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GREEN ENGINEERING AND GATE-TO GATE LIFE CYCLE ASSESSMENTS  
FOR PHARMACEUTICAL PRODUCTS

by

Daniel Fichana

A Thesis

Submitted in partial fulfillment of the requirements of the  
Master of Science Degree  
of  
The Graduate School  
at  
Rowan University  
December 1st 2005

Approved by  
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Date Approved 12/1/2005

## **Abstract**

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Green Engineering and Gate-to Gate Life Cycle Assessments for Pharmaceutical  
Products  
2004/2005  
Dr. C. Stewart Slater  
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The research of this thesis focused on the environmental and processing metrics during the development of two different drugs. Previous research in life cycle assessments and green engineering have focused on other products and processes, but only a limited amount of studies have been conducted for pharmaceutical applications. This analysis concerned a gate-to-gate analysis of two distinct pharmaceutical products along with the development of a solvent selection table. The goal of this research was to determine how various processing and environmental metrics were affected by process improvements.

The first drug was the pravastatin, which was made via a fermentation route. Four lab scale routes were investigated for this drug. The second study tracked the processing and environmental metrics of another drug through three different scales; lab-scale, glass-scale, and pilot-scale. A solvent selection table was also developed as part of the research for this project and included in this paper.

Some of the conclusions for this analysis were that over time the processing metrics and the environmental metrics decreased for different reasons. The factors that contributed to a decrease in environmental factors were increased yield, solvent substitution and the removal of process equipment.

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# Chapter 1: Introduction and Background

## *Introduction*

Green engineering is a relatively new concept that is partially based lean product methods. Green engineering is a term used to describe engineering, which attempts to minimize the pollution at the source while also minimizing the risk to human health and the environment. There is also an economic aspect to green engineering. The design and use of products and processes have to be economically feasible [1].

One principle of green engineering is applying life cycle assessment to products and processes. Life cycle assessment is a methodology of analyzing the various mass and energy balances in and out of the process. A list of environmental factors are then applied to these masses and emissions from the energy. This typically consists of 4 steps [2]. These steps include the goal and scope step, the inventory step, the impact step, and the interpretation step. Once the a life cycle assessment study has been conducted, problem areas can be identified and green engineering solutions can be applied and alternatives can be found to make the process more sustainable.

A life cycle assessment on a process is usually conducted in the research and development to determine if there are other options such as replacement of a solvent or chemical with a less environmentally harmful ones, comparison of the process to processes used by competitors, and also to reduce liability [3], [4].

There were two studies considered for the green engineering analysis described in this thesis. These took into account two important aspects during drug development. These two important aspects are the analysis of a fermentation-based pharmaceutical

which compares improvements made by different people over a certain time period and the scale up of another product. There has not been a study that focused solely on the lab-scale of a fermentation-based product, which compares the drug made 20 years ago to more recent process improvements in the manufacturing process. Another goal of this study was to study a drug throughout the discovery stages and process modifications by the initial investigational team in the early 1980's and improvements made by another team more recently in 2004. This analysis was used to determine if any trends were present.

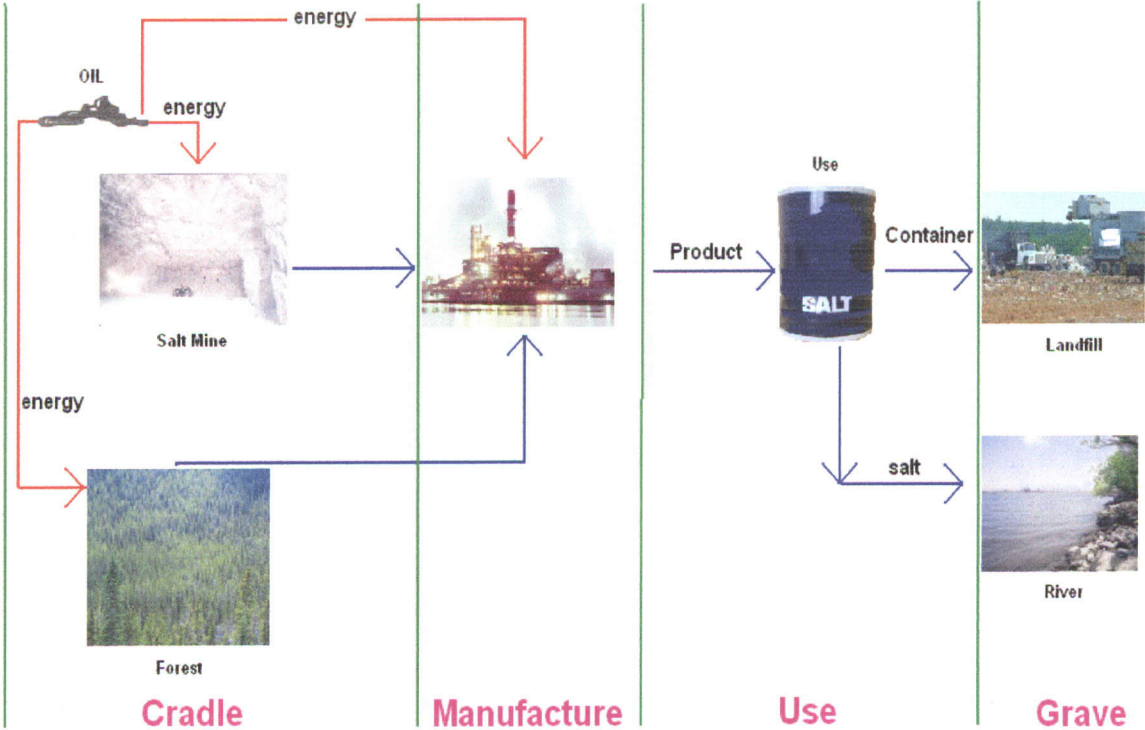
Pravastatin was specifically chosen as the lab-scale drug because it is a drug that is available as a name-brand drug and the patent expires in 2006, which will result in generic manufactures having a wide array of processes to make pravastatin.

A second study was also conducted on the scale up of another pharmaceutical product. This will show how various environmental metrics can be used to show how environmental impacts change as a pharmaceutical product goes through scale-up in the process development stages. Between this study and the previous study, the full life-cycle of a drug can be investigated and a full analysis can be conducted.

### ***Background on Life Cycle Assessment*** [ 5]

Life cycle assessment is a way to determine the environmental impact of the products or processes by using the masses of materials and energy that are input into the process and the outputs from the process. These studies are typically conducted on a cradle to grave approach, but could be conducted as a gate-to gate approach depending on the level of information available. A list of environmental metrics are applied to these

metrics to determine which process or product is more environmentally friendly or more sustainable. A simple life cycle assessment (LCA) is shown in Figure 1. This is a general life cycle assessment for the manufacture of salt and includes a cradle to gate analysis. In a full there would be many more streams to account for all of the inputs and outputs for the process.



**Figure 1: General LCA for Salt**

Life cycle impact assessment methodology has been in foreground of sustainability since the 1960's. The early studies focused solely on energy usage and solid waste while little consideration was paid to the various environmental risks associated with these compounds. During the oil crisis in the 1970's a large amount of energy studies were conducted on various industries [3], [6]. These studies were the

basis of life cycle inventories. An example of a mass and energy balance can be seen by Beaver et al. [7]. This study was a very simplified version of a life cycle assessment and only included 4 criteria; mass, energy, water and greenhouse gas emissions [7]. There was a practice called the “Best Practicable Environmental Option (BPEO)” which was practiced during the late 1980’s and early 1990’s and was practiced in Europe [6]. This approach was not the best approach to use since it tried to minimize the environmental burdens at the practitioner’s plant. BPEO did not analyze the entire life cycle. Life cycle assessments came into fruition in the late 1980’s, but were preformed by private companies [3]. Unfortunately these studies did not have a common framework. In 1993 the Society of Environmental Toxicology and Chemistry introduced principles on how to conduct, review, use and present the findings of a life cycle assessment [3]. The International Standardization Organization introduced an internal standard concerning life cycle assessments in 1997. This standard is known as ISO 14000 and outlined the various procedures for conducting a life cycle analysis.

Life cycle assessment is a process of analyzing various environmental criteria of a certain product or process to minimize waste and environmental impact. Life cycle impact assessments typically consist of 4 steps [8]. The first step includes the definitions of the system boundary, scope, and the functional unit. The second step consists of an inventory of the inputs and outputs of the system. Many life cycle assessments are brought to an end at this stage and conclusions are based on how to minimize mass and energy usage [3]. Unfortunately, this approach of making recommendations based solely on the life cycle inventory does not consider “whether some categories in the inventory analysis are more hazardous than others” [3]. The third step is comprised of transforming

the values obtained in step 2 into factors of environmental performance. The last step is interpreting the results of step 3 and recommending process improvements if feasible [9]. SETAC has a different, but similar 4<sup>th</sup> step, which is termed “improvement assessment” which is a way to improve the impact assessment [6] .

Life cycle assessments are typically conducted for user products, but can also be used proactively for process selection, design, and optimization [6]. Burgess, et al. stated that a life cycle assessment conducted on a product is also valid for the processing steps involved in the manufacture of the product [3]. The purpose for conducting an LCA for a process is different than an LCA conducted on a product [3]. Contrary to the previous claim, Chevalier et al., stated that a life cycle conducted on a process is more thorough than a life cycle conducted on a product [4]. A life cycle assessment on a process is usually conducted in the research and development to determine if there are other options such as replacement of a solvent with a less environmentally harmful solvent, comparison of the process to the processes used by competitors, and also to reduce liability [3], [4]. A product life cycle analysis is typical done for the purpose of marketing and policy making [3]

### **Goal and Scope of a Life Cycle Assessment**

Defining a boundary for a life cycle assessment is a difficult task. The International Standards Organization 14040 standardized life cycle impact assessments in 1997 [10], [11]. This states that a life cycle assessment should be conducted in terms of elementary flows. This was typically understood as from the cradle to the grave, which

included raw material mining to the disposal of the product. This included all the supply chains for a specific life cycle assessment [9]. The standard was further refined by ISO 14041. This stated that certain processes, inputs, and outputs can be omitted if these processes are deemed insignificant [3]. Burgess, et al. stated that assumptions concerning the boundary conditions are necessary to maintain manageability and the law of diminishing returns can be seen after three upstream processes. Unfortunately according to ISO standards, this data must be collected before it can be disregarded. The functional unit is typically 1 ton of product for processes, but can be specified where product effectiveness is an issue [3].

Suh et al. stated that the ISO standards for excluding and including processes in system boundaries are difficult to determine because the cutoff criteria typically do not have a scientific basis [12]. Also excluding or including a process to extend the boundaries can be difficult if the practitioner has no experience on the specific process.

## **Methods for life cycle inventory**

This portion of a life cycle analysis is the collection of all the data that will be used in the life cycle analysis. The quality of the data is an important part of the life cycle inventory process. According to Burgess et al., the results of the life cycle assessment are only as good as the input data. The data obtained in some life cycle analysis may be controversial due to the source of the data. This is usually the case when the data is proprietary or from a confidential source [3]

There are four main methods of conducting a life cycle impact inventory. These methods are economy scale, life cycle scale, equipment scale, and a hybrid LCI [9]. There are advantages and disadvantages to each of these methods. The methods listed are listed from the most general to the most detailed. The most general analysis contains all the information from cradle-to-grave, but is not specific for an individual process, while the most detailed method is typically used for gate-to-gate analysis.

The first method is the economy scale [9], [13]. This type of method typically uses national statistics about resource use and emissions from a specified sector and considers the whole economy. Typically this is an advantage in this process because the boundary can be defined as cradle to grave. The most well known method in this category is the EIOLCA software developed by Carnegie Mellon [13]. There are two disadvantages to this approach. Typically an assumption must be made concerning the products. This assumption assumes there is a linear relationship between the dollars spent on the product and its environmental impact. For some cases this may be true, such as in the case of obtaining a higher purity for a chemical, but in other cases, it does not

hold true, such as cars [13]. The researchers to this method clearly state the limitations and use a car for an example for the limitations. There is also another drawback to using this type of method. The data typically used is that most of the data is collected from the entire industry. This assumption may be valid assuming that the company is around the average, but the given company may be a leader in sustainability or may be operating inefficiently or may be using an out of date process.

The second method that is typically used is the life cycle scale [9]. This scale typically focuses on a specific sector. These life cycle inventories are the typical inventories used in industry. This type of data is more detailed than the data offered in economic scale analysis, but does not include a large degree of details about the individual processes, pieces of equipment, or other reactants/catalysts that could be considered negligible. There is a small issue about boundary selection in this type of inventory. The results of any life cycle analysis are highly dependent on the boundary selection of the system. For example, if a person was comparing two drugs which did the same thing, but for one drug they conducted a gate-to-gate analysis and for the other drug they conducted a cradle to gate, the analysis could lead to a different conclusion.

The third type of method for conducting a life cycle inventory is on the equipment scale [9]. This method is not used often for a full life cycle assessment even though the most accurate data can be obtained from this method. The issue with this method is the amount of time, resources and access needed to conduct a full life cycle inventory. This type of method is used for gate-to-gate analysis of various processes. Another issue with this method of conducting an LCI is that a comparison is relatively difficult to obtain since a gate-to-gate inventory does not account for how the given raw materials are being



produced. This type of method is usually supplemented with data from the previous 3 LCI methods.

The fourth type of method is the use of a hybrid life cycle inventory [9]. This method combines the features of the economic, life cycle and equipment scale. The motivation behind this method was to try to overcome the shortcomings of the various methods. The hybrid methods combined the economy scale with the life cycle scale to give a cradle to grave analysis with more detailed information on the specific industry or can be a combination of life cycle scale analysis combined with equipment scale analysis [12]. The advantage to this method is that it fills in the gaps that are left from the life cycle scale with data from the economic scale, which enables the person conducting the life cycle assessment to have a full cradle to gate life cycle. This type of life cycle also has the limitations of the economic scale for the data that is taken from the economic scale.

There are other methods that can be used for a life cycle inventory which include a limited life cycle inventory [7]. This only considers a small amount of metrics such as mass, water usage, energy, toxics emitted and overall pollutants emitted. This uses in-depth calculations, but does not consider all of the metrics stated by Allen and Shonnard [8]. Another method for life cycle assessment was proposed by Lei et al. called “the Most of the Most” [14]. This consisted of finding the most significant impact factors and then selecting the most significant phases. This process was meant to consider the whole process life cycle, but severely limits the size of an LCA.

Another way to conduct a life cycle assessment is in terms of exergy. Exergy is the available energy for the specific process [15]. This method reduced the amount of

double counting involved in a process [15]. According to Cornelisen et al., an exergetic life cycle assessment is a good tool to use in the area of depletion of natural resources and stated that life cycle assessments are weak in evaluating the depletion of natural resources [16]. An exergetic analysis compares the irreversibility of the different products and whichever product has the lower irreversibility is more sustainable [15], [16], [17]. Cornelisen et al. compared coal, green wood, and dried wood in an exergetic life cycle assessment. According to the study mentioned above using waste wood as chipboard instead of as an energy source gives less depletion [16]. It was also found that using green wood for electricity than for chipboard gives less depletion of resources than using waste wood for electricity production mainly due to the factor that the green wood would have to be dried prior to being used in chipboard production [16]. Ukidiwe et al., stated that the exergetic life cycle assessment does not account for various ecological resources and suggests that a thermodynamic life cycle assessment can be used in place of an exergetic LCA [18].

If there is limited information given on a specified process from the manufacturer, there are a series of heuristics that can be used to determine various parameters that are not given [19]. Jimenez-Gonzalez et al., proposed a methodology that can be used if the information is not given or is unknown [20]. This includes the inlet temperature and pressure, reflux ratio, fugitive losses and to account for any water in contact with other chemicals as contaminated. Jimenez-Gonzalez et al., mentioned that by using this approach will give a 20% error, but the error is smaller than not having any data for the process [19].

## **Impact assessment and analysis**

There are many factors that could be considered in the impact assessment stage of a life cycle analysis. There are 3 steps that are conducted in an impact analysis which are classification, characterization and valuation. The first step is classification. In this step the compounds are grouped according to impact categories. Xun et al., stated that there are 4 classes of metrics that can be used in the impact portion of the life cycle assessment [21]. The first of these categories is generic for both chemical and site. The second category is chemical specific, but does not account for environmental conditions. The third class is chemical specific in a generic environment, such as a chemical's global effects. The fourth class is site and chemical specific, such as releases into a specific waterway. Typical impact categories include global warming, ozone depletion, smog formation, human carcinogenicity, atmospheric acidification, aquatic and terrestrial toxicity, habitat destruction, eutrophication, and depletion of non-renewable resources [3], [8], [22].

Characterization is the second step on an impact analysis. In the characterization step, the mass or dollar amount of material is multiplied by the potential for the compound to cause an impact on a specified criterion such as global warming. When two similar products are compared and one product is higher for all impact categories are, no further analysis is needed, but this is rarely the case [8].

The valuation step consists of determining which impact categories are the most significant from the characterization step. Also in the valuation step, the total amount of ocean and land that are needed to "buffer" the various environmental impacts are calculated [8]. It is also possible to conduct the valuation stage in terms of monetary

value [3], [13]. Burgess, et al. stated that is difficult to develop a set standard for assigning relative weights to the categories because there is no clear consensus on how to carry out the stage of valuation [3]. Shonnard et al., developed a way to determine the specific weighting of the category using the relevance of the category in a specific country [22]. Shonnard et al., also showed how weighted factors can be used to determine which factor contributes most using societal factors [22]. Shonnard et al., use a process called Eco-Efficiency to determine which process causes the least environmental impact at the lowest normalized cost.

### **Previous Studies in Life Cycle Assessment**

Typical life cycle assessments are conducted in the product review stage during a process [23]. During the product review, the plant, prototypes, and detailed design of the product have already been done.

Mueller et al. stated that life cycle evaluation is needed at the planning stage of product development [23]. Mueller et al. investigated the disposal of multifunctional chip cards, which are used in a wide variety of electronics [23]. This article breaks down the amount of material used for each board, how much is recycled, how much material is incinerated, the toxic emissions and the energy required to mine/produce the material. This shows that the board is made of roughly half PVC, which accounts for 2/3 of the toxic emissions, but only 8.1% of the total energy to produce. On the other side, the silver oxide is only used in 2.5% of the product by weight, but takes the most energy to produce.

There have been studies conducted for electricity generation. One of these studies focused on the use of natural gas, heavy oil, or coal for use in a co-generation plant [24]. This paper used a numerical eco-load total standardized evaluation system developed by the authors to determine which type of fuel would be best to used in the co-generation plant. This article found that coal, and not natural gas had the lowest eco-load. The study by Goralczyk compared hydroelectric, photovoltaic cells, wind turbines, oil, coal, and natural gas [25]. Goralczyk found that electricity from hydropower had the least environmental impact [25]. Another study was conducted by Schleisner, which focused on wind farms [26]. This study was a typical life cycle inventory study that focused on the materials used to manufacture the windmills, but stopped short on the analysis portion. In the study conducted by Schleisner, it was found that 2% of the electricity generated during the windmill's lifetime was used to manufacture the windmill components [26].

A life cycle assessment for various forms of production for hydrogen has also been conducted. Koroneos et al., cited 6 ways to manufacture hydrogen [27]. These are photovoltaic cells, solar thermal energy, wind power, hydroelectric power, biomass degradation and natural gas steam reforming [27]. Generation of hydrogen from wind has the least environmental impacts for greenhouse gas formation, acidification, eutrophication and smog formation [27]. Hydrogen formation using photovoltaic cells has the largest total environmental impact [27]. The recommendation of Koroneos et al., is to use wind power, hydropower and solar thermal power to produce hydrogen since these are the “most environmentally friendly methods” [27].

There was also a life cycle assessment on two different anodizing processes [28]. This consisted of six life cycle stages and two different ways to anodize metal. The two processes were a mixture of boric and sulfuric acid and the other process used chromic acid. This article used a series of matrices to determine the environment impacts of the two processes. According to Eagan et al., the process using the mixture of boric and sulfuric acid is a better choice over the process using chromic acid [28].

Tan et al., have conducted a life cycle assessment for an aluminum supply chain [29]. This was a cradle to gate life cycle assessment of an aluminum billet, which included the mining of bauxite, the processing of the alumina and the final casting process for 3 plants located in Australia. Four different scenarios were analyzed, a base case, a reduction in scrap metal, a reduction of scrap metal and a more sustainable practice for the smelter, and the latter with clean coal technology. Implementation of the last case decreased the global warming potential by 21%, and also decreased the all other emissions [29].

A few life cycle assessments have been conducted on the pharmaceutical industry. One study conducted by Jodicke et al., focused on one processing aspect of an intermediate with a metal catalyst or bio-catalyzed with yeast [30]. It was shown that the solvents used in the extraction of the product played a large role in the environmental impacts.

Life cycle assessments have also been conducted on desalination technologies. One study was conducted by Raluy et al. and used SimaPro 5.0 software for the analysis portion. There were 3 desalination technologies that were compared. These were multi-effect distillation, multi-stage flash and reverse osmosis [31]. The study focused on the

environmental criteria of carbon dioxide, nitrogen oxides, non-methane volatile organic compounds, and sulfur oxides. The analysis of the paper published by Raluy et al. focused on integrating the distillation process and flash process with a cogeneration plant and with reverse osmosis. This study also compared different regions. These regions are dependent on different types of fuels for electricity. It was found that in the average European, Spanish, and Portuguese regions that a multi-stage flash had the least environmental burdens, but in the French and Norwegian models, reverse osmosis had the least environmental negative effects using Eco-indicator 99, Ecopoint 97 and CML 2 baseline [31]. Raluy et al. also stated that using a hybrid plant cuts down energy usage by 75% [31].

There are also a number of studies done on industrial paint coatings. One study done by Shonnard et al., compared 5 different coating processes for wooden doors [22]. From this analysis the UV coating process has the least risk potential, raw material consumption, emissions and energy consumption [22]. Papasavva et al., also conducted a life cycle assessment on paints which focused on paints used in the automotive industry [32]. This study focused on 3 types of coating materials; primer, basecoat and clear coat. Three primers were investigated, one solvent borne and 2 powders. One powder was acrylic and the other powder was polyester. The 2 basecoats that were used were waterborne which are white and pewter. The 2 clear coats were both acrylic, but one was a solvent clear coat while the other was a powder clear coat. The white basecoat was chosen for the article since the energy required produced either basecoat “use about the same amount of energy” [32]. The criteria used by Papasavva et al. were material requirements, energy consumption, atmospheric emissions, water emissions, solid waste

emissions, particulate matter, SO<sub>x</sub>, NO<sub>x</sub>, CO, VOC, and CO<sub>2</sub>. Papasavva et al. show that there is a trade-off between environmental factors. This is evident from the combination of the powder primer, water basecoat and powder clear coat “the PP2-WB1-PC2 is associated with the least energy, water consumption, solid waste and VOC. However it exceeds the other scenarios in PM, SO<sub>x</sub>, and CO<sub>2</sub> equivalent air emissions”[32]. There was another life cycle assessment conducted on car painting. Dobson shows from the analysis that incineration of the VOC compounds has the same environmental impact as the water based paint [33]. Dobson used the same criteria as Papasavva et al.[33].

The pulp and paper industry is another industry where life cycle assessment methodology has been applied. One example was a paper by Lopes et al., which compared two types of fuels, heavy fuel and natural gas, which were used in the pulp and paper industry [34]. The environmental categories were the same categories listed by Shonnard et al. [8]. The use of methane in place of fuel oil decreased all of the environmental parameters except photochemical ozone formation, which did not vary between fuel options [34].

Other life cycle assessments have been conducted on recycling. One of these studies by Rio et al., focused on the end of life recycling of plastics used in electronics [35]. The focus of this paper was on the separation and sorting of various types of plastics for recycling. Another study conducted by Shonnard et al., compared PET bottles to glass bottles with and without recycling. It was found that recycling the PET bottles had the least environmental impact and the same normalized cost as the glass bottle [35]. Song et al., focused on the recycling aspects of PET bottles for 11 different scenarios and showed that as the collection ratio increases, the energy used for collection



also increases [36]. Song et al., cited that the recycle pathway which produces the least  $\text{CO}_2$ ,  $\text{SO}_x$  and  $\text{NO}_x$  was the closed loop and landfill pathway while the pathway which produced the least solid waste was the pathway for pyrolysis and incineration [36]. There was also a study for another commonly recycled product, which is paper. Ekvall conducted a life cycle analysis for recycling newsprint in Sweden [37]. Shiojiri et al. conducted a life cycle assessment on recycling sulfur hexafluoride used in the electronics industry. [38]. There were different ways to use and to recycle the sulfur hexafluoride. From the study conducted on sulfur hexafluoride “energy consumption as well as global warming risk can be reduced by using a mixture of  $\text{SF}_6$  with nitrogen as an insulating gas compared to  $\text{SF}_6$ ”, but the other environmental impacts will increase due to transportation to the recycling plant [38].

There have been life cycle assessments conducted on waste management. Jimenez-Gonzalez et al., conducted a partial life cycle inventory on 3 different waste treatments for pharmaceutical waste [20]. These life cycle inventories were conducted on wastewater treatment plant, an incinerator, and solvent recovery [20]. Chevalier et al., compared two flue gas treatment processes for waste incineration using life cycle assessment [4].

Gasoline and other fuels have also had life cycle assessments completed on their manufacture and use. Major uses of these fuels are in vehicles, which is a concern of a few of these studies. Furuholt conducted a study comparing gasoline and diesel [39]. This study focused on the production of diesel, gasoline, and gasoline with MTBE. This study focused on the manufacture of 1000 L of fuel in Norway. The factors that were considered in this study were global warming, photo-oxidant formation, acidification,

eutrophication, fossil energy and solid waste. The impacts in the environmental categories listed above were also conducted on the basis of 1 MJ of energy. Both studies found that gasoline with MTBE contributed the most to the categories listed above. It was also found that diesel fuel and gasoline have approximately the same scaled values for acidification, eutrophication, and solid waste, but gasoline without additives has 1.5 times the global warming, 2.6 times the photo-chemical oxidant formation, and uses 1.5 times the fossil energy as diesel [39]. Another study on automobile fuel options was conducted by MacLean et al. [40]. This study focused on light duty vehicles and the CO<sub>2</sub> equivalent gases released during manufacture, gasoline refining, operation, maintenance, and other services. The author cites that 73% of the greenhouse equivalent gases are released during operation. MacLean et al. proposes viable alternatives to the use of gasoline in vehicles. MacLean et al. emphasized that although battery powered vehicles have zero emissions there were other factors, which have a negative environmental impact such as the use of heavy metals [40]. Hybrid vehicles are also discussed as an alternative, but “the higher sales price of the Prius is not justified by fuel savings, emissions reductions, or a combination of the two.” [40]. Diesel fuel is also another alternative, which has a well to tank efficiency of 24% while gasoline only has 20% efficiency [40]. There are also some drawbacks to the use of diesel, which include higher NO<sub>x</sub> and particulate matter emissions [40]. Ethanol is a viable alternative as an alternative fuel source, and there are two renewable processes that can be used to obtain ethanol. The first way is from plant cellulosic material. The well to tank efficiency for this material ranges from 80-95% and the emissions are 15 g CO<sub>2</sub> equivalent gases/MJ [40]. The other way is to use corn to manufacture ethanol. This process releases 6 times as

much CO<sub>2</sub> equivalent gases/MJ as the previous process [40]. MacLean et al., also cited that fuel cell vehicles are 20 years away from having a large number of these vehicles on the road [40].

Other than fuels, life cycle assessments have been performed on other sectors of the transportation industry. One study focused on the catalytic converters for passenger cars [41]. The goal of the life cycle study conducted by Amatayakul and Ramnas was to compare the life cycle impacts of a catalytic converter and the environmental benefits in terms of emission reductions through the exhaust pipe [41]. The study on catalytic converters focused on a cradle to grave study, but excluded the mining and transportation of raw materials since no data was available. The criteria used for environmental loads were global warming potential, waste, eutrophication, acidification, resource use and photochemical ozone creation potential [41]. It was found from this study that waste and global warming are drastically increased, but acidification, eutrophication, and photochemical ozone creation potential are drastically decreased [41]. Auxiliary power units for diesel trucks were compared by Baratto et al [42]. The environmental criteria used were the same criteria as mentioned by Shonnard et al. [8], but also included the toxicity for humans, terrestrial species and aquatic species. It was found the auxiliary power unit had the least impact for all the categories [42]. An economic analysis was also conducted and it was found that the payback period was slightly over two years [42].

Other life cycle assessments have been done on consumer products. A life cycle assessment was conducted by Shonnard et al., in which processes for various indigo dyes for dying denim were analyzed. A 2-D plot was used with the axis being cost and normalized environmental impact [22]. It was found that the dying the denim

electrochemically in a 40% vat solution has the least environmental impact and the least cost while dying the denim using indigo plants has the most environmental impact and the most cost.

There have also been life cycle assessments conducted on the food industry. A life cycle assessment was conducted on milk production by Cederberg et al. [43]. The study conducted by Cederberg et al. compared organic milk farms to conventional milk farms. For this study there was an increase in global warming due to organic farming, but a decrease in other compounds such as carbon dioxide and N<sub>2</sub>O. Most of the acidification potential for both of the systems was due to “ammonia evaporation from farmyard manure” [43]. The eutrophication parameter was estimated for this study and was based off of the manure application rate and a higher phosphorous surplus on conventional farms [43]. Cederberg et al., stated that organic farming reduces pesticide use, global warming, acidification and eutrophication [43].

Zabaniotou et al. conducted a study on two types of egg packaging material, recycled paper and polystyrene. The functional groups for this study were done on a packaging basis instead of a mass basis. The environmental factors used in the study for egg containers were global warming, ozone depletion, acidification, eutrophication, particulate matter, heavy metals, carcinogenic substances and photochemical ozone creation potential [44]. This study concluded “PS packages contribute more to acidification potential, winter and summer smog formation, while recycled paper egg packages contribute more to heavy metal and carcinogenetic substances impact.” [44].

Another study on food packaging was conducted by Bohlmann, which focused on a comparison of polypropylene and biodegradable packaging [45]. The functional

unit for this case study was the packaging required to fill 1000 kg of yogurt. The environmental criteria used for this comparison were energy and greenhouse gases. The biodegradable package consumes less energy, but has slightly higher greenhouse gas emissions. Bohlmann cited that the greenhouse gas emissions are equivalent if the biodegradable packaging is fully decomposed in the landfill [45].

Another study by Anderson et al. conducted a life cycle assessment on tomato ketchup [46]. The study on tomato ketchup was intended to identify “hot spots” in the life cycle of the product [46]. In this study, it was found that food processing contributes the most to greenhouse gases, human toxicity (CML provisional method), and acidification. From the study conducted by Anderson et al. the major contributor to eutrophication is the agriculture sector [46].

There has only been a limited number of life cycle assessments conducted on pharmaceutical products. The pharmaceutical sector has a unique situation unlike other sectors. Improvements to the processing of various pharmaceutical ingredients can not be made once a new drug application is filed with the FDA. There has only been one study conducted by Jimenez-Gonzalez et al on a pharmaceutical product.

Jimenez-Gonzalez et al. conducted a cradle to gate life cycle for a pharmaceutical product for GSK [47]. The criteria used for this study were eutrophication, acidification, greenhouse gases, photochemical ozone creation, energy and mass. It was found from this cradle to gate study that the process contributes most to eutrophication, ozone creation, total organic carbon, energy and raw materials while energy contributes most to greenhouse gas formation and acidification [47]. The manufacturing process is broken down further and shows the impact of solvents, chemicals, and internal drug manufacture

on the environmental criteria listed above. Jimenez-Gonzalez et al., also stated that solvent selection contributes significantly to the impact of the manufacture of a pharmaceutical product [47]. Solvents contribute 75% to the energy use, 80% of the mass excluding water, and 70% of the ozone depletion [47]. Energy also contributes 70% to resource depletion and 90% to green house gas emissions [47]. Jimenez-Gonzalez et al. also compared two processes for making sertaline. These were the THF and TOL processes [48]. These two processes were analyzed from the lab scale to the production scale. It was found that in the processes the energy usage decrease by 70% and 73% [48]. It was also found that there is no significant energy difference during the final production stage of the product with regard to the 2 different processes [48]. The criteria used for this study were eutrophication, acidification, greenhouse gases, photochemical ozone creation, energy and mass. It was found from this cradle to gate study that the process contributes most to eutrophication, ozone creation, total organic carbon, energy and raw materials while energy contributes most to greenhouse gas formation and acidification [47]. The manufacturing process is broken down further and shows the impact of solvents, chemicals, and internal drug manufacture on the environmental criteria listed above. It was also found that there is no significant energy difference during the final production stage of the product with regard to the 2 different processes [48],[ 49].

