Green Manufacturing in the Medical Device Industry: A Case Study

by

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Dedication and Acknowledgements

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I. Introduction

I.1 Introduction to Med Dev and Motivations for the Thesis

Med Dev (name changed to protect confidentiality), is a medical device start-up using tissue engineering and drug delivery techniques to help combat the negative effects associated with secondary injury. Med Dev's first generation technology is a polymer scaffold that will be inserted into the injury site immediately post injury during a routine procedure. The scaffold prevents secondary injury (bruising and scarring) formation by filling the void space left by the injury, promoting cell growth over deleterious apoptosis (cell death), and slowly degrading away over the course of approximately one month. Med Dev's second generation technology is a photopolymerizable hydrogel which would function identically to the first generation, except that it would be injected into the injury rather than surgically inserted.

Med Dev's first and second generation technologies, differ not only in their method of administration, but also in their manufacture. Commercially available polymers are mechanically processed for scaffold manufacture, whereas Med Dev must synthesize their own polymers for hydrogel manufacture. Polymer synthesis requires vast quantities of often toxic solvents to solubilize and later extract the polymer. In the first generation technology toxic solvent responsibilities lie with Med Dev's suppliers, whereas in the second generation technology Med Dev is directly responsible for their toxic solvents use. This is not to say Med Dev should not be aware of their supplier's use of toxic solvents when they are producing polymers for Med Dev's end-use, but rather to point out that Med Dev is more directly responsible for toxic solvent use when they produce their own polymers.

In January, as Med Dev's director of operations I applied for a grant which required that I detail how Med Dev intended to build a green manufacturing facility. Understanding all the toxic solvents involved in a polymer synthesis, I thought while building a green manufacturing facility was a positive step toward becoming more environmentally sustainable, why stop there, why not incorporate green thinking into polymer synthesis process design. A thesis was born.

I.2 Intro to Green Chemistry/Manufacturing

The US EPA defines green chemistry as: "...the design of chemical products and processes that reduce or eliminate the use or generation of hazardous substances. Green chemistry applies across the life cycle, including the design, manufacture, and use of a chemical product." [i] Green chemistry is essentially a pollution prevention methodology, resulting in resource conservation, waste reduction, and enhanced product safety. Companies are beginning to realize that pursuing green chemistry is not only good for the environment, but also for their bottom line; they are becoming increasingly aware that continued competitiveness in the allied chemicals industry actually requires the implementation of green chemistry principles. Paul Anastas and John Warner published what have become the central tenets of green chemistry in their 1998 book entitled "Green Chemistry: Theory and Practice"[ii]; The 12 Principles of Green Chemistry include:

12 Principles of Green Chemistry

1. **Prevent waste:** Design chemical syntheses to prevent waste, leaving no waste to treat or clean up.
2. **Design safer chemicals and products:** Design chemical products to be fully effective, yet have little or no toxicity.
3. **Design less hazardous chemical syntheses:** Design syntheses to use and generate substances with little or no toxicity to humans and the environment.
4. **Use renewable feedstocks:** Use raw materials and feedstocks that are renewable rather than depleting. Renewable feedstocks are often made from agricultural products or are the wastes of other processes; depleting feedstocks are made from fossil fuels (petroleum, natural gas, or coal) or are mined.
5. **Use catalysts, not stoichiometric reagents:** Minimize waste by using catalytic reactions. Catalysts are used in small amounts and can carry out a single reaction many times. They are preferable to stoichiometric reagents, which are used in excess and work only once.
6. **Avoid chemical derivatives:** Avoid using blocking or protecting groups or any temporary modifications if possible. Derivatives use additional reagents and generate waste.
7. **Maximize atom economy:** Design syntheses so that the final product contains the maximum proportion of the starting materials. There should be few, if any, wasted atoms.
8. **Use safer solvents and reaction conditions:** Avoid using solvents, separation agents, or other auxiliary chemicals. If these chemicals are necessary, use innocuous chemicals.
9. **Increase energy efficiency:** Run chemical reactions at ambient temperature and pressure whenever possible.
10. **Design chemicals and products to degrade after use:** Design chemical products to break down to innocuous substances after use so that they do not accumulate in the environment.
11. **Analyze in real time to prevent pollution:** Include in-process real-time monitoring and control during syntheses to minimize or eliminate the formation of byproducts.
12. **Minimize the potential for accidents:** Design chemicals and their forms (solid, liquid, or gas) to minimize the potential for chemical accidents including explosions, fires, and releases to the environment.

