ventilation, wear suitable respiratory equipment. If ingested, seek medical advice immediately and show the container or the label. Avoid contact with skin and eyes. Keep away from incompatibles such as acids.

Storage:
Hygroscopic. Keep container tightly closed. Keep container in a cool, well-ventilated area. Do not store above 24°C (75.2°F). Hygroscopic

Section 8: Exposure Controls/Personal Protection

Engineering Controls:
Use process enclosures, local exhaust ventilation, or other engineering controls to keep airborne levels below recommended exposure limits. If user operations generate dust, fume or mist, use ventilation to keep exposure to airborne contaminants below the exposure limit.

Personal Protection:
Splash goggles. Lab coat. Dust respirator. Be sure to use an approved/certified respirator or equivalent. Gloves.

Personal Protection in Case of a Large Spill:
Splash goggles. Full suit. Dust respirator. Boots. Gloves. A self contained breathing apparatus should be used to avoid inhalation of the product. Suggested protective clothing might not be sufficient; consult a specialist BEFORE handling this product.

Exposure Limits: Not available.

Section 9: Physical and Chemical Properties

Physical state and appearance: Solid. (Solid powder.)

Odor: Odorless.

Taste: Alkaline.

Molecular Weight: 105.99 g/mole

Color: White.

pH (1% soln/water): 11.5 [Basic.]

Boiling Point: Not available.

Melting Point: 851°C (1563.8°F)

Critical Temperature: Not available.

Specific Gravity: Density: 2.532 (Water = 1)

Vapor Pressure: Not applicable.

Vapor Density: Not available.

Volatility: Not available.

Odor Threshold: Not available.

Water/Oil Dist. Coeff.: Not available.

Ionicity (in Water): Not available.

Dispersion Properties: See solubility in water.

Solubility:

Soluble in hot water, glycerol. Partially soluble in cold water. Insoluble in acetone, alcohol.

Section 10: Stability and Reactivity Data

Stability: The product is stable.

Instability Temperature: Not available.

Conditions of Instability: Incompatible materials, moisture

Incompatibility with various substances:
Reactive with acids. Slightly reactive to reactive with moisture.

Corrosivity: Non-corrosive in presence of glass.

Special Remarks on Reactivity:
Hygroscopic. Combines with water with evolution of heat. Incompatible with phosphorus pentoxide, lithium, fluorine, fluoride, ammonia + silver nitrate, 2,4,6-trinitrotoluene, ammonia, acids, sodium sulfide + water, hydrogen peroxide, red hot alumium metal, sodium sulfide, zinc, calcium hydroxide. Sodium Carbonate is decomposed by acids with effervescence. Reacts violently with F2, Lithium, and 2,4,6-trinitrotoluene. Sodium begins to decompose at 400 C to evolve CO2.

Special Remarks on Corrosivity: Hot concentrated solutions of sodium carbonate are mildly corrosive to steel.

Polymerization: Will not occur.

Section 11: Toxicological Information

Routes of Entry: Inhalation. Ingestion.

Toxicity to Animals:
WARNING: THE LC50 VALUES HEREUNDER ARE ESTIMATED ON THE BASIS OF A 4-HOUR EXPOSURE. Acute oral toxicity (LD50): 4090 mg/kg [Rat]. Acute toxicity of the dust (LC50): 1200 mg/m3 2 hours [Mouse].

Chronic Effects on Humans: May cause damage to the following organs: upper respiratory tract, skin, eyes.

Other Toxic Effects on Humans: Hazardous in case of skin contact (irritant), of ingestion, of inhalation (lung irritant).

Special Remarks on Toxicity to Animals: LDL (Lowest Published Lethal Dose) [Man] - Route: Oral; Dose: 714 mg/kg

Special Remarks on Chronic Effects on Humans: May cause adverse reproductive effects based on animal test data

Special Remarks on other Toxic Effects on Humans:
Acute Potential Health Effects: Skin: Causes skin irritation with possible burns depending on the concentration, site (abraded or intact skin), and duration of exposure. Eyes: Causes eye irritation and possible burns. Concentrated solutions may cause permanent corneal injury (permanent corneal opacity). Ingestion: Sodium carbonate ingestion may cause irritation of the digestive tract resulting in nausea, vomiting, diarrhea, thirst, abdominal pain depending on concentration and amount ingested. May also affect the cardiovascular system . Inhalation: Dust may cause respiratory tract and mucous membrane irritation with coughing and shortness of breath (dyspnea), pulmonary edema. Chronic Potential Health Effects: Chronic inhalation may result in decreased pulmonary function, nasal congestion, nosebleeds, perforation of the nasal septum. Other effects of chronic exposure are skin (dermatitis and ulceration), and gastrointestinal complaints. However, the effects of chronic exposure seem to be reversible if exposure is decreased.

Section 12: Ecological Information

Ecotoxicity: Not available.

BOD5 and COD: Not available.

Products of Biodegradation:
Possibly hazardous short term degradation products are not likely. However, long term degradation products may arise.

Toxicity of the Products of Biodegradation: The products of degradation are less toxic than the product itself.

Special Remarks on the Products of Biodegradation: Not available.

Section 13: Disposal Considerations

Waste Disposal:
Waste must be disposed of in accordance with federal, state and local environmental control regulations.

Section 14: Transport Information

DOT Classification: Not a DOT controlled material (United States).

Identification: Not applicable.

Special Provisions for Transport: Not applicable.

Section 15: Other Regulatory Information

Federal and State Regulations: TSCA 8(b) inventory: Sodium carbonate

Other Regulations: EINECS: This product is on the European Inventory of Existing Commercial Chemical Substances.

Other Classifications:

WHMIS (Canada): CLASS D-2B: Material causing other toxic effects (TOXIC).

DSCL (EEC):
R36/37/38- Irritating to eyes, respiratory system and skin. S22- Do not breathe dust. S26- In case of contact with eyes, rinse immediately with plenty of water and seek medical advice.

HMIS (U.S.A.):

Health Hazard: 2

Fire Hazard: 0

Reactivity: 1

Personal Protection: E

National Fire Protection Association (U.S.A.):

Health: 2

Flammability: 0

Reactivity: 1

Specific hazard:

Protective Equipment:
Gloves. Lab coat. Dust respirator. Be sure to use an approved/certified respirator or equivalent. Wear appropriate respirator when ventilation is inadequate. Splash goggles.

Section 16: Other Information

References: Not available.

Other Special Considerations: Not available.

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Material Safety Data Sheet
Sodium sulfate anhydrous MSDS

Section 1: Chemical Product and Company Identification

Product Name: Sodium sulfate anhydrous

Catalog Codes: SLS3685, SLS1465, SLS2089, SLS3511, SLS1294

CAS#: 7757-82-6

RTECS: WE1650000

TSCA: TSCA 8(b) inventory: Sodium sulfate anhydrous

CI#: Not available.

Synonym:

Chemical Name: Sodium Sulfate Anhydrous

Chemical Formula: Na2SO4

Contact Information:

Sciencelab.com, Inc.
14025 Smith Rd.
Houston, Texas 77396

US Sales: **1-800-901-7247**
International Sales: **1-281-441-4400**

Order Online: ScienceLab.com

CHEMTREC (24HR Emergency Telephone), call: 1-800-424-9300

International CHEMTREC, call: 1-703-527-3887

For non-emergency assistance, call: 1-281-441-4400

Section 2: Composition and Information on Ingredients

Composition:

Name	CAS #	% by Weight
Sodium sulfate anhydrous	7757-82-6	100

Toxicological Data on Ingredients: Sodium sulfate anhydrous: ORAL (LD50): Acute: 5989 mg/kg [Mouse].