Jimenez-Gonzalez et al. also explained the limitations of life cycle analysis for a pharmaceutical process [49]. Along with each route, the materials used in the processing were taken back to preliminary starting materials such as crude oil, pre-filtered water or corn. For these processes a life cycle assessment was conducted to determine which

process is the more environmentally friendly process. For this analysis, terrestrial toxicity, land use, and resource depletion were not considered during the life cycle assessment [49]. Transportation of the raw materials was included in this analysis. Allocation of energy and pollutants if a plant produced more than 1 material was allocated on a mass basis. Solvent recovery for this process was assumed to be 75% for full production and 0% for laboratory scale [49]. Waste treatment was also considered in this paper. The waste treatment considered organic compounds, inorganic salts and solvent incineration

The analysis was conducted using a life-cycle assessment software package, ECOPRO<sup>®</sup> 1.5 but the author cites that other software packages were compared to ECOPRO<sup>®</sup>. These software packages included PEMS<sup>®</sup>, SIMAPRO<sup>®</sup>, and LCAIT<sup>®</sup>. Several different models were also used during the analysis portion. These included BUWAL, CML and Eco-indicator 95 [49]. There is a newer version of Eco-indicator, which was released in 1999, which was not used for the analysis. A comparison was made between various refineries using the various types of software packages. There are some technical errors in the software programs that are not physically possible. When comparing the methodologies and software packages the authors cited the example of ammonia production as a case study to prove the point that different literature values give different results in terms of materials used, water used, energy and emissions. The values the authors obtained were approximately the same as the values obtained from EFMA and BUWAL for most of the parameters investigated. The authors concluded the compounds in a typical LCA database are only a small portion of the compounds present in any given pharmaceutical product and that it is difficult to obtain LCA data on the

compounds that are not in a database due to legal ramifications [49]. Jimenez-Gonzalez et al. further stated that a gate-to-gate estimation method is better than missing data. [49]. It appears as though there are some inconsistent values, which are present in all of the software packages. Unfortunately, the author does not recommend which software package to use in place of another software package, which could be useful information. The graphs given in the paper show that SIMAPRO<sup>®</sup> and PWMI<sup>®</sup> give the median to low values as compared to ECOPRO<sup>®</sup>, PEMS<sup>®</sup>, and FRANKLIN<sup>®</sup> [49].

A heating and cooling sub-module was developed to determine the heating, cooling, and waste treatment that is used in a process. This gave heuristics about how to calculate the heating and cooling for each process and to back calculate the heating and cooling emissions for the processes. Heuristics on lowering the energy input was not included in the thesis. Using a methodology for lowering the energy is more important for future projects than lowering the energy in one specific project. One example for this case would be switching the process from batch to continuous which would allow heat integration to be conducted on the final process. It should be noted that at the pilot scale the largest decrease was noticed. The authors attribute this decrease to the reduction of mechanical energy and that all the energy is being provided by electricity at the laboratory scale. There was another issue with this article, which is that no processing conditions are listed. It should be noted that most pharmaceutical processes do not have significant heating/cooling and energy requirements simply because most operate close to ambient temperature and pressure. For fermentation-based products, such as pravastatin, there is very little heating or cooling required for the process, and the largest energy usage can be attributed to the RO pumps and the mixers. In other processes, fugitive



emissions from the process are approximately the same magnitude as emissions from energy consumption. Heating and cooling could be neglected because these do not constitute a large amount of energy usage in an LCA for many pharmaceutical processes.

Jimenez-Gonzalez et al described a methodology for comparing different processes using 4 main categories for a comparison. These categories are environment, safety, efficiency, and energy. These categories have a list of indicators for each category. For example, for the environment category there are 4 mass indicators, which are mass intensity, solvent intensity, waste intensity, and process emissions. These are calculated on a weight-by-weight basis such as kg mass/ kg active pharmaceutical product (API). The advantage to using a weight-by-weight method is that it incorporates the percent yield into the category indirectly. The life cycle category only includes CO<sub>2</sub>. The individual indicators are compared and are given a score of 0, 5 or 10 with 0 have a disadvantage, 5 being neutral and 10 having an advantage [49]. The scores were averaged and the numerical average is correlated with a color that is put into the main categories with 2.5 or lower being red, 2.5-7.5 being yellow and above 7.5 green [49]. From the life cycle assessment, it appeared as though the route that used ethanol as the starting solvent was the most efficient and the most environmentally friendly process. The criteria that were used in other portions of the paper were global warming potential, ozone depletion potential, acidification, nitrification, carcinogens, smog formation, and complexity of steps [49]. From the life cycle analysis, it appeared as though most of the global warming potential came from the energy generation while the process emissions contributed the most to acidification, nitrification, carcinogens, smog formation [49]. Transport related emission contributed to a large degree to the ozone depletion potential.

The author cites that these percentages can be used to find the problem areas in each process and to decrease the “problem” areas. The process that used ethanol as the starting solvent also had the smallest mass intensity [49].

With the larger indicators, the engineer or scientist can then look at the chart and determine which category is “more” important and add a weighting factor to that specific category. This method is open to interpretation of the engineer or scientist making the decision on which process to use for the plant. This method also has a disadvantage which is knowledge about the analyst’s own plant. The analyst may not know of a piece of equipment that is being underused that could be used to clean up a waste stream which would skew the results of the method. The alternative is also true; another project may be in the process of being built which would push a certain process unit to capacity without the analyst’s knowledge. The numerical method in general is also a disadvantage. Having a scale from 0-10 is not the most accurate way to gauge environmental criteria and could bias the analysis portion. A better way would be to normalize the data using the highest or lowest value.

Complexity was considered as a criterion by Jimenez-Gonzalez et al. [49]. They do not address the societal ramifications that could be considered when using complexity as a criterion specifically for this drug that is an anti-depressant. Decreasing the complexity for a process makes it easier for the manufacturer to make the drug, but it also makes it easier for another person to make the drug illegally. For pain relievers and anti-depressants, making a more complex process may decrease the societal impacts. There are other drugs such as anti-cancer medicines where this is not the case, due to the well known and documented side effects of chemotherapy.

Jimenez-Gonzalez et al. also use substance trees in their analysis. Substance trees are a simple way to account for raw materials, but do not count multiple products from the same plant. This makes it very easy to double count the mass and energy of side products. For example, in the manufacture of NaOH, there are several ways for purifying sodium chloride where some processes use more energy and some processes use less [50]. Also, a byproduct of sodium hydroxide production is chlorine gas, which is typically used to make HCl, but the product tree shows these compounds in two completely different areas [50]. HCl could potentially be made from methylene chloride production, dichlorobenzene production, sodium hydroxide production or all of these processes as a side product [50]. Another concern with this analysis is that everything is on a comparison basis, thereby downplaying some areas of importance and making negligible criterion as important problems that should be addressed in the process.

Solvent recovery, incineration, landfill, and waste treatment are all considered [49]. The energy requirements and limitations are outlined effectively for each disposal method. There was one disposal option that was left out. This option was selling the solvent waste to another facility for use as a paint solvent. Use as a paint solvent would drastically change the dynamics and environmental implications listed in this chapter. The methods mentioned only account for the soil and water releases along with chemically modified releases into the air. The compounds released during painting are a direct solvent release into the air and will have a completely different impact. This also provides an environmental justification for recovery and recycling of solvents vs. disposal, but still does not consider solvent usage for other purposes outside the plant. If an outside vendor was using the waste solvents as a solvent for another purpose, than

using solvent recovery would contribute more to the environmental factors since fresh solvent would have to be made for the outside vendor. In the case of solvent recovery, more energy would be spent to purify the solvent for internal use inside the plant.

## ***Background of the Pharmaceutical Industry***

There are a large number of issues that are present in the pharmaceutical field that make the field unique. These issues include the manufacture multiple unique products, a large number of constraints by the FDA, limiting factors within a process and separation techniques that are benign to the compound. Some of these constraints are outline by the FDA [51]

There are a number of issues with applying green engineering and life cycle assessment to pharmaceutical products. The first issue is that comparative life cycle assessment studies are difficult to conduct. Pharmaceutical companies make similar products, but may have different processes. A given pharmaceutical company will not give their various process parameters for a drug to a competitor for a comparison.

Another issue is that the green engineering and life cycle assessment studies are typical conducted for internal documentation and not used when the new drug application (NDA) is submitted to the FDA for approval. The primary concerns for consumers are how well the drug works, the side effects of the drug, cost, and supply. Normally the environmental sustainability of a drug is not a concern to the end consumer or the FDA. There is another disadvantage that makes life cycle assessment difficult for drug manufacturers. This is that most pharmaceutical companies make a variety of drugs ranging from mild over the counter pain relievers to anti-cancer agents. One day a drug company may be making a statin drug and the next day making a drug, which has anti-cancer properties or is an antibiotic.

The benefits are that the company does not have to invest heavily in other equipment costs and maintenance and this approach lends itself well when fermentation is involved since the time it takes from initiating fermentation to harvest usually takes 7 to 10 days. Another positive aspect is that fewer pieces of equipment save floor space. It is much easier to provide space for 1 piece of equipment than 7 pieces of equipment. Another negative aspect is that most of the equipment is not specifically made for each drug. For example, the centrifuge may be made to handle 10000 L/hr, while the fermentation beer for the drug that is being processed that day may be only 3000 L total. To relate this to another industry that uses a distillation column. If the flow rate for a distillation column was decreased by 70%, there would be a large amount of issues such as weeping. The other option available is to not separate or recycle the solvents. This is typically the case since the volume of waste solvents produced is not worth recovery or cannot be reused due to FDA regulations unless certain certifications are obtained for the recycled solvent. There are other constraints that the drug manufacturers have to follow.

Pharmaceutical manufacturing can be broken down into two distinct categories, biochemical and organic synthesis, which have distinct equipment for each. Within each category the equipment used in the manufacture of one drug is typically the same equipment used to make all the drugs; there may be a few specific pieces of equipment for each drug, but most of the equipment is the same. For example a filter used to separate a crystalline API from a liquid solvent may be used for 10 different products in a given year. This approach has both positive and negative consequences for the company.

Developing an LCA for this process is rather difficult because it is not a continuous process. Allocation of the specific piece of equipment is also difficult since

there is not a “good” way to allocate each process. Using the cost to manufacture a specific drug is not an accurate way to determine the allocation of the equipment.

One drug may be 10 times the cost of another drug because of a raw material cost or inclusion of a precious metal in the drug itself. An example of this would be in the case of cis-platinum, which is an anti-cancer agent. If Platinum cost approximately \$900/ounce and accounts for 65% of the API weight then this would be a significant cost.

Another way to allocate the materials equipment is by using weight. There are also drawbacks to this approach, which are related to dosage. One drug may “work” better than another drug, but may be made in a similar way.

There are some benefits for the use of green engineering in the pharmaceutical field. Many drugs that go “off patent” are produced by other suppliers and are known as “generic drugs.” A substantial portion of the generic drug industry success is dependent on decreasing the solvent usage and gaining a competitive advantage. A way of achieving a competitive advantage is to reduce liability and environmental risk. Competitive advantage is also gained by managing resources properly. A life cycle analysis can be used to generate proper resource management and identify “problem” areas in a process.

Another advantage is that life cycle assessment and green engineering allows scientists and engineers to track their progress through drug development. This allows the analyst to determine what aspect of the process has the most environmental impact. The analysts can further adjust the process to minimize the impact on the category by changing the process.

A third advantage is that potential drugs can be flagged because of increased legal liability during the early stages of drug development. Once a life cycle study is conducted, some software packages give results in either life-years or disability affected life years (DALY). If the projected amount of lives saved is less than either the DALY or the Life-Years, the drug should not be made or a large number of modifications should be made to the process prior to the manufacture of the drug.

Most pharmaceuticals are produced in batch processes and the processing is limited by some factor within the process. The limiting factor could be volume, concentration, heat transfer, or stability of the product or an intermediate. This is especially true for microbial produced drugs. Most drugs and intermediates are poisons to microbes at various concentrations, so there may be a limited amount of drug that can be produced per batch, regardless of how much intermediate is added or how much time passes. There are also other unique factors, which make pharmaceutical processing different and include separation techniques employed.

Separation of the drug from a solvent is very difficult process compared to the separation techniques applied by other industries. Traditional distillation and crystallization will not work. Traditional distillation could potentially destroy the product. In traditional crystallization, approximately 10% by weight of material is used to seed the solution, but this cannot be used in the pharmaceutical industry due to cross contamination problems. The techniques employed consist of liquid-liquid extraction, vacuum filtration, adsorption, crystallization with extremely small amounts of API, and to some extent chromatography [53]. In chromatography there are a large amount of scale up problems and this technique is usually avoided. The main focus of these



separation techniques is to obtain a very high purity product. In order to obtain this high purity product, the overall yield is sacrificed for the safety of the end consumer. In many cases the recovery of other phase or medium is not considered because it is not cost effective to safely recover an API, active pharmaceutical ingredient, from the waste due to impurities.

### **Background for Green Analysis of a lab-scale fermentation based API**

One way to produce a drug is by having microorganisms metabolize a certain compound and change the compound into the desired drug. Although this manufacturing route is typically greener than drugs made by organic synthesis, it is still is raw material and separation intensive and consequently is an environment concern. Most of the solvents used in these processes are volatile organic compounds. Strong acids and bases are also typically used in the processing to change the solubility properties of the desired compound in a solvent.

Manufacturing pharmaceuticals by a fermentation route originated over 80 years ago. Many organic chemicals were made via fermentation in the early 20<sup>th</sup> century before alternative synthetic routes were discovered. Some chemicals previously made by fermentation include citric acid and acetic acid [52]. Fermentation involves many steps in the production of a chemical. Most of these steps involve separating the desired product from the microorganisms and the by-products and wastes produced by the microorganisms.

There are a lot of material specifications that must be met for the raw materials that are input into the process. The plants that are used to manufacture pharmaceuticals are much like the clean rooms in the manufacture of microchips. Even water for these processes has to meet a certain specification. This specification is usually met by using reverse osmosis followed by deionization to remove molecules that may inhibit microbial growth, which is followed by a UV treatment. These molecules are typically added to water to inhibit microbial growth. Treating water in this way allows microbes to grow uninhibited by antimicrobial agents present in tap water [53].

The water cannot be used directly from a public water supply because any microbes that are added may die. On the other hand, treating the water and storing it under “open conditions” allows undesired microbes to grow in the water prior to use, which would result in the water having to be retreated. This contributes substantially to the energy required for a process.

Most pharmaceuticals made by biochemical engineering routes are produced in batch processes [53]. The use of a continuous process for fermentation is typically not feasible. The problems with continuous fermentation include having an extremely large reactor, the growth rate of the microbes, control of the microbes, and other problems.

The manufacture of drugs using biochemical methods from microbes is very separation intensive. For many pharmaceutical processes, the desired materials are relatively unstable at high temperatures and require specialized separation techniques. These compounds include proteins, amino acids along and other compounds. These chemicals can also change the crystal structure at higher temperatures. This could result in lost product at best and at worst the formation of a toxic substance. These compounds

require separation techniques that are typically solvent intensive. The techniques employed consist of liquid-liquid extraction, vacuum filtration, adsorption, crystallization, and to some extent chromatography [53]. Typically drugs made from fermentation are produced in relatively low concentration in the process. For example, pravastatin made via fermentation is only present in 3 grams per liter in the initial fermentation broth [54]. Even ethanol produced via fermentation is on the order of 50 grams per liter [55]. The main focus of these separation techniques is to obtain a very high purity product. In order to obtain this high purity product, the overall yield is sacrificed for the safety of the end consumer. In many cases the recovery of the other phase or medium is not considered because it is not cost effective to safely recover an API, active pharmaceutical ingredient, from the waste due to impurities.

Over a period of time, drugs are replaced with newer drugs that have more benefits and/or less side effects. Also generic manufacturers produce their own versions of the drug, which is the case of pravastatin (sodium). Life cycle analysis plays a role in developing these new drugs so that these drugs can be made using the same technology or more advanced technology. Environmental management not only contributes to recovering investment costs, but also allows for greater efficiencies in the process.

There are also drugs, which are not made by fermentation, but by organic synthesis. Products made in this way have processing that is completely unique from products made by fermentation.

## **Scale up of an active pharmaceutical ingredient**

The majority of pharmaceutical products are made by organic synthesis. The drug studied in this section of the thesis was made by an organic synthesis route. For this drug the scale up that is involved during the production of a drug was analyzed. The scale up is more useful to a pharmaceutical company that invented the drug since this is extremely different than other industry.

During the scale up of a specific drug, the R&D scientists and engineers have to be mindful of various health, safety, and processing of the drug while scaling up. In this industry, most of the lab scale equipment is very similar to the pilot and full-scale equipment to minimize scale-up difficulties, but there are always other problems that arise.

For this analysis data for one specific drug, Drug A, was obtained and was tracked from the lab-scale to the pilot plant scale. Typically there were a wide range of changes that are made from the lab scale to pilot scale. These changes include, but are not limited to, solvent substitution, reagent substitution, equipment substitution, etc. It was found that there was need for an easy to use solvent selection table so that the scientist and engineers could determine the environmental effects of the replacement of solvent with another solvent.

## **Chapter 2: Definitions for the Green Analysis of the Pharmaceutical Products**

There are wide ranges of metrics that can be applied to the processing of the drug. These metrics are dependent on where the boundary of process is set. The boundary of study limits the analysis to processes, which are pertinent to the process. The boundary conditions are the same for each comparison. Once the boundary is set, an analysis can be conducted regarding the various metrics used.

### ***Boundary, Scope and Functional Unit***

As an initial estimate the boundaries for this analysis will be designated as basic raw material input and drug output. Drug output in a crystallized form was chosen. Within these boundaries there are manufacturing processes consisting of various reaction, and separation processes. The scope of this life cycle assessment and life cycle inventory includes the drug prior to formulation. Formulation of the drug was not included in this analysis due to the variability of the dosage.

The functional unit for both drugs was 1 kg of API. A functional unit was used to normalize the data so a valid comparison could be made. All data was averaged and expressed in terms of a 1 kg unit of this drug. This unit was chosen because it could easily be converted to other functional units in the industry.

For the scale up of an active pharmaceutical product (API) a gate-to-gate analysis was used. This was chosen because some steps were outsourced to another company. The company who was making the drug does not have a large amount of control over how the intermediate is made.

### ***Types of Metrics used by Pharmaceutical Companies***

There are a number of different metrics that are used to determine the safety and sustainability of a process. These included metrics (both public and proprietary) used by individual pharmaceutical industries and various chemical engineering societies. There was some overlap between the methods, but each organization has their own unique metric representation. These include mass, energy, water usage, waste management, along with other processing conditions and environmental considerations.

There is a broad category called processing metrics. The metrics in this category include mass, energy, water, and solvent usage along with waste management issues and solvent recovery. These factors are considered more frequently than the other metrics since these are the basic operating parameters of a chemical plant. All of these factors are typically used in pharmaceutical applications.

There are number of ways that mass can be reported. Gonzalez et al., used mass intensity as metric [56]. Mass intensity is the amount of total mass needed to make 1 kilogram or pound of a product. This metric can be found by using the yield for the upstream process, and the summation of the mass of solvents and water used in the process. This approach is used by two engineering societies; AIChE and IChemE as

complementary metrics [57] [58]. There is a method described by Schwarz et al, which is called “material intensity” [59]. This is the same metric, except with a name variation. Another method to compare mass can be found by using the mass and dividing it by the dollar amount of the final product. This is the method that is recommended by the AIChE and is also used as a metric by IChemE [57], [58]. There is a third way that can be used to determine the mass of material. This approach uses a mass balance on the material and does not take into account the mass of product or dollar value of the product. This approach is used by Cue and is also used by IChemE as complimentary method to report mass [58], [60]. There are other metrics by AIChE Sustainability Institute and IChemE, but these metrics are not typically used. These include the percentage of mass recycled, the percentage of renewable resources used, and the total mass divided by the value of money added to the product by the processing steps.

There are 3 unique methods in reporting the energy usage for a process. The simplest method is an energy balance on the process, which only takes into consideration the total energy used for the process [57], [58], [60]. The second method for reporting energy is reporting the value in the form of energy intensity, which is calculated similar to the mass intensity (total energy used for the process divided by the mass of product produced). This technique was used by Jimenez-Gonzalez et al, Schwarz et al, and is a complimentary metric of the AIChE energy metric [56], [59], [57]. The other approach to calculate energy intensity is on a per dollar basis. The energy is found by dividing the total energy used by the value of the product sold. This is the preferred method of AIChE [57]. There are other metrics by AIChE and IChemE that are not used in a typical

analysis. These include the percentage renewable energy used, and the total mass divided by the value of money added to the product in the processing steps.

The AIChE metric for water usage uses a water balance on the process to report the water used, but does not consider the amount of product or the price of product [57]. This method is also used by IChemE, but reported on a yearly basis [58]. IChemE uses other methods for determining the water usage [58]. The first of these methods is found similar to the energy and mass intensities and is calculated by dividing the amount of water consumed by the total mass of the product. This method was also used by Schwarz et al. [58] [59]. The other method of reporting water usage is used by Tallis et al. this was found by dividing the total water usage by the value added to the chemical because of processing [58].

Waste is another metric that is frequently considered. There are a few methods of reporting waste and waste generation. Cue measured the total waste of the process [60]. Jimenez-Gonzalez et al. and Taylor both used waste intensity as a metric [56], [61]. The waste intensity is found similar to the mass intensity (total amount of waste divided by the mass of product). Taylor utilized a unique approach to waste intensity by further delineating the waste into two different categories, liquid waste and solid waste [61].

Solvent usage is another factor that is considered in sustainability. This factor is specifically a problem in the pharmaceutical industries. Jimenez-Gonzalez et al. used solvent intensity as a factor for sustainability [56]. Solvent intensity is defined as the amount of solvents including volatile organic compounds (VOCs) needed to make 1 kilogram of final pharmaceutical product. In Taylor's Greenness Scorecard, there is a solvent rating guide. This allows the user to determine which chemical is less or more



harmful based on a 0 to 4 scale. Solvents which are 4 are the most environmentally friendly solvents, such as ethanol and water [61]. Taylor's Greenness Scorecard used percent solvent recovery as one of the criteria [61]. Cue did not consider solvent recovery but used fresh solvent usage as a criterion. This would result in the same conclusion as the Greenness Scorecard. There is another consideration when solvents are considered in a process. This metric considered the recovery and reuse of solvent from another company's waste [58].

Volume is typically a limiting factor in most pharmaceutical applications since the volume is typically the bottleneck in the manufacture of pharmaceuticals. Volume is also used as a metric in pharmaceutical processing. Many liquid chemicals, such as the solvents used in processing are typically expressed as volume instead of mass. Cue used the maximum volume to find the volume of the process [60]. The maximum volume is defined as the processing step where the largest volume is present. This is approach is typically used in batch processing to find bottlenecks in the process, since the size of the reactor limits the amount of solvents that can be used in it in a given batch and therefore the material that can be produced. Taylor used volume intensity as a metric [61]. Taylor's approach was similar to Cue's approach except that the maximum volume was divided by the mass of the product produced.

Fugitive emissions are the amount of released material that is attributed to unavoidable emissions. There are two methods that are used for reporting the fugitive emissions. Schwarz et al. and Cue used one method, which was to count the total fugitive emissions for the process [59], [60]. There are disadvantages and advantages to this approach. The advantages is that most simulation programs for emissions give total

emissions in a form used by most government agencies. The disadvantage is that process improvements will not show up if there is an increased yield of the drug. The second method is used by Gonzalez et al. and Taylor and is called the fugitive emission intensity [56], [61]. This is calculated in a similar fashion as the mass intensity. This is the fugitive emissions divided by the total mass of product produced, typically in kilograms. Gonzalez et al., used the same mass units for all of the intensities, which is kg/kg API [56]. Taylor used different mass units to differentiate between solid, liquid and fugitive emissions, which are given in kg/kg API, L/kg API, and lb/kg API respectively [61].

Time is another factor that is used as a metric [56], [60], [61]. Time is not direct metric, but has environmental implications. Typically fugitive emissions are a function of time; the longer the process, the more fugitive emissions are released. The second environmental impact with time is with solvent usage and solvent recycling. More solvent could be recycled if the process was continuous or a processing step only took a short amount of time. Typically longer times reflect negatively on the processing conditions. Also since most pharmaceuticals are made in batch processes, longer times to make the product also limit the amount of API that can be made since some drugs can take weeks to months to produce.

Yield is another factor that is routinely considered as a metric. All the yields are calculated on a mole basis. This is the traditional method for reporting yield. The reason for including yield as a metric is because as the yield increases for a given batch the various other metrics will decrease. Yield, also to some degree, reflects on the complexity and number of processing steps. As a process becomes more complex or more steps are included the overall yield decreases due to loss of product in various waste

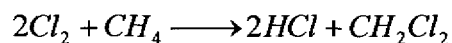
streams. Jimenez-Gonzalez et al, Cue, and Taylor used this metric [56], [60], [61]. Taylor's Greenness Scorecard has a unique algorithm for calculating the yield. This method also included the increased difficulty of reaching extremely high yields. This also factors in the step yields. For example if a process has two steps each with a 50% yield, the overall yield would be 25%. Obtaining a 10 to 20% overall yield is relatively easy compared to having a yield of 90 or 99%.

There is also another step related to yield which is the number of unit operations. This is the number of unit processes involved in each processing step. Both Jimenez Gonzalez et al. and Taylor use the number of unit operations as a metric [56], [61]. As the number of unit operations increases, the amount of mass, energy, and water needed increases. As the number of steps increases, the yield typically decreases due to product left in a previous pieces of equipment.

Conversion was also used as a metric by Gonzalez et al. and Taylor [56], [61]. The same reasoning for the inclusion of yield also applies for conversion. Conversion is slightly different than yield in that conversion is a reflection of the conversion of raw material to product while yield is the total usable output of drug. For example, a given process may convert 95% of an intermediate to product, but only have a 50% yield due to isolation losses.

Safety metrics were also taken into consideration. Jimenez-Gonzalez and Taylor both gave a broad view of occupational hazards and process hazards [56], [61]. Taylor gave specific examples of process hazards in the Greenness Scorecard such as worker exposure limits [61].

Process hazards could be independent of the occupational hazards. These are exclusive to Taylor's Green Scorecard [61]. These metrics include dust explosion potential, charge dissipation, pressure rise rate, explosion energy, use of excessive reagents, and the formation of gaseous byproducts. Most of these factors are based on process safety. These issues are typically a large concern in the pharmaceutical industry since small particles are typically produced. The use of excessive reagents and the formation of gaseous by-products can be found through a balanced reaction. An example is given below for a typical chlorination reaction



There are chemicals that a few companies do not use because of the liability associated with these chemicals. Taylor uses this metric as "number of listed reagents" in his Greenness Scorecard [61]. This metric can vary from company to company, and is dependent on past problems with the chemical compound. For example, these chemicals could include benzene, cyanide complexes, and certain organic compounds.

There is also a classification of environmental metrics based on overall ecological concerns. These metrics include a human health metric, carcinogenicity, ozone depletion, global warming potential, eutrophication, smog formation, an eco-toxicity metric, acidification, biopersistent materials, societal implications, and land use.

The human health metric is a metric cited by AIChE as a sustainability metric [57]. The formula for this metric is shown in Equation 1.

### Equation 1

$$HHM = \frac{Mass * BCF * \frac{1}{2} Life}{TLV}$$

Where:

HHM is the human health metric

Mass is the Mass of the compound

BCF is the Bio-concentration factor

$\frac{1}{2}$  life is the multimedia-weighted half-life

The PEL and TLV are set by various organizations as the maximum exposure a worker can have without adverse effects. The threshold limit values can be found on MSDS sheets from various chemical suppliers such J.T. Baker or Fisher Scientific and is set by OSHA [62], [63]. There are cases when the TLV data was unavailable because of the lack of study of the chemical, lack of use for the certain chemical or the chemical is deemed safe. Some chemicals that are deemed safe are meat extract, which is an ingredient for microbial growth, water, and sugar. When this was the case, the specific chemicals are not included in the toxicity criteria. This is because the human health metric for the chemical is close to zero. The persistence is the time it takes for the material to decompose. The bioconcentration factor is the propensity of the compound to be absorbed by the body and not metabolized. The persistence and the bioconcentration factor can be calculated using group contribution theory. The calculation used for the persistence and bioconcentration take into account every bond in the molecule and the time it takes for the bonds to break down. This is somewhat redundant of some of the safety metrics, which are mentioned by Taylor and Jimenez-Gonzalez et al, but this

metric takes into account the half-life of the material of interest. Taylor also counts the bio-persistent as a separate metric [61].

The eco-toxicity metric is a metric cited by AIChE as a sustainability metric [57] and is calculated in a similar manner to the human health metric. The eco-toxicity represents the toxicity to aquatic species. This metric is found by multiplying the mass of the compound by the bioconcentration factor and the multimedia weighted half-life divided by the lethal concentration to kill 50% of fish over 14 days. Most of this data can be found from MSDS sheets and calculated using group contribution theory for the persistence and bioconcentration factor. IChemE has tabulated a small list of compounds with eco-toxicity potency factors [58]. This list contains heavy metals, along with selected organic and inorganic compounds.

Carcinogenicity is another metric of concern. Carcinogenicity is hidden within other categories such as worker exposure limits, process hazards and process safety [56], [61]. The sustainability metrics by IChemE include carcinogenicity as a stand-alone metric. IChemE gives various potency factors for the carcinogens listed with the baseline carcinogen, benzene, having a carcinogenicity value of 1 [58].

Global warming potential is another metric that is a concern. There are a few methods available on reporting this metric. The first method is by analyzing the global warming potential of the materials present in the process. The table provided by IChemE gives guidance about which materials should be considered contributors of global warming. Most of the compounds listed are halogenated hydrocarbons, but carbon dioxide and monoxide are included in the table along with a blanketed category for volatile organic compounds [58]. AIChE has the core metric that is expressed in terms of

CO<sub>2</sub> equivalents per dollar value of the product. There are other complementary metrics listed by AIChE, which are CO<sub>2</sub> equivalents per mass of product sold, and CO<sub>2</sub> equivalents per dollar value added from processing [57]. Another technique of determining global warming is by using life cycle assessment software. Jimenez-Gonzalez et al. employed this method in the life cycle analysis of pharmaceutical compound, which used a complementary metric mentioned by AIChE [57], [64].

Ozone depletion is an environmental metric that is considered by various organizations. All of the compounds that are ozone-depleting compounds are halogenated hydrocarbons. The table provided by IChemE gives guidance about which materials should be considered contributors of ozone depletion. Typically, CFC-11, which is a chlorofluorocarbon, is used as the baseline for ozone depleting substances and is given a potency factor of 1.

Photochemical smog formation is a category typically considered as a sustainability metric. AIChE has a core metric that is expressed in terms of kilograms of ethylene equivalents per dollar value of the product. There are other complementary metrics listed by AIChE, which are kilograms of ethylene equivalents per mass of product sold, and kilograms of ethylene equivalents per dollar value added from processing [57].

Eutrophication is a criterion, which is used as a metric for sustainability. Eutrophication is the process where bodies of water receive excessive nutrients. This is mainly attributed to phosphorus and nitrogen containing compounds. There are a few methods on reporting eutrophication. AIChE has a core metric that is expressed in terms of phosphate equivalents per dollar value of the product. There are other complementary

metrics listed by AIChE that include phosphate equivalents per mass of product sold, and phosphate equivalents per dollar value added from processing [57]. Another technique of determining eutrophication is by using life cycle assessment software. Jimenez-Gonzalez et al. employed this method in the life cycle analysis of pharmaceutical compound, which used a complementary metric mentioned by AIChE [57], [64]. Another method of reporting eutrophication is by using the potency factors given by IChemE. The table given by IChemE represents the typical factors that contribute to eutrophication [58].