Figure 1: 12 Principles of Green Chemistry, reproduced from the EPA[iii]

Historically, limits placed on exposure have been the first line of defense against toxic substances, green chemistry suggests further minimizing risk by eliminating the use of these substances altogether wherever possible. The twelve principles of green chemistry speak to waste reduction, resource conservation, increased reaction and energy efficiencies, the use of safer alternative solvents, and product stewardship.

Design for the environment is a holistic methodology in which green chemistry is considered at each stage of a product's life cycle (supply chain, research and development, manufacturing, and end use) in a quest to minimize the product's impact on the environment. Green manufacturing, in particular, refers to manufacturing processes that have benefitted from the implementation of design for the environment and are as a consequence more efficient, safe, and environmentally friendly.

The allied chemicals industry has long suffered a very unfavorable reputation, today it ranks very low in the public's perception, narrowly outranking the nuclear power and tobacco industries at the bottom of the scale according to attitude and perception studies.[iv] This perception is not without merit, as the allied chemicals industry has been at the center of some of the twentieth century's most catastrophic manmade disasters, most notably the Bhopal disaster in Bhopal, India and the Love Canal in Niagra Falls, New York.

The Bhopal disaster occurred at a Union Carbide carbaryl (trade named: Sevin) pesticide plant on December 3, 1984, when large amounts of water seeped into a tank containing 42 metric tons of methyl isocynate gas. The methyl isocynate and water reacted, increasing the temperature within the tank to over 200°C and causing the pressure to skyrocket. The tank, not designed to withstand such high temperatures and pressures, began emergency venting thereby releasing massive quantities of the toxic gas to the environment. The water-methyl isocynate reaction was further catalyzed by the iron in the corroding non-stainless steel pipelines designed to vent the tank. In the end, approximately 500,000 people in Bhopal were exposed to the poisonous methyl isocynate gas (as well as: phosgene, hydrogen cyanide, carbon monoxide, hydrogen chloride, nitrous oxides, and monomethyl amines). Of the 500,000 exposed, approximately 8,000 people died in the two weeks immediately following the incident, and another 8,000 people are thought to have died since due to gas related illnesses, in what has become known as the "world's worst industrial disaster".[v] Post mortem investigations of the incident have revealed that poor maintenance, poor design, storage of methyl isocynate in one large tank rather than several small tanks, and economic pressures to use methyl isocynate over a safer, though more expensive, alternative all precipitated the incident. If green chemistry principles and safety had been considered in the design of the Union Carbide pesticide plant, the disaster could have been averted.

The Love Canal was named after the developer William T Love, who, in the early 1890's envisioned building a canal to connect the two levels of the Niagra River. Love's plan to build the canal never materialized due to financial and preservationist pressures, rather than deter the developer however, it simply returned him to the drawing board where he devised a plan for a shipping lane that would reach Lake Ontario without passing Niagra Falls. The developer was again plagued by financing troubles and had to abandon his project when the canal was only 1 mile long (50 ft wide and 10 to 40 ft deep). The one mile stretch of canal gradually filled with water, then in the 1920s the municipality of Niagra Falls converted it to a dumping site. In the 1940s Hooker Electrochemical Company (Hooker Chemical Company) began searching for a dump site for its toxic chemical waste and was granted permission to dump in the Love Canal by the Niagra Power and Development Company. Hooker drained the canal, lined it with clay and commenced placing 55 gallon drums of hazardous chemical waste at the site, a practice it continued until 1952, when the site, containing 21,000 tons of chemicals (caustics, alkalines, fatty acids, chloronated hydrocarbons), was covered in dirt. In 1953, the Niagra Falls school board tried to purchase the Love Canal site to construct a school, Hooker Chemical Company warned the school board against the purchase, but they persisted and the land was developed into a school; though its original location was moved by 85 ft to avoid being directly atop the landfill. In 1957, development of the areas directly adjacent to the landfill commenced, the eventual inhabitants of these developments were unaware of the canals history however. Finally, in 1977, the Love Canal landfill's protective clay lining was breached by the construction of the La Salle