Section 3: Hazards Identification

Potential Acute Health Effects:
Hazardous in case of eye contact (irritant). Slightly hazardous in case of skin contact (irritant), of ingestion, of inhalation.

Potential Chronic Health Effects:
CARCINOGENIC EFFECTS: Not available. MUTAGENIC EFFECTS: Not available. TERATOGENIC EFFECTS: Not available. DEVELOPMENTAL TOXICITY: Not available. Repeated or prolonged exposure is not known to aggravate medical condition.

Section 4: First Aid Measures

Eye Contact:
Check for and remove any contact lenses. In case of contact, immediately flush eyes with plenty of water for at least 15 minutes. Cold water may be used. Get medical attention.

Skin Contact:
Wash with soap and water. Cover the irritated skin with an emollient. Get medical attention if irritation develops. Cold water may be used.

Serious Skin Contact: Not available.

Inhalation:
If inhaled, remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Get medical attention.

Serious Inhalation: Not available.

Ingestion:
Do NOT induce vomiting unless directed to do so by medical personnel. Never give anything by mouth to an unconscious person. Loosen tight clothing such as a collar, tie, belt or waistband. Get medical attention if symptoms appear.

Serious Ingestion: Not available.

Section 5: Fire and Explosion Data

Flammability of the Product: Non-flammable.

Auto-Ignition Temperature: Not applicable.

Flash Points: Not applicable.

Flammable Limits: Not applicable.

Products of Combustion: Not available.

Fire Hazards in Presence of Various Substances: Not applicable.

Explosion Hazards in Presence of Various Substances:
Risks of explosion of the product in presence of mechanical impact: Not available. Risks of explosion of the product in presence of static discharge: Not available.

Fire Fighting Media and Instructions: Not applicable.

Special Remarks on Fire Hazards: Not available.

Special Remarks on Explosion Hazards: At a temperature of 800 C, sodium sulfate and aluminum will explode.

Section 6: Accidental Release Measures

Small Spill:
Use appropriate tools to put the spilled solid in a convenient waste disposal container. Finish cleaning by spreading water on the contaminated surface and dispose of according to local and regional authority requirements.

Large Spill:
Use a shovel to put the material into a convenient waste disposal container. Finish cleaning by spreading water on the contaminated surface and allow to evacuate through the sanitary system.

Section 7: Handling and Storage

Precautions:
Do not ingest. Do not breathe dust. Avoid contact with eyes. Wear suitable protective clothing. If ingested, seek medical advice immediately and show the container or the label. Keep away from incompatibles such as oxidizing agents, metals.

Storage: Keep container tightly closed. Keep container in a cool, well-ventilated area. Hygroscopic

Section 8: Exposure Controls/Personal Protection

Engineering Controls:
Use process enclosures, local exhaust ventilation, or other engineering controls to keep airborne levels below recommended exposure limits. If user operations generate dust, fume or mist, use ventilation to keep exposure to airborne contaminants below the exposure limit.

Personal Protection:
Splash goggles. Lab coat. Dust respirator. Be sure to use an approved/certified respirator or equivalent. Gloves.

Personal Protection in Case of a Large Spill:
Splash goggles. Full suit. Dust respirator. Boots. Gloves. A self contained breathing apparatus should be used to avoid inhalation of the product. Suggested protective clothing might not be sufficient; consult a specialist BEFORE handling this product.

Exposure Limits: Not available.

Section 9: Physical and Chemical Properties

Physical state and appearance:
Solid. (Crystals solid. Crystalline powder. Granular solid. Powdered solid.)

Odor: Odorless.

Taste: Bitter. Saline.

Molecular Weight: 142.06 g/mole

Color: White.

pH (1% soln/water): Not available.

Boiling Point: 1100°C (2012°F)

Melting Point: 888°C (1630.4°F)

Critical Temperature: Not available.

Specific Gravity: 2.671 (Water = 1)

Vapor Pressure: Not applicable.

Vapor Density: Not available.

Volatility: Not available.

Odor Threshold: Not available.

Water/Oil Dist. Coeff.: Not available.

Ionicity (in Water): Not available.

Dispersion Properties: See solubility in water.

Solubility:
Soluble in cold water, hydrogen iodide, and glycerol.. Insoluble in alcohol.

Section 10: Stability and Reactivity Data

Stability: The product is stable.

Instability Temperature: Not available.

Conditions of Instability: Excess dust generation, incompatible materials

Incompatibility with various substances: Reactive with oxidizing agents, metals.

Corrosivity: Non-corrosive in presence of glass.

Special Remarks on Reactivity:
Hygroscopic. Sodium sulfate reacts violently with magnesium. Also incompatible with aluminum, potassium, mercury, lead, calcium, silver, barium, ammonium ions, and strontium. Sulfates give precipitates with salts of lead, barium, strontium, and calcium. Silver and mercury form slightly soluble salts. Alcohol preciptates most sulfates out of solution.

Special Remarks on Corrosivity:
The rates of corrosion of iron and steel in water are a function of the specific mineral quality as well as the alkalinity and pH values. Sodium sulfate ... is a strong contributor to the rate of corrosion. For example, in water with 400 mg/l of alkalinity (as CaCO3) at pH 7, the corrosion rate will be zero at 200 mg/l of Na2SO4, but when the concentration of sodium sulfate is 400 mg/l, the corrosion rate will be about 100 mg per square cm per day.

Polymerization: Will not occur.

Section 11: Toxicological Information

Routes of Entry: Inhalation. Ingestion.

Toxicity to Animals: Acute oral toxicity (LD50): 5989 mg/kg [Mouse].

Chronic Effects on Humans: Not available.

Other Toxic Effects on Humans: Slightly hazardous in case of skin contact (irritant), of ingestion, of inhalation.

Special Remarks on Toxicity to Animals: Not available.

Special Remarks on Chronic Effects on Humans:
May cause adverse reproductive effects (fetotoxicity) based on animal studies. Human human data found May cause cancer (tumorigenic) based on animal studies. No human data found. Placental absorption of sulfate ion has been characterized. Sulfate ion levels at term are somewhat higher in fetal than in maternal blood.

Special Remarks on other Toxic Effects on Humans:
Acute Potential Health Effects: Skin: May cause irritation, although it is not known to be an irritant. Eyes: May cause eye irritation. Ingestion: Saline cathartics (laxitives) are poorly absorbed from the gastrointestinal tract; hence, systemic toxicity is unlikely unless massive amounts have been ingested. Ingestion of large amounts may cause gastrointestinal (digestive) tract irritation with abdominal pain, nausea, vomiting, diarrhea. Low hazard for usual industrial handling. Inhalation: May cause respiratory tract irritation. Low hazard for usual industrial handling.

Section 12: Ecological Information

Ecotoxicity: Not available.

BOD5 and COD: Not available.

Products of Biodegradation:
Possibly hazardous short term degradation products are not likely. However, long term degradation products may arise.

Toxicity of the Products of Biodegradation: The product itself and its products of degradation are not toxic.

Special Remarks on the Products of Biodegradation: Not available.

Section 13: Disposal Considerations

Waste Disposal:
Waste must be disposed of in accordance with federal, state and local environmental control regulations.

Section 14: Transport Information

DOT Classification: Not a DOT controlled material (United States).

Identification: Not applicable.

Special Provisions for Transport: Not applicable.

Section 15: Other Regulatory Information

Federal and State Regulations:
Pennsylvania RTK: Sodium sulfate anhydrous Massachusetts RTK: Sodium sulfate anhydrous TSCA 8(b) inventory: Sodium sulfate anhydrous

Other Regulations: EINECS: This product is on the European Inventory of Existing Commercial Chemical Substances.