Acidification is considered as a sustainability metric and is defined as the emissions that cause acid rain. These emissions can result from direct processing, or as a result of combustion. AIChE has a core metric for acidification that is expressed in terms of kilograms of SO<sub>2</sub> equivalents per dollar value of the product. There are other complementary metrics listed by AIChE that are given as kilograms of SO<sub>2</sub> equivalents per mass of product sold and kilograms of SO<sub>2</sub> equivalents per dollar value added from processing [57]. Another technique for determining acidification is by using life cycle assessment software. Jimenez-Gonzalez et al. employed this method in the life cycle analysis of pharmaceutical compound, which used the complementary metric mentioned by AIChE [57], [64]. Acidification can also be calculated by using the potency factors given by IChemE. The table given by IChemE represents the typical factors that contribute to acidification that is given on a basis of tons of H<sup>+</sup> ions released per year [58].

There are two more environmental categories that are still in development. These include the societal impact of a product or process and land usage. The publication by IChemE offers some guidelines for each of these two categories, but these are not widely



used or developed. The societal impacts include meetings with external shareholders, benefits from the company, the number of complaints, and legal actions that are taken against the company. This can either be established on a monetary or yearly basis [58]. The land use metric is also described by IChemE and accounts for waste disposal and some of the environmental parameters [58].

From these metrics, a list of metrics was chosen to compare the pharmaceutical products discussed in this paper. The processing metrics for this paper included total mass, water, solvent, and waste intensities. Also included were energy intensity and fugitive emissions.

A list of environmental criteria was also developed. The environmental criteria included weighted factors for global warming potential, ozone depletion, smog formation, carcinogenicity and acidification. Other factors were also included which are derivatives of the human health and the environmental metrics, but do not account for the bioconcentration factor or half-life of the compound. These are the inhalation toxicity metric and aquatic toxicity metric. The inhalation toxicity has the same formula as the human health metric, but without the BCF and half-life factors. The aquatic toxicity has the same formula as inhalation toxicity, but uses the  $LC_{50}$  for fish instead of the TLV. There was another metric added. This metric is the ingestion toxicity. This can be found similar to the inhalation toxicity, but uses the  $LD_{50}$  for rats instead of the TLV.

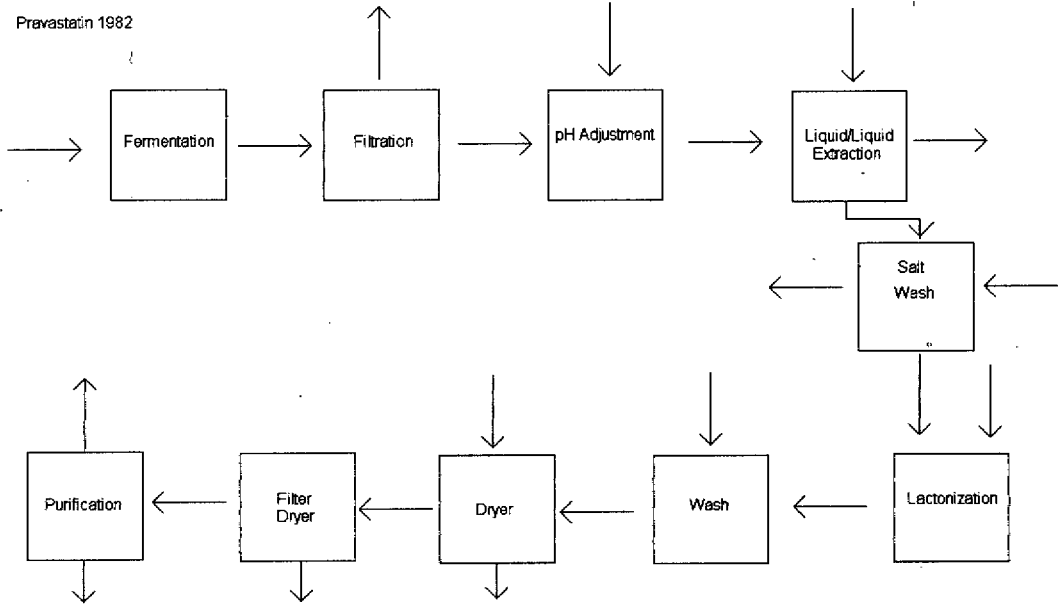
These metrics were applied to two studies to determine if there were any trends present. One study consisted of the green analysis of a lab-scale fermentation based pharmaceutical product. The other study focused on the scale up of an active pharmaceutical ingredient made by organic synthesis.

## **Chapter 3: Green Analysis of a lab-scale fermentation based API**

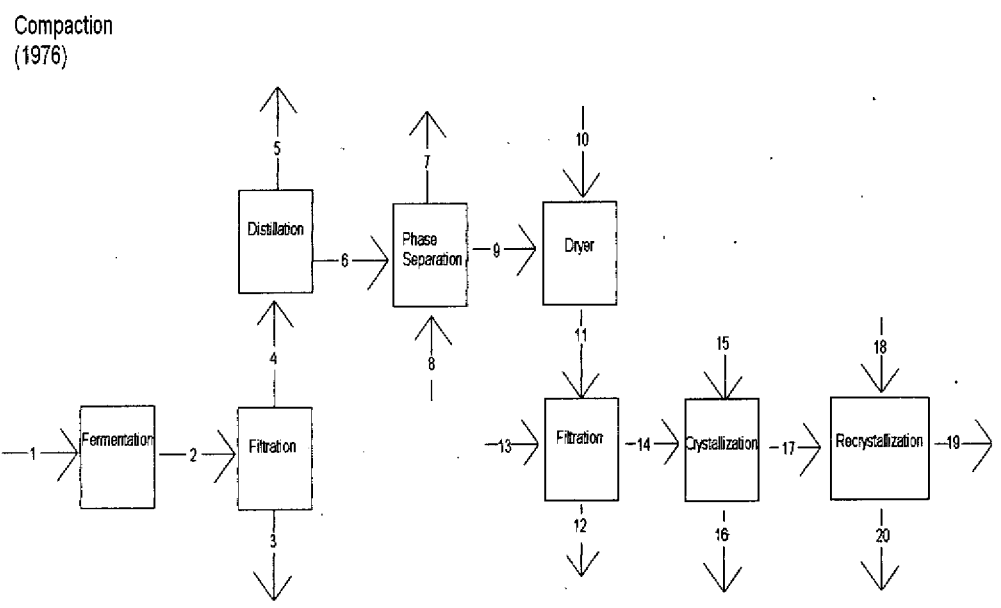
Pravastatin, which is made by Bristol Myers Squibb, was chosen for this analysis since a number of processes have been investigated for the manufacture of the drug. There are two fermentation steps involved in the manufacture of pravastatin. ML-236B is the intermediate and is made in the first fermentation step by one type of fungi [65]. In the second fermentation, an intermediate is converted to pravastatin by another type of fungi [54], [66], [67], [68]. These processes were defined following two patents, one for pravastatin and one for the intermediate. Variations and improvements in the intermediate process is beyond the scope of this analysis. For this process the emissions released by the fungi are assumed to be zero since the mass of microbes is insignificant in the fermentation beer [53].

### ***Processing***

The first process in the manufacture of pravastatin was in 1982, which had an extremely low yield. This is given in Figure 2 and Figure 3 [66]. The flows from the patent do not reflect the actual operating procedures used in large-scale production, but are lab-scale applications. If the intermediate process is not included and a linear scale up is assumed, the amount of waste generated would constitute over 1,307 drums which hold 55-gallons each of waste for each kilogram of active pharmaceutical ingredient (API) produced [66]. Most of this waste is water, but the water still has to be treated since it may contain microbes or harmful microbial by-products and unused reactants.



**Figure 2: Pravastatin Process from Patent**



**Figure 3: Intermediate Process from Patent**

These two processes are given on different scales so both these processes need to be scaled up. Each chemical was totaled for use in the processes for the LCI: For the pravastatin and intermediate processes the scale up can be seen in Table 1 and Table 2.

**Table 1: Scale up of Pravastatin Process**

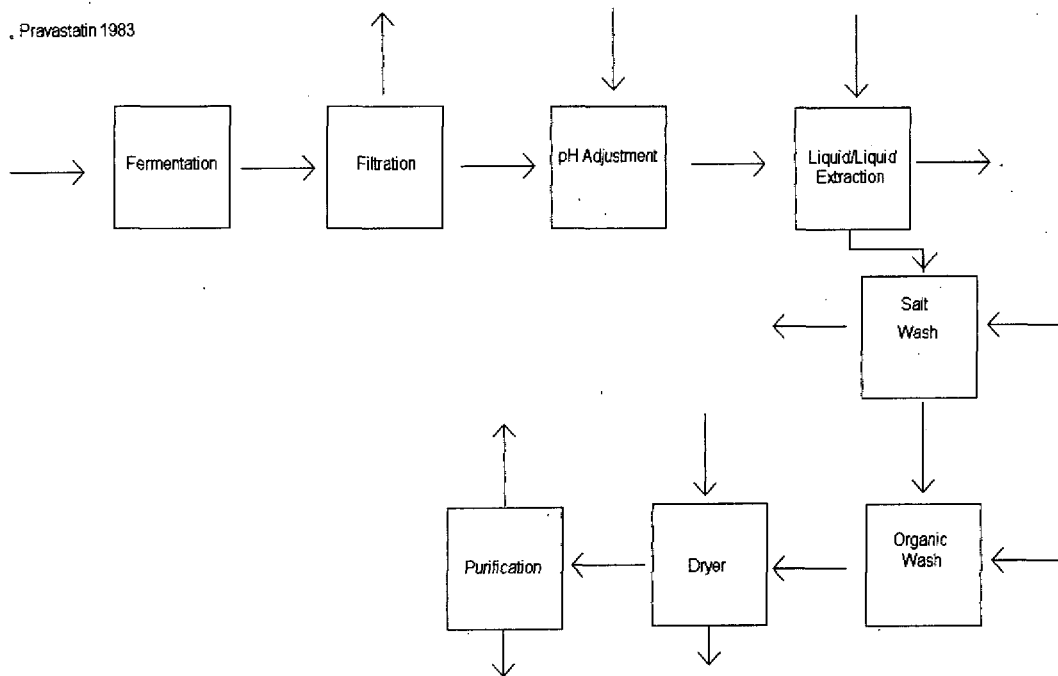
Pravastatin 1982	Amount of Material needed to make 50.1 mg of pravastatin	To make 1 kg
Compounds (kg)		
Water	8.55	170,659
Glucose	0.04	798
K <sub>2</sub> HPO <sub>4</sub>	0.003	60
MgSO <sub>4</sub> * 7 H <sub>2</sub> O	0.003	60
NH <sub>4</sub> NO <sub>3</sub>	0.002	40
Peptone	0.002	40
Corn extract	0.004	80
Yeast Extract	0.002	40
Intermediate	0.01	200
C <sub>2</sub> H <sub>3</sub> F <sub>3</sub> O <sub>2</sub>	0.1218	2,431
Ethyl acetate	2.7	53,892
NaCl	0.1	1,996
Sodium bicarbonate	0.03	599
Sodium sulfate	3	59,880

**Table 2: Scale up of Intermediate Process**

Compounds (kg)	Kg needed to make 12.8 g of intermediate	Kg needed to make 200 kg of intermediate
Water	3000	46,875,000
Glucose	63	984,375
Peptone	3	46,875
Penicillium	95	1,484,375
HCL	1.875	29,296.88
Ethyl Acetate	450	7,031,250
Silica Gel	5.18	80,937.5
Hexane	282.5	4,414,063
Acetone	25.5	398,437.5
Benzene	2.7	42,187.5
Ethanol	1.2	18,750

Figure 4 and Table 3 show the amount of material needed to make pravastatin in 1983, one year after the original patent was filed. There was a substantial improvement in the overall yield due mainly to optimal microbe selection. The microbe selected for this patent had over a 10-fold increase in the amount of material obtained than the patent in 1982. In the 1983 patent there were other processes mentioned to make statin drugs. These methods were more energy and waste intensive and involve live animals such as dogs, along with other processes that involved animal by-products such as homogenized rabbit liver. The process flow sheet is given in Figure 4. The two tables show amount of material needed for each process. These tables can be seen in Table 3 and Table 4.

Pravastatin 1983



**Figure 4: Pravastatin Process from Patent**

**Table 3: Scale up of Pravastatin Patent**

Pravastatin 1983	Material (Kg) needed to make 600 mg pravastatin	Material (Kg) needed to make 1 kg
Compounds (kg)		
Water	2.24	3733
Glucose	0.021	33
Peptone	0.0020	7
Corn Liquor	0.0061	10
Yeast Extract	0.0020	3
Intermediate	0.0010	17
Meat Extract	0.0020	3
C <sub>2</sub> H <sub>5</sub> F <sub>3</sub> O <sub>2</sub>	0.009	15
Ethyl acetate	1.24	2067
NaCl	0.1	167
ether	0.216	360
diazomethane	0.024	40
Benzene	1	1667

**Table 4: Scale up of Intermediate Process**

Compounds	Material (Kg) needed to make 12.8 g of intermediate	Kg needed to make 17 kg of intermediate
Water	3000	3,984,375
Glucose	63	83,672
Peptone	3	3,984
Penicillium	95	126,172
HCL	1.875	2,490
Ethyl Acetate	450	597,656
Silica Gel	5.18	6,880
Hexane	282.5	375,195
Acetone	25.5	33,867
Benzene	2.7	3,586
Ethanol	1.2	1,594

In one year, the waste production decreased by over 92%. From the patents, the main reason for the decrease was due to microbe substitution for this process. For this example given in the patent, 35.3 drums which hold 55-gallons of waste are produced per kilogram of drug. Also it should be noted that less intermediate was used so all of the processing masses in the intermediate process can be decreased by over 91%. This is a large decrease for a one-year period of time. There was still a net decrease in the amount of benzene needed due to the amount of benzene used in the intermediate process.

In 1985, another patent was filed on the production of pravastatin. In this patent, pravastatin was made in a similar way, but another microbe was chosen. With the



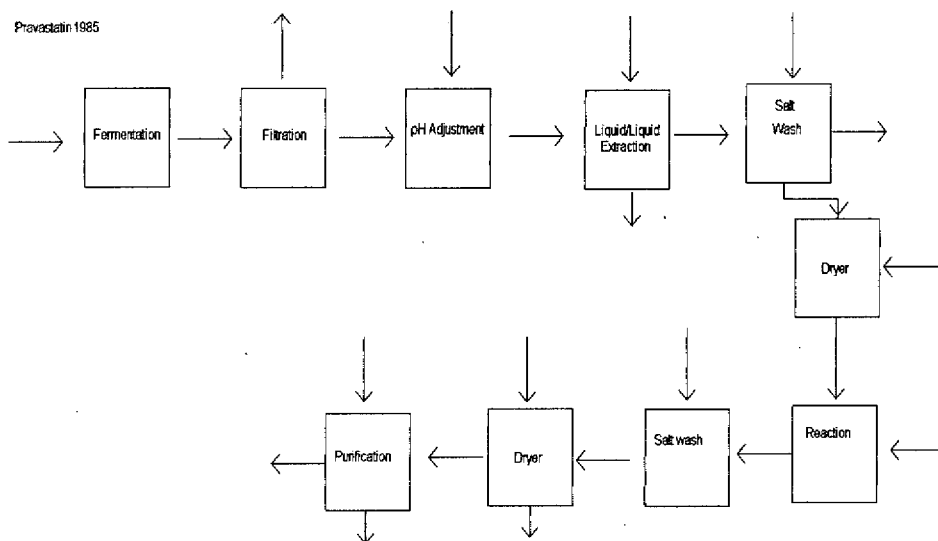
microbe *nocardi autotropica* subspecies amethystine FERM 6183 approximately 5 times the amount of pravastatin was obtained compared to the patent in 1983 [68]. The table for the materials used for this patent is given in Table 5 and Table 6. The decrease in the amount of intermediate needed can also be seen in Table 5. Again there was another decrease in the amount of materials needed to make pravastatin. The process flow sheet did not change significantly and can be seen in Figure 5.

**Table 5: Scale up of Pravastatin Patent**

Compounds	Material (Kg) needed to make 2.6 g pravastatin	Material (Kg) needed to make 1 kg
Water	4	1379
Glucose	0.02	7
Peptone	0.002	1
Yeast Extract	0.002	1
Intermediate	0.0008	5.5
Meat Extract	0.002	1
C <sub>2</sub> H <sub>3</sub> F <sub>3</sub> O <sub>2</sub>	0.0902	31
Ethyl acetate	3.4	1172
NaCl	0.356	123
Sodium sulfate	2	690
Sodium bicarbonate	0.05	17
Benzene	0.7	241
Acetone	0.3	103

**Table 6: Scale up of Intermediate Patent**

Compounds	Material (Kg) needed to make 12.8 g of intermediate	Material (Kg) needed to make 5.5 kg of intermediate
Water	3000	1,289,063
Glucose	63	27,070
Peptone	3	1,289
Penicillium	95	40,820
HCL	1.875	806
Ethyl Acetate	450	193,359
Silica Gel	5.18	2,226
Hexane	282.5	121,387
Acetone	25.5	10,957
Benzene	2.7	1,160
Ethanol	1.2	516



**Figure 5: Process Flow Sheet for the 1985 Pravastatin Patent**

Another patent to make pravastatin was also filed in 2004. In this patent there was another significant decrease in the amount of materials needed to produce pravastatin. The decrease was attributed to process improvements. This can be seen in Figure 6 and in Table 7. For this process, six 55 gallons drums of waste are produced per kilogram pharmaceutical product. Again this is another improvement for the processes. The intermediate process is shown in Table 8.

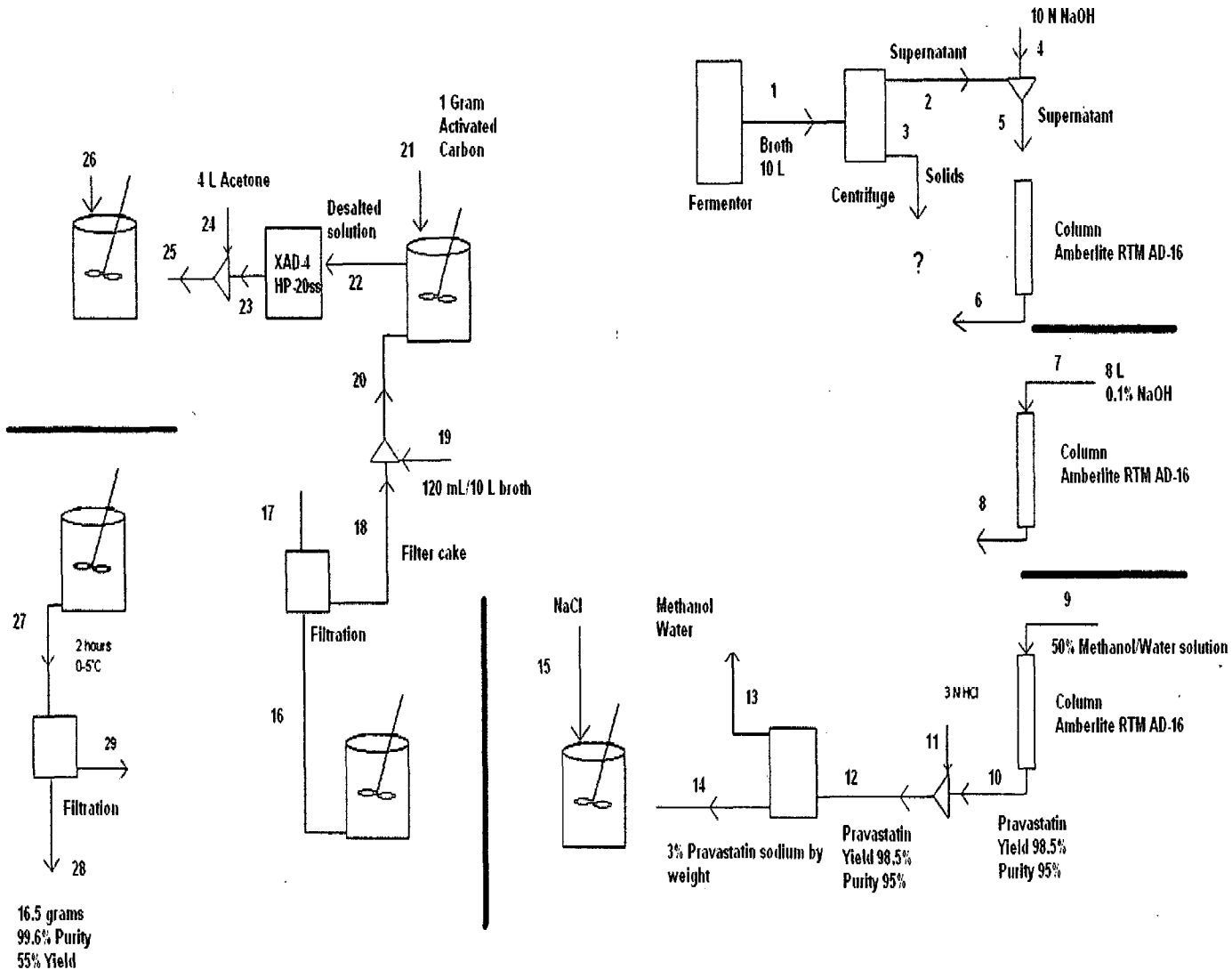


Figure 6: Pravastatin Process from 2004 patent

**Table 7: Scale up of 2004 Pravastatin Patent**

Compounds	Material (Kg) needed to make 16.5 g pravastatin	Material (Kg) needed to make 1 kg
Water	18.92	1146
NaOH	0.01	.607
Methanol	0.916	55.6
HCl	0.000075	.0045525
Acetone	5.06	307.3
Carbon	0.001	0.0607
Intermediate	0.0275	1.67

**Table 8: Scale up of Intermediate Process**

Compounds (kg)	Material (Kg) needed to Make 12.8 g of intermediate	Material (Kg) needed to make 1.67 kg of intermediate
Water	3000	391,406
Glucose	63	8,220
Peptone	3	391
Penicillium	95	12,395
HCL	1.875	245
Ethyl Acetate	450	58,711
Silica Gel	5.18	676
Hexane	282.5	36,857
Acetone	25.5	3,327
Benzene	2.7	352
Ethanol	1.2	157

## ***Energy usage***

For all of these processes, the mixing operation and reverse osmosis system (used to make the pharmaceutical grade water) contributed the most to the energy usage. With respect to the pravastatin process in 2004, the energy required by the reverse osmosis system accounted for 25 % of the total energy usage in the entire process. The liquid in the other pumps is assumed to be at ambient pressure and temperature and only a minimal pressure drop is required. The other large contributor to energy consumption is the mixer/compressors used for agitation within the fermentation tank. This accounted for 58.9% of the total energy usage. Table 9 shows the energy usage for the lab-scale pravastatin process for 2004. A comparison of the energy required for the other processes to make the intermediate and pravastatin is unnecessary since there is a direct correlation between the volume of water needed and the energy consumption, mainly due to reverse osmosis and mixing. A linear relationship can be developed for the energy required for the other processes based on the water usage since there was not a large difference in the processing equipment for all four patents.

**Table 9: Energy Usage for the 2004 Lab-scale Fermentation for Pravastatin**

Pravastatin process	MJ used/kg drug
RO pump	126
Pump 1	1.65
Pump 2	0
Pump 3	1.65
Pump 4	0.68
Pump 5	0.68
Pump 6	0.72
Pump 7	0.3
Pump 8	0.35
Pump 9	21.69
Pump 10	0.04
Pump 11	0.04
Pump 12	0.04
Pump 13	0.01
Pump 14	0.01
Pump 15	0.01
Pump 16	0.35
Pump 17	0.35
Pump 18	0.35
Cooling unit 1	21.5
Cooling unit 2	15.6
Centrifuge 1	0.2
Mixer 1	289.9
Mixer 2	8.05
Mixer 3	0.53
Mixer 4	4.83

For this process it was assumed that the fuel for the generation of electricity was fuel oil number 2. Fuel oil number 2 is a typical fuel used in chemical plants for electricity generation. The heat of combustion for fuel oil number 2 is 44812 KJ/Kg. It was assumed that the efficiency between the generation of electricity and resistance is 50% due to frictional losses. For the pravastatin process there are a total of 991 MJ used.

Since the mass is known the amount of emissions released was determined by a mole balance. From this calculation it was found that for this process 163 lbs of CO<sub>2</sub>, 0.1 lbs of NO<sub>x</sub> and 0.22 lbs of SO<sub>2</sub> are released per kilogram of pravastatin.

There was another reason to ignore the negligible energy consumption. There is a way to recover the energy of the retentate water, which is still at the feed pressure. The pressurized water in most industries is used to spin a turbine. With respect to other reverse osmosis systems approximately 30% of the energy used is recovered for a typical desalination plant [69]. This can be extrapolated for this specific system. Approximately 6% of the energy can be recovered from this specific reverse osmosis system. This amounted to 59.46 MJ, which is enough energy to power most of the other pieces of equipment and would save 9.8 lbs of CO<sub>2</sub>, 0.006 lbs of NO<sub>x</sub>, and .014 lbs of SO<sub>2</sub> from being released. Table 10 lists the emissions if the reverse osmosis and mixing are taken into consideration for all these processes without including any other pieces of equipment. The intermediate and pravastatin processes are included in each of the years listed. Figure 7 also shows the decrease in energy related emissions. The decrease was attributed to less energy that was needed to purify water and in mixing.



**Table 10: Energy Related Emissions for the intermediate and Pravastatin Processes**

Patent Year	CO2 (lbs)	NOX (lbs)	SOX (lbs)
1982	6,691,486	4,105	9,031
1983	567,244	348	766
1985	183,545	113	248
2004	55,834	34	75

The energy related emissions are shown in Figure 6. There is a significant decrease from patent years 1982 to 2004 for CO<sub>2</sub>. The trend for NO<sub>x</sub> and SO<sub>x</sub> are the same as CO<sub>2</sub>, but on a smaller scale since composition of fuel oil did not change. The energy decrease is a function of the yield increase since a large amount of the energy is used to manufacture the water and to stir the fermentation tank.

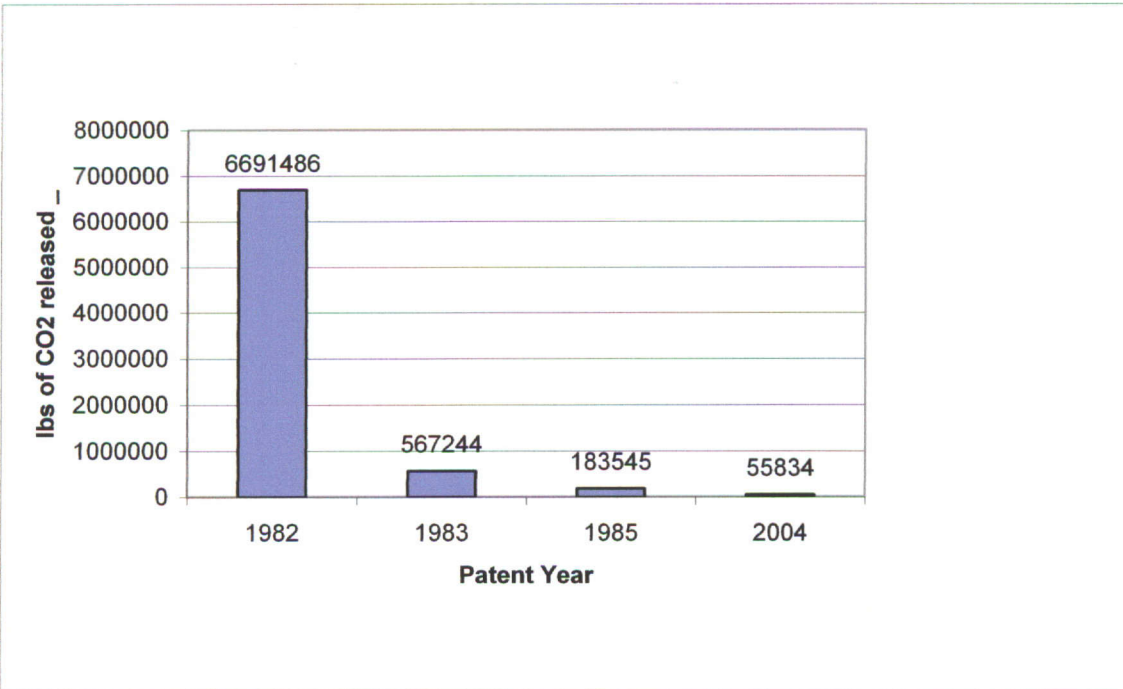


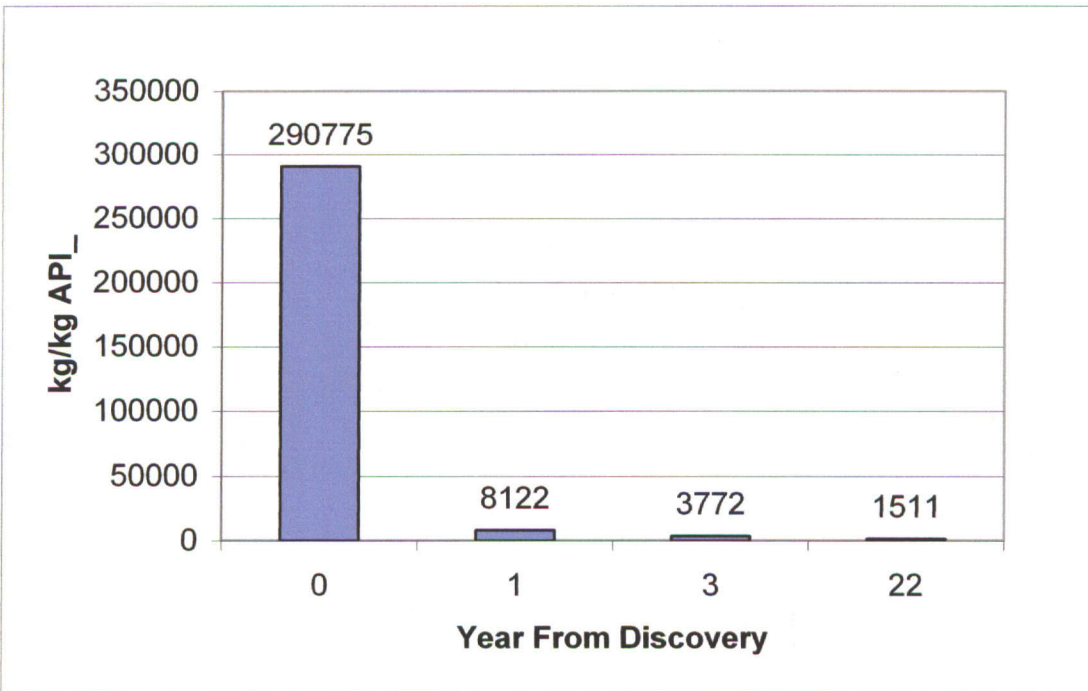
Figure 7: Energy Related CO<sub>2</sub> Emissions for the Combined Intermediate and Pravastatin Patents

## *Process Metrics*

For the process metrics there were a few factors that were considered. These factors include water intensity, solvent intensity and mass intensity. The intermediate process was not included in the water, solvent, or mass intensity, but as another criteria called intermediate intensity since the intermediate process would dwarf the pravastatin process in some areas. Waste intensity was not included in the analysis since the analysis was based on patents, which are lab scale processes. Recycling and reuse is not typically conducted at the laboratory scale. If this study was conducted at larger scales, the results would vary significantly, but there are some trends shown in these studies at the laboratory scale in making the process greener.