Expressway and pools of oil and colored liquids began appearing in people's back yards. Residents complained of smelling strange odors and witnessing substances surface in their back yards that killed off vegetation. Perhaps most tragic of all Niagra Falls had an inordinately high number of unexplained illnesses, miscarriages, and mentally retarded children. In fact 56% of children born in Niagra Falls between 1974 and 1978 had birth defects and 33% of the city's residents had chromosomal damage compared to 1 % of the general populus.[vi] Benzene along with eleven other known or suspected carcinogens have been found at the site of what has become known as: "one of the most appalling environmental tragedies in American history"[vii] and one of the major impetuses behind the Comprehensive Environmental Response Compensation and Liability Act (CERCLA) which holds pollution generators accountable for the clean-up of their waste sites. The Love Canal tragedy also could have been prevented had green chemistry principles been used at Hooker Chemical Company, certainly waste minimization and solvent substitution could have ameliorated the environmental burdens of Hooker's landfill.

Designing for the environment by considering green chemistry at every step along a product's lifecycle, particularly during manufacturing, is a methodology to ensure that such travesties as the Bhopal disaster and the Love Canal are never repeated. In the Bhopal instance, had safer alternative chemicals or processes been used and had more care been taken to prevent accidents from happening, the methyl isocynate tank would never have existed or if it had proper safety precautions surrounding it would have prevented it from venting. Meanwhile, the Love Canal case, highlights the importance of pollution prevention, had Hooker Chemical Company reduced the amount and toxicity (through substitution) of waste they generated the effects on the Niagra Falls community would not have been so vast. Green chemistry can help the allied chemicals industry regain its lost appeal, by preventing future accidents and maintaining the health and safety of its employees.

II Why is Green Chemistry Important at this Stage of Med Dev's Development?

Implicit in designing for the environment is a certain robustness; the process is designed right the first time, in full anticipation of future legislation that might ban the use of a particular solvent or of cost efficiencies that could be gained by using an alternative reaction route. Designing for the environment not only allows companies to pre-empt legislation and recognize cost savings, but it also demarcates them as environmental stewards, helping them gain all the associated accolades with such a distinction.

Designing for the environment is particularly pertinent in the strictly regulated pharmaceutical industry, where a robust process, that won't suffer from supply chain disruptions or changes in production methods, is essential. Late stage changes in a pharmaceutical production process can be time consuming and costly, even without considering the effects of production stoppages:

"It is especially important for the pharmaceutical companies to explore alternative processes early on, because once a drug and its associated manufacturing process receives FDA approval, it may be cost prohibitive to make changes and risk having to repeat the regulatory review process."-Vicki Glaser[viii]

By designing for the environment a pharmaceutical company mitigates the risk of having to repeat its regulatory review process, by avoiding toxic substances that might be subject to bans and minimizing their waste profiles as much as possible.

Today more than ever before, attention is being focused on the environmental performance of companies and while this performance remains largely voluntary, the future will probably hold much stricter mandates. Strict mandates on chemical production are already beginning to appear in the form of legislation and public pressure; the European Union's REACH legislation and Massachusetts Toxics Use Reduction Act are two examples of stiffening chemicals legislation that will be discussed in this thesis.