Other Classifications:

WHMIS (Canada): Not controlled under WHMIS (Canada).

DSCL (EEC):
R36- Irritating to eyes. S36- Wear suitable protective clothing. S46- If swallowed, seek medical advice immediately and show this container or label.

HMIS (U.S.A.):

Health Hazard: 2

Fire Hazard: 0

Reactivity: 0

Personal Protection: E

National Fire Protection Association (U.S.A.):

Health: 2

Flammability: 0

Reactivity: 0

Specific hazard:

Protective Equipment:
Gloves. Lab coat. Dust respirator. Be sure to use an approved/certified respirator or equivalent. Splash goggles.

Section 16: Other Information

References: Not available.

Other Special Considerations: Not available.

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Material Safety Data Sheet
Tetrahydrofuran MSDS

Section 1: Chemical Product and Company Identification

Product Name: Tetrahydrofuran

Catalog Codes: SLT3136, SLT2254

CAS#: 109-99-9

RTECS: LU5950000

TSCA: TSCA 8(b) inventory: Tetrahydrofuran

CI#: Not available.

Synonym: Tetrahydrofuran stabilized with BHT; THF; Butylene Oxide; Cyclotetramethylene oxide; 1,4-Epoxybutane

Chemical Name: Tetrahydrofuran

Chemical Formula: C4H8O

Contact Information:

Sciencelab.com, Inc.
14025 Smith Rd.
Houston, Texas 77396

US Sales: **1-800-901-7247**
International Sales: **1-281-441-4400**

Order Online: ScienceLab.com

CHEMTREC (24HR Emergency Telephone), call: 1-800-424-9300

International CHEMTREC, call: 1-703-527-3887

For non-emergency assistance, call: 1-281-441-4400

Section 2: Composition and Information on Ingredients

Composition:

Name	CAS #	% by Weight
Tetrahydrofuran	109-99-9	100

Toxicological Data on Ingredients: Tetrahydrofuran: ORAL (LD50): Acute: 1650 mg/kg [Rat]. VAPOR (LC50): Acute: 21000 mg/m 3 hours [Rat].

Section 3: Hazards Identification

Potential Acute Health Effects:
Hazardous in case of skin contact (irritant), of eye contact (irritant). Slightly hazardous in case of skin contact (permeator), of ingestion, of inhalation.

Potential Chronic Health Effects:
CARCINOGENIC EFFECTS: Not available. MUTAGENIC EFFECTS: Mutagenic for mammalian somatic cells. Mutagenic for bacteria and/or yeast. TERATOGENIC EFFECTS: Not available. DEVELOPMENTAL TOXICITY: Not available. The substance may be toxic to blood, kidneys, lungs, liver, upper respiratory tract, skin, eyes, central nervous system (CNS). Repeated or prolonged exposure to the substance can produce target organs damage.

Section 4: First Aid Measures

Eye Contact:
Check for and remove any contact lenses. In case of contact, immediately flush eyes with plenty of water for at least 15 minutes. Cold water may be used. Get medical attention.

Skin Contact:
In case of contact, immediately flush skin with plenty of water. Cover the irritated skin with an emollient. Remove contaminated clothing and shoes. Cold water may be used.Wash clothing before reuse. Thoroughly clean shoes before reuse. Get medical attention.

Serious Skin Contact:
Wash with a disinfectant soap and cover the contaminated skin with an anti-bacterial cream. Seek immediate medical attention.

Inhalation:
If inhaled, remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Get medical attention.

Serious Inhalation:
Evacuate the victim to a safe area as soon as possible. Loosen tight clothing such as a collar, tie, belt or waistband. If breathing is difficult, administer oxygen. If the victim is not breathing, perform mouth-to-mouth resuscitation. WARNING: It may be hazardous to the person providing aid to give mouth-to-mouth resuscitation when the inhaled material is toxic, infectious or corrosive. Seek medical attention.

Ingestion:
Do NOT induce vomiting unless directed to do so by medical personnel. Never give anything by mouth to an unconscious person. If large quantities of this material are swallowed, call a physician immediately. Loosen tight clothing such as a collar, tie, belt or waistband.

Serious Ingestion: Not available.

Section 5: Fire and Explosion Data

Flammability of the Product: Flammable.

Auto-Ignition Temperature: 321°C (609.8°F)

Flash Points: CLOSED CUP: -14.5°C (5.9°F). OPEN CUP: -20°C (-4°F).

Flammable Limits: LOWER: 2% UPPER: 11.8%

Products of Combustion: These products are carbon oxides (CO, CO2).

Fire Hazards in Presence of Various Substances:
Highly flammable in presence of open flames and sparks, of heat. Non-flammable in presence of shocks.

Explosion Hazards in Presence of Various Substances:
Risks of explosion of the product in presence of mechanical impact: Not available. Explosive in presence of open flames and sparks, of heat.

Fire Fighting Media and Instructions:
Flammable liquid, soluble or dispersed in water. SMALL FIRE: Use DRY chemical powder. LARGE FIRE: Use alcohol foam, water spray or fog.

Special Remarks on Fire Hazards: Vapor may travel considerable distance to source of ignition and flash back. May form explosive mixtures with air.

Special Remarks on Explosion Hazards:
Reacts explosively with lithium-aluminum alloys, and Sodium Aluminum Hydride, Potassium hydroxide, Calcium Hydride.
It is normally stable, however, prolonged storage, and exposure to air and light may cause formation of unstable explosive peroxides especially when anhydrous and unless it is inhibited against peroxide formation. Explosive in the form of vapor when exposed to heat or flame.

Section 6: Accidental Release Measures

Small Spill:
Dilute with water and mop up, or absorb with an inert dry material and place in an appropriate waste disposal container.

Large Spill:
Flammable liquid. Keep away from heat. Keep away from sources of ignition. Stop leak if without risk. Absorb with DRY earth, sand or other non-combustible material. Do not touch spilled material. Prevent entry into sewers, basements or confined areas; dike if needed. Be careful that the product is not present at a concentration level above TLV. Check TLV on the MSDS and with local authorities.

Section 7: Handling and Storage

Precautions:
Keep away from heat. Keep away from sources of ignition. Ground all equipment containing material. Do not ingest. Do not breathe gas/fumes/ vapor/spray. Wear suitable protective clothing. In case of insufficient ventilation, wear suitable respiratory equipment. If ingested, seek medical advice immediately and show the container or the label. Avoid contact with skin and eyes. Keep away from incompatibles such as oxidizing agents.

Storage:
Store in a segregated and approved area. Keep container in a cool, well-ventilated area. Keep container tightly closed and sealed until ready for use. Avoid all possible sources of ignition (spark or flame). Prolonged exposure to air and light may form unstable explosive peroxides unless it is inhibited against peroxide formation

Section 8: Exposure Controls/Personal Protection

Engineering Controls:
Provide exhaust ventilation or other engineering controls to keep the airborne concentrations of vapors below their respective threshold limit value. Ensure that eyewash stations and safety showers are proximal to the work-station location.

Personal Protection:
Splash goggles. Lab coat. Vapor respirator. Be sure to use an approved/certified respirator or equivalent. Gloves.

Personal Protection in Case of a Large Spill:
Splash goggles. Full suit. Vapor respirator. Boots. Gloves. A self contained breathing apparatus should be used to avoid inhalation of the product. Suggested protective clothing might not be sufficient; consult a specialist BEFORE handling this product.