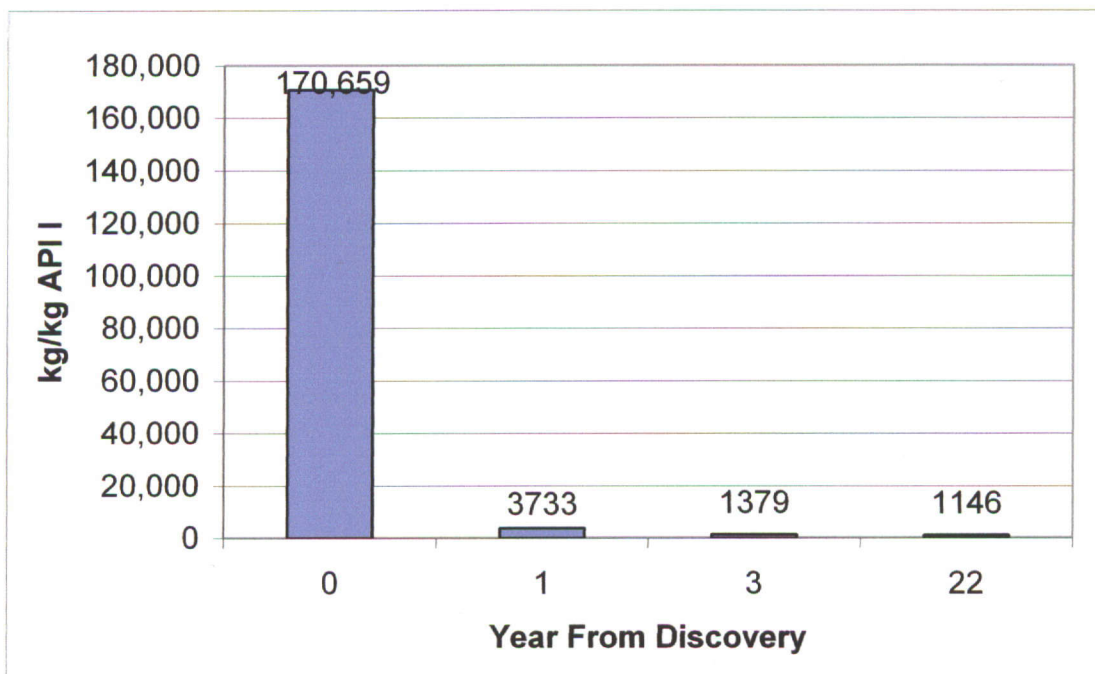
There was a decrease in the mass intensity from the original 1982 patent. The primary reason is better microbe selection. In 1982, the typical microbial yield was on the order of 50 milligrams [66]. In year 3, 1985, the amount of pravastatin obtained from the process was over 2000 milligrams (2 grams) for the same batch size. In 2004 there was a slight improvement in which the total batch yield was 16.5 grams for a batch, which had a volume of 10 L [54]. Back calculation for comparison yielded 3,300 milligrams for a 2 L batch size. This is an improvement, but not as large an improvement as the first few years. The second reason for the trend would be a better understanding of the process and better separation techniques that were used. There were changes over the time period that made aided in obtaining more API from the process. This can be seen in Figure 8. In 1982, the chemicals were environmentally benign compared to the other years, but a large amount of chemicals were used. Approximately half of the decrease from the original patent was attributed to the yield increase. The second

decrease in mass usage was attributed to solvent substitution and other improvements. In the 1983 data, the water decreased by a factor of three, the glucose decreased by a factor of two, decreased the ethyl acetate used by a factor of two, and the research team removed sodium sulfate. All of this was done while the yield increased by a factor of twelve. In 1985, the water increased by 1.75 times the 1983 value, the amount of intermediate decreased by 1/5 and the ethyl acetate and sodium chloride increased by a factor of three. When the increased yield was taken into consideration, the water decreased by a 2.63 times, and the ethyl acetate and sodium chloride decreased by a factor of 1.33 times the 1983 value. These chemicals included mostly organic solvents, which were soluble in water. In 2004 ethyl acetate was removed along with sodium sulfate and sodium bicarbonate. This was because a liquid-liquid extraction was removed from the process. Also in 2004 benzene was removed and replaced with acetone. These solvents had different solubility limits for the drug and made the drug more easily recovered.



**Figure 8: Mass Intensity for the Pravastatin Patents**

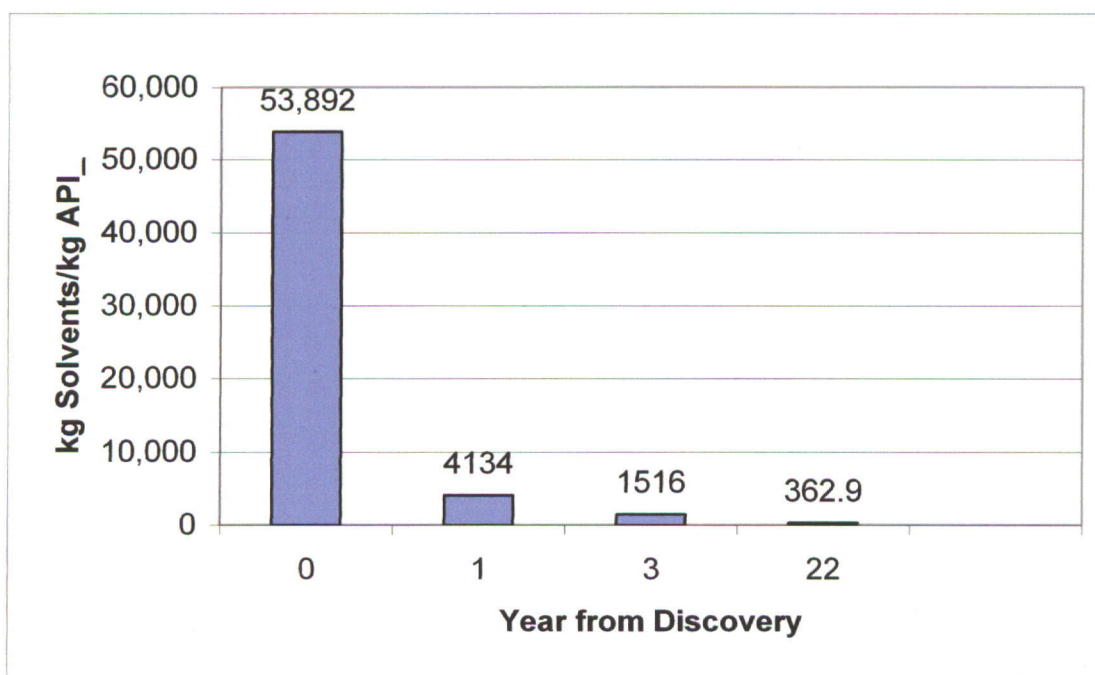
Water intensity followed a similar pattern to that of the mass intensity. This is because most of the mass that was used was water. The decrease in water intensity can be attributed to a larger concentration of drug out of the process. Fermentation based products use a large amount of water so any increase in yield would result in a substantially lower water usage. This can be seen in Figure 9.



**Figure 9: Water Intensity for Pravastatin Patents**

In terms of the water, there was a finite limit for the process, which is 1,000-kg/kg of drug. For many microbial processes, there is a certain concentration of water that is needed so that the microbes will grow. The yield attributed to 25% of the decrease in the water usage for 1983 and 1985, and 80% in 2004. The other decrease in water usage in 1983 was attributed to the removal of the lactonization step. Another reason for this decrease was because microbe selection. A significant amount of water was used in the fermentation broth and for the 1983 data; a lower amount of water was used. In 1985, the processing was similar to the 1983 data and the same reasoning applied for the decrease in water usage. In 2004, the yield only accounted for an 80% decrease in the water intensity. The other decreases were attributed to the use of resin absorption in place of liquid-liquid extraction and the removal of water from the wash steps.

There was a large decrease in the solvent intensity, which can be seen in Figure 10. There was a point at which the decrease in solvent usage tapered off. This is mainly attribute to the physical limitations of the chemistry involved and chemical separation techniques used. The 1983 data decreased slightly more then the yield increase. The reason for the decrease was the removal of a lactonization step in the process. The 1985 data point does follow the trend with respect to yield increase. The 2004 data point was less then what was expected from the yield increase. The main reason for the large decrease in the 2004 data was because of the removal of a liquid-liquid extraction step.



**Figure 10: Solvent Intensity of the Pravastatin Patents**

Figure 11 shows the decrease in the amount of intermediate needed for each process. Only one patent was analyzed for the manufacture of the intermediate. A decrease in the amount of intermediate needed directly corresponded to a decrease in the

life cycle materials, the total amount of materials needed to make pravastatin starting at the most rudimentary chemicals, used to make pravastatin. Other processes to manufacture intermediate were beyond the scope of this study. The main decrease in intermediate usage was attributed to a yield increase. The yield increase was mainly because of better microbe selection, but in the 2004 data, it was because of the recovery techniques employed. In the 2004 data, resin absorption was used in place of liquid-liquid extraction and very little waste streams were produced

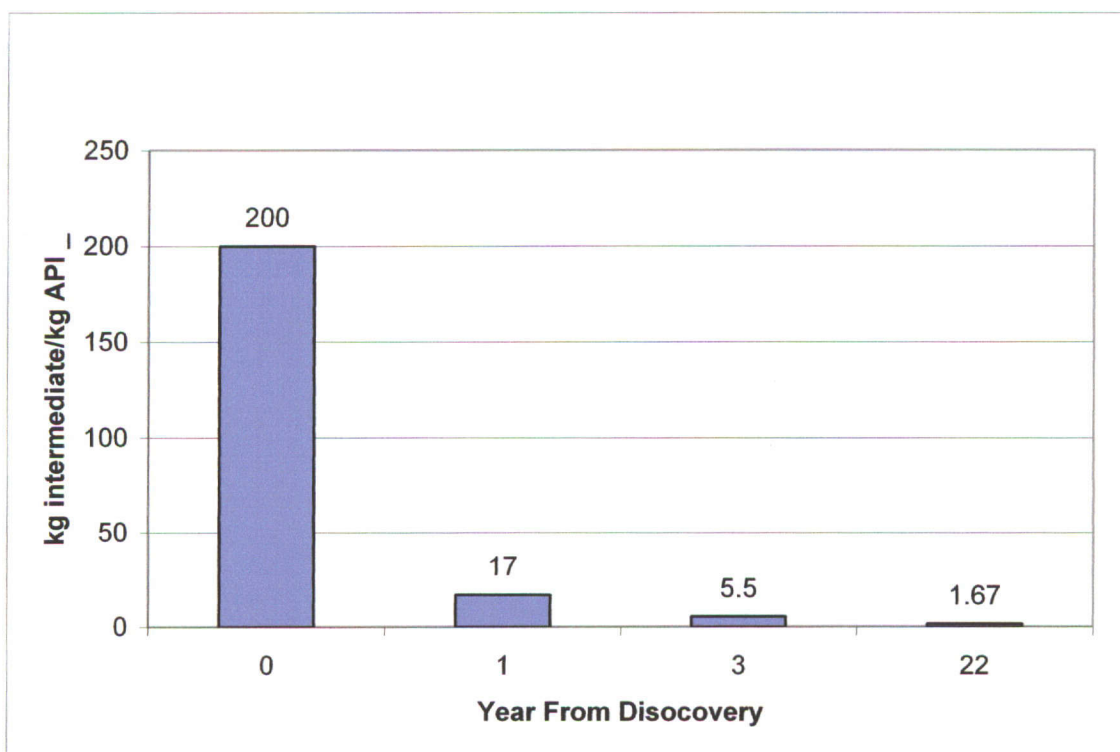


Figure 11: Amount of Intermediate Needed to Make Pravastatin



The percentage decrease in the various parameters over the period of time was also analyzed. This is shown in Figure 12. The largest increase occurred in the year immediately following drug discovery.

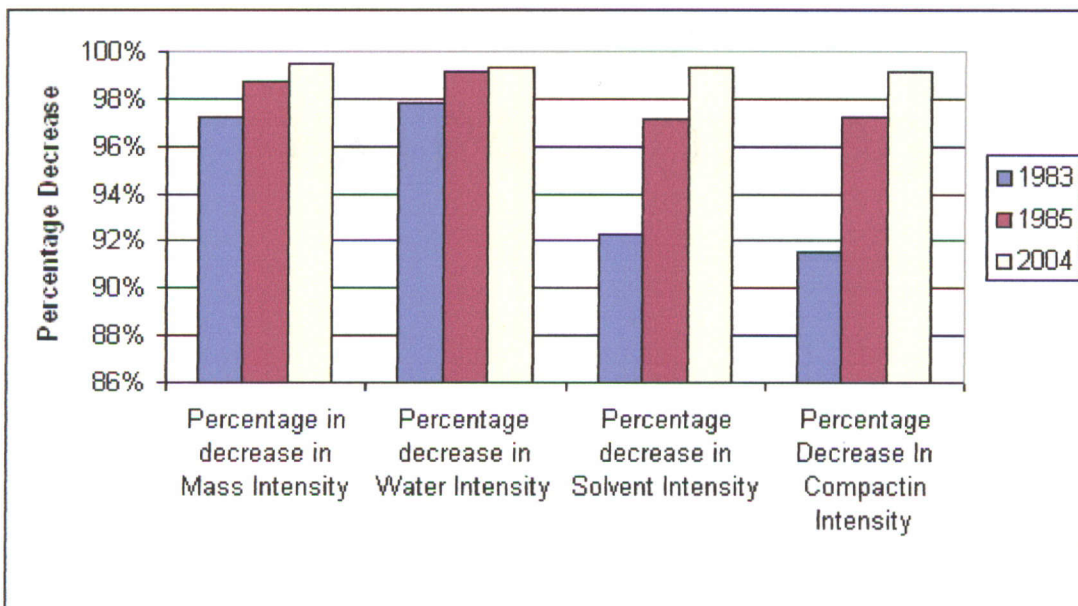
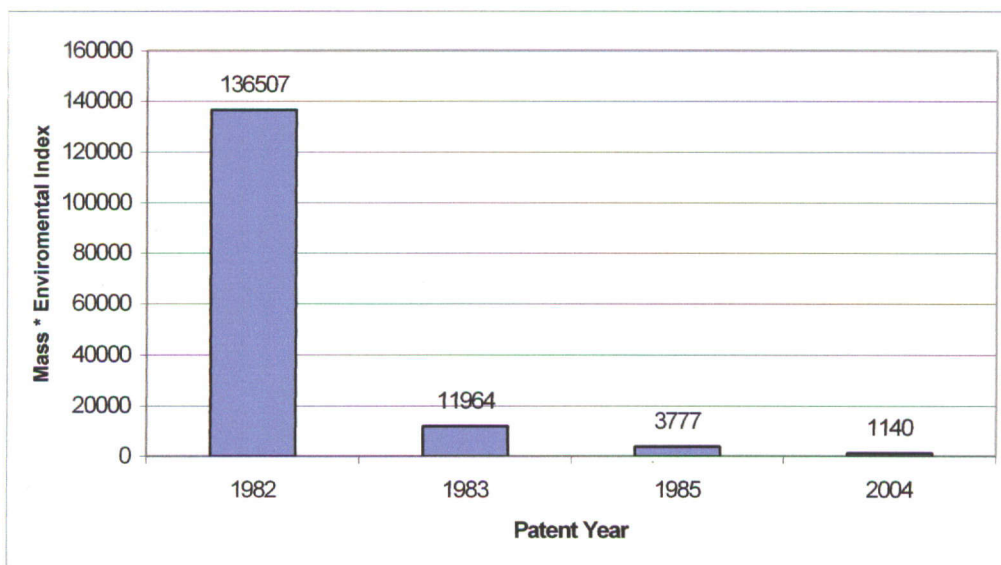


Figure 12: Percentage Decrease in Mass Criteria Using the Initial Patent as a Baseline

## ***Environmental Analysis***

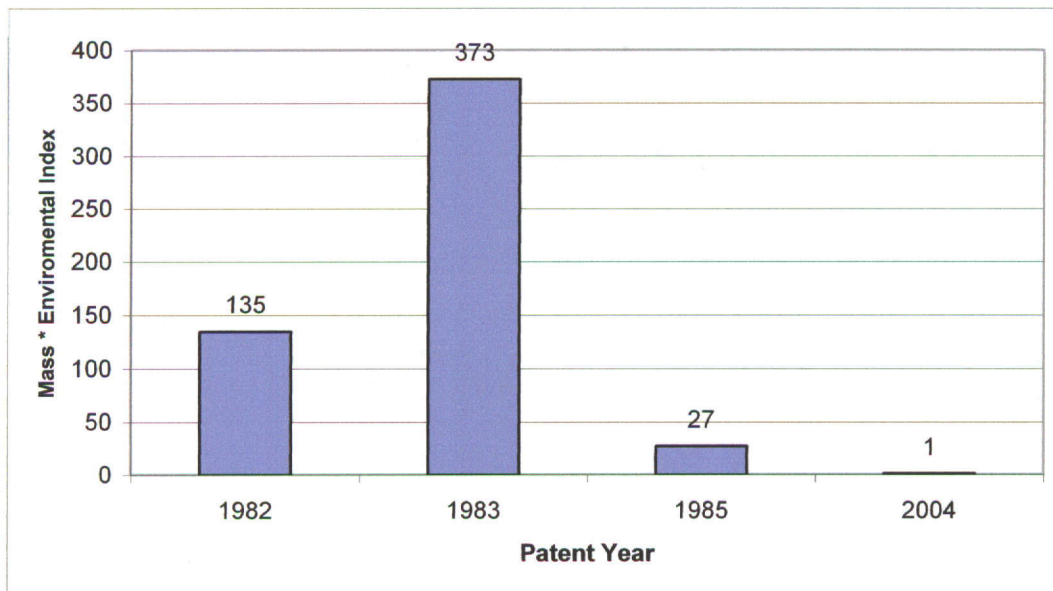
There are several environmental factors that were considered during the analysis. These factors included inhalation, ingestion and aquatic toxicity, global warming potential, smog formation, carcinogenicity and acidification. These factors aided in determining which process was the most sustainable. The various toxicity factors along with carcinogenicity illustrated the various degrees of exposure of a substance along with the environmental harm caused by the substance. Global warming potential, smog formation and acidification are gauges of global and regional environmental impacts from the chemicals in the process. Eutrophication was not included in this analysis since very little phosphates were used or produced.

For the inhalation toxicity category, the threshold limit values for the chemicals were used. This was used to determine the potential environmental impact of each process if there was a leak and the chemicals would be released into the air. Figure 13 shows the weighted inhalation toxicity for each process lab-scale manufacturing process for pravastatin. The intermediate process was included since this would drastically decrease with respect to the various processes and there were hazardous chemicals involved in the intermediate process. The environmental criteria decreased in proportion to Figure 11.



**Figure 13: Weighted Environmental Index Including the Intermediate Process**

The vast majority of the environmental index was attributed to the use of the intermediate. Removal of the intermediate process shows the “green progress” of the pravastatin processes over time. This is shown in Figure 14. There was no correlation between the environmental index and the year of the patent. This was because the compounds in 1982 were relatively benign. The most toxic chemicals for inhalation in 1982 were ammonium nitrate that is not an extremely toxic chemical. In 1983, benzene and ether were used in place of ethyl acetate. From 1983 to 1985, there was a large decrease in the inhalation toxicity. 25% of the decrease from 1983 to 1985 was attributed to by yield. Another decrease was because of the use of acetone in place of benzene.



**Figure 14: Weighted Environmental Index of the Pravastatin Patents Only**

Figure 15 shows the weighted ingestion toxicity for only pravastatin process patents. The end product is going to be ingested by people and there may be trace amounts of the various processing chemicals trapped within the crystal structure and in the final tabulated formulation. Again in 1982 the chemicals were relatively benign, but there were a lot of chemicals used. In 1983, benzene and ether were used which are extremely toxic. From 1983 to 1985 the use of benzene decreased by 85% and no ether was used in the 1985 data. In 2004, no benzene or ether were used, but the value for the ingestion toxicity is slightly higher when the increased yield was taken into consideration. There are a few reasons for the increased aquatic toxicity for 2004. The first reason is because of the increased usage of methanol. Methanol is more toxic to marine life than the compounds used in 1982. Another reason is the use of acids and bases. In 1982, the acids and bases used were weak, such as sodium sulfate and sodium

bicarbonate. In 2004 sodium hydroxide and hydrochloric acid were used in place of the weak acids and bases. There was a trend in the weighted ingestion toxicity, which is mainly due to the process becoming more efficient. There is also another reason why the weighted ingestion toxicity decreased. Most of the chemicals involved, mainly benzene, were decreased and eliminated from the most recent process patent.

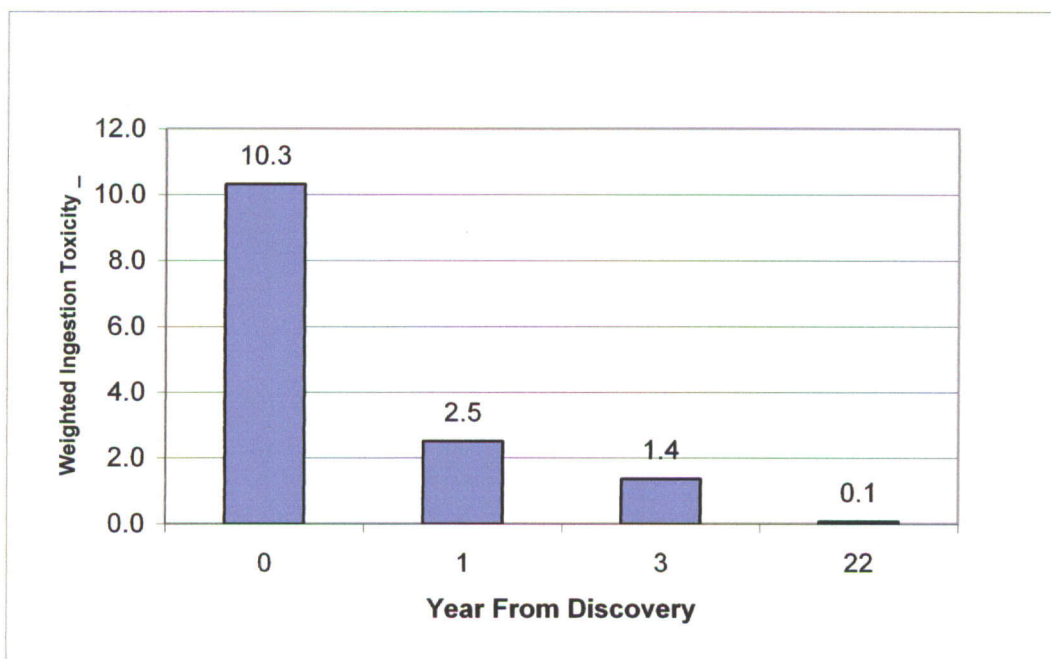


Figure 15: Weighted Ingestion Toxicity of the Pravastatin Patents Only

Figure 16 shows the weighted ingestion toxicity with the intermediate process included. The trend for weighted ingestion toxicity is directly related to the increase in yield for the pravastatin process. The ingestion toxicity can be found on MSDS sheets from chemical suppliers like J.T. Baker or other references [62], [63]. Figure 16 followed the same trend as the intermediate graph, which is Figure 11.

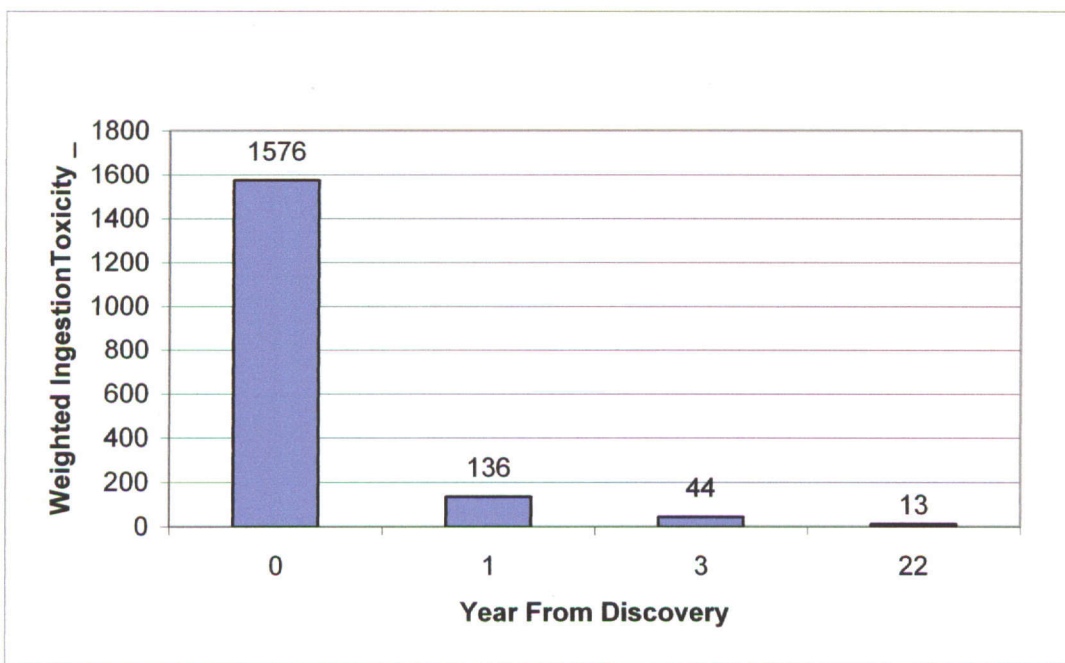


Figure 16: Weighted Ingestion Toxicity including the Process to Make the Intermediate

The first comparison for the weighted aquatic toxicity was made without the intermediate process. This showed the decrease in aquatic toxicity over time with respect to pravastatin. This can be seen in Figure 17. The decrease did not follow the same pattern as the other environmental parameters. This was attributed to process improvements, which directly impacted the yield. This is evident from drug discovery to the first few years. The researchers increased the yield, but by using chemicals such as benzene. Even though the use of extremely toxic chemicals increased, the aquatic toxicity decreased because of the substantial increase in yield. Theoretically, the aquatic toxicity should have dropped to 8% of the drug discovery value, but this was not the case due to the use of more toxic chemicals. There was a trade off between yield and aquatic toxicity. In 1983, the aquatic toxicity should be 4.39, but was 18.9. The increase in

aquatic toxicity was attributed to the usage of benzene and ether in the 1983 data. In 1985, there was an increase in the yield, but also there was less benzene used and no ether used. In the 2004 data, 25% of the decrease was attributed to the yield increase. The other 75% of the decrease was attributed to because of two reasons. The first reason was the removal of a liquid-liquid extraction step, which contributed significantly to the aquatic toxicity. The second reason was the use of ethyl acetate as a replacement solvent in 2004 in place of other solvents.

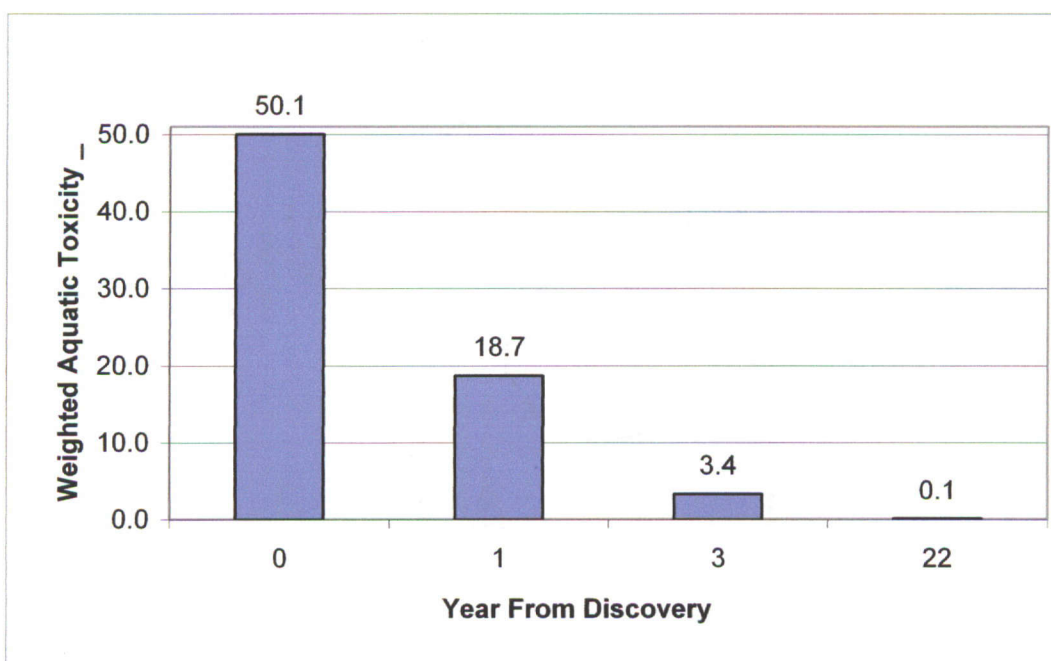


Figure 17: Aquatic Toxicity for the Pravastatin Patents

The analysis for aquatic toxicity was conducted with the intermediate processes included. There was a large increase in the aquatic toxicity mainly attributed to hexane and benzene. A significant amount of benzene and hexane were used to make intermediate. The weighted aquatic toxicity when the intermediate process is included

follows the same trend as Figure 11. This can be seen in the Figure 18. A major issue within the intermediate patent is the use of hexane, which is extremely toxic to marine life.

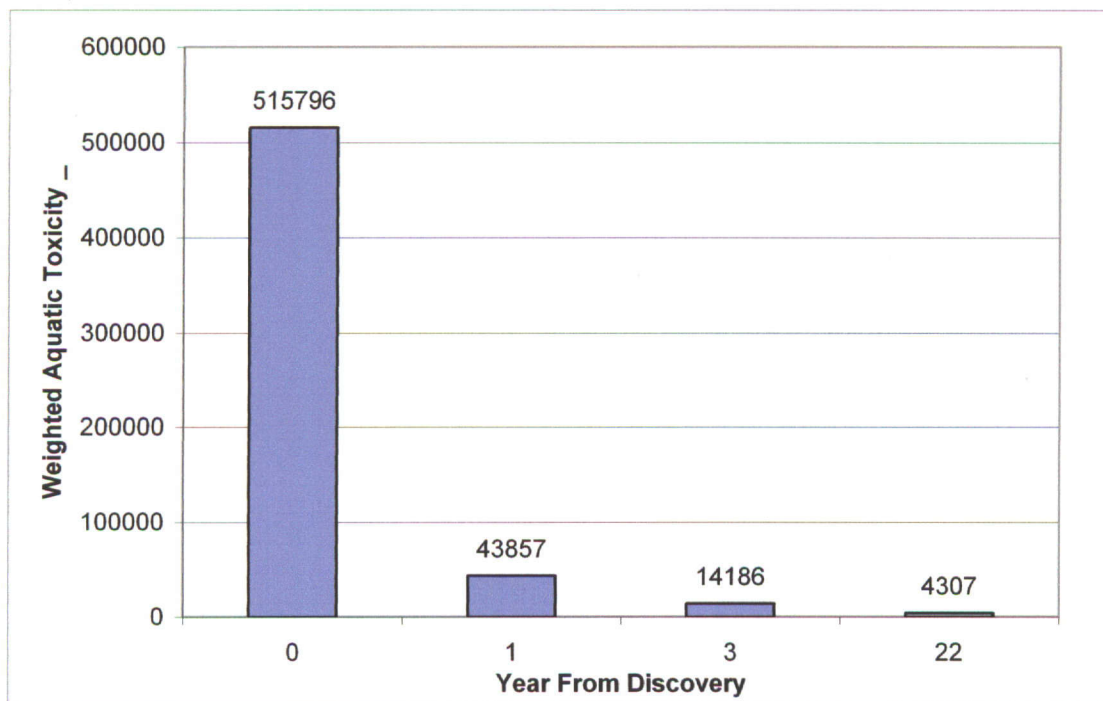
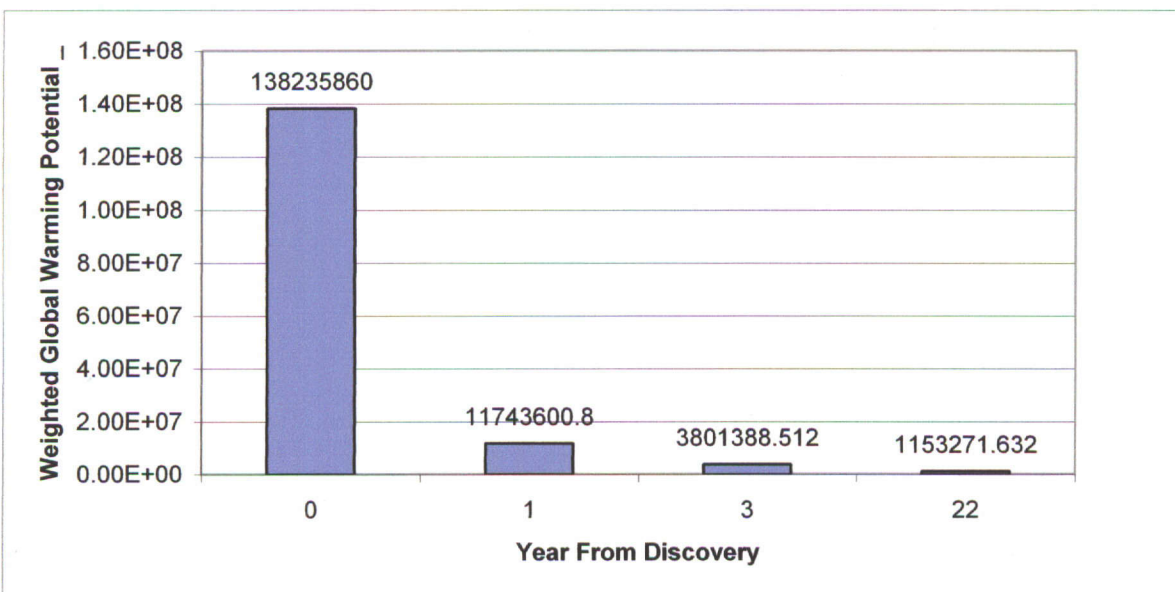


Figure 18: Aquatic Toxicity with the Intermediate Process Included

The organic solvents used in the processing contributed the most to the global warming potential [58]. The vast majority of the global warming potential can be attributed to the process to make intermediate. The global warming potential for both processes is shown in Figure 19. The weighted global warming potential follows the same trend as the usage of intermediate.