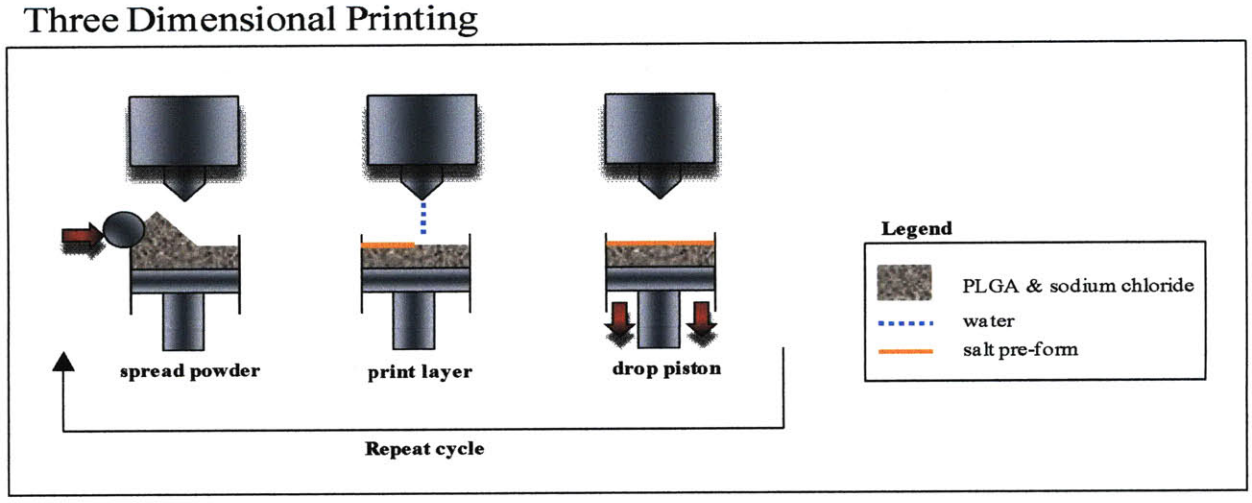
Large Pharmaceutical companies have realized the importance of environmental stewardship and have begun to track their environmental metrics in accordance with the global reporting initiatives (GRI) G3 guidelines[ix], "the world's most widely used sustainability reporting framework."[x] Pharmaceutical companies have not stopped at merely tracking their environmental metrics (things like green house gas emissions, volatile organic compound emissions, hazardous waste generation, and water use), rather they are actively pursuing green chemistry campaigns which will be outlined in the body of this thesis. As a signal of this commitment many of the top pharmaceutical companies (Merck, Pfizer, Astra Zeneca, Glaxo Smith Kline, Schering Plough, Johnson & Johnson, Lilly, and Boehringer Ingelheim) belong to the American Chemical Society's Green Chemistry Institute's Pharmaceutical Roundtable[xi]. Pharmaceutical companys' assessment of their environmental performance is not limited to activities that take place within their confines, they also assess the performance of their suppliers and are making strides to ensure that pharmaceuticals won't accumulate in the environment after their end use (in an initiative called pharmaceuticals in the environment). The environmental initiatives many pharmaceutical companies have taken have helped them decrease production costs, but have also garnered them recognition through various green chemistry awards and grants, the most notable awards are the EPA's Presidential Green Chemistry Challenge Awards[xii] and the IChemE Sustainable Technology Awards[xiii]. Most pharmaceutical companies view green chemistry as one of the major requirements for maintaining competitive advantage; since green chemistry enables them to realize cost savings while avoiding possible future supply chain disruptions that could occur due to more stringent legislation.

Med Dev is a burgeoning start-up about to design its first manufacturing facility that will launch it into human clinical trials. Against a backdrop of increasingly stringent chemical legislation and a pharmaceutical industry progressively more aware of their environmental performance, that of their suppliers and their acquisitions, it is logical that Med Dev would investigate greening their manufacturing processes. This thesis aims to lay out the arguments for adopting green chemistry early, designing for the environment to stave off the possibility of costly process changes that might be required by stiffer environmental legislation in the future. Med Dev's manufacturing process and its associated environmental issues are described, followed by a discussion of current and pending legislation and the impact these laws might have on Med Dev, then a summary of large pharmaceutical company's environmental initiatives, and finally a green chemistry approach to Med Dev's manufacturing process is suggested.

II.1 Med Dev's First Generation Technology

Med Dev's first generation product will be a three dimensionally printed scaffold made of poly(lactic-co-glycolic acid) (PLGA). Three dimensional printing is an adaptation of ink jet printing where a liquid 'binder' is printed onto a powder bed rather than ink onto paper. This binder is printed so that it dissolves and re-solidifies specific areas of powder, in order to construct the desired shape. This

process is iterated in a layer-by-layer fashion until the three-dimensional structure is formed, upon which the excess unbound powder is carefully removed.



For Med Devs' purposes, a three dimensional printer will be used to print an aqueous binder (water) onto a powder bed of sodium chloride (NaCl) and PLGA. NaCl is used to construct the mold for the PLGA scaffold. It is fully removed once it has performed its function, leaving only the scaffold with a precise micro-architecture and customized macro-structural shape tailored to patient requirements.