Exposure Limits:
TWA: 590 STEL: 737 (mg/m3) from ACGIH (TLV) [United States] Inhalation TWA: 200 STEL: 250 (ppm) from ACGIH (TLV) [United States] Inhalation TWA: 590 STEL: 735 (mg/m3) from NIOSH [United States] Inhalation TWA: 200 STEL: 250 (ppm) from NIOSH [United States] Inhalation TWA: 200 STEL: 250 (ppm) from OSHA (PEL) [United States] Inhalation TWA: 590 STEL: 735 (mg/m3) from OSHA (PEL) [United States] Inhalation TWA: 100 STEL: 200 (ppm) [United Kingdom (UK)] Inhalation TWA: 300 STEL: 599 (mg/m3) [United Kingdom (UK)] Inhalation3 Consult local authorities for acceptable exposure limits.

Section 9: Physical and Chemical Properties

Physical state and appearance: Liquid.

Odor: Ethereal. Fruity.

Taste: Pungent.

Molecular Weight: 72.11 g/mole

Color: Colorless.

pH (1% soln/water): Not available.

Boiling Point: 65°C (149°F) @ 760 mm Hg

Melting Point: -108.3°C (-162.9°F)

Critical Temperature: 267°C (512.6°F)

Specific Gravity: 0.8892 (Water = 1)

Vapor Pressure: 19.3 kPa (@ 20°C)

Vapor Density: 2.5 (Air = 1)

Volatility: 100% (v/v).

Odor Threshold: 20 ppm - 50 ppm

Water/Oil Dist. Coeff.: The product is more soluble in oil; log(oil/water) = 0.5

Ionicity (in Water): Not available.

Dispersion Properties: See solubility in water, diethyl ether, acetone.

Solubility:
Easily soluble in diethyl ether, acetone. Partially soluble in cold water. Solubility in water is 30%. Miscible with alcohols, ketones, esters, hydrocarbons, and ethers. Very soluble in benzene, ethanol, and chloroform.

Section 10: Stability and Reactivity Data

Stability: The product is stable.

Instability Temperature: Not available.

Conditions of Instability: Heat, ignition sources (sparks, flames), light, air, and incompatible materials

Incompatibility with various substances: Reactive with oxidizing agents, acids, alkalis.

Corrosivity: Non-corrosive in presence of glass.

Special Remarks on Reactivity:
Reacts violently with Bromine. Addition of anhydrous chlorides (hafnium tetrachloride, titanium tetrachloride, and zirconium tetrachloride) directly to tetrahydrofuran will cause a violent exothermic reaction. Also incompatible with Calcium Hydride + heat, caustics (e.g. ammonia, ammonium hydroxide, calcium hyroxide, potassium hydroxide, sodium hydroxide), metal halides, moisture, lithium tetrahydroaluminate, borane, 2-aminophenol + potassium dioxide, sodium tetrahydroaluminate, and 2-aminophenol. Prolonged exposure to air and light may form unstable peroxides especially when anhydrous and unless it is inhibited against peroxide formation.

Special Remarks on Corrosivity: It will attack some forms of plastics, rubber, coatings.

Polymerization: Will not occur.

Section 11: Toxicological Information

Routes of Entry: Absorbed through skin. Dermal contact. Eye contact.

Toxicity to Animals:
WARNING: THE LC50 VALUES HEREUNDER ARE ESTIMATED ON THE BASIS OF A 4-HOUR EXPOSURE. Acute oral toxicity (LD50): 1650 mg/kg [Rat]. Acute toxicity of the vapor (LC50): 24000 mg/m3 2 hours [Mouse].

Chronic Effects on Humans:
MUTAGENIC EFFECTS: Mutagenic for mammalian somatic cells. Mutagenic for bacteria and/or yeast. May cause damage to the following organs: blood, kidneys, lungs, liver, upper respiratory tract, skin, eyes, central nervous system (CNS).

Other Toxic Effects on Humans:
Hazardous in case of skin contact (irritant). Slightly hazardous in case of skin contact (permeator), of ingestion, of inhalation.

Special Remarks on Toxicity to Animals: Not available.

Special Remarks on Chronic Effects on Humans:
It is excreted in mother's milk. May cause cancer based on animal data. No human data found at this point. May cause adverse reproductive effects (fetotoxicity) based on animal data. No human data found at this point. May affect genetic material.

Special Remarks on other Toxic Effects on Humans:
Acute Potential Health Effects: Skin: Causes skin irritation. May be absorbed through skin and cause symptoms similar those of inhalation and ingestion. Eyes: Contact with eyes may cause severe irritation with possible eye burns. Vapors may cause eye irritation. Inhalation: May cause upper respiratory tract (nose, throat) irriation. High concentrations may affect behavior/ central nervous system (central nervous system depression/effects characterized by headache, general anesthetic, dizziness, somnolence, muscle weakness, loss of conciousness, and coma), respiration (respiratory stimulation, dyspnea), and gastrointestinal tract (nausea, vomiting). Ingestion: May cause gastrointestinal irritation with nausea, vomiting, and diarrhea, abdominal pain. May also affect the liver and behavior/central nervous system with symptoms similar to inhalation. Chronic Potential Health Effects: Skin: Prolonged or repeated skin contact may cause defatting and dermatitis. Eyes: Prolonged or repeated eye contact may cause conjunctivitis. Inhalation: Prolonged or repeated exposure to vapors may affect the liver, kidneys, muculosketal system, endrocrine system (spleen and thymus), blood, cardiovascular system, thymus, spleen, and lungs (lung damage). Ingestion: Prolonged or repeated exposure from ingestion may affect the blood, and metabolism.

Section 12: Ecological Information

Ecotoxicity: Ecotoxicity in water (LC50): 2160 mg/l 96 hours [Fish (Fathead Minnow)].

BOD5 and COD: Not available.

Products of Biodegradation:
Possibly hazardous short term degradation products are not likely. However, long term degradation products may arise.

Toxicity of the Products of Biodegradation: The products of degradation are less toxic than the product itself.

Special Remarks on the Products of Biodegradation: Not available.

Section 13: Disposal Considerations

Waste Disposal:
Waste must be disposed of in accordance with federal, state and local environmental control regulations.

Section 14: Transport Information

DOT Classification: CLASS 3: Flammable liquid.

Identification: : Tetrahydrofuran UNNA: 2056 PG: II

Special Provisions for Transport: Not available.

Section 15: Other Regulatory Information

Federal and State Regulations:
Connecticut hazardous material survey.: Tetrahydrofuran Illinois toxic substances disclosure to employee act: Tetrahydrofuran Illinois chemical safety act: Tetrahydrofuran New York release reporting list: Tetrahydrofuran Rhode Island RTK hazardous substances: Tetrahydrofuran Pennsylvania RTK: Tetrahydrofuran Minnesota: Tetrahydrofuran Massachusetts RTK: Tetrahydrofuran Massachusetts spill list: Tetrahydrofuran New Jersey: Tetrahydrofuran New Jersey spill list: Tetrahydrofuran Louisiana spill reporting: Tetrahydrofuran California Director's List of Hazardous Substances: Tetrahydrofuran TSCA 8(b) inventory: Tetrahydrofuran TSCA 4(a) proposed test rules: Tetrahydrofuran TSCA 8(a) PAIR: Tetrahydrofuran TSCA 8(a) IUR: Tetrahydrofuran TSCA 8(d) H and S data reporting: Tetrahydrofuran: effective data: 3/11/94; sunset date: 6/30/98 CERCLA: Hazardous substances.: Tetrahydrofuran: 1000 lbs. (453.6 kg)

Other Regulations:
OSHA: Hazardous by definition of Hazard Communication Standard (29 CFR 1910.1200). EINECS: This product is on the European Inventory of Existing Commercial Chemical Substances.