**Figure 19: Weighted GWP for the Pravastatin with the Intermediate Included**

The weighted global warming for the four-pravastatin patents was also compared excluding the intermediate patent. This can be seen in Figure 20. The main reason for the decrease is due to the increased conversion and yield. The second reason is due to decreased solvent usage. The vast majority of the global warming potential was caused by organic solvents used in the process. The energy related global warming potential accounted for 4% of the total global warming potential in 1982 and 2004, and accounted for approximately 1% in 1983 and 1985. In 1983, the yield improvement contributed to 88% of the decrease in global warming. There were other improvements in which the solvent usage was decreased by 10%, which accounts for the other improvement in global warming potential. In 1985 the improvement in the global warming potential was entirely attributed to by the yield increase. In 2004, 81% of the global warming potential

was attributed to by the yield increase. There was also a 24% decrease in solvent usage when the yield was taken into consideration from 1982 to 2004.

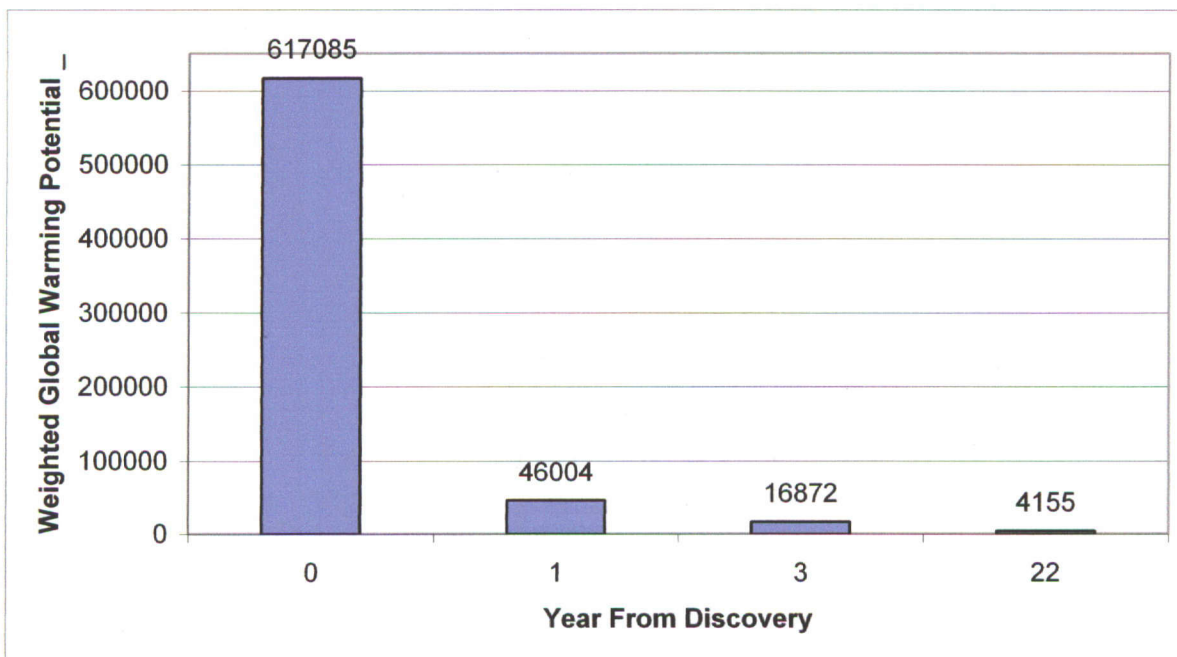
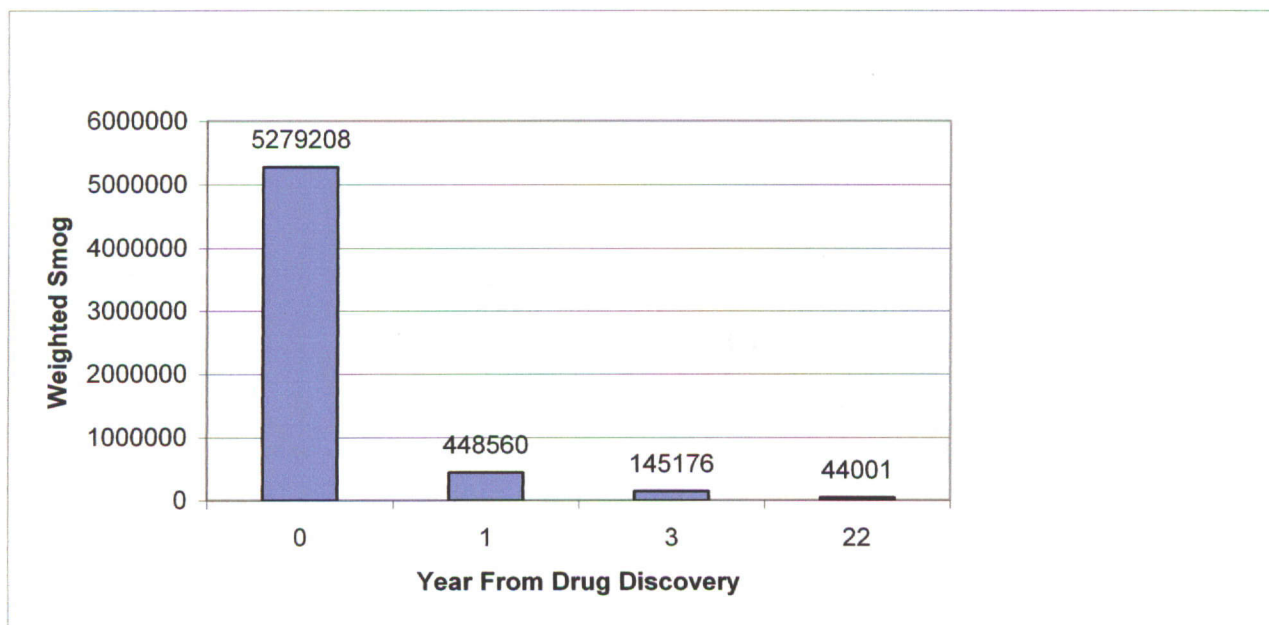


Figure 20: Weighted GWP for the manufacture of Pravastatin

For this process, no ozone depleting substances were used in the processing of pravastatin directly. All of the compounds listed as ozone depleting chemicals are chlorinated and brominated hydrocarbons. All of the patented processes do not contain any halogenated hydrocarbons.

Figure 21 shows the weighted smog for both the intermediate and pravastatin processes. There was a significant decrease in the photochemical smog formation after drug discovery. In Figure 21, most of the smog can be attributed to the production of the

intermediate. In the intermediate process, 98% of the photochemical smog formation was attributed to hexane and ethyl acetate.



**Figure 21: Weighted Photochemical Smog Formation for Pravastatin and Intermediate**

Figure 22 shows the decrease in photochemical smog formation from the pravastatin patents. This portion of the analysis was needed to determine if the decrease in photochemical smog formation was attributed to the efficiency or an actual “green” improvement. The weighted smog formation is shown in Figure 22. In 1983, 88% of the improvement in photochemical smog formation can be attributed to by a yield increase. The other 11.2% was attributed to the decrease usage of solvents and the usage of ether in place of ethyl acetate. In 1985, the yield contributed to all of the decrease in smog formation. In 2004, the yield increase attributed 46% to the decrease in

photochemical smog formation. Approximately 50% of the decrease in 2004 was attributed to the use of methanol and acetone in place of ethyl acetate.

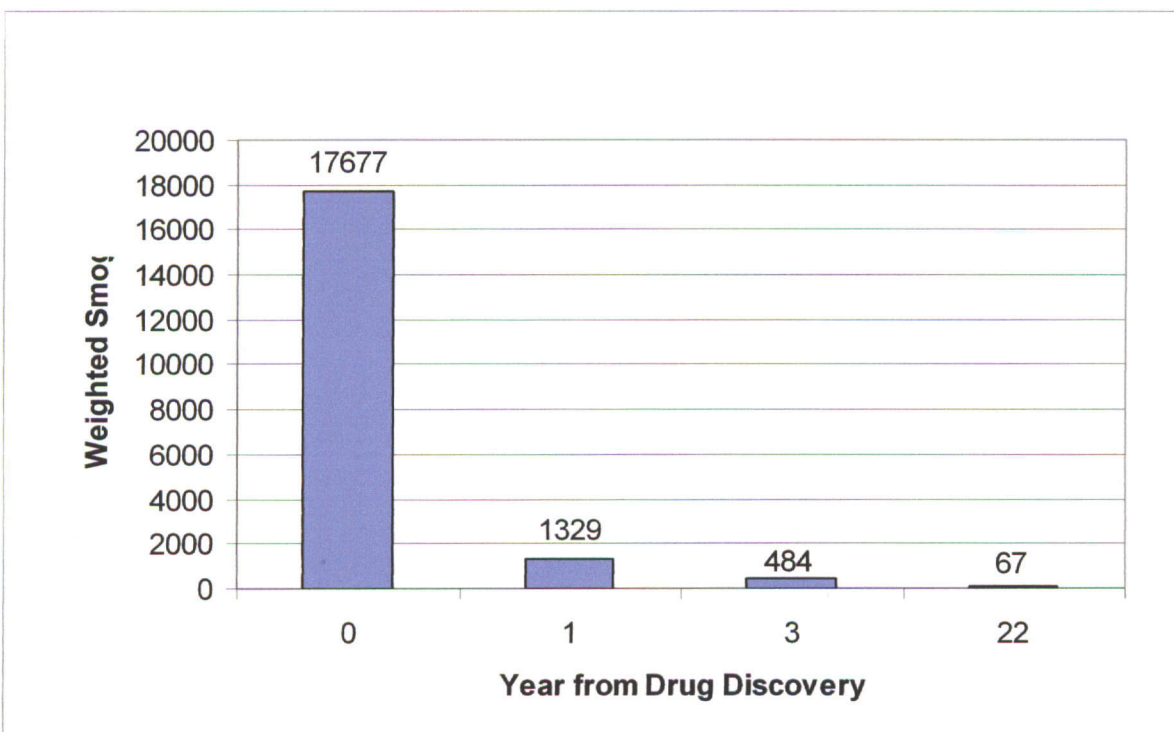


Figure 22: Weighted Smog Formation for the Manufacture of Pravastatin Only

Carcinogenicity was also considered as a criterion. For this criterion, the carcinogenicity was scaled on a factor of 0-5; 0 was non-carcinogenic and 5 was a known carcinogen. An example would be 1000 kg of water, which is non-carcinogenic. Water would have a scaled factor of 0. The mass was multiplied by  $(10^0-1)$  to give a scaled carcinogenic score of 0. There was an exception, which was for the intermediate. For this compound the carcinogenic score was calculated in a similar fashion. When the intermediate was included in the pravastatin process, the sum of the carcinogenic score of the intermediate process was used and multiplied by the mass of intermediate used in the

process. Figure 23 shows the weighted carcinogenicity for the intermediate and pravastatin processes. Figure 23 was similar to Figure 11.

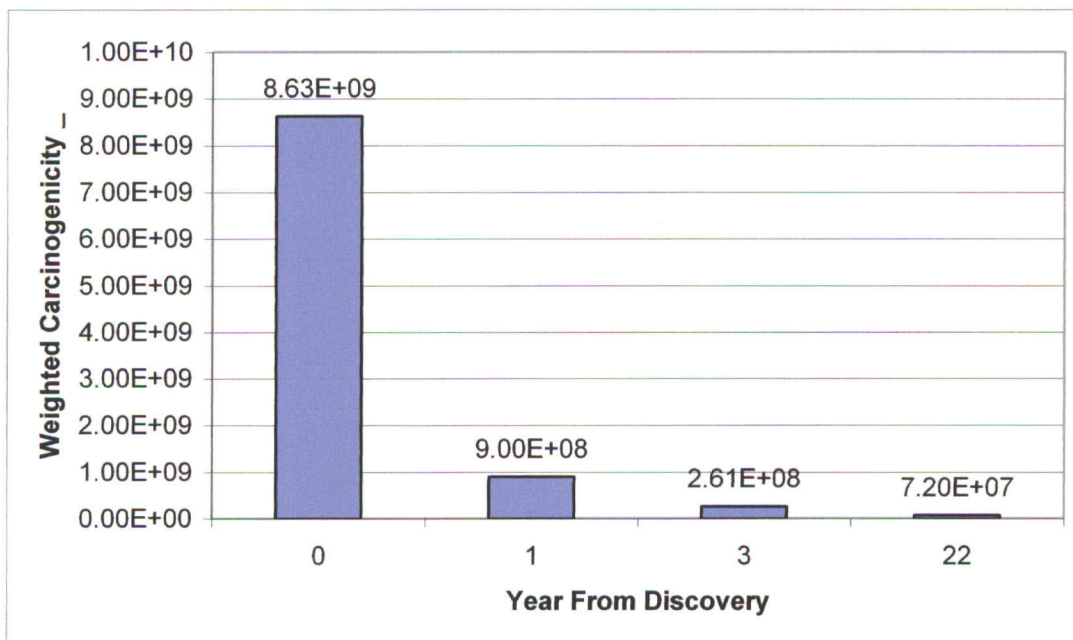
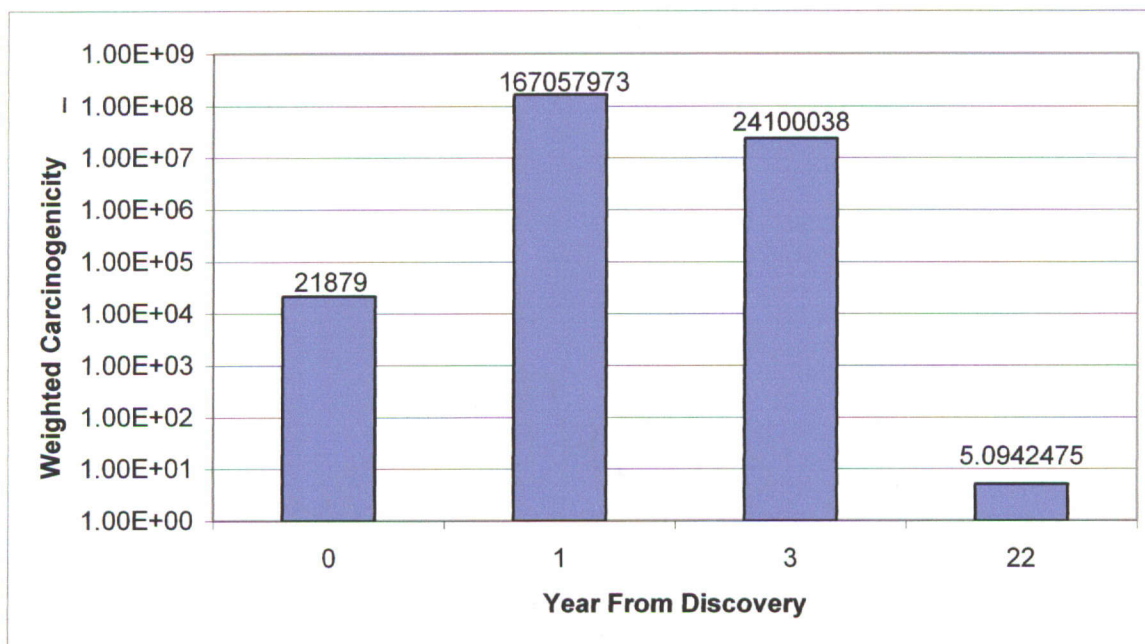


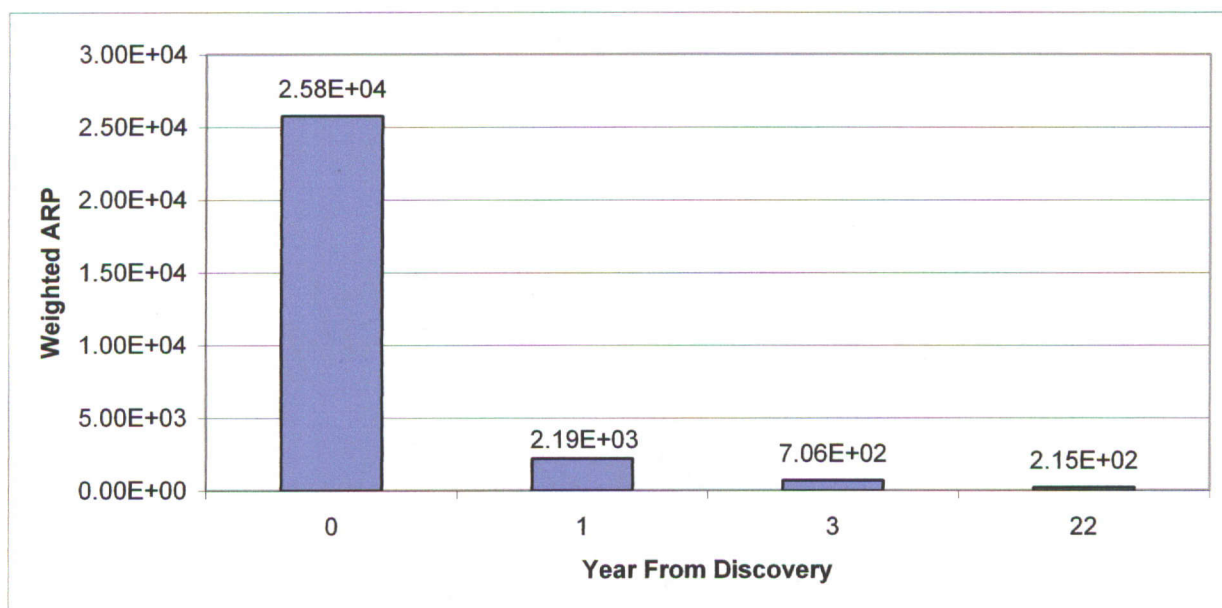
Figure 23: Weighted Carcinogenicity for the Intermediate and Pravastatin Combined Processes

Since there was a trend that seemed to follow the decrease in intermediate usage, the carcinogenicity of only the pravastatin processes was investigated. Figure 24 shows the carcinogenicity of the pravastatin process. This graph was prepared on a logarithmic scale since there is a huge variation between the carcinogenicity for each year. The weighted carcinogenicity actually increased for years 1 and 3 after drug discovery by a factor of 7,500 for year 1, which corresponds to 1983 due to the use of benzene in the process, but the weighted carcinogenicity decreased significantly in year 22, which corresponds to 2004, which was attributed to removal of benzene from the process.



**Figure 24: Weighted Carcinogenicity of the Pravastatin Patents Only**

The potential for acidification in the processes, was another metric that was used for an environmental comparison. This analysis only included acids used or produced in the direct processing of pravastatin and not the acidification due to the emissions related to energy. The analysis of both the intermediate and pravastatin patents can be seen in Figure 25. The graph followed the same trend as Figure 11, which is the intermediate usage.



**Figure 25: Weighted ARP for the Intermediate and Pravastatin Processes**

The acid rain potential (ARP) of the different lab-scale processes to make pravastatin were compared. This was used to determine if there was a significant decrease in the acid rain potential of the manufacture of the drugs. This can be seen in Figure 26. The Between 1983 and 1985, the weighted acidification increased significantly. The reason for the increase was due to the use of sodium hydrogen carbonate. In 1983, year 1, no materials were used in the pravastatin patent that could contribute to the acid rain potential. In 2004, a negligible amount of acids were used.

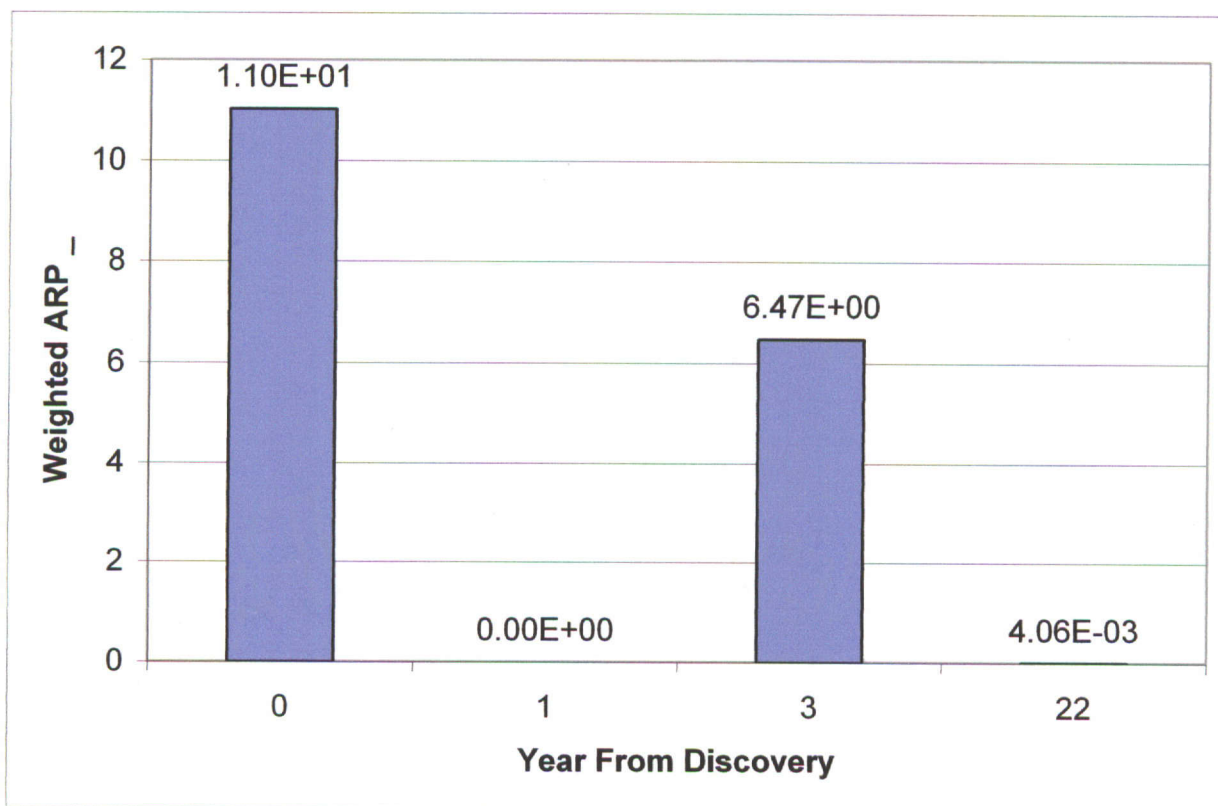


Figure 26: Weighted ARP of the Pravastatin Patents Only

### ***Chemical Tree Development***

Resource depletion was another key issue that was considered with sustainable drug development. This analysis portion was used to determine the resources used to make the various compounds used during drug manufacture. This analysis was a further aid in determining sustainable technologies and shows the broader impact on the environment of green engineering improvements to the drug manufacturing process. The diagrams on the next few pages show the chemical trees for each patent. The data



obtained from these chemical trees can then be input into LCA software such as SIMAPRO<sup>®</sup> so that a cradle to gate life cycle analysis can be obtained and coupled with the gate to gate analysis which was conducted earlier. The chemical tree for the process to make intermediate is given in Figure 27. [52],[65].

During construction of the chemical tree, there was a choice between renewable and non-renewable processes. The renewable pathway was used if over 50% of the chemical was produced by a renewable route. A renewable route is defined as any pathway in which the starting material is made by plants or animals in the eco-system. An example of a renewable and non-renewable pathway is the manufacture of ethyl acetate. Ethyl acetate is made by reacting ethanol with acetic acid with sulfuric acid as a catalyst [71]. The sulfuric acid is recycled in this process. Ethanol and acetic acid can be made in a variety of ways. Ethanol made via a fermentation route is fairly common while acetic acid is not traditionally made via fermentation [71]. For this process, the fermentation ethanol was chosen because 92% of the ethanol in the world is made via the fermentation route. [71].

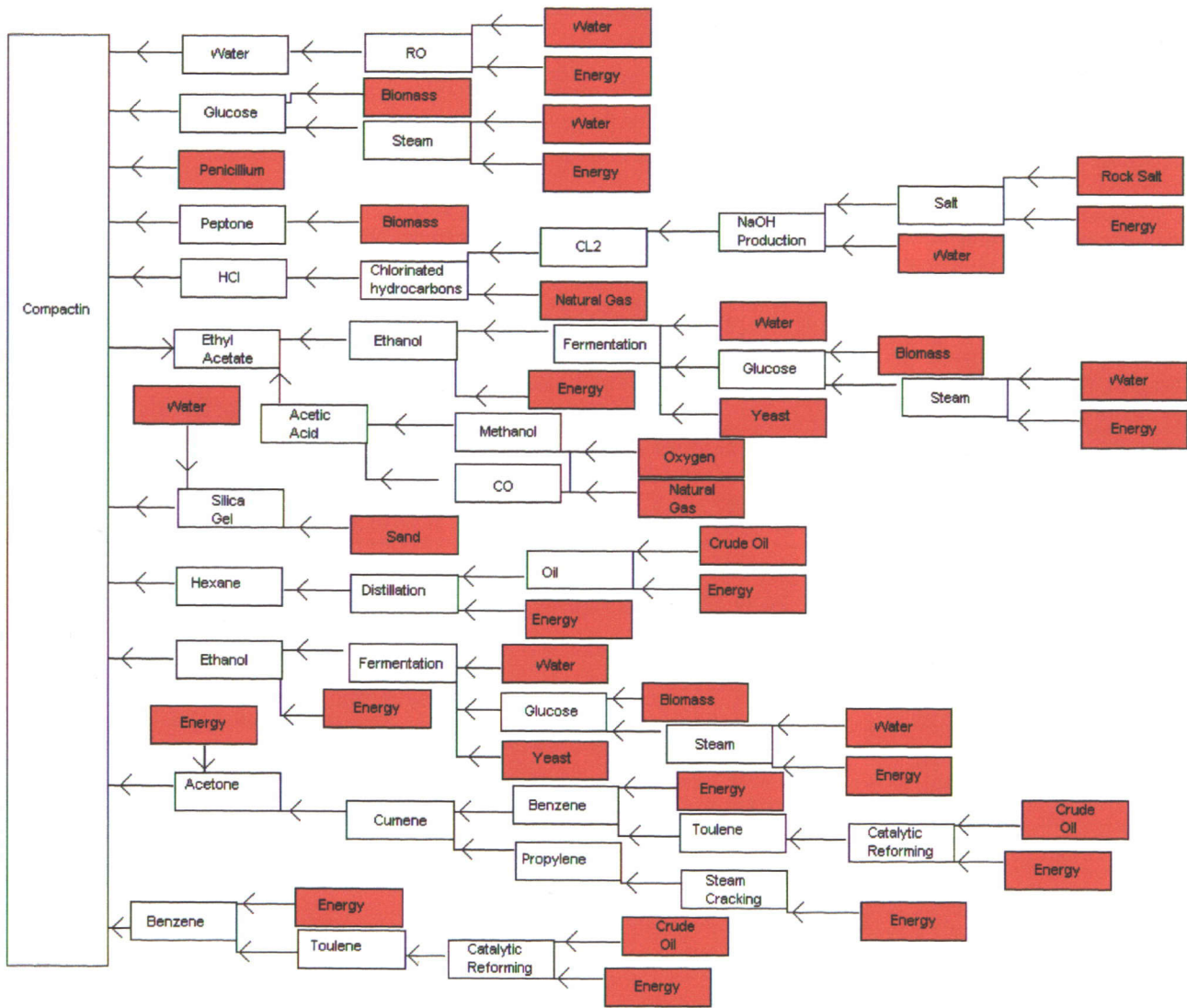


Figure 27: Chemical Tree for the Intermediate

The next figures are the diagrams of the pravastatin processes. These are shown in Figure 28, Figure 29, Figure 30, and Figure 31 [52], [54], [66], [67], [68].