II.1.1 Materials and Packaging:

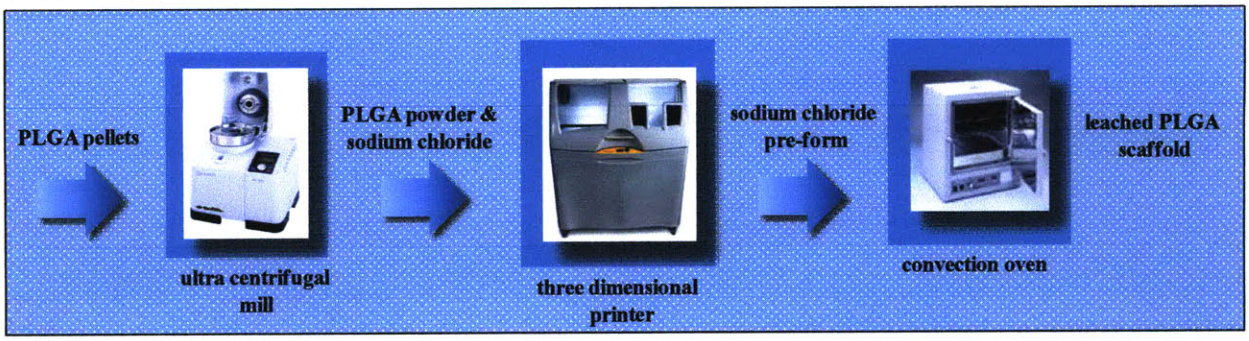
PLGA used to construct the scaffold is sourced from Boehringer Ingelheim Pharma GMBH and CO. KG, Ingelheim, Germany. The particular lactide to glycolide ratio used is 50:50 and is marketed as RESOMER RG504 or RG504H. This formulation of PLGA has an inherent viscosity of 0.55-0.75, a glass transition temperature of 45-50°C, and an approximate resorption time of 1-2 months. The fabricated scaffolds will be placed in eppendorf tubes, sealed, and then placed in Tyvek pouches that are sealed with a heat bar sealer prior to exposure to the electron beam sterilization device.

II.1.2 Process:

PLGA, commercially available in pellet form only, must be milled into a powder for use with three dimensional printing. Pellets are frozen with liquid nitrogen and then milled with an ultra centrifugal mill, before they are sieved through screens rated at the appropriate particle size. The PLGA powder is then blended with the appropriate amount of salt for use in three dimensional printing.

The aqueous binder binds the sodium chloride, forming a printed pattern; whilst entrapping surrounding water-insoluble PLGA particles. Once the three-dimensional scaffold is completed, it is moved to a convection oven and heated to 80 °C (the glass transition temperature of PLGA) for 1 hour to melt the PLGA particles within the salt pre-form. Melted PLGA fills the voids in the salt structure. Upon cooling, the PLGA solidifies, and then the scaffold is placed in a distilled-deionized water bath to leach out the sodium chloride.

PLGA Scaffold Fabrication Process



Once the scaffold has formed and solidified, electron beam sterilization (e-beam sterilization) is used to sterilize it. During this sterilization process, a linear accelerator generates electrons, which then excite the electrons within the scaffold producing "secondary energetic species" which include: electrons, ion pairs, and free radicals. These "secondary energetic species" disrupt the DNA of contaminating microorganisms and inactivate them affecting full 10^6 bioburden removal as required by the FDA[xiv]. The scaffolds will be packaged in e-beam compatible, sterile tyvek packaging that will enable them to be processed and stored prior to emergency room delivery, the appropriate tyvek packaging for this task will be evaluated. Electron beam sterilization represents the quickest, most efficient, least damaging method of sterilizing Med Dev's PLGA scaffold.

II.1.3 Environmental Implications of the first generation technology

Med Dev's first generation technology is environmentally innocuous, outside of the use of liquid nitrogen for freezing the PLGA pellets prior to pulverizing them. The environmental concerns lie with Med Dev's suppliers and echo those outlined in the discussion of Med Dev's second generation technology. According to an article in *Polymer Degradation and Stability* by Dieter Bendix[xv] describing Boehringer Ingelheim's synthesis of polylactide and its copolymers (poly(lactic-co-glycolic acid)) for medical applications the process follows these steps:

1.) Lactic acid undergoes direct condensation to form oligo(lactate)
2.) A thermal unzipping reaction with a thermolysis catalyst is performed to yield lactide, a cyclic diester of lactic acid
3.) The cyclic diesters are then re-crystallized from different solvents to ensure that no oligomers contaminate the monomer prior to final polymerization.
4.) Ring opening polymerization of the purified cyclic monomers is performed in the presence of the catalyst tin octoate
5.) Extraction or dissolution/precipitation is finally performed to remove any residual monomers.