Other Classifications:

WHMIS (Canada):
CLASS B-2: Flammable liquid with a flash point lower than 37.8°C (100°F). CLASS D-2B: Material causing other toxic effects (TOXIC).

DSCL (EEC):
R11- Highly flammable. R19- May form explosive peroxides. R36/37- Irritating to eyes and respiratory system. S16- Keep away from sources of ignition - No smoking. S29- Do not empty into drains. S33- Take precautionary measures against static discharges.

HMIS (U.S.A.):

Health Hazard: 2

Fire Hazard: 3

Reactivity: 0

Personal Protection: h

National Fire Protection Association (U.S.A.):

Health: 2

Flammability: 3

Reactivity: 1

Specific hazard:

Protective Equipment:
Gloves. Lab coat. Vapor respirator. Be sure to use an approved/certified respirator or equivalent. Wear appropriate respirator when ventilation is inadequate. Splash goggles.

Section 16: Other Information

References: Not available.

Other Special Considerations: Not available.

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Material Safety Data Sheet
Thionyl chloride MSDS

Section 1: Chemical Product and Company Identification

Product Name: Thionyl chloride

Catalog Codes:

CAS#: 7719-09-7

RTECS: XM5150000

TSCA: TSCA 8(b) inventory: Thionyl chloride

CI#: Not available.

Synonym: Sulfurous oxychloride; Sulfinyl chloride; Sulfur chloride oxide; Sulfurous dichloride; Thionyl dichloride

Chemical Name: Thionyl chloride

Chemical Formula: Cl2OS

Contact Information:

Sciencelab.com, Inc.
14025 Smith Rd.
Houston, Texas 77396

US Sales: **1-800-901-7247**
International Sales: **1-281-441-4400**

Order Online: ScienceLab.com

CHEMTREC (24HR Emergency Telephone), call: 1-800-424-9300

International CHEMTREC, call: 1-703-527-3887

For non-emergency assistance, call: 1-281-441-4400

Section 2: Composition and Information on Ingredients

Composition:

Name	CAS #	% by Weight
Thionyl chloride	7719-09-7	100

Toxicological Data on Ingredients: Thionyl chloride: VAPOR (LC50): Acute: 500 ppm 1 hours [Rat].

Section 3: Hazards Identification

Potential Acute Health Effects:
Very hazardous in case of skin contact (irritant), of eye contact (irritant), of ingestion, of inhalation. Hazardous in case of skin contact (corrosive, permeator), of eye contact (corrosive). Liquid or spray mist may produce tissue damage particularly on mucous membranes of eyes, mouth and respiratory tract. Skin contact may produce burns. Inhalation of the spray mist may produce severe irritation of respiratory tract, characterized by coughing, choking, or shortness of breath. Severe over-exposure can result in death. Inflammation of the eye is characterized by redness, watering, and itching. Skin inflammation is characterized by itching, scaling, reddening, or, occasionally, blistering.

Potential Chronic Health Effects:
CARCINOGENIC EFFECTS: Not available. MUTAGENIC EFFECTS: Not available. TERATOGENIC EFFECTS: Not available. DEVELOPMENTAL TOXICITY: Not available. The substance may be toxic to upper respiratory tract, skin, eyes. Repeated or prolonged exposure to the substance can produce target organs damage. Repeated or prolonged contact with spray mist may produce chronic eye irritation and severe skin irritation. Repeated or prolonged exposure to spray mist may produce respiratory tract irritation leading to frequent attacks of bronchial infection. Repeated exposure to a highly toxic material may produce general deterioration of health by an accumulation in one or many human organs.

Section 4: First Aid Measures

Eye Contact:
Check for and remove any contact lenses. In case of contact, immediately flush eyes with plenty of water for at least 15 minutes. Get medical attention immediately.

Skin Contact:
In case of contact, immediately flush skin with plenty of water for at least 15 minutes while removing contaminated clothing and shoes. Cover the irritated skin with an emollient. Wash clothing before reuse. Thoroughly clean shoes before reuse. Get medical attention immediately.

Serious Skin Contact:
Wash with a disinfectant soap and cover the contaminated skin with an anti-bacterial cream. Seek immediate medical attention.

Inhalation:
If inhaled, remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Get medical attention immediately.

Serious Inhalation:
Evacuate the victim to a safe area as soon as possible. Loosen tight clothing such as a collar, tie, belt or waistband. If breathing is difficult, administer oxygen. If the victim is not breathing, perform mouth-to-mouth resuscitation. WARNING: It may be hazardous to the person providing aid to give mouth-to-mouth resuscitation when the inhaled material is toxic, infectious or corrosive. Seek immediate medical attention.

Ingestion:
Do NOT induce vomiting unless directed to do so by medical personnel. Never give anything by mouth to an unconscious person. If large quantities of this material are swallowed, call a physician immediately. Loosen tight clothing such as a collar, tie, belt or waistband.

Serious Ingestion: Not available.

Section 5: Fire and Explosion Data

Flammability of the Product: Non-flammable.

Auto-Ignition Temperature: Not applicable.

Flash Points: Not applicable.

Flammable Limits: Not applicable.

Products of Combustion: Not available.

Fire Hazards in Presence of Various Substances: Not applicable.

Explosion Hazards in Presence of Various Substances:
Risks of explosion of the product in presence of mechanical impact: Not available. Risks of explosion of the product in presence of static discharge: Not available.

Fire Fighting Media and Instructions: Not applicable.

Special Remarks on Fire Hazards: When heated to decomposition it emits toxic fumes.

Special Remarks on Explosion Hazards:
It will explode in the presence of several chemicals: Azidoacetylacid, Chlorylperchlorate, N,N-Dimethylformamide, Dimethyl sulfoxide and acyl halides, Hexafluoropropylideneaminolithium, Linseed oil + quinoline, o-Nitrobenzoylacetic acid, p-Nitrobenzoyl and cold ammonia solution, o-Nitrophenylacetic acid; Sodium hydroxide, Sulfur dioxide, Toluene + ethanol+ water, water.

Section 6: Accidental Release Measures

Small Spill: Absorb with an inert material and put the spilled material in an appropriate waste disposal.

Large Spill:
Corrosive liquid. Poisonous liquid. Stop leak if without risk. Absorb with DRY earth, sand or other non-combustible material. Do not get water inside container. Do not touch spilled material. Use water spray curtain to divert vapor drift. Use water spray to reduce vapors. Prevent entry into sewers, basements or confined areas; dike if needed. Call for assistance on disposal. Be careful that the product is not present at a concentration level above TLV. Check TLV on the MSDS and with local authorities.

Section 7: Handling and Storage

Precautions:
Keep container dry. Keep away from heat. Keep away from sources of ignition. Keep away from direct sunlight or strong incandescent light. Do not ingest. Do not breathe gas/fumes/ vapor/spray. Never add water to this product. Avoid shock and friction. In case of insufficient ventilation, wear suitable respiratory equipment. If ingested, seek medical advice immediately and show the container or the label. Avoid contact with skin and eyes. Keep away from incompatibles such as metals, acids, alkalis, moisture.

Storage: Keep container tightly closed. Keep container in a cool, well-ventilated area.

Section 8: Exposure Controls/Personal Protection

Engineering Controls:
Provide exhaust ventilation or other engineering controls to keep the airborne concentrations of vapors below their respective threshold limit value. Ensure that eyewash stations and safety showers are proximal to the work-station location.