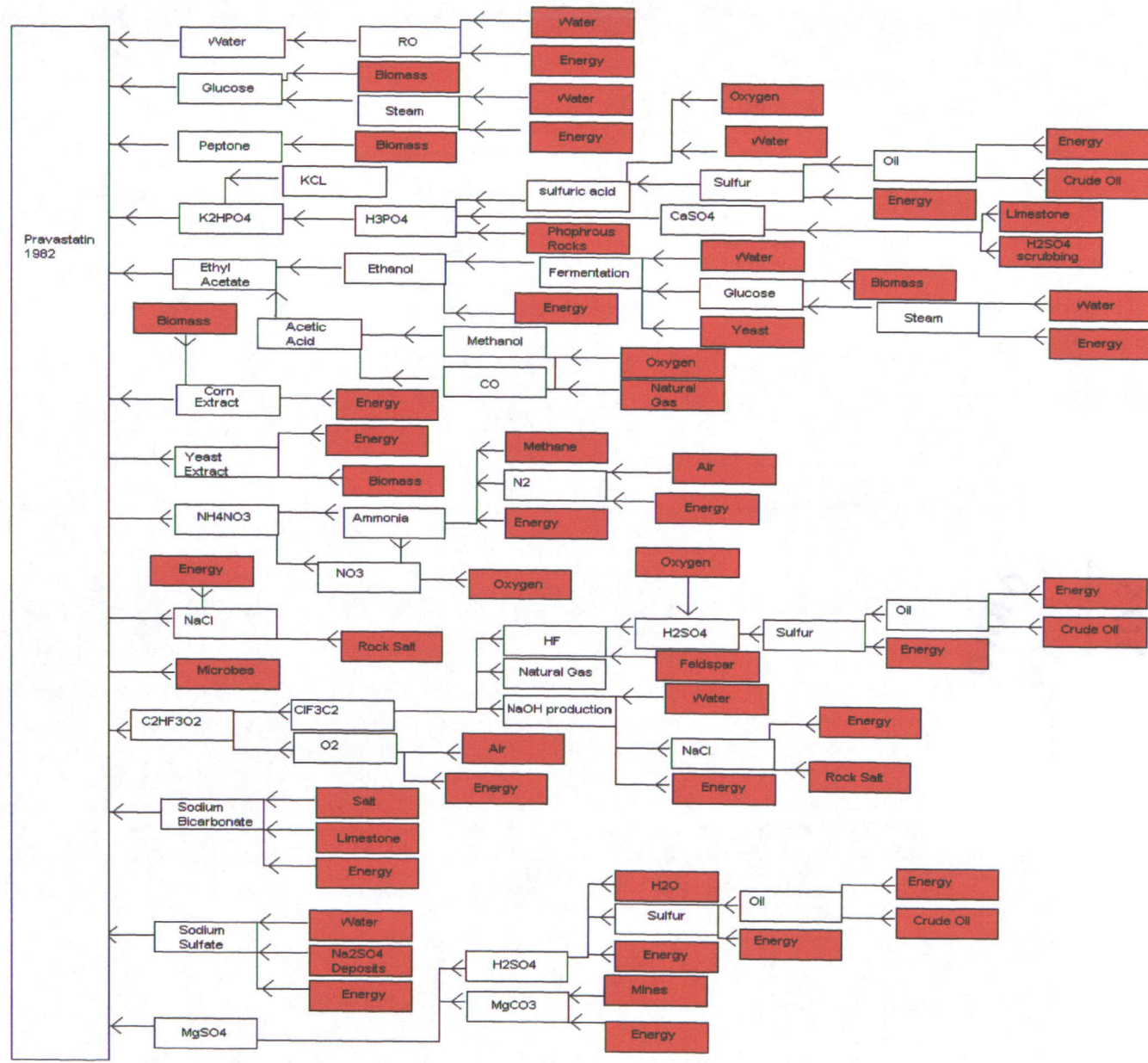


Figure 28: Chemical tree of the 1982 Pravastatin Patent

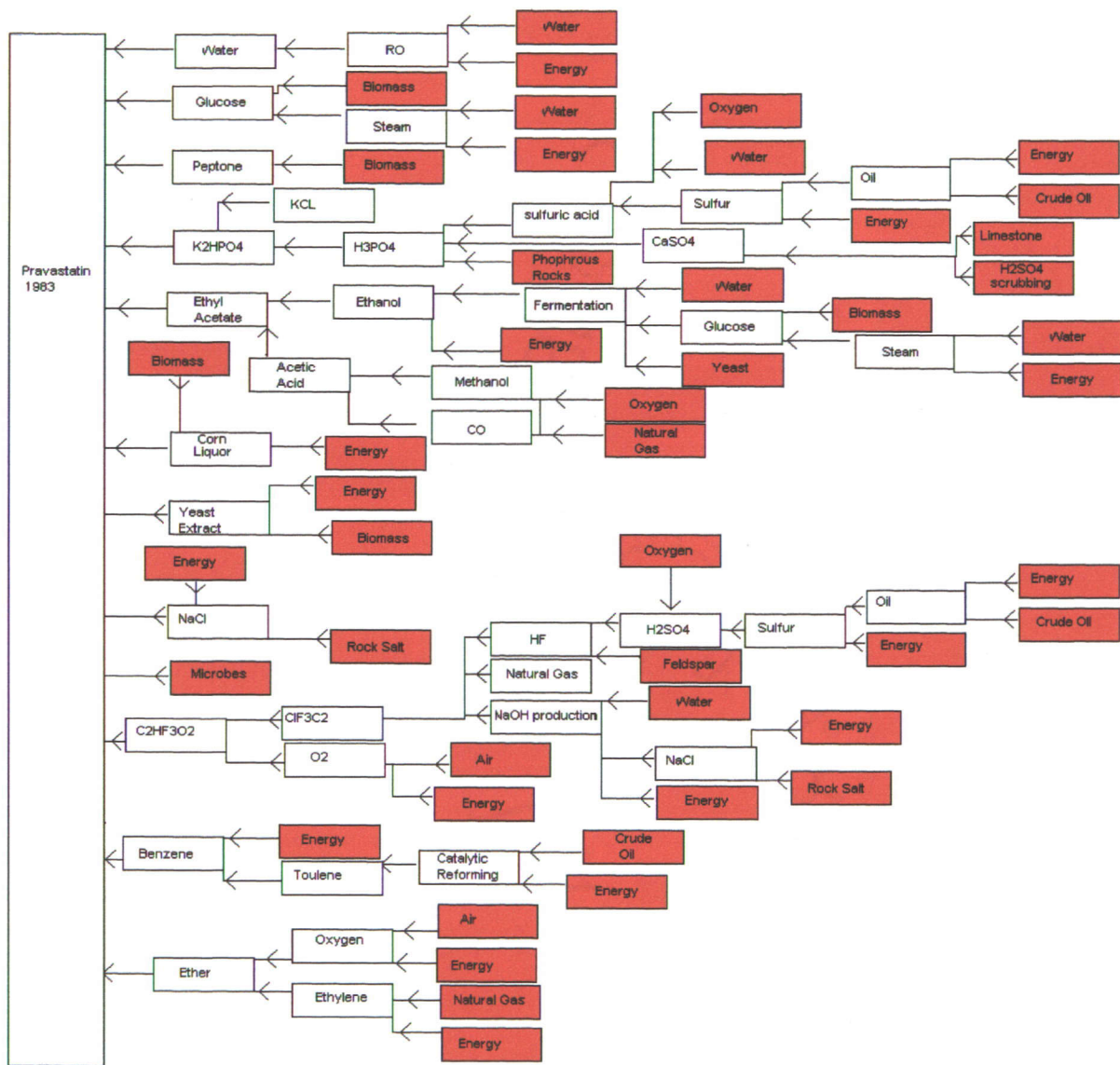


Figure 29: Chemical Tree of the 1983 Pravastatin Patent

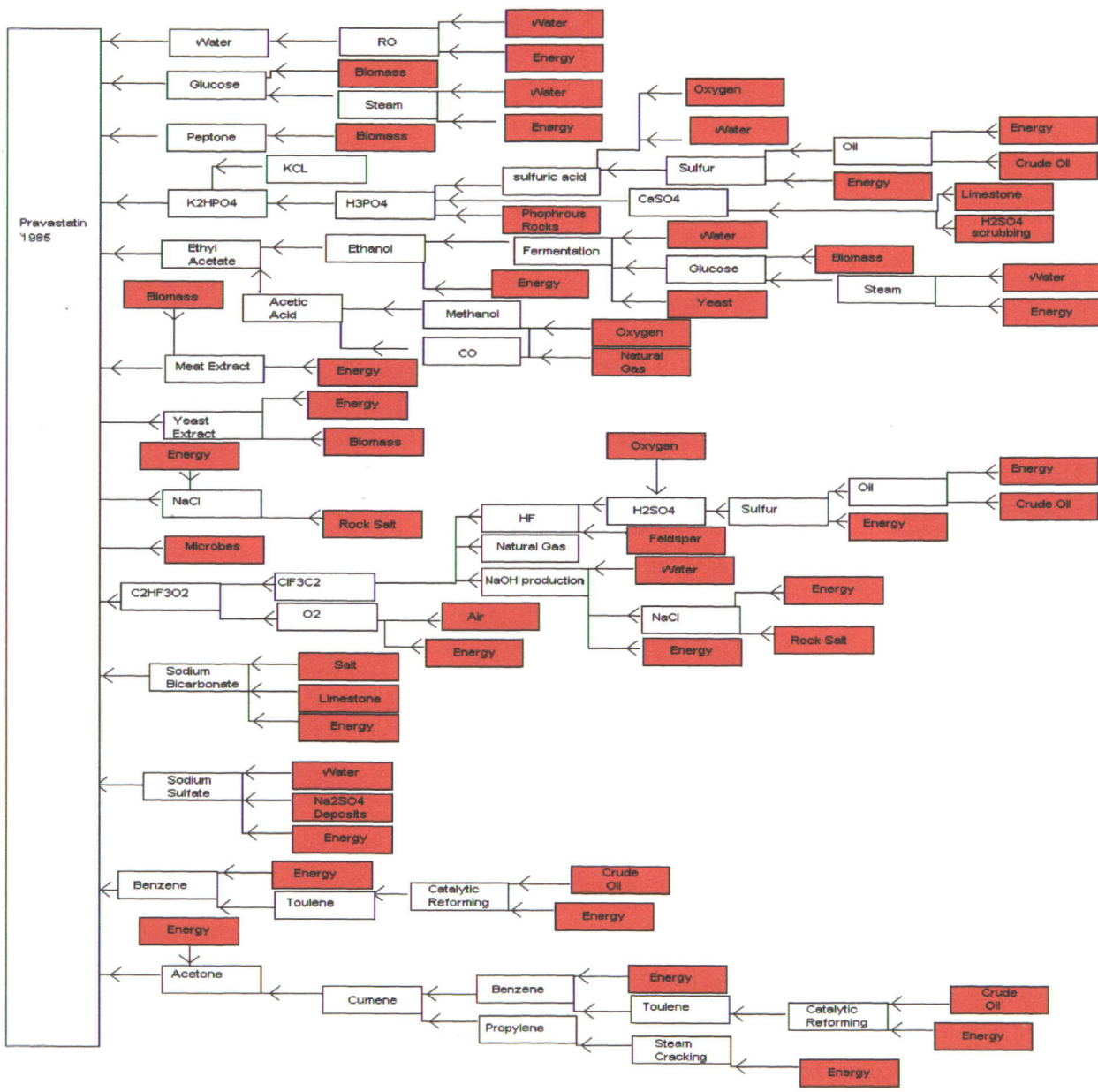


Figure 30: Chemical Tree for the 1985 Pravastatin Patent

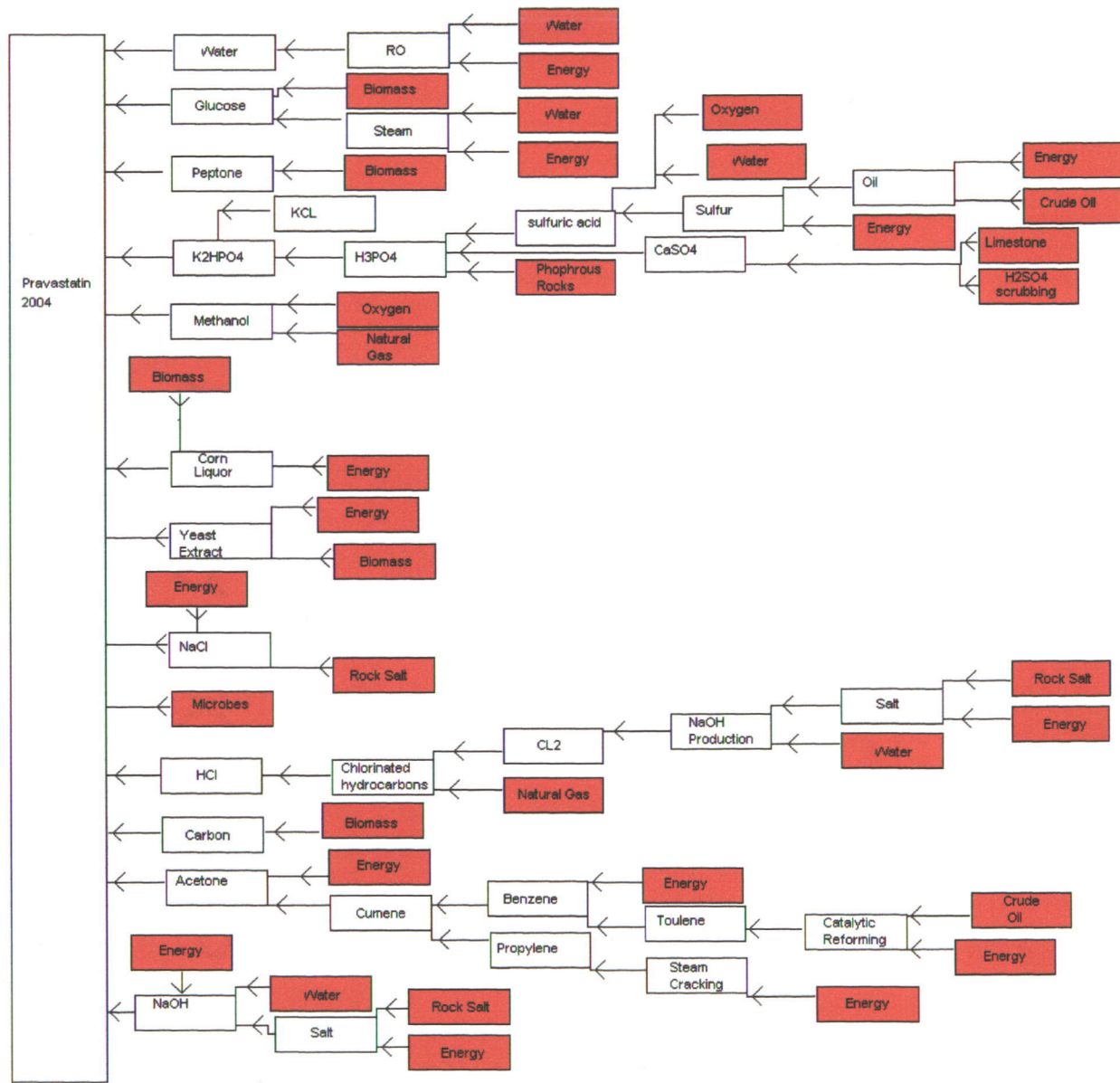


Figure 31: Chemical Tree for the 2004 Pravastatin Patent

From these chemical tree diagrams, a table was developed to determine the resource depletion of each patent. Resource depletion for this analysis considers energy, natural gas, and crude oil. Biomass, water, and naturally occurring minerals were not considered since these resources will not run out in the foreseeable future. Energy was found via the EIOLCA software for the processes [13]. Since the data was given in terms of 1992 dollars, the inflation rate was adjusted to 2004 dollars for calculation of the amount of fuel needed per million dollars. Petroleum refining and nitrogen and phosphorous containing compounds were the most significant compared to the other materials in terms of energy consumption. The other factors in terms of energy consumption were insignificant compared to these larger energy usages. The manufacture of lime for use as calcium carbonate used only 2.5% of the energy used in the manufacture of the previous mentioned compounds. Only materials based on petroleum, natural gas and nitrogen containing compounds were included in the energy analysis. The masses of the materials from each patent were applied to this data. The life cycle energy requirements are given in Table 11.

**Table 11: Energy Resource Depletion**

Patent	KJ/kg	Kg of fuel oil #2 depleted/kg API
Intermediate (1976)	18793638.6	438.9
Pravastatin (1982)	16985058.3	396.7
Pravastatin (1983)	1302044.64	30.4
Pravastatin (1985)	477479.36	11.1
Pravastatin (2004)	114300.418	2.7

The resource depletion due to energy was insignificant as compared to the mass of materials used. The total resource depletion can be seen in Table 12. Most of the resource depletion was attributed to the solvents, which were used in the process. There are other issues involved with the solvents, which cannot be answered at this time. These issues include the final disposal of the solvents.

The pharmaceutical industry has a limited range of disposal options for spent solvents. This analysis assumed that the waste generated was incinerated and no work was obtained from these solvents and other materials. In many cases, this may not be the case and the solvents may serve another purpose. Possible alternative solvent disposal routes include; use as fuel, in-process recycling, off-site recovery, spent solvents sold to another company, or possibly used as a generic solvent in paint. If any of these situations are the case, the resource depletion due to these processes will decrease since the solvents would be directly substituted for “new” solvents in alternative disposal routes



**Table 12: Total Resource Depletion**

Patent	Total Resource Depletion (kg/kg API)
Intermediate (1976)	60023
Pravastatin (1982)	45941
Pravastatin (1983)	4446
Pravastatin (1985)	1429
Pravastatin (2004)	350

## Chapter 4: Scale up of a active pharmaceutical ingredient

### *Batch comparison*

A secondary analysis was conducted on the scale up of a product that was produced through organic synthesis. A comparison of the lab scale, glass and pilot plant batches was conducted. The glass plant is slightly smaller than the pilot plant and is used for an intermediate amount of material. For example, a pilot run may produce 100-300 kg of API product and the glass plant batch may be 10% of this value. This comparison used mass and energy balance factors, fugitive emissions, the chemistry of the reaction(s) and environmental criteria as metrics. These critical factors were used to determine the process greenness of a pharmaceutical product. The flow sheets were found from patent literature at the lab scale and detailed process flow sheets provided by Bristol-Myers Squibb of the batch manufacturing for the glass and pilot scales [71]. During the production in the pilot plant batch, side-product was formed instead of an intermediate. This accounted for approximately 9% of lost yield. Instead of a large increase due to the formation of a by-product, most of the metrics still decreased.

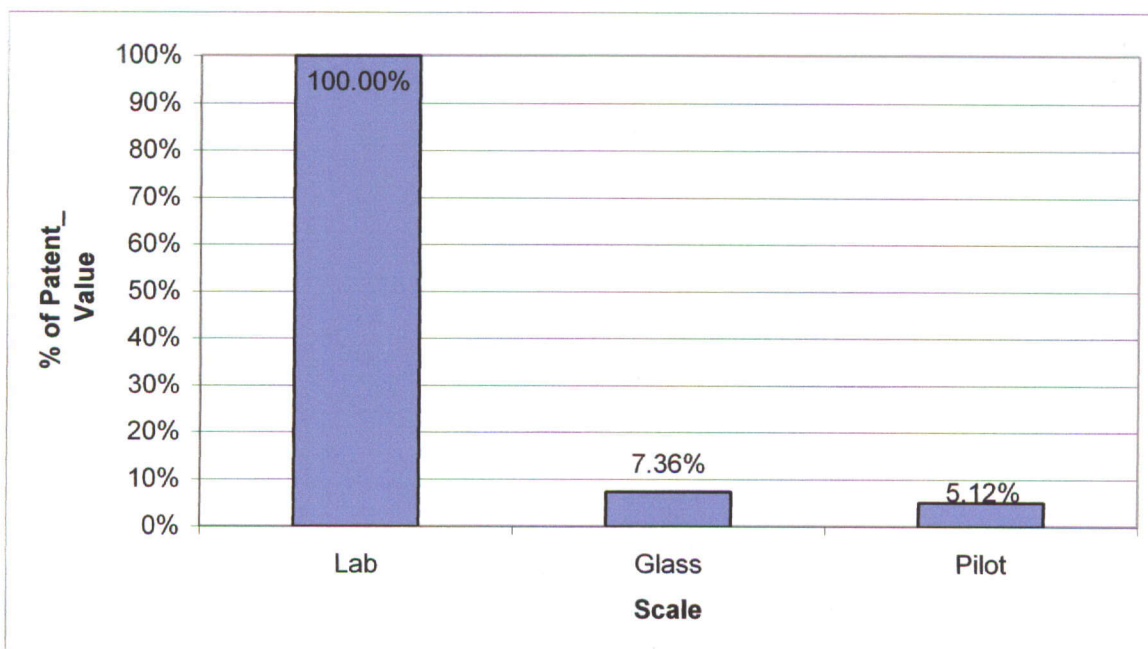
For all of the process metrics there was a large decrease from the lab-scale to glass scale production and a slight decrease from the glass to pilot scale. This decrease from the lab to glass scale was attributed to equipment substitution. The improvements from the glass plant to pilot plant were attributed to an increase in the yield, a decrease in solvent and water usage, and solvent substitution.

Figure 32 shows the material (mass) intensity criteria for three different production scales. The total mass intensity decreased as the batch size increased in the

overall batch processing. Table 13 shows the percentage of the three scales. There was a 29% relative yield increase from the glass to pilot plant batches. This accounted for most of the decrease in the criterion from the glass to pilot plant batches. Theoretically, the mass intensity should have decreased by 29% from the glass to pilot plant because of the 29% relative yield increase. The total decrease in mass intensity was 30.4%. The other 1.4% relative decrease was attributed to less solvent and water usage along with a decreased amount of processing steps. A major reason for the high mass intensity for the laboratory scale was the use of HPLC as a separation method and the use of ethyl acetate as another separation method. This method was substituted for liquid-liquid extraction and crystallization. The decrease in the mass intensity from the glass plant to the pilot plant was attributed to an increased yield in the pilot plant. There was a small slight decrease in the mass intensity not attributed to the increased yield, but attributed to the substitution of solvents along with a slight decrease in water usage.

**Table 13: Relative Mass Intensity of Three Scales**

Lab	100.00%
Glass	7.36%
Pilot	5.12%

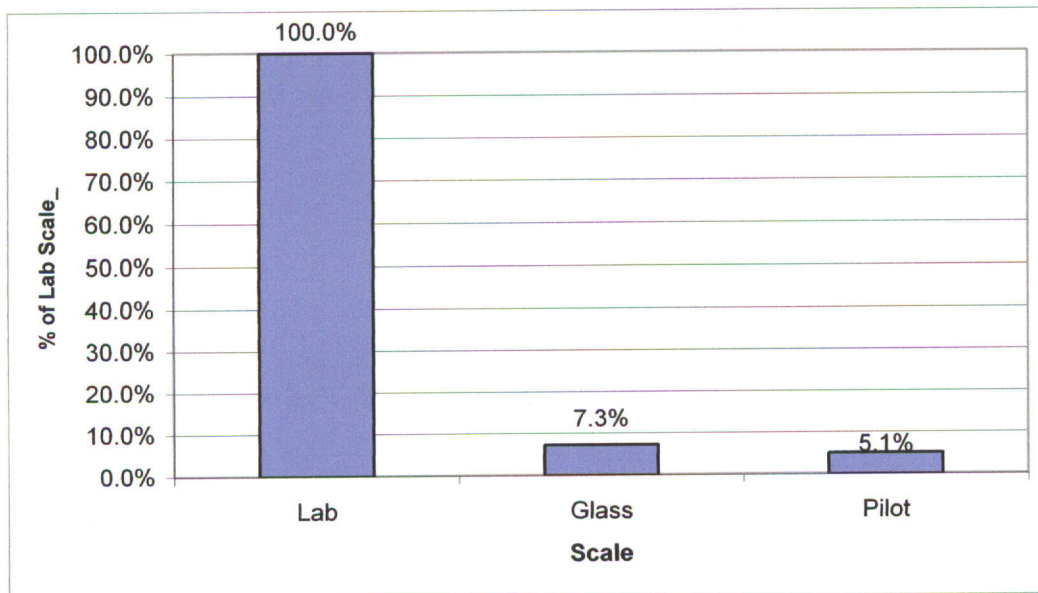


**Figure 32: Relative Mass Intensity of Three Scales**

Figure 33 shows the water intensity criteria for three batch sizes. Table 14 shows the relative percentage for the water intensity of the three batch scales. The large amount of water in the lab scale was attributed to the use of HPLC. This contributed significantly to the mass intensity for the lab scale. There was a decrease from the glass scale to the pilot scale not attributed to by the yield increase from the glass to pilot scale. Theoretically, the water should have decreased by 29% from the glass to pilot plant because of the yield increase. The total decrease was 29%.

**Table 14: Relative Percentage of Water Intensity in the Lab, Glass and Pilot Batches**

Lab	100%
Glass	7.3%
Pilot	5.1%

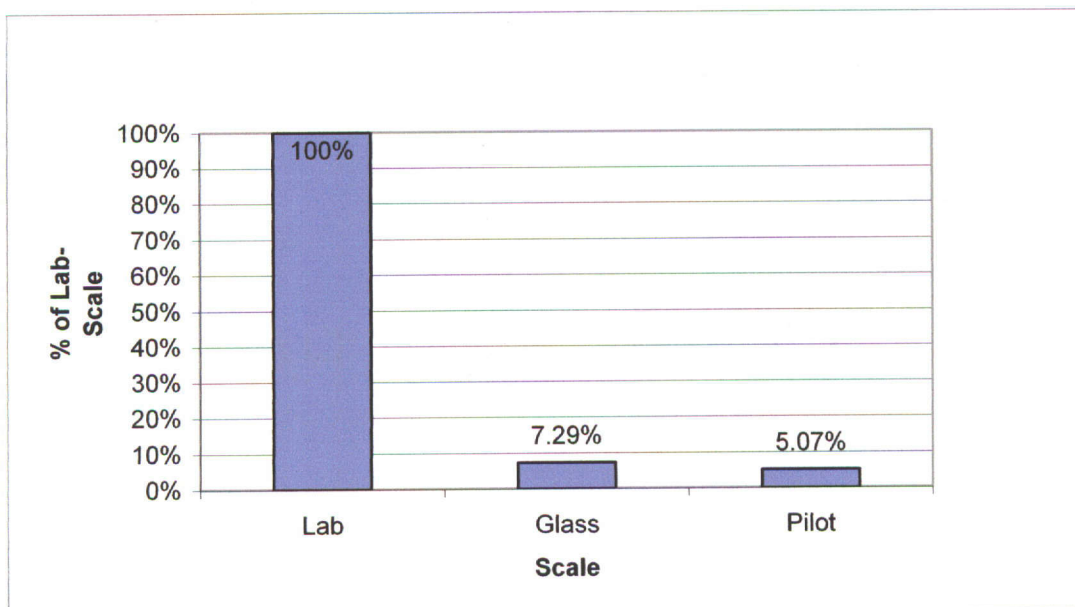


**Figure 33: Relative Percentage of Water Intensity in the Lab, Glass and Pilot Batches**

Figure 34 shows the waste intensity criteria for the different batch sizes. Table 15 shows the relative percentage of the three scales. There was a large difference in the equipment used at the laboratory scale than the other two scales. The lab scale equipment focused on obtaining a “high purity” product for initial tests at a large cost for solvents and water. Theoretically, the waste should have decreased by 29% from the glass to pilot plant, but decreased by 30.46%. This is the same as the mass intensity since no solvents or water are recycled or recovered from these scales.

**Table 15: Relative Percentage of Waste Intensity in the Lab, Glass and Pilot Batches**

Lab	100%
Glass	7.29%
Pilot	5.07%



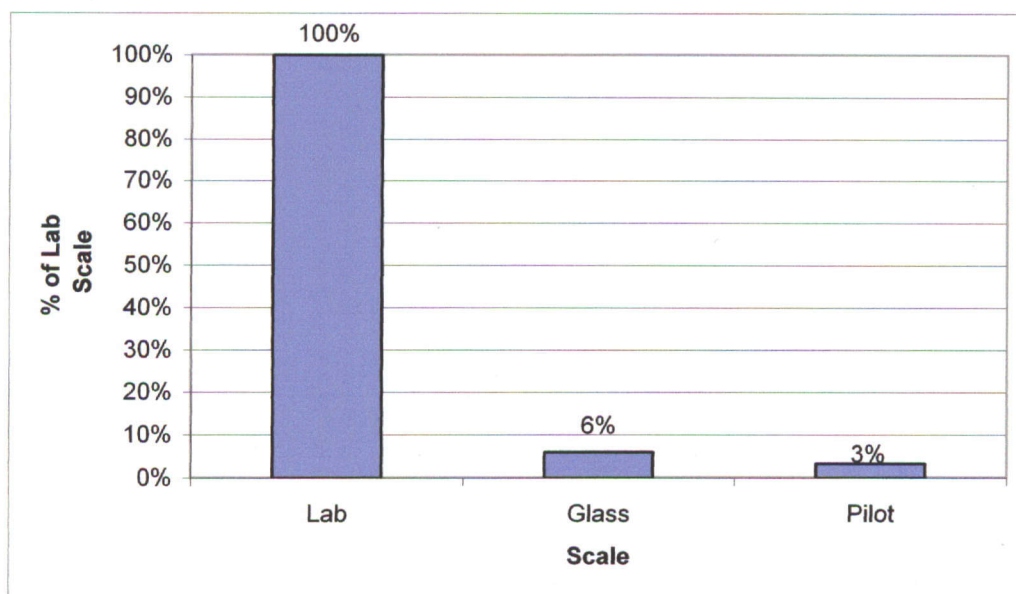
**Figure 34: Relative Percentage of Waste Intensity in the Lab, Glass and Pilot Batches**

Figure 35 shows the solvent intensity percentage for the three batch sizes. Table 16 shows the relative percentage of the solvent intensity for the three scales. The lab scale equipment focused on obtaining a “high purity” product for initial tests at a large cost for solvents and water. In the lab scale the solvent intensity was extremely high because of the excessive use of HPLC for purification purposes. In another step, in a purification process, excessive amounts of ethyl acetate were used to purify the product. This method was not used in either the glass or pilot plants. With the solvent intensity, from the glass to pilot plant, there was a 45.7% decrease in solvent usage. There are two factors that contributed to the decreased usage of solvents. The first is the increased yield

that resulted in the pilot plant. There was a 16.8%, which was not accounted for because of the yield. This was attributed to a few causes. The first cause for the large decrease was the because of two steps in the processing. In one step, a reaction was removed from the process. In another step, the amount of acetonitrile used was decreased by a factor of 2.25. The toluene was substituted for half the amount of ethyl acetate. A small percentage of acetone was also used.

**Table 16: Relative Percentage of Solvent Intensity in the Lab, Glass and Pilot Batches**

Lab	100%
Glass	6%
Pilot	3%



**Figure 35: Relative Percentage of Solvent Intensity in the Lab, Glass and Pilot Batches**

The energy required for the three batches was also compared. These factors were estimated using engineering heuristics and the flow sheets obtained from each batch. For these estimates, no heat loss was assumed for the heating or cooling in all the

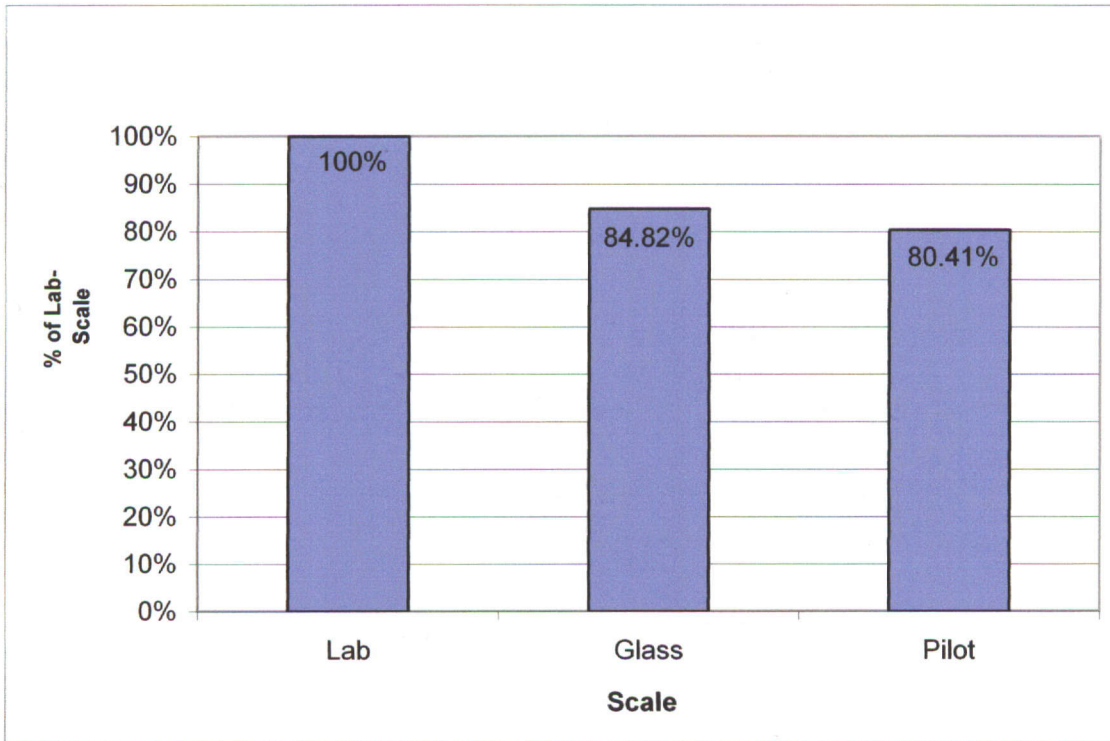
processes. The use of the heuristics and any assumptions concerning heat loss would decrease as the scale increase since heat loss is a function of surface area.

The processing conditions for this pharmaceutical product are those typically found in other pharmaceutical products. The comparison of the energy can be seen in Figure 36 and in Table 17. The pumping energy was found to be negligible for this process while the heating and cooling were the most significant energy consumers in the processes. Table 17 and Figure 36 are given for energy related emissions, but could also be used for the energy used in the various process stages. All three of these processes did not have a lot of energy associated with them. In the lab scale there was a lot of heating and not much cooling. It was not uncommon to find temperature raise by 50 degrees in many of the steps at the laboratory scale. In the glass and pilot scales the temperatures were kept close to ambient temperature in pressure with temperature differences of 20 degrees, but in both the glass and pilot plants there was heating and cooling occurring, many times in the same vessel. Some of this heating and cooling involved heating and cooling vessels, which contained salt solutions that did not occur at the lab scale. When the increased yield was taken into consideration, the energy usage increased slightly. The increased energy usage was attributed to the substitution of water in place of solvents and also the heating and cooling of salt solutions.