The solvents used in recrystalization, extraction, or dissolution and precipitation of the polymer include: methylene chloride, n-hexane, and diethyl ether. Each of these solvents is hazardous, methylene chloride and n-hexane are both listed in the US Environmental Protection Agency's (EPA) Toxics Release Inventory (TRI) chemical list, while diethyl ether is extremely flammable. Thus while Med Dev's

first generation technology does not have a primary environmental impact, it has a secondary one, which may be ameliorated through co-operation with its suppliers.

II.2 Med Dev's Second Generation Technology

Med Dev's second generation product will be a photopolymerizable hydrogel. The hydrogel will be injected into the injury site during a typical surgery and polymerized in situ using a curing light (Curing Light 2500, 3M Dental Products).[xvi] A hydrogel is comprised of a macromer and a photoinitiator. The macromer, PEG-co-poly (lactic acid)-diacrylate, has three structural domains: a water soluble central polymer (PEG), two hydrolytically sensitive oligomeric extenders (ring opened lactide), and two photopolymerizable termini (acrylate groups). Piantino et al[i] adapted a two step PEG-co-poly(alpha hydroxy acid)-diacrylate macromer synthesis technique from Sawhney et al[xvii] which involves : 1.) copolymerizing poly(ethylene glycol) with an alpha-hydroxy acid and 2.) functionalizing this copolymer with acrylate groups to facilitate photopolymerization. Eosin, a photoinitiator, is added to the final macromer solution and a curing light is used to initiate polymerization. The method discussed herein is that developed by Piantino et al[i] with slight variations.

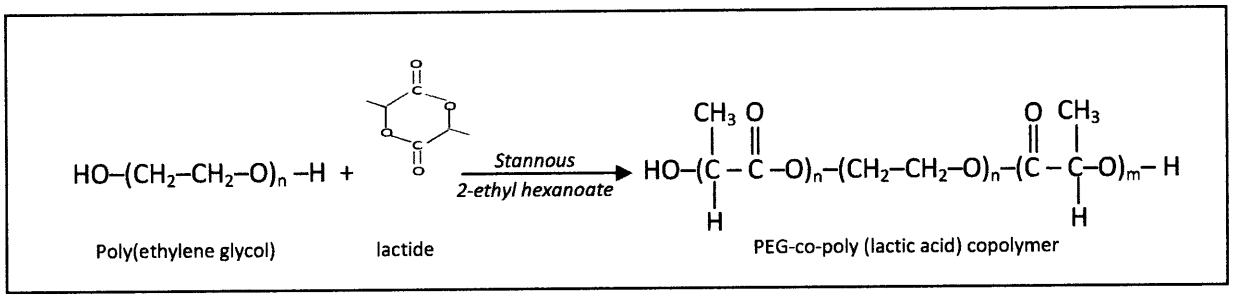


Figure 2: Ring Opening Polymerization. Synthesis of PEG-co-poly(lactic acid) copolymer from Poly(ethylene glycol) and lactide.

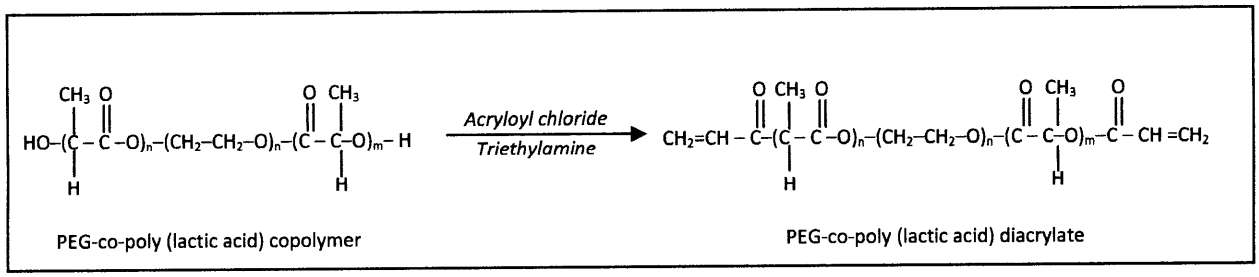


Figure 3: Acrylation. Synthesis of PEG-co-poly (lactic acid) diacrylate from PEG-co-poly (lactic acid) copolymer.