Personal Protection:
Face shield. Full suit. Vapor respirator. Be sure to use an approved/certified respirator or equivalent. Gloves. Boots.

Personal Protection in Case of a Large Spill:
Splash goggles. Full suit. Vapor respirator. Boots. Gloves. A self contained breathing apparatus should be used to avoid inhalation of the product. Suggested protective clothing might not be sufficient; consult a specialist BEFORE handling this product.

Exposure Limits:
CEIL: 1 (ppm) from OSHA (PEL) [United States] CEIL: 1 from ACGIH (TLV) [United States] CEIL: 1 (ppm) from NIOSH [United States] TWA: 1 (ppm) [Denmark] STEL: 1 (ppm) [Belgium] STEL: 1 (ppm) [United Kingdom (UK)] Consult local authorities for acceptable exposure limits.

Section 9: Physical and Chemical Properties

Physical state and appearance: Liquid. (Fuming liquid.)

Odor: Suffocating.

Taste: Not available.

Molecular Weight: 118.98 g/mole

Color: Colorless to light yellow.

pH (1% soln/water): Not applicable.

Boiling Point: 76°C (168.8°F)

Melting Point:
-104.5°C (-156.1°F) Decomposition temperature: >140 deg. C

Critical Temperature: Not available.

Specific Gravity: 1.638 (Water = 1)

Vapor Pressure: 13.3 kPa (@ 21°C)

Vapor Density: 4.1 (Air = 1)

Volatility: Not available.

Odor Threshold: Not available.

Water/Oil Dist. Coeff.: Not available.

Ionicity (in Water): Not available.

Dispersion Properties: Not available.

Solubility:
Insoluble in cold water. Miscible with chloroform, benzene, carbon tetrachloride

Section 10: Stability and Reactivity Data

Stability: The product is stable.

Instability Temperature: Not available.

Conditions of Instability: Incompatible materials, moisture/moist air, temperatures above 140 deg. C

Incompatibility with various substances:
Reactive with metals, acids, alkalis, moisture. The product may undergo hazardous decomposition, condensation or polymerization, it may react violently with water to emit toxic gases or it may become self-reactive under conditions of shock or increase in temperature or pressure.

Corrosivity: Non-corrosive in presence of glass.

Special Remarks on Reactivity:
Thionyl chloride fumes on exposure to moist air. In the presence of moisture/water it decomposes and liberates toxic gases of hydrogen chloride and sulfur dioxide. Decomposes when heated above 140 deg. C forming chlorine, sulfur dioxide, sulfur monochloride, hydrogen chloride. Thionyl chloride decomposes in acids, alcohols, alkalies. It is also incompatible with amines, ammonia, chloryl perchlorate, dimethyl sulfoxide, hexafluoro isopropylidene amino lithium, linseed oil, quinoline, sodium, sulfinyl chloride, N,N-Dimethylformamide, metals. It reacts with Grignard reagents to form suloxides.

Special Remarks on Corrosivity: Not available.

Polymerization: Will not occur.

Section 11: Toxicological Information

Routes of Entry: Absorbed through skin. Dermal contact. Eye contact. Inhalation. Ingestion.

Toxicity to Animals:
WARNING: THE LC50 VALUES HEREUNDER ARE ESTIMATED ON THE BASIS OF A 4-HOUR EXPOSURE. Acute toxicity of the vapor (LC50): 500 1 hours [Rat].

Chronic Effects on Humans: May cause damage to the following organs: upper respiratory tract, skin, eyes.

Other Toxic Effects on Humans:
Extremely hazardous in case of inhalation (lung corrosive). Very hazardous in case of skin contact (irritant), of ingestion, . Hazardous in case of skin contact (corrosive, permeator), of eye contact (corrosive).

Special Remarks on Toxicity to Animals: Not available.

Special Remarks on Chronic Effects on Humans: Not available.

Special Remarks on other Toxic Effects on Humans:
Acute Potential Health Effects: Skin: Corrosive. Causes skin burns. May be absorbed through skin in harmful amounts. Eyes: Corrosive. Causes eye burns. Lachrymator. May cause conjunctivitis, corneal damage. Inhalation: Corrosive. Harmful if

inhaled. Causes chemical burns to the respiratory tract. Inhalation may be fatal as a result of spasm, inflammation, edema of the larynx and bronchi, chemical pneumonitis, and pulmonary edema. Toxic exposure to fumes of Thionyl chloride reacting with water may result in delayed pulmonary response, bronchiolitis Oblitereans(inflammmation of the bronchioles). Ingestion: Corrosive. Harmful if swallowed. Causes gastrointestinal/digestive tract burns. May cause severe and permanent damage to the digestive tract.

Section 12: Ecological Information

Ecotoxicity: Not available.

BOD5 and COD: Not available.

Products of Biodegradation:
Possibly hazardous short term degradation products are not likely. However, long term degradation products may arise.

Toxicity of the Products of Biodegradation: The products of degradation are more toxic.

Special Remarks on the Products of Biodegradation: Not available.

Section 13: Disposal Considerations

Waste Disposal:
Waste must be disposed of in accordance with federal, state and local environmental control regulations.

Section 14: Transport Information

DOT Classification: Class 8: Corrosive material

Identification: : Thionyl chloride UNNA: 1836 PG: I

Special Provisions for Transport: Not available.

Section 15: Other Regulatory Information

Federal and State Regulations:
Connecticut hazardous material survey.: Thionyl chloride Illinois toxic substances disclosure to employee act: Thionyl chloride Rhode Island RTK hazardous substances: Thionyl chloride Pennsylvania RTK: Thionyl chloride Florida: Thionyl chloride Minnesota: Thionyl chloride Massachusetts RTK: Thionyl chloride Massachusetts spill list: Thionyl chloride New Jersey: Thionyl chloride California Director's List of Hazardous Substances: Thionyl chloride TSCA 8(b) inventory: Thionyl chloride

Other Regulations:
OSHA: Hazardous by definition of Hazard Communication Standard (29 CFR 1910.1200). EINECS: This product is on the European Inventory of Existing Commercial Chemical Substances.

Other Classifications:

WHMIS (Canada):
CLASS D-1A: Material causing immediate and serious toxic effects (VERY TOXIC). CLASS E: Corrosive liquid. CLASS F: Dangerously reactive material.

DSCL (EEC):

HMIS (U.S.A.):

Health Hazard: 3

Fire Hazard: 0

Reactivity: 2

Personal Protection:

National Fire Protection Association (U.S.A.):

Health: 4

Flammability: 0

Reactivity: 2

Specific hazard:

Protective Equipment:
Gloves. Full suit. Vapor respirator. Be sure to use an approved/certified respirator or equivalent. Wear appropriate respirator when ventilation is inadequate. Face shield.

Section 16: Other Information

References: Not available.

Other Special Considerations: Not available.

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Material Safety Data Sheet
Zinc chloride MSDS

Section 1: Chemical Product and Company Identification

Product Name: Zinc chloride

Catalog Codes: SLZ1225, SLZ1060, SLZ1165

CAS#: 7646-85-7

RTECS: ZH1400000

TSCA: TSCA 8(b) inventory: Zinc chloride

CI#: Not available.

Synonym:

Chemical Name: Zinc Chloride

Chemical Formula: ZnCl2

Contact Information:

Sciencelab.com, Inc.
14025 Smith Rd.
Houston, Texas 77396

US Sales: **1-800-901-7247**
International Sales: **1-281-441-4400**

Order Online: ScienceLab.com

CHEMTREC (24HR Emergency Telephone), call:
1-800-424-9300

International CHEMTREC, call: 1-703-527-3887

For non-emergency assistance, call: 1-281-441-4400

Section 2: Composition and Information on Ingredients

Composition:

Name	CAS #	% by Weight
Zinc chloride	7646-85-7	100

Toxicological Data on Ingredients: Zinc chloride: ORAL (LD50): Acute: 350 mg/kg [Rat]. 329 mg/kg [Mouse].