**Table 17: Relative Percentage of Lab-Scale Energy Related Emissions**

Lab	100%
Glass	84.82%
Pilot	80.41%



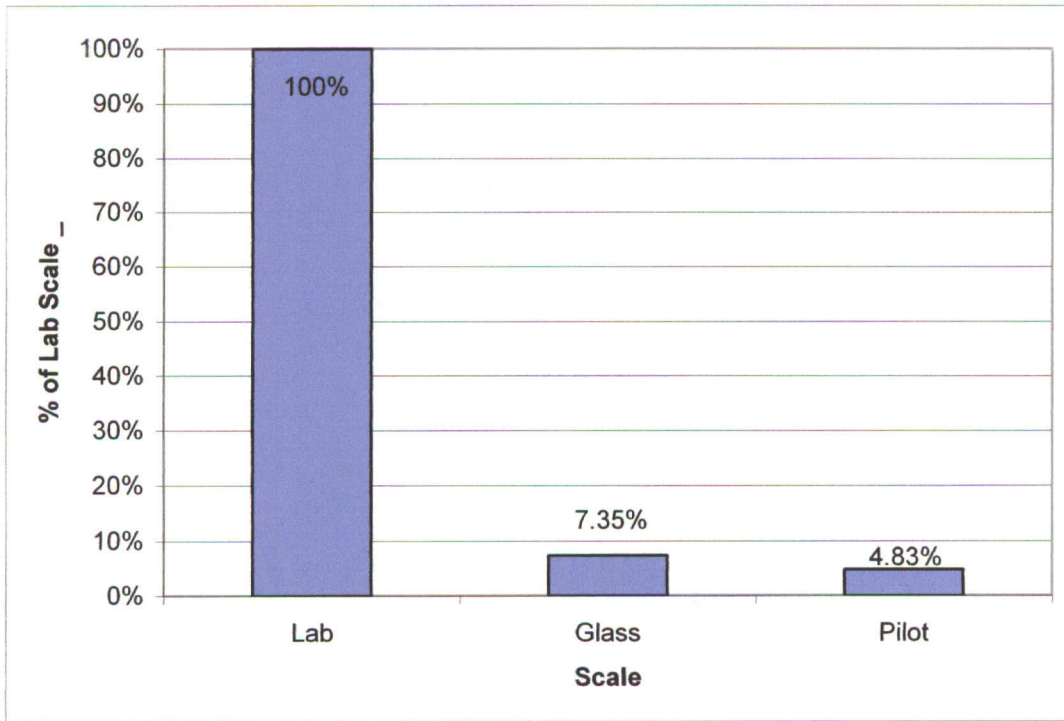


**Figure 36: Relative Percentage of Lab-Scale Energy Related Emissions**

A comparison of the fugitive emission was also made. These emissions are negligible compared to the waste intensity in the material intensities graph. The fugitive emissions tended to follow the mass intensity. This can be seen in Table 18 and Figure 37.

**Table 18: Relative Percentage of Fugitive Related Emissions for 3 Different Batch Sizes**

Lab	100%
Glass	7.35%
Pilot	4.83%



**Figure 37: Relative Percentage of Fugitive Related Emissions for 3 Different Batch Sizes**

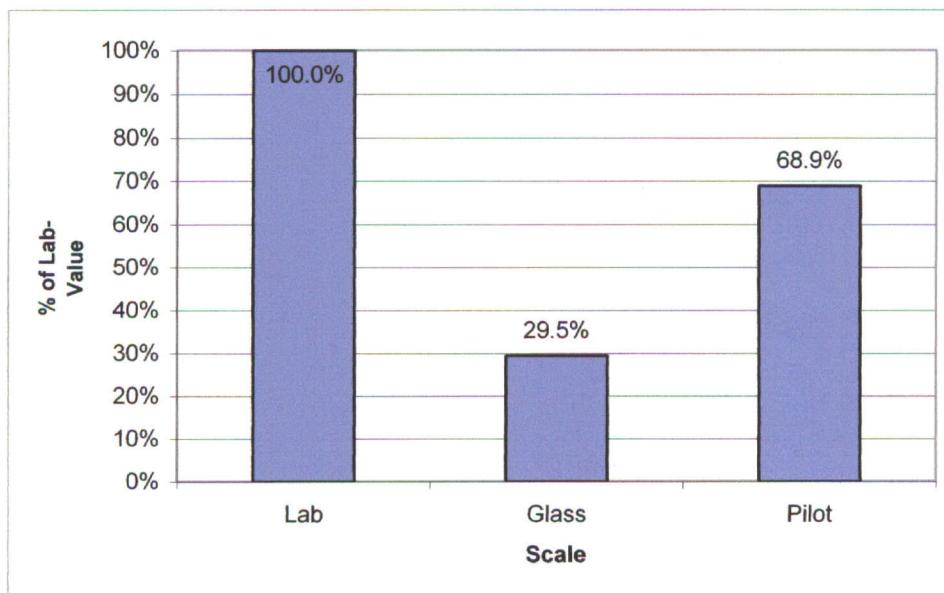
## ***Environmental Criteria***

The environmental factors were also considered. For these environmental criteria, all of the information was given in the pilot scale and the glass scale, but not for the lab-scale batch, which was obtained from a patent [71]. To make a valid comparison, the side reactions were not included for this analysis since the side reactions for the patent were not known.

Most of the factors decreased in their environmental impact category except the aquatic toxicity. The increase in aquatic toxicity was caused by the use of solvents that were more toxic to aquatic species. From the glass plant to pilot plant batch, there was a solvent replacement in which double the amount of heptane was used as a replacement for an butyl acetate. Heptane is many times more toxic to fish, but the ingestion toxicity was two times less toxic than the butyl acetate.

Figure 38 shows the weighted inhalation toxicity graph. For the weighted inhalation toxicity, despite having certain process controls in place such as scrubbers, the relative percentage still decreased from the lab scale. The percentage decrease from the lab-scale to the glass scale was 70%. The percentage decreased from the lab-scale to the pilot scale was 32%. There were two reasons for the increase from the glass plant to the pilot plant. The increase from the glass plant to the pilot plant was attributed to the increase usage of a reactant in the first step of the process. The second reason for the increase from the glass to pilot plant batches was attributed to an increased usage of a reagent in the process. The reagent in question has a very low TLV and 3 times more of the specific chemical was used in the pilot scale batch. If the side reactions are included

in this process, the glass plant had a substantially higher percentage than both the lab scale and pilot plant values.



**Figure 38: Relative Inhalation Toxicity for the Lab, Glass and Pilot batches**

The weighted ingestion toxicity was calculated by converting  $LD_{50}$  to a unitless kg/kg value. Figure 39 shows the weighted ingestion toxicity graph. The ingestion toxicity decreased as the scale increased. The reason why the lab scale was extremely high was because of two reasons. The first reason was because of excessive chemical usage. The second reason for the large number for the ingestion toxicity was the use of acetonitrile. Acetonitrile is a compound that can cause cyanide poisoning and was used in excessive amounts for purification techniques in the lab scale. The excessive use of this chemical was changed in the glass and pilot plants. Instead of using HPLC which used the acetonitrile, liquid-liquid extraction was used more often which are considered “food grade”. These chemicals included heptane, ethyl acetate, and butyl acetate. The decrease for the pilot plant was 39.04% while the yield increase was 29% from the glass

plant value. There were two factors that increased this effect; the first was a usage of more environmentally benign solvents, such as acetone and various acetates, but was countered with the increased usage of the toxic reagent, which is a proprietary compound. The second portion was the decreased use of butyl acetate in the last step of the process. Some butyl acetate was replaced with heptane in the process. Butyl acetate is not a toxic chemical, but heptane is even less toxic when ingested.

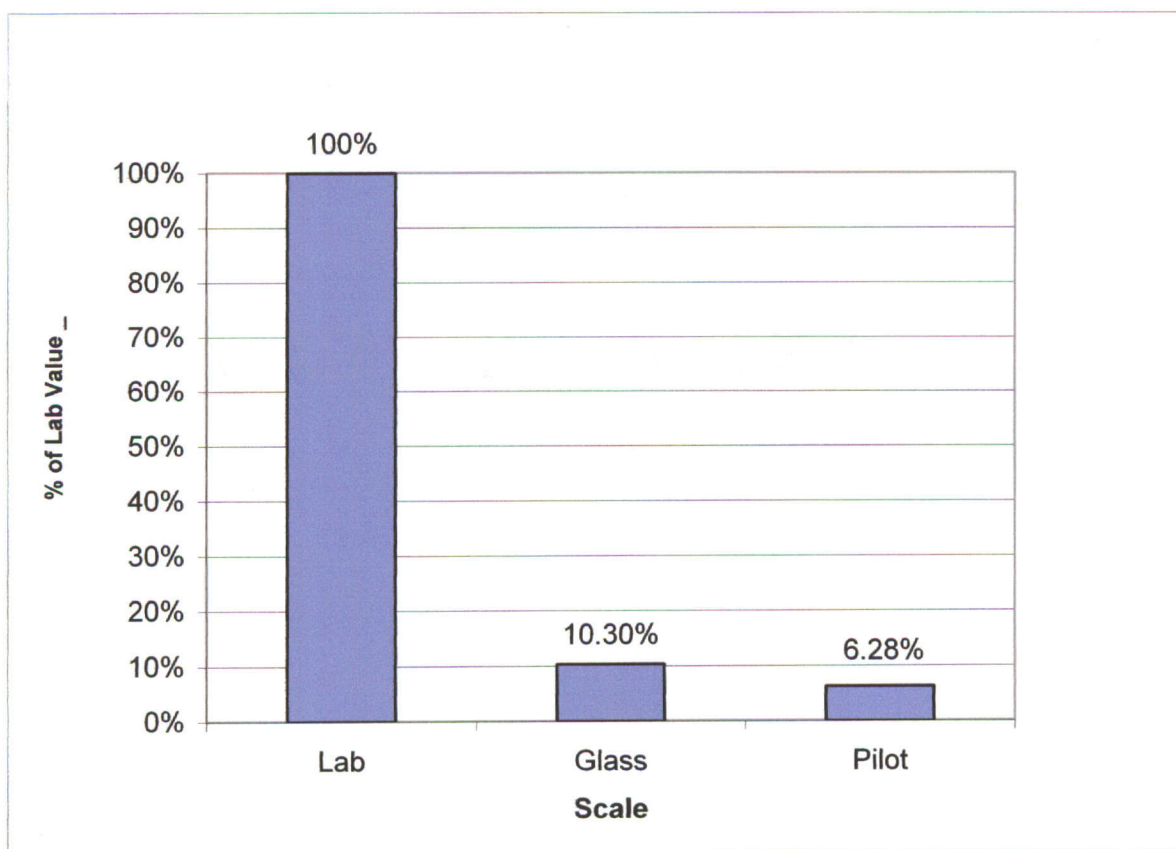
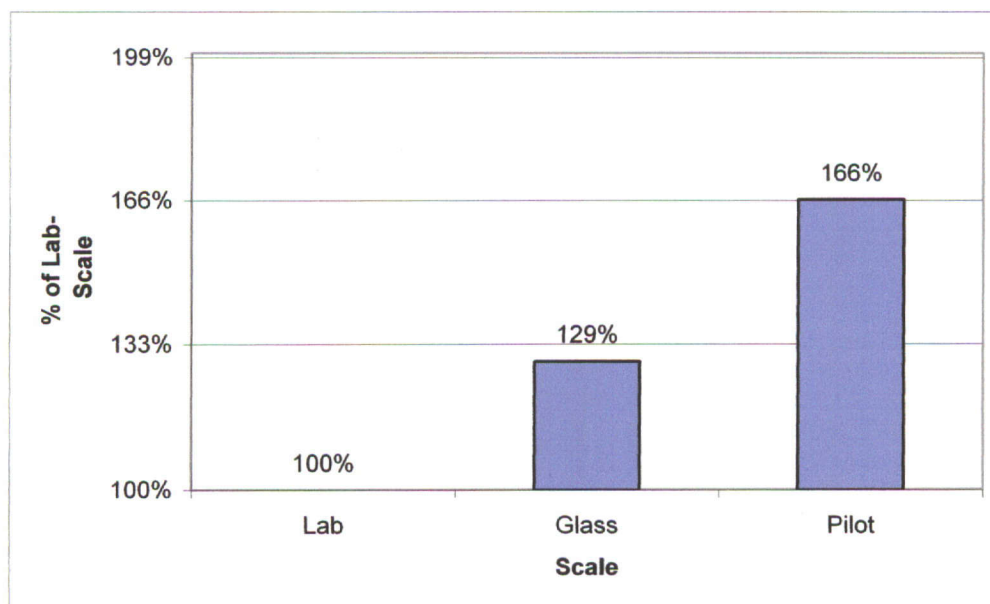


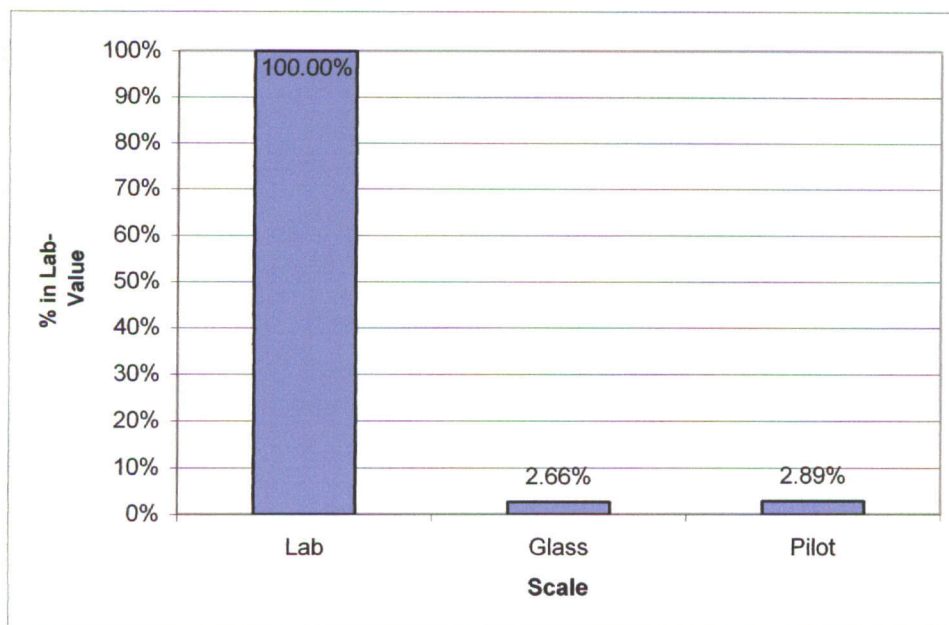
Figure 39: Relative Ingestion Toxicity for the Lab, Glass Plant and Pilot Plant scales

Figure 40 shows the weighted aquatic toxicity graph. The aquatic toxicity increased caused by a change in solvents. In the lab scale, a lot of substances were used, but these chemicals were relatively non-toxic to aquatic life. These chemicals include water, acetonitrile, and salts. There are mixed results for the glass and pilot scales. In the first step for the glass plant, toluene was used which is more toxic than the other compounds. The other steps for the pilot plant had more substances that were toxic to aquatic species. These substances included the use of acetonitrile in place of methanol and acetone and the replacement of butyl acetate with heptane. The increased usage of heptane and the decreased usage of butyl acetate caused the increase in aquatic toxicity. There was a trade off between the environmental criteria and the mass criteria. This is because of the properties of the drug itself, most organic drugs are more soluble in organic phases and this drug is not an exception. To lower the mass intensity and volume of the reactors, the aquatic toxicity was sacrificed.



**Figure 40: Relative Aquatic Toxicity as a Percentage of the Lab-Scale Value**

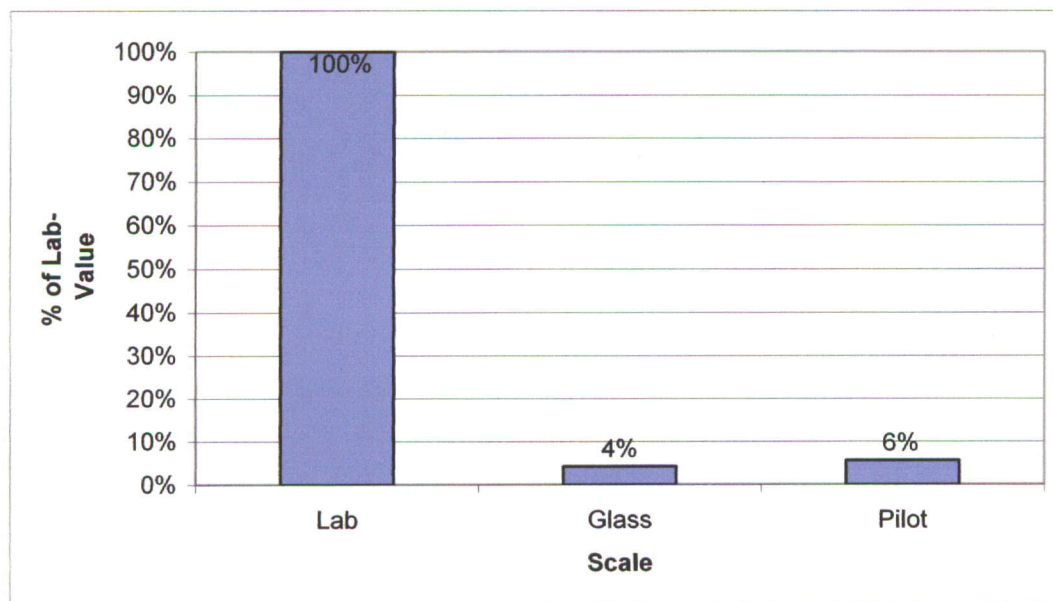
The global warming potential was also analyzed. This can be seen in Figure 41. This effect was a combination of the volatile organic compounds and various other compounds that contributed to global warming. There was a reduction from the lab-scale to the glass scale batch. The value for the global warming potential stayed approximately the same for the glass and batch scale batches. The global warming potential should have decreased because of the increased yield, but this was not the case. The reason for the increase was that every solvent was given the same global warming potential, so any increase in solvent usage would increase the global warming potential.



**Figure 41: Relative Global Warming Potential as a Percentage of the Lab Scale Value**

The weighted photochemical smog formation was also analyzed for these three batches. There was a large decrease from the lab to the glass scale, which was due to the substitution of water in place of solvents along with decreased solvent usage. In the lab scale, a significant portion of the photochemical smog formation was attributed to the

ethyl acetate used in one of the steps for purification in the process and also to acetonitrile that was used in the HPLC for purification. There was a slight increase in the photochemical smog formation from the glass to pilot plant scale despite decreased solvent usage. This occurred for the same reason as the aquatic toxicity. The only reason why there was an increase from the glass plant to pilot plant scale was because of the use of heptane in the last step in the process. Heptane is a relatively persistent chemical and contributes significantly to smog formation. The value for heptane is 0.77 while the value for butyl acetate, the chemical in which it was substituted for has a value of 0.51. [58]



**Figure 42: Relative Photochemical Smog Formation as a Percentage of the Lab Scale Value**

An analysis for carcinogenicity was also prepared. This was conducted on a scale of 0-5 with the number 5 denoting a proven carcinogen to humans. The scale of 0 would denote that the substance was proven to be non-carcinogenic to humans. Some substances in the 0 category include water and ethanol. A category 2 would be a possible



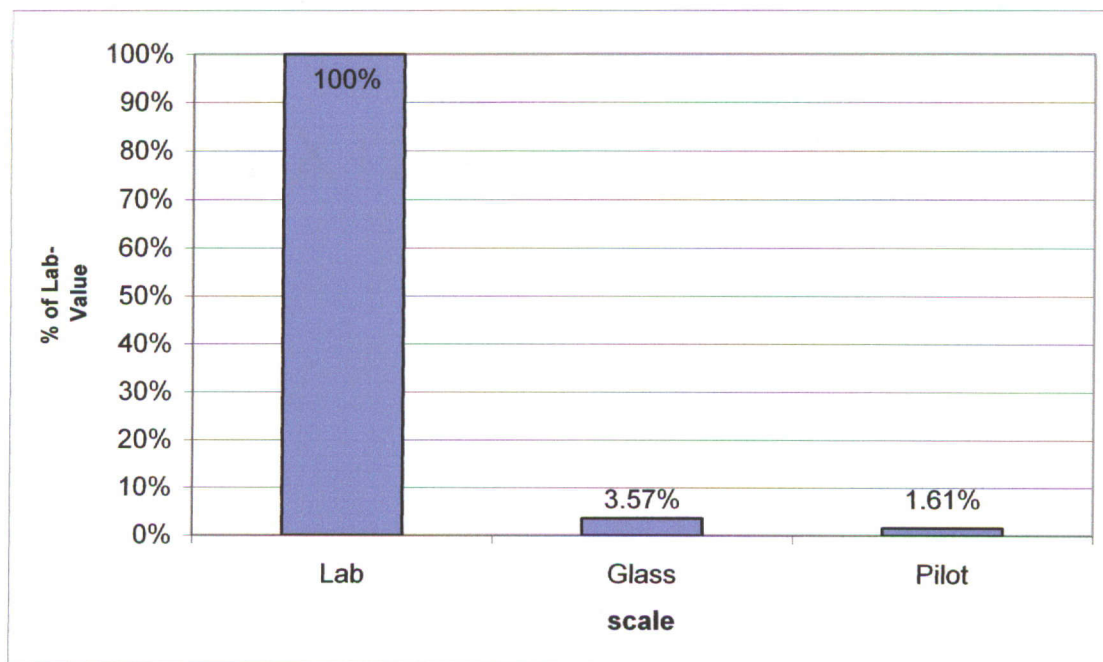
human carcinogen, a substance in category 3 would be potentially carcinogenic based on animal tests, and a substance in the fourth category would be potentially a carcinogenic based on limited human data. The equation used for carcinogenicity can be seen in Equation 1.

**Equation 1**

$$\text{Carcinogenicity} = \text{Mass} * (10^{\text{classification number}} - 1)$$

This was a simple method to estimate the carcinogenicity of all the compounds without making extreme assumptions. An example of the logic of this method was with benzene and toluene, which are 5 and 3 respectively. Using this method, benzene was 100 times more carcinogenic than toluene. Figure 43 shows the carcinogenicity for the three batch scales.

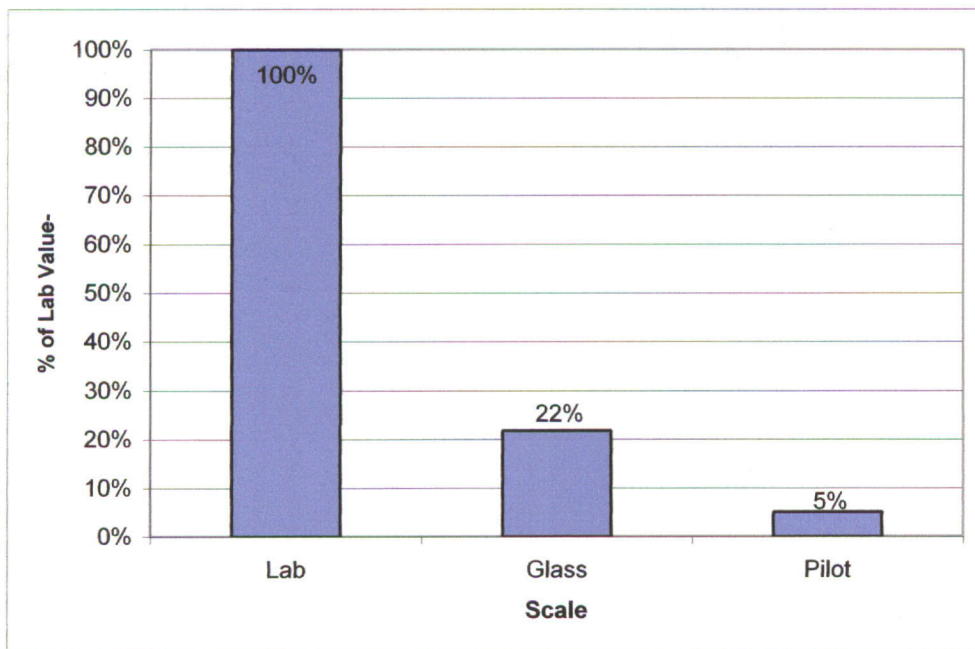
In the laboratory scale, there was low yield and some substances were used which had high potentials to cause cancer. These substances include dichloromethane, toluene, formaldehyde, and DMF. All of these substances were removed for the glass plant. There was an improvement from the glass plant to the pilot plant that was not based on yield improvement. This was the removal of THF from one of the steps.



**Figure 43: Relative Carcinogenicity as a Percentage of the Lab Scale Value**

A graph for the weighted acidification was also prepared. This was the amount of acid producing compounds that are released such as sulfuric acid, carbonic acid, and hydrochloric acid. In general, there was a decrease in the acid rain potential for the processes from the input materials. There was not as large of a drop between the lab-scale and the glass-batch scale mainly due to the pieces of processing equipment that were added for safety reasons. In the laboratory scale, hydrochloric acid was used in one of the steps. In both the glass plant and pilot plant very little hydrochloric acid was used. In both the glass and pilot scales phosphoric and sulfuric acids were used. The sulfuric acid was not present in the laboratory scale because this chemical was part of a process control within a step in the process. There was a slight difference in the acidification between the glass plant and the pilot plant. This was attributed to an

increased yield and the telescoping of one reaction step. The decrease can be seen in Figure 44.



**Figure 44: ARP as a Percentage of the Lab Scale Value**

## Chapter 5: Solvent Selection Guide

There was a need for a quick method to determine the various environmental factors that are related to solvent selection. Previous methods to determine the most efficient solvent for a specific process took into consideration various factors. These considerations included basic engineering, economics, chemistry principles, and safety concerns, which are typically the primary concerns for solvent selection. This table provides guidance for selected solvents from an environmental perspective. The environmental categories are typically secondary consideration for solvent usage in the pharmaceutical industry. There are a large number of databases and information available for the various environmental criteria, but most of this information is not readily available for comparison. The user has to search for the data and re-enter the data into a spreadsheet if a comparison of two solvents is desired. This data is available from MSDS sheets, the EPISUITE software package, SOLV-DB and the metrics developed by IChemE [58] [72], [73], [74].

A simple excel spreadsheet was developed which includes inhalation toxicity, ingestion toxicity, aquatic toxicity, ozone depletion, smog formation, global warming potential, carcinogenicity and acidification for 39 typical solvents. The environmental metrics used for this solvent selection guide take into account safety and liability.

This solvent selection guide is different from previous solvent selection guide because it takes into account parameters, which were not previously considered in other solvents selection tables. This table also provides the user with raw data, so a direct

comparison can be made very quickly to determine if any process improvements were made in the environmental categories.

Another advantage to this solvents selection guide is that the data can be expanded to include solvents, which are proprietary or have been newly developed. For this data, a person using a proprietary solvent only has to enter the data into the spreadsheet for the compound. This allows the user to compare the solvent to the other solvents in the spreadsheet. The data for their proprietary solvent can be found on the material safety data sheets for the solvent. The other environmental parameters can be found by estimation using similar compounds as reference sources.

There has been previous efforts in the development of solvent selection tables. Most of these guides were in the form of logic-tree programs that determined the best solvents from a set list of parameters. Most of these methods take into account processing, solubility, regulatory, and health parameters, but were not easy to use in terms of user interfaces and learning curves and were used primarily for initial process development.

A program developed by the EPA called the Green Chemistry Expert System, and contains 649 chemicals and has many of the physical properties listed, but does not list any toxicological information [75]. Also a direct comparison is not available. Therefore, a pen and paper method is still needed if a comparison is desired.

The EPA also released the Solvents Alternatives Guide (SAGE), which is used for cleaning processes for equipment [76]. This method works well for its intended purpose, but does not translate well to solvent selection for pharmaceutical processes.

There is also another solvent selection guide by Curzons et al., which accounts for a few environmental factors [77]. This guide takes into account various environmental parameters such as bioconcentration, inhalation toxicity, aquatic toxicity, and water solubility. This guide lacks a feature to account for the mass of the solvent used.

Gani et al. proposed another method for solvent selection [78]. This method proposed a series of rules for solvent selection and used a point system to “score” different solvent alternatives. This used various physical parameters and lumped all the environmental parameters into one category. This approach is methodical, but is time consuming.

There are life cycle assessment packages that take various solvents into consideration, but these take a relatively long time to set up for a simple comparison. A second disadvantage to life cycle assessment packages is that most of the solvents are not listed. This severely limits the effectiveness of the life cycle software for solvent selection. If an analyst desires a more accurate comparison of the solvents using a life cycle assessment software package, the analyst must define the specific solvent in the program. This is a time consuming and research intensive.

All of these programs have a specified list of solvents that cannot be changed. The only method that takes into account mass is the life cycle assessment packages, which are inconvenient to use and require the user to learn a new software program or a new type of interface. The other programs cannot be changed, and in some cases, are not available to the average user.

## Metrics Used

Inhalation toxicity was chosen to represent the airborne health hazards associated with each chemical. This metric is considered in hazard and operability studies, HAZOP, and is considered a local to regional issue depending on the hazard and amount released. The values used for this analysis are the permissible exposure limit or the threshold limit value of the chemical. This criterion is often considered for worker safety, but can also affect most terrestrial species outside of the plant boundaries if there is an accidental release. There are other factors that were not considered with the inhalation toxicity which include, dispersion models and the atmospheric half-life of each chemical. Dispersion models were not included since every manufacturing plant will have a unique geographical position and the atmospheric half-life was unavailable for a few of the chemical species.

Carcinogenicity was another category, which was considered as a metric. This metric is typically considered along with inhalation toxicity for worker safety in a HAZOP report. Carcinogenicity is typically considered to be a local environmental metric, but can be considered regional depending on the size, extent of a spill and exposure method. The carcinogenic value can be found on any MSDS sheet and is given for all chemicals. There are other sources, which only have a small number of chemicals listed. These sources were not used since there was missing data. The carcinogenicity was scaled on a factor of 0-5. A chemical with a value of 0 was denoted as non-carcinogenic and a chemical with a value of 5 was denoted as a known carcinogen. This can be seen in Equation 2.

$$\text{Equation 2}$$
$$\text{Carcinogenicity} = \text{Mass} * (10^{\text{scaled value}} - 1)$$

An example would be 1000 kg of water, which is non-carcinogenic. Water has a scaled factor of 0. The mass was multiplied by  $(10^0-1)$  to give a scaled carcinogenic score of 0. Carcinogenicity is used as supplemental information for inhalation, ingestion and aquatic toxicity.

Ingestion toxicity was chosen to represent the impact that the chemical can have on species that ingests the solvent. This also represents the potential impact on terrestrial life if there is a liquid spill or if the vapor precipitates out of the atmosphere. This metric is considered a local to regional issue dependent on the hazard and amount released. The  $LD_{50}$ , the lethal dose to kill 50% of a given population, was chosen for rats to represent typical ingestion toxicity for the solvent for mammalian species. Rats were used to represent mammalian ingestion toxicity because toxicological studies are typically conducted on rats or mice. There are some concerns with this data specifically with the alkane groups. Rats can drink 1.2% of their weight in hexane, 2.5% of their weight in heptane, and there is no limit to octane and higher alkanes, without surpassing the  $LC_{50}$  for this species. Care should be taken when comparing the alkane groups to other groups because of the resistance of rats to the alkanes.

Aquatic toxicity was used to determine the impact of the solvent associated with environmental impact to marine life. This metric is considered a local to regional issue dependent on the hazard, amount released, previous concentration in the water, the size of the water source, and the amount of other water sources affected. The  $LC_{50}$  for freshwater fish over 14 days was used for the comparative measurement. This is a typical metric used to represent aquatic toxicity. Aquatic toxicity accounted for any accidental discharges into lakes or streams and the resulting ecological impact.