II.2.1 Materials and Packaging:

The ring opening polymerization of D,L-lactide with the hydroxyl end groups of poly(ethylene glycol) is conducted using D,L-lactide and PEG (MW~4000 Da) from Polysciences. PEG was chosen as the central polymer based on the facts that its nontoxic, its water soluble, it doesn't illicit an immune response, and it is readily cleared from the body. D,L-lactide was chosen as an extender for the central PEG molecule because it has very well understood degradation characteristics and its degradation

products (lactate) occur naturally and are easily metabolized. The transesterification catalyst for this ring opening reaction, stannous 2-ethyl hexanoate, is sourced from Sigma. The acrylation step is conducted using acryloyl chloride and triethylamine from Sigma. Acrylates were chosen as the end groups for their ability to undergo rapid photopolymerization with the appropriate initiator (eosin). The degradation products of acrylates, oligo(acrylic acid) with a degree of polymerization of 2 or 3, are relatively innocuous as they are both water soluble and nontoxic. For the photopolymerization step, both eosin and PBS were purchase from Aldrich. All reagents used for dissolution or precipitation (notably: diethyl ether, methylene chloride, and hexane) are reagent grade and were purchased from Aldrich. A curing light (Curing Light 2500) is used to initiate polymerization and is sourced from 3M Dental Products.

II.2.2 Process:

1. ***Synthesis of PEG-co-poly(lactic acid) copolymers***

Dry PEG 4k, D,L-lactide, and stannous 2-ethyl hexanoate are all charged into a stainless steel, pressurizable/vacuum compatible jacketed reactor under nitrogen. The jacketed reactor is used to tightly control reaction conditions as the reaction mixture is stirred under vacuum at 200°C for four hours and 160°C for 2 hours, prior to being cooled to room temperature. The resultant polymer is dissolved in methylene chloride, then precipitated with diethyl ether before being filtered through a large Bruckner funnel. Once filtration is complete, the filter cake is removed from the funnel and placed in a vacuum oven to dry.

2. ***Synthesis of PEG-co-poly(lactic acid) diacrylate macromers***

Once the PEG-co-poly(lactic acid) copolymer is dry, it is dissolved in methylene chloride and placed in a stainless steel jacketed reactor. Then triethylamine and acryloyl chloride dissolved in methylene chloride are added to the copolymer solution and the reaction is allowed to proceed for 36 hours. Once the reaction is complete, the macromer solution is diafiltered to remove triethanolamine hydrochloride. Then the macromer is poured into a large excess of diethyl ether to initiate precipitation. The resultant solution (and precipitate) are filtered through a large Bruckner funnel and the resultant solids are redissolved in methylene chloride to be precipitated again with hexane. The hexane precipitants are filtered through a Bruckner funnel and allowed to vacuum dry at 70°C, prior to being dissolved in phosphate buffered saline (PBS). The PBS-macromer solution is then diafiltered to remove all possible contaminants. At the close of the diafiltration, the macromer solution is concentrated, frozen, and then lyophilized. The lyophilized product can be reconstituted in PBS and can be investigated for purity using proton NMR, Infrared spectrophotometry, and a gas chromatograph (each of which will detect excess reagents/solvents that were not removed by the purification procedures). Once the purity of the macromer is established it can be combined with the photoinitiator, eosin (0.02%) and triethanolamine, then the entire hydrogel is filtered through a 0.2 μm filter to sterilize it for use. The solution will not polymerize unless the photoinitiator is activated with the curing light, and this activation process will be carried out in situ.

II.2.3 Environmental Implications of the Second Generation Technology

Med Dev's second generation technology requires the use of vast amounts of toxic solvents such as dichloromethane, hexane, and diethyl ether. Dichloromethane is used to dissolve the polymer prior to its reaction with acryloyl chloride, while hexane and diethyl ether are used to affect polymer extraction once the reaction is complete. Dichloromethane, hexane, and diethyl ether are health as well as a flammability hazards. Extensive solvent use creates risks for employees directly exposed to the solvents, and the environment (both during processing and final disposal). Solvents are relatively costly as well, thus steps should be taken to replace or eliminate toxic solvents wherever possible.

Another area of possible concern in Med Dev's synthesis of its second generation technology, is the use of stannous 2-ethyl hexanoate as a ring opening catalyst, as studies have demonstrated that the catalyst is a possible neurodegenerative agent. Substitution of this catalyst, in addition to the solvents above, should be explored.

III What are the Hazards Associated With the Materials Med Dev Uses?