Section 3: Hazards Identification

Potential Acute Health Effects:
Very hazardous in case of skin contact (irritant), of eye contact (irritant), of ingestion, of inhalation. Hazardous in case of skin contact (corrosive, permeator), of eye contact (corrosive). The amount of tissue damage depends on length of contact. Eye contact can result in corneal damage or blindness. Skin contact can produce inflammation and blistering. Inhalation of dust will produce irritation to gastro-intestinal or respiratory tract, characterized by burning, sneezing and coughing. Severe over-exposure can produce lung damage, choking, unconsciousness or death. Inflammation of the eye is characterized by redness, watering, and itching. Skin inflammation is characterized by itching, scaling, reddening, or, occasionally, blistering.

Potential Chronic Health Effects:
CARCINOGENIC EFFECTS: Not available. MUTAGENIC EFFECTS: Classified POSSIBLE for human. Mutagenic for mammalian somatic cells. Mutagenic for bacteria and/or yeast. TERATOGENIC EFFECTS: Not available. DEVELOPMENTAL TOXICITY: Not available. The substance may be toxic to kidneys, pancreas. Repeated or prolonged exposure to the substance can produce target organs damage. Repeated exposure of the eyes to a low level of dust can produce eye irritation. Repeated skin exposure can produce local skin destruction, or dermatitis. Repeated inhalation of dust can produce varying degree of respiratory irritation or lung damage.

Section 4: First Aid Measures

Eye Contact:
Check for and remove any contact lenses. In case of contact, immediately flush eyes with plenty of water for at least 15 minutes. Cold water may be used. Get medical attention immediately.

Skin Contact:
In case of contact, immediately flush skin with plenty of water for at least 15 minutes while removing contaminated clothing and shoes. Cover the irritated skin with an emollient. Cold water may be used.Wash clothing before reuse. Thoroughly clean shoes before reuse. Get medical attention immediately.

Serious Skin Contact:
Wash with a disinfectant soap and cover the contaminated skin with an anti-bacterial cream. Seek immediate medical attention.

Inhalation:
If inhaled, remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Get medical attention.

Serious Inhalation:
Evacuate the victim to a safe area as soon as possible. Loosen tight clothing such as a collar, tie, belt or waistband. If breathing is difficult, administer oxygen. If the victim is not breathing, perform mouth-to-mouth resuscitation. WARNING: It may be hazardous to the person providing aid to give mouth-to-mouth resuscitation when the inhaled material is toxic, infectious or corrosive. Seek immediate medical attention.

Ingestion:
Do NOT induce vomiting unless directed to do so by medical personnel. Never give anything by mouth to an unconscious person. If large quantities of this material are swallowed, call a physician immediately. Loosen tight clothing such as a collar, tie, belt or waistband.

Serious Ingestion: Not available.

Section 5: Fire and Explosion Data

Flammability of the Product: Non-flammable.

Auto-Ignition Temperature: Not applicable.

Flash Points: Not applicable.

Flammable Limits: Not applicable.

Products of Combustion: When heated to decomposition, it emits toxic fumes of Hydrochloric Acid, and Zinc Oxide.

Fire Hazards in Presence of Various Substances: Not applicable.

Explosion Hazards in Presence of Various Substances:
Risks of explosion of the product in presence of mechanical impact: Not available. Risks of explosion of the product in presence of static discharge: Not available.

Fire Fighting Media and Instructions: Not applicable.

Special Remarks on Fire Hazards: Not available.

Special Remarks on Explosion Hazards: A mixture of potassium and zinc chloride produces a strong explosion on impact.

Section 6: Accidental Release Measures

Small Spill: Use appropriate tools to put the spilled solid in a convenient waste disposal container.

Large Spill:
Corrosive solid. Stop leak if without risk. Do not get water inside container. Do not touch spilled material. Use water spray to reduce vapors. Prevent entry into sewers, basements or confined areas; dike if needed. Call for assistance on disposal. Be careful that the product is not present at a concentration level above TLV. Check TLV on the MSDS and with local authorities.

Section 7: Handling and Storage

Precautions:
Keep locked up.. Keep container dry. Do not ingest. Do not breathe dust. Never add water to this product. In case of insufficient ventilation, wear suitable respiratory equipment. If ingested, seek medical advice immediately and show the container or the label. Avoid contact with skin and eyes. Keep away from incompatibles such as oxidizing agents, metals.

Storage:
Deliquescent. Keep container tightly closed. Keep container in a cool, well-ventilated area. Do not store above 25°C (77°F).

Section 8: Exposure Controls/Personal Protection

Engineering Controls:
Use process enclosures, local exhaust ventilation, or other engineering controls to keep airborne levels below recommended exposure limits. If user operations generate dust, fume or mist, use ventilation to keep exposure to airborne contaminants below the exposure limit.

Personal Protection:
Splash goggles. Synthetic apron. Vapor and dust respirator. Be sure to use an approved/certified respirator or equivalent. Gloves.

Personal Protection in Case of a Large Spill:
Splash goggles. Full suit. Vapor and dust respirator. Boots. Gloves. A self contained breathing apparatus should be used to avoid inhalation of the product. Suggested protective clothing might not be sufficient; consult a specialist BEFORE handling this product.

Exposure Limits:
TWA: 1 STEL: 2 (mg/m3) [United Kingdom (UK)] TWA: 1 STEL: 2 (mg/m3) from ACGIH (TLV) [United States] TWA: 1 STEL: 2 (mg/m3) from OSHA (PEL) [United States]Consult local authorities for acceptable exposure limits.

Section 9: Physical and Chemical Properties

Physical state and appearance: Solid. (Deliquescent solid.)

Odor: Odorless.

Taste: Not available.

Molecular Weight: 136.29 g/mole

Color: White.

pH (1% soln/water): Not available.

Boiling Point: 732°C (1349.6°F)

Melting Point: 290°C (554°F)

Critical Temperature: Not available.

Specific Gravity: 2.907 (Water = 1)

Vapor Pressure: Not applicable.

Vapor Density: 4.7 (Air = 1)

Volatility: Not available.

Odor Threshold: Not available.

Water/Oil Dist. Coeff.: Not available.

Ionicity (in Water): Not available.

Dispersion Properties: See solubility in water.

Solubility: Easily soluble in cold water.

Section 10: Stability and Reactivity Data

Stability: The product is stable.

Instability Temperature: Not available.

Conditions of Instability: Incompatible materials, moisture.

Incompatibility with various substances: Reactive with oxidizing agents, metals.

Corrosivity: Non-corrosive in presence of glass.

Special Remarks on Reactivity:
Very deliquescent. Incompatible with cyanides, sulfides

Special Remarks on Corrosivity: Zinc Chloride fumes are corrosive to metals

Polymerization: Will not occur.

Section 11: Toxicological Information

Routes of Entry: Absorbed through skin. Dermal contact. Inhalation. Ingestion.

Toxicity to Animals: Acute oral toxicity (LD50): 329 mg/kg [Mouse].

Chronic Effects on Humans:
MUTAGENIC EFFECTS: Classified POSSIBLE for human. Mutagenic for mammalian somatic cells. Mutagenic for bacteria and/or yeast. May cause damage to the following organs: kidneys, pancreas.