Acid rain potential was another metric that typically has a regional impact. This is the potential for a compound to lower the pH of rain. Typically solvents do not contribute to the acid rain potential unless the solvents are oxidized to carbon dioxide via a non-biological route. It was assumed for this analysis that the solvents would be recycled, biologically treated or used for another purpose instead of being incinerated, which is typically the case. If the user chose to account for the combustion of the solvent, the ARP can be modified by finding the amount of SO<sub>2</sub>, CO<sub>2</sub>, NO and NO<sub>2</sub> released by the combustion of the solvent.

There was a metric for used to gauge photochemical smog formation. Typically organic solvents tend to react and form smog in the lower atmosphere, which can cause harm to terrestrial species. Smog formation can either be a local or regional issue dependent on the amount of chemicals released.

Ozone depletion and global warming potential are factors that have global environmental impacts. Ozone depletion is a measure of how the solvent will react and destroy ozone in the upper atmosphere. Most of the solvents do not contribute to ozone depletion, except compounds that contain halogenated groups. The other metric is global warming potential. This metric was the same for all the solvents since a generic value is given for volatile organic compounds and all of the solvents besides water are organic compounds. The global warming potential is a direct function of the mass of solvent used. These two metrics can be used to compare the global environmental impact of different solvents. The list of the various solvents available for comparison are shown in Table 19.

**Table 19: Solvents in Spreadsheet**

Acetic Acid	Dimethyl Acetamide	Isopropyl Ether
Acetic Anhydride	1,4-Dioxane	Methanol
Acetonitrile	Ethanol	Methyl Cellosolve
Acetone	Ethyl Bromide	Methylene Chloride
Amyl Acetate	Ethyl Acetate	Methyl Ethyl Ketone
Benzene	Ethyl Ether	Methyl Formate
1-Butanol/n-butanol	Formaldehyde	Methyl Isobutyl Ketone
2-Butanol/sec-Butanol	Formamide	Pyridine
Butyl Acetate	n-Heptane	Tetrahydrofuran
Carbon Tetrachloride	n-Hexane	Toluene
Chloroform	Isobutanol/isobutyl alcohol	Trichloroethane
o-Dichlorobenzene	Isopropanol	Water
Diethylamine	Isopropyl Acetate	Xylene

For the inhalation toxicity, ingestion toxicity, and aquatic toxicity, a higher value denotes a less toxic material. For these three criteria the inverse toxicity value of the chemical was used to represent that a more toxic substance is more harmful. The other environmental values were obtained from the IChemE [58]. Some data was unavailable since some of these solvents are not used to a large degree. This data may be obtained in the future or the category can be neglected for the comparison.

A simple spreadsheet was set up with the solvents and the various environmental metrics. The only information the user needs to enter into the spreadsheet is the mass of material being used and the spreadsheet will calculate the various environmental parameters. These values can then be compared to other value obtained for other compounds. The full table is given in Table 20. The user can also further adjust the impact of each category by including a weighting factor. This is dependent on the

concern for each category and for a specific location. An example of when the environmental parameters could be adjusted is when a plant is located in the middle of a desert. The aquatic toxicity would be of very little concern since there are no outside water sources close to the plant.

**Table 20: Environmental Solvent Selection Table**

Solvent	How Used (order in use in kg)	Reportable Quantity Limit (kg)	Weighted Inhalation	Weighted Ingestion Toxicity	Weighted Aquatic Toxicity	Weighted Global Warming	Weighted Ozone Depletion	Weighted Smog	Weighted Carcinogenicity	Weighted Acclimation	Log Octanol/Water Partition Coef (log Kow)	Henry's Law Constant at 25°C (mm <sup>3</sup> /mole)	Soil Adsorption Coefficient (log Koc)	Bio Concentration Factor
<b>ACETATES</b>														
Ethyl Acetate		2272.7	0	0	0	0	0	0	0	0	0.73	1.34E-04	0.789	3.16
Isopropyl Acetate		None	0	0	0	0	0	0	0	0	1.29	2.78E-04	0.977	1.94
Butyl Acetate		None	0	0	0	0	0	0	0	0	1.78	2.81E-04	1.319	4.69
Amyl Acetate		2272.7	0	0	0	0	0	0	0	0	2.3	3.88E-04	1.966	11.70
<b>ACIDS</b>														
Acetic Anhydride		2272.7	0	0	0	0	0	0	0	0	-0.98	5.71E-06	0	3.16
Acetic Acid		2272.7	0	0	0	0	0	0	0	0	-0.17	1.00E-07	0	3.16
<b>ALCOHOLS</b>														
Methanol		2272.7	0	0	0	0	0	0	0	0	-0.77	4.59E-06	0	3.16
Ethanol		None	0	0	0	0	0	0	0	0	-0.31	5.00E-06	0	3.16
Isopropanol		None	0	0	0	0	0	0	0	0	0.05	8.80E-06	0.025	3.16
1-Butanol/Isobutanol		2272.7	0	0	0	0	0	0	0	0	0.88	8.81E-06	0.389	3.16
Isobutanol/Isobutyl alcohol		2272.7	0	0	0	0	0	0	0	0	0.76	9.78E-06	0.311	3.16
2-Butanol/Sec-Butanol		None	0	0	0	0	0	0	0	0	0.61	9.08E-06	0.311	3.16
<b>ALKANES</b>														
n-Hexane		None	0	0	0	0	0	0	0	0	3.9	1.8	2.173	200.91
n-Heptane		None	0	0	0	0	0	0	0	0	4.66	2	2.439	772.69
<b>ETHERS</b>														
Ethyl Ether		45.5	0	0	0	0	0	0	0	0	0.89	1.29E-03	0.643	3.16
Isopropyl Ether		None	0	0	0	0	0	0	0	0	1.52	2.28E-03	1.021	2.95
<b>HALOGENATED COMPOUNDS</b>														
Carbon Tetrachloride		4.5	0	0	0	0	0	0	0	0	2.83	2.78E-02	1.687	30.13
Chloroform		4.5	0	0	0	0	0	0	0	0	1.97	3.67E-03	1.545	6.56
Ethyl Chloride		None	0	0	0	0	0	0	0	0	1.61	7.49E-03	1.376	3.47
Methylene Chloride		454.5	0	0	0	0	0	0	0	0	1.34	3.29E-03	1.376	1.83
p-Dichlorobenzene		45.5	0	0	0	0	0	0	0	0	3.43	1.92E-03	2.646	87.30
Trichloroethane		454.5	0	0	0	0	0	0	0	0	2.49	1.72E-02	1.687	16.49
<b>KETONES</b>														
Acetone		2272.7	0	0	0	0	0	0	0	0	-0.24	3.97E-06	0.297	3.16
Methyl Ethyl Ketone		2272.7	0	0	0	0	0	0	0	0	0.29	5.69E-06	0.903	3.16
Methyl Isobutyl Ketone		2272.7	0	0	0	0	0	0	0	0	1.31	1.39E-04	1.039	2.04
<b>NITROGEN CONTAINING NON-IONIC ORGANICS</b>														
Acetanilide		2272.7	0	0	0	0	0	0	0	0	-0.34	3.46E-06	0.663	3.16
Diethylamine		454.5	0	0	0	0	0	0	0	0	0.58	2.59E-05	1.699	3.16
Dimethyl Acetamide		None	0	0	0	0	0	0	0	0	-0.77	1.31E-08	0.969	3.16
Formamide		45.5	0	0	0	0	0	0	0	0	-1.51	1.53E-08	0.175	3.16
<b>NON-ORGANICS</b>														
Water		None	0	0	0	0	0	0	0	0	-1.39	8.41E-09	1.165	3.16
<b>OXYGEN CONTAINING ORGANICS</b>														
Formaldehyde		45.5	0	0	0	0	0	0	0	0	0.35	3.37E-07	0	3.16
Methyl Cellulose		None	0	0	0	0	0	0	0	0	-0.77	3.33E-07	0	3.16
Methyl Formate		454.5	0	0	0	0	0	0	0	0	0.03	2.23E-04	0.332	3.16
<b>IONS/COMPOUNDS</b>														
Benzene		4.5	0	0	0	0	0	0	0	0	2.13	5.56E-05	2.219	8.71
1,4-Dioxane		45.5	0	0	0	0	0	0	0	0	-0.27	4.89E-06	0	3.16
Pyridine		454.5	0	0	0	0	0	0	0	0	0.65	1.01E-05	1.519	3.16
Tetrahydrofuran		454.5	0	0	0	0	0	0	0	0	0.46	7.05E-06	0.689	3.16
Toluene		454.5	0	0	0	0	0	0	0	0	2.73	6.64E-03	2.429	26.23
Xylene		454.5	0	0	0	0	0	0	0	0	3.12	5.18E-03	2.646	90.35

## Example of Solvent Selection

An example of the application of this solvent selection table for the environmental criteria would be if a scientist or engineer narrowed down the desired properties to three viable solvents. For this example case, the projected amount of solvents needed would be either 100 kg of benzene, 200 kg of acetone or 150 kg of n-hexane. The results for this analysis are shown on the next page in Table 21.

**Table 21: Results of Solvent Selection Table for the Example Compounds**

Solvent	Mass Used (enter in mass in kg)	Reportable Quantity limit (kg)	Weighted Inhalation	Weighted Ingestion toxicity	Weighted Aquatic toxicity	Weighted Global Warming	Weighted Ozone depletion	Weighted Smog	Weighted Carcinogenicity	Weighted Acidification	Log Octanol- Water Partition Coef (log Kow)	Henry's Law Constant at 25C (atm m <sup>3</sup> /mole)	Soil Adsorption Coefficient (log Koc)	Bio Concentration Factor
Acetone	200	2272.7	0.4	34462.75862	101.4575066	2200	0	36.4	0	0	-0.24	3.97E-05	0.297	3.16
n-Hexane	150	None	3	6000	7568240.925	1650	0	97.2	0	0	3.9	1.8	2.173	200.91
Benzene	100	4.5	10	107526.8817	2241.436201	1100	0	33.4	99900	0	2.13	5.55E-03	2.219	8.71

These results can be compared to one another either by direct comparison or by converting every metric to a percentage to find the net increase or decrease if solvent substitution is considered. The results from the table show that in terms of inhalation, toxicity, ingestion toxicity, aquatic toxicity, and carcinogenicity that acetone has the least impact, while benzene has the least impact in terms of smog and global warming, but the largest impact in terms of carcinogenicity.

## Chapter 6: Conclusions

### *Green Analysis of a lab-scale fermentation based API*

From a review of the various patents of the drug pravastatin, there was a significant decrease in the water, energy, and solvent usage as time progressed. There was also a decrease in the environmental categories. This was attributed to the process becoming more efficient. It was also found that the largest contributor of all of these categories was the process to make the intermediate. The intermediate process used significantly more energy, water, and solvents than all of the pravastatin processes. The trends that each of the graphs followed were related to a form exponential decay, which indicated that there will be a minimum value to each trend which means that the value will never reach zero or be a perfectly sustainable process.

Decreasing the material usage in a process is an important green engineering objective and can be accomplished in two different methods. Direct process improvements are one way to decrease the material and energy usage. This was investigated in this paper. The second method of decreasing mass usage is by increasing the conversion and yield of the intermediate. This was apparent in the analysis since less intermediate was needed as the years progressed.

For this process the use of the Best Practical Environmental Option (BPEO) would be a disadvantage and result in a process, which would do more harm to the environment. For this specific example, it was not the process to make the drug that was a large concern, but the manufacture of the intermediate which was the concern. In 1982, the substances that were used in the process to make pravastatin were relatively benign,

but there were a lot of chemicals used and a great deal of waste was produced. Also a great deal of intermediate was used. In the next few years, the primary focus was on increasing the yield of the product. This resulted in the lower criteria for the entire life cycle of the product, but a higher numbers for some of the criteria for 1983 and 1985.

It was also found that there is a direct relationship between intermediate usage and energy usage. Most of the energy usage in all of the process came directly from the mixers and the reverse osmosis systems to make pure water. Resource depletion from energy contributed small fraction to the total material depleted. The emission attributed by energy decreased by a factor of over 100 in the 22-year span of the four patents for this analysis.

The trend for the environmental categories were analyzed for the pravastatin process. Inclusion of the intermediate process in the environmental categories would have trivialized the decrease in the environmental categories.

For the environmental index and carcinogenicity solely for the pravastatin patents, no trend could be found to fit the four patents. This was due to the usage of benzene in 1983 and 1985 patents. There was a decreasing trend for the environmental index when 1983 value is removed, but the 1985 and the 2004 values could potential be with the same confidence limit.

For this study it can be concluded that the BPEO is not the best approach to use. For this specific drug, it was better to increase the yield by using hazardous solvents because in the total life cycle the use of hazardous solvents would decrease.

### ***Scale up of a active pharmaceutical ingredient***

The scale up of another pharmaceutical product offers another perspective on the pharmaceutical industry. There are a few considerations that were taken into account for the scale up. The first consideration is purity. There was a large concern about purity for this drug so many environmental solutions could not be used. The second consideration was yield. The greater the yield, the better the process to some degree. It was found for this process that yield improvement and high yields do not directly correlate to a green process since the lab scale had 100% yield in the last step, but used a substantial amount of solvents and energy to maintain this yield. The third consideration for this scale up was lowering the volume of the reactors, which had mixed results for the processes.

The lab scale production maintained an extremely high purity drug and had an extremely large yield for the last step. There was a cost for this yield though. The cost for the yield was excessive use of water and another solvent in a certain piece of equipment. When this factor was taken into consideration and compared to the glass plant and the pilot plant, the use of this specific piece of equipment was not worth the amount of product recovered from either an economic or an environmental perspective. For the last step in the lab scale, it would cost more money to recover the API than the API is worth.

There were decreases in most of the environmental factors as the scale of the process increased from the lab scale to the glass scale to the pilot scale in many of the categories. In some of the categories there was a decrease in some of the environmental factors.

The large decrease from the lab scale to the glass scale for mass, solvent, and water usage and most of the environmental parameters was attributed the use of different equipment and the use of different reagents, catalysts, and solvents. At the laboratory scale, there was a large use of exotic reagents and techniques that would result in large scale contamination if conducted at a larger scale.

There was a slight decrease from the glass plant to the pilot plant. This is mainly attributed to because of a yield increase. This was the case of the mass, solvent and water usage along with the ingestion toxicity. The yield increase had mixed results in the environmental categories. For instance, in order to obtain the higher yield a reactant was used in excess. This reactant is an extremely toxic and reactive chemical so the environmental index increased.

There was also telescoping which occurred between the glass plant and the pilot plant. Telescoping is defined as the processing of removing process steps or equipment. By removing this equipment, the processing steps became smaller and not as much equipment was used. Because the equipment was not used the vessel did not need to be cleaned with water or solvent and also intermediate was not lost in the vessel.

In terms of energy, it was not expected that there was a huge decrease in the amount of energy used for the processing. There are a few reasons why there was not a large drop. The first reason is that the process occurs around ambient temperature and pressure so there is not much energy involved to begin with. The second reason was because of different operating conditions of the lab scale compared to the other two scales. In the laboratory scale, very little cooling was present, but there was a large amount of heat and mechanical energy. In the glass scale and pilot scale, water with salt



was heated so that a salt would dissolve quickly into solution and then the solution was cooled. This was unnecessary since the salt was well below its solubility limit. Use of room temperature water would have solved the heating and cooling need used for the process. Also in the glass scale and pilot scale there was negligible mechanical energy compared to the laboratory scale.

There was a trade off between a solvent substitution that took place between the glass scale and the pilot scale. In the glass scale a large amount of acetates were used, but these were substituted in for an alkane in the pilot plant. This caused the ingestion toxicity to decrease significantly, but caused the aquatic toxicity and smog formation to increase. This is because heptane contributes more to smog formation than the butyl acetate and heptane is extremely toxic to fish.

There was also a decrease in the carcinogenicity of the processes. For this analysis, the intermediate compounds are treated as potential human carcinogens and one of the intermediates is treated as suspected human carcinogen because this is a traditional practice in the pharmaceutical industry for unknown compounds. For this case there was a decrease of the period of time because the yield increased. This analysis where the intermediates are treated as potential carcinogens is the most accurate way to analyze this process until further testing can be conducted on the intermediates or they are proven to be non- carcinogenic.

## ***Solvent Selection guide***

The solvent selection guide developed with the input of industry representatives is helpful in determining which solvents will cause less damage from an environmental perspective. This solvent selection guide is different from previous solvent selection guide because it takes into account parameters, which were not previously considered in other solvents selection tables. This table also provides the user with raw data, so a direct comparison can be made very quickly to determine if any process improvements were made in the environmental categories. Unlike previous solvent selection tables, this allows the user to factor in the mass of the chemical and offers a direct comparison to alternative solvents. This avoids the pen and paper approach previously used to determine the optimal solvent from an environmental perspective.

Unlike previous solvent selection tables that have the data imbedded in the program, this software allows the user to quickly and easily add in data for various other solvents if another solvent is desired.

In conclusion, a recommendation is to use this solvent selection table along with the solvent selection approaches already employed by various organizations, such as the EPA and Glaxo-Smith-Kline to determine the optimal solvent.

## References

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- 1) <http://www.epa.gov/oppt/greenengineering/>
- 2) Allen, David, Shonnard, David, Green Engineering: Environmentally Conscious Design of Chemical Processes, Prentice Hall, Upper Saddle River, NJ, 2002
- 3) Burgess, A.A., Brennan, D.J. Application of Life cycle assessment to chemical processes, *Chemical Engineering Science*, Volume 56, issue 8, April 2001, pages 2589, 2609
- 4) Chevalier, Jacques, Rousseaux, Patrick, Benoit, Valerie, Benadda, Balkacem, Environmental assessment of flue gas cleaning processes of municipal solid waste incinerators by means of the life cycle assessment approach, *Chemical engineering Science*, Volume 58, Issue 10, May 2003, pages 2053-2064
- 5) Kent, James A., *Handbook of Industrial Chemistry and Biotechnology 11th edition: Chapter 2: Green Engineering – Integration of Green Chemistry, Pollution Prevention, and Risk Based Considerations*, Springer, 2006
- 6) Azapagic, Adisa, Life cycle assessment and its application to process selection, design, and optimization, *Chemical Engineering Journal*, Volume 73, Issue 1, April 1999, pages 1-21
- 7) Beaver, Earl R. Calculating Metrics for Acetic acid production, *AIChE Sustainability Engineering Conference Proceedings*, Austin, Texas, November 2004, pages 7-15
- 8) Allen, David, Shonnard, David, Green Engineering: Environmentally Conscious Design of Chemical Processes, Prentice Hall, Upper Saddle River, NJ, 2002
- 9) Ukidwe, Nandan W. Bakshi, Bhavik R., A Multiscale Bayesian Framework for Designing Efficient and Sustainable Industrial Systems, *AIChE Sustainability Engineering Conference Proceedings*, Austin, Texas, November 2004, pages 179-187
- 10) Ekvall, Tomas, Finnveden, Goran, Allocation in ISO 14041 – a critical review, *Journal of Cleaner Production*, Volume 9, Issue 3, June 2001, pages 197-208
- 11) Bakshi, Bhavik R., Hau, Jorge L., A Multiscale and Multiobjective Approach for Environmentally Conscious Process Retrofitting, *AIChE Sustainability Engineering Conference Proceedings*, Austin, Texas, November 2004, pages 229-235
- 12) Suh, Sangwon, Lenzen, Manfred, Treloar, Graham J., Hondom Hiroki, Harvath, Arpad, Huppel, Gjalte, Joliet, Olivier, Klann, Uwe, Krewitt, Wolfram, Morguchi, Yuichi, Munksgaard, Jesper, Norris, Gregory, System Boundary Selection in Life-Cycle Inventories Using Hybrid Approaches, *Environmental Science & Technology*, volume 38, Issue 3, 2004, pages 657-663
- 13) <http://www.eiolca.net/index.html>, developed by Green Design Initiative, Carnegie Mellon University, last logon March 21, 2005
- 14) Lei, Liu, Zhifeng, Liu, Fung, Richard, “The Most of the Most”-Study of a New LCA Method, *IEEE proceedings*, 2003, pages 177-182

- 
- 15) Bakshi, Bhavik R., Hau, Jorge L, Using Exergy Analysis for Improving Life Cycle Inventory Databases, AIChE Sustainability Engineering Conference Proceedings, Austin, Texas, November 2004, pages 131-134
- 16) Cornelissen, Rene L., Hirs, Gerard G., The value of the exergetic life cycle assessment besides the LCA, *Energy Conversion and Management*, volume 43, 2002, pages 1417-1424
- 17) Becalli, Giorgio, Cellura, Maurizio, Mistretta, Marina, New exergy criterion in the “multi-criteria” context: a life cycle assessment of two plaster products, *Energy Conservation and Management*, Volume 44, 2003, pages 2831-2838
- 18) Ukidwe, Nandan W. Bakshi, Bhavik R. Economic versus natural Capital Flows in Industrial Supply Networks- Implications to Sustainability, AIChE Sustainability Engineering Conference Proceedings, Austin, Texas, November 2004, pages 145-153
- 19) Jimenez-Gonzalez, Concepcion, Kim, Seungdo, Overcash, Micheal R., Methodology for Developing Gate-to-Gate Life Cycle Inventory Information, *International Journal of Life Cycle Assessment*, Volume 5, 2000, pages 153- 159
- 20) Jimenez-Gonzalez, Concepcion, Overcash, Micheal R., Curzons, Alan, Waste treatment modules- a partial life cycle inventory, *Journal of Chemical Technology and Biotechnology*, Volume 76, 2001, pages 707-716
- 21) Jin, Xun, High, Karen A. Comparative vs. Absolute Performance Assessment with Environmental Sustainability Metrics, AIChE Sustainability Engineering Conference Proceedings, Austin, Texas, November 2004, pages 27-35
- 22) Shonnard, David R., Kichere, Andreas, Saling, Peter, Industrial Applications Using BASF Eco-Efficiency Analysis: Perspectives on Green Engineering Principles Engineering Design for End-of-Life Electronics Resource Recovery, *Environmental Science and Technology*, 2003, issue 37, pages 5340-5348
- 23) Mueller, Jutta, Griese, Hansjoerg, Schischke, Karsten, Stobbe, Irina, Norris, Gregory A., Udo de Haes, Helias A., Life Cycle Thinking for Green Electronics: Basics in EcoDesign and the UNEP/SETAC Life Cycle Initiative, *International IEEE Conference on Asian Green Electronics*, 2004, pages 193-199
- 24) Widiyanto, Anugerah, Kato, Seizo, Maruyama, Naoki, Kojima, Yoshimasa, Environmental Impact of Fossil Fuel Fired Co-Generation Plants Using a Numerically Standardized LCA Scheme, *Journal of Energy and Resource Technology*, 2003, volume 125, pages 9- 16
- 25) Goralczyk, Malgorzata, Life-cycle assessment in the renewable energy sector, *Applied Energy* Volume 75, 2003, pages 205-211
- 26) Schleisner, L., Life cycle assessment of a wind farm and related externalities, *Renewable Energy*, volume 20, 2000, pages 279-288
- 27) Koroneos, C., Dompros, A., Roumbas, G., Moussiopoulos, N., Life cycle assessment of hydrogen fuel production processes, *International Journal of Hydrogen Energy*, Volume 29, 2004, pages 1443-1450
- 28) Eagan, Patrick, Weinberg, Laurence, Application of Analytic Hierarchy Process Techniques to Streamlined Life-Cycle Analysis of Two Anodizing Processes, *Environmental Science and Technology*, 1999, volume 33, pages 1495-1500
- 29) Tan, Reginald, B.H., Khoo, Hsien, H., An LCA study of a primary aluminum supply chain, *Journal of Cleaner Production*, Volume 13, Issue 6, May 2005, pages 607-618

- 
- 30) Jodicke, Gerald, Zenklusen, Oliver, Weidenhaupt, Andre, Hungerbuhler, Konrad, Developing environmentally sound processes in the chemical industry: a case study on pharmaceutical intermediates, *Journal of Cleaner Production*, Volume 7, Issue 2, March 1999, pages 159-166
- 31) Raluy, R.G., Serra, L., uche, J., Valero, A., Life-cycle of desalination technologies integrated with energy production systems, *Desalination*, Volume 167, 2004, pages 445-458
- 32) Papasavva, Stella, Kia, Sheila, Claya, Jospeh, Gunther, Raymond, Characterization of automotive paints: an environmental impact analysis, *Progress In Organic Coatings*, Volume 43, 2001, pages 193-206
- 33) Dobson, Ian D., Life cycle assessment for painting processes, putting the VOC issue in perspective, *Progress In Organic Coatings*, Volume 27, 2001, pages 55-58
- 34) Lopes, E., Dias, A., Arroja, L., Capela, I., Pereira, F., Application of life cycle assessment to the Portuguese pulp and paper industry, *Journal of Cleaner Production*, Volume 11, 2003, pages 51-59
- 35) Rios, Pedro, Stuart, Julie Ann, Grant, Ed, Plastics Disassembly versus Bulk Recycling: Engineering Design for End-of-Life Electronics Resource Recovery, *Environmental Science and Technology*, 2003, issue 37, pages 5463-5470
- 36) Song, Hyun-Seob, Hyun, Jae Chun, A study on the comparison of the various waste management scenarios for Pet bottles using life-cycle assessment (LCA) methodology, *Resources, Conservation, and Recycling*, Volume 27, 1999, pages 267-284
- 37) Ekvall, Tomas, Key Methodological issues for life cycle inventory analysis of paper recycling, *Journal of Cleaner production*, Issue 7, 1999, pages 281-294
- 38) Shiojiri, K., Yanagisawa, Y., Fujii, M., Kiyono, F., Yamasaki, A., A Life Cycle Impact Assessment Study on Sulfur Hexafluoride as a Gas Insulator, *AIChE Sustainability Engineering Conference Proceedings*, Austin, Texas, November 2004, pages 135-143
- 39) Furuholt, Edgar, Life Cycle assessment of gasoline and diesel, *Resources, Conservation, and Recycling*, Volume 14, 1995, pages 251-263
- 40) MacLean, Heather L., Lave, Lester B., Life Cycle Assessment of Automobile/Fuel Options, *Environmental Science and Technology*, Volume 37, 2003, pages 5445-5452
- 41) Amatayakul, Wathanyu, Ramnas, Olle, Life cycle assessment of a catalytic converter for passenger cars, *Journal of Cleaner Production*, Volume 9, 2001, pages 395-403
- 42) Baratto, Francesco, Diwekar, Urmila M. Life cycle of fuel cell-based APUs, *Journal of Power Sources*, Volume 139, 2005, pages 188-196
- 43) Cederberg, Christel, Mattson, Berit, Life cycle assessment of milk production – a comparison of conventional and organic farming, *Journal of Cleaner Production*, Volume 8, 2000, pages 49-60
- 44) Zabaniotou, A, Kassidi, E., Life cycle assessment applied to egg packaging made from polystyrene and recycled paper, *Journal of Cleaner Production*, Volume 11, 2003, pages 549-559
- 45) Bohlmann, Gregory M., Biodegradable Packaging Life-Cycle Assessment, *Environmental Progress*, Volume 23, Issue 4, pages 342-346

- 
- 46) Anderson, Karin, Ohlsson, Thomas, Olsson, Par, Screening life cycle assessment of tomato ketchup: a case study, *Journal of Cleaner production*, volume 6, 1998, pages 277-288
- 47) Jimenez-Gonzalez, Concepcion, Curzons, Alan D., Constable, David J.C., Cunningham, Virginia L. Cradle-To-Gate Life Cycle Inventory and Assessment of Pharmaceutical Compounds, *International Journal of Life Cycle Assessment*, Volume 9, 2004, pages 114- 121
- 48) Jimenez-Gonzalez, Concepcion, Overcash, Micheal R. Energy Optimization during early drug development and the relationship with environmental burdens, *Journal of Chemical Technology and Biotechnology*, Volume 75, 2000, pages 983-990
- 49) Jimenez-Gonzalez, Concepcion, Life Cycle Assessment in Pharmaceutical Applications, PhD thesis, North Carolina State University, Department of Chemical Engineering, 2000
- 50) Chenier, Philip J. Survey of Industrial Chemistry, 3rd edition, Kluwer academic/plenum publishers, 2002, New York
- 51) U.S. Departemnt of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Guidance for Industry Q3C-Tables and Lists, November 2003, Revision 1
- 52) Kroschwitz ,Jacqueline I. Kirk-Othmer Encyclopedia of Chemical Technology, 2nd edition, Wiley, New York, 1991
- 53) Belter, Paul A. Cussler, E.L., Bioseparations: Downstream Processing For Biotechnology, John Wiley & Sons, 1988
- 54) Mai, Jing-Chen, et al. US patent 6790984, September 14th 2004
- 55) Quershi, Nasib, Dien, Bruce, Nichols, Nancy, Liu, Siging, Hughes, Stephen, Iten, Loren, Saha, Badal, Cotto, Michael, Continuous Production of Ethanol in High Productivity Bioreactors Using Genetically Engineered Escherichia Coli Fbr5: Membrane and Fixed Cell Reactors, American Institute Of Chemical Engineers Annual Meeting, November 2004
- 56) Jimenez-Gonzalez, Concepcion, Constable, David J.C., Curzons. Alan D. Cunningham, Virginia L., Developing GSK's Green Technology Guidance: Methodology for Case-Scenario Comparison of Technologies, *Journal of Clean Technology and Environmental Policy*, Volume 4, 2002
- 57) AIChE sustainability metrics, <http://www.aiche.org/cwrt/projects/sustain.htm>
- 58) Tallis, Bill, et al. Sustainable Development Progress Metrics, <http://www.icheme.org>
- 59 ) Schwarz, Jenaette, Beloff, Beth, Beaver, Earl, Use of Sustainability Metrics to Guide Decision-Making, *Chemical Engineering Progress*, July 2002
- 60) Cue, Berkeley W. Roch Colorado Corporation, "Green Chemistry in the Pharmaceutical Industry: Accomplishments and Opportunities"
- 61) Taylor, Stephen, Incorporation of the BMS Process Greenness Scorecard into the Commercial S-88 Recipe Base Software Applications.
- 62) <https://www1.fishersci.com/index.jsp>

- 
- 63) Crowl, Daniel A. Louvar, Joseph F., Chemical Process Safety, 2nd edition, Prentice Hall, 2002
- 64) Jimenez-Gonzalez, Concepcion, Curzons, Alan D., Constable, David J.C., Cunningham, Virginia L. Cradle-To-Gate Life Cycle Inventory and Assessment of Pharmaceutical Compounds, International Journal of Life Cycle Assessment, Volume 9, 2004, pages 114- 121
- 65) Endo, Akira, et al. US patent 4049495, September 20th 1976
- 66) Terahara, Akira, Tanaka, Minoru, ML-236B Derivatives and their preparation., US patent 4346227, August 24,1982
- 67) Terahara, Akira, Tanaka, Minoru, ML-236B Derivatives and their preparation., US patent 441629, October 18, 1983
- 68) Terahara, Akira, Tanaka, Minoru, Process for Preparing 3-hydroxy-ML-236B Derivatives known as m-4 and M-4', US patent 4537859, August 27,1985
- 69) Baker, Richard M., Membrane Technology and Application, 2nd edition, John Wiley, 2004
- 70) Chenier, Philip J. Survey of Industrial Chemistry, 3rd edition, Kluwer academic/plenum publishers, 2002, New York
- 71) Bhine, Rajeev, Cai, Zhen-Wei, Qian, Ligang, Barbosa, Stephanie, Novel Inhibitors of Kinases, WO2004/009784 A2, 2003
- 72) <http://www.jtbaker.com>
- 73) EPISUITE software package version 3.12, Developed by EPA's Office of Pollution Prevention, 2000
- 74) SOLV-DB, Developed by the National Center for Manufacturing Science, Funded by the EPA and DOE
- 75) Green Chemistry Expert System, Version 9.0, Developed by the Environmental Protection Agency
- 76) Solvent Alternative Guide (SAGE ) <http://clean.rti.org/>
- 77) Curzons, A.D., Constable D.C. Cunningham, V.L., Solvent selection guide: a guide to the integration of environmental, health and safety criteria into the selection of solvents, Clean products and Processes, Volume I, 1991, pages 82-90
- 78) Gani, Rafiqul, Jimenez-Gonzalez, Concepcion, Constable, David J., Method for selection of solvents for promotion of organic reactions, Computers and Chemical Engineering, Volume 29, 2005, pages 1661-1676