The hazardous materials Med Dev uses in the synthesis of its second generation technology include: n-hexane, dichloromethane, diethyl ether, and stannous 2-ethylhexanoate. The exact hazards, flammability and possible adverse health effects, associated with each chemical are expanded upon here. Each chemical's use guidelines or limitations are also described.

III.1 n-Hexane

n-Hexane, C_6H_{14}, (CAS No. 110-54-3) is used to effect precipitation of the PEG-co-poly(lactic acid) diacrylate macromers during hydrogel synthesis.

Flammability n-hexane is a colorless liquid with a boiling point of 69°C and a flash point of -23°C. The term flash point is used to describe the temperature above which a flammable liquid can form an ignitable mixture with air, with a flash point of -23°C n-hexane is extremely flammable. Lower and upper explosion limits of a material give the lowest and highest concentration a material required to support its combustion in air, for hexane its lower explosion limit (lel) is 1.2 (% by volume), and its upper explosion limit (uel) is 7.7 (% by volume).

Possible Adverse Health Effects In addition to its flammability, n-hexane is harmful or fatal if swallowed, harmful if inhaled, and causes irritation to the skin, eyes, and respiratory tract. Furthermore, n-hexane may impair fertility, may cause depression of the central nervous system (CNS), and may cause serious health effects after prolonged exposure. The MSDS sheet from J.T. Baker[xviii] elaborates on some of the side effects resulting from inhalation, ingestion, skin and eye contact, as well as chronic exposure. Inhalation of n-hexane may irritate the respiratory tract, while over exposure may result in lightheadness, nausea, headache, blurred vision, and extreme exposure may result in muscle weakness, numbness in the extremities, unconsciousness, and even death. Ingestion may cause abdominal pain and/or nausea, the ingestion case becomes more dire if n-hexane is aspirated into the lungs where it may cause serious lung damage. Skin and eye contact both cause irritation and redness. Chronic skin exposure may de-fat the skin

and result in dermatitis; while chronic inhalation exposure may create peripheral or central nervous system effects.

Use Guidelines and Limitations Lethal dose 50 (LD50) is a term used to describe the dose of a substance at which 50% of exposed specimens will die, the LD50 for oral ingestion by rats is 28,700 mg/kg. Lethal concentration 50 (LC50) is the concentration of a substance at which 50% of exposed specimens will die, the LC50 for inhalation by rats is 48,000 ppm/4hrs.

The permissible exposure limits (PEL) legally limit the chemical substance concentration an employee may be exposed to in the United States and are determined by the Occupational Safety and Health Administration (OSHA). The PEL for n-hexane is given in the regulations (Standards-29CFR 1910.1000 Table Z1) as an 8 hour time weighted average of 500 ppm[xix].

The US Food and Drug Administration (FDA) has issued a Guidance for Industry on permissible residual solvent levels in drug products called "QC3 Impurities: Residual Solvents"[xx]. Manufacturing techniques only effect the partial removal of solvents, residual solvents are those solvents which remain, un-removed, in the final pharmaceutical product. The FDA prescribes a "permitted daily exposure" (PDE) which represents the pharmaceutically acceptable residual solvent intake. In establishing PDEs the FDA groups solvents into 3 classes: class 1 (solvents to be avoided) include "known human carcinogens, strongly suspected human carcinogens, and environmental hazards", class 2 (solvents to be limited) include "nongenotoxic animal carcinogens, possible causative agents of other irreversible toxicities, and solvents suspected of significant but reversible effects", and class 3 (solvents w/low toxic potential) include those with "low toxic effects on man"[x]. Hexane is a class 2 solvent according to the FDA classification and has a PDE of 2.9 mg/day (or, in terms of concentration, 290 ppm). In addition, hexane's use as a food additive is also regulated by the FDA. Residual hexane concentrations should not exceed: 25 ppm in spice oleoresins (21CFR 173.270), 2.2% in hops extract (21CFR 173.270), 25 ppm in modified hop extract for beer (21CFR 172.560), or 5 ppm in fish protein isolates (21CFR 172.340)[xxi].

Hexane is classified as a hazardous air pollutant under section 112 of the US EPA's Clean Air Act[xxii] Major sources of HAP, those that emit 20,000 lbs of a HAP/yr must implement the maximum achievable control technology (MACT), while small HAP sources, those that emit 2,000 lbs of a HAP/year must implement generally available control technology (GACT).

III.2 Dichloromethane