Other Toxic Effects on Humans:
Very hazardous in case of skin contact (irritant), of ingestion, of inhalation. Hazardous in case of skin contact (corrosive, permeator), of eye contact (corrosive).

Special Remarks on Toxicity to Animals: Lowest Published Lethal Dose[Rat] - Route: Inhalation; Dose: 1960 mg/m3/10M

Special Remarks on Chronic Effects on Humans:
May cause adverse reproductive effects (paternal effects, effects on fertility (post-implantation mortality, fetoxicity) and birth defects based on animal data. May cause cancer based on animal data. May affect genetic material. Animal: passes through placental barrier, excreted in maternal milk.

Special Remarks on other Toxic Effects on Humans:
Acute Potential Health Effects: Skin: Causes skin irritation with possible burns, especially if skin is wet or moist. May be absorbed by the skin. Eyes: May cause severe irritation with posssible eye burns and irreversible eye injury. May cause corneal ulceration, and opacification, and glaucoma and severe iritis. Eye or skin contact may result in mild, moderate, or severe irritation and burns depending on the concentration and duration of exposure. Inhalation: May cause severe respiratory tract irritation, and may affect behavior. Symptoms may include sore throat, coughing, shortness of breath, dyspnea, chest tightness, headache, cyanosis (bluish discoloration of skin due to deficient oxygenation of the blood), delayed lung edema, bronchial asthma . Inhalation of fumes may cause metal fume fever. It is characterized by flu-like symptoms (fever, chills, cough, muscle pain, weakness), chest pain. Ingestion: Harmful if swallowed. May cause severe digestive tract irritation with nausea, vomiting, diarrhea abdominal pain, possible burns(corrosion and permanent tissue destruction) of the esophagus and digestive tract and perforation of the stomach and possible death. It may also affect behavior/Central nervous system (central nervous system depression), the urinary system (kidney damage - hematuria, oliguria, renal failure), cardiovascular system, respiration (dyspnea), metabolism, pancreas (elevated amylase, and glucose levels), liver enzymes, and blood (changes in white and red blood cell count, changes in serum composition). Zinc chloride is irritating or caustic depending on the concentration ingested. Chronic Potential Health Effects: Skin: Prolonged or repeated skin contact may cause defatting and dermatitis.

Section 12: Ecological Information

Ecotoxicity: Not available.

BOD5 and COD: Not available.

Products of Biodegradation:
Possibly hazardous short term degradation products are not likely. However, long term degradation products may arise.

Toxicity of the Products of Biodegradation: The products of degradation are less toxic than the product itself.

Special Remarks on the Products of Biodegradation: Not available.

Section 13: Disposal Considerations

Waste Disposal:
Waste must be disposed of in accordance with federal, state and local environmental control regulations.

Section 14: Transport Information

DOT Classification: Class 8: Corrosive material

Identification: : Zinc Chloride, anhydrous UNNA: 2331 PG: III

Special Provisions for Transport: Not available.

Section 15: Other Regulatory Information

Federal and State Regulations:
Connecticut hazardous material survey.: Zinc chloride Illinois toxic substances disclosure to employee act: Zinc chloride Illinois chemical safety act: Zinc chloride New York release reporting list: Zinc chloride Rhode Island RTK hazardous substances: Zinc chloride Pennsylvania RTK: Zinc chloride Minnesota: Zinc chloride Massachusetts RTK: Zinc chloride Massachusetts spill list: Zinc chloride New Jersey: Zinc chloride New Jersey spill list: Zinc chloride Louisiana spill reporting: Zinc chloride California Director's List of Hazardous Substances: Zinc chloride TSCA 8(b) inventory: Zinc chloride CERCLA: Hazardous substances.: Zinc chloride: 1000 lbs. (453.6 kg)

Other Regulations:
OSHA: Hazardous by definition of Hazard Communication Standard (29 CFR 1910.1200). EINECS: This product is on the European Inventory of Existing Commercial Chemical Substances.

Other Classifications:

WHMIS (Canada):
CLASS D-1B: Material causing immediate and serious toxic effects (TOXIC). CLASS D-2A: Material causing other toxic effects (VERY TOXIC). CLASS E: Corrosive solid.

DSCL (EEC):

HMIS (U.S.A.):

Health Hazard: 3

Fire Hazard: 0

Reactivity: 0

Personal Protection: j

National Fire Protection Association (U.S.A.):

Health: 3

Flammability: 0

Reactivity: 0

Specific hazard:

Protective Equipment:
Gloves. Synthetic apron. Vapor and dust respirator. Be sure to use an approved/certified respirator or equivalent. Wear appropriate respirator when ventilation is inadequate. Splash goggles.

Section 16: Other Information

References: Not available.

Other Special Considerations: Not available.

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Appendix N - Waste Disposal Costs

Appendix N-1 Solvent Waste Costs

Solvent	Process	Contaminants	Purity	Quantity per batch (L)	Quantity per batch (gal)	Cost ($/gal)	Waste Cost per batch
IPA	100	Thionyl chloride, L-alanine, HCl, L-alanine isopropyl ester	95%	130,000	34,342	$1.60	$54,948
DCM	200	DIEA, phenyl dichlorophosphate, L-alanine isopropyl ester, 2-chloro-6-hydroxypyridine	92%	170,000	44,909	$1.60	$71,855
Sodium Sulfate	200	DIEA, phenyl dichlorophosphate, L-alanine isopropyl ester, 2-chloro-6-hydroxypyridine	99%	8*	8*	$100*	$800
Water	200	DIEA, phenyl dichlorophosphate, L-alanine isopropyl ester, 2-chloro-6-hydroxypyridine	90%	200,000	52,834	$0.55	$29,059
THF	300	A1, DIEA, Zinc Chloride, Methyluridine	82-90%	60,000	15,850	$1.60	$25,361
Ethyl Acetate	300	THF, A1, DIEA, Zinc Chloride, Methyluridine	90-95%	110,000	29,059	$1.60	$46,494
DCM	300	Acetone	85%	63,000	16,643	$1.60	$26,629
Sodium Sulfate	300	HCl, Buffer Solution, Sodium Carbonate, NH4Cl	99%	8.7*	8.7*	$100*	$870
Water	300	HCl, Buffer Solution, Sodium Carbonate, NH4Cl	90%	225,000	59,439	$0.55	$32,691
Cost of disposal of only organic solvents							$61,750
Cost of disposal of only organic solvents							($226,956)
Paid disposal of all solvents							**($288,706)**
Disposal of contaminated organics		**5% of**					**($11,348)**

*Quantities for Sodium Sulfate are reported in yd^3, and Costs for Sodium Sulfate are reported in $/$yd^3$, as per the figures provided by the industrial consultants.

Appendix N-2 Organic Solvent Resale Values

Solvent	Process	Contaminants	Purity	Quantity per Batch (L)	Resale Value ($/kg)	Resale Value per batch
IPA	100	Thionyl chloride, L-alanine, HCl, L-alanine isopropyl ester	95%	130,000	$0.05	$4,630
DCM	200	DIEA, phenyl dichlorophosphate, L-alanine isopropyl ester, 2-chloro-6-hydroxypyridine	92%	170,000	$0.02	$4,805
THF	300	A1, DIEA, Zinc Chloride, Methyluridine	82-90%	60,000	$0.09	$4,534
Ethyl Acetate	300	THF, A1, DIEA, Zinc Chloride, Methyluridine	90-95%	110,000	$0.02	$1,480
DCM	300	Acetone	85%	63,000	0.02	$178
Total Resale Value						$15,627
Resale Value of 95% Pure Solvents						**$14,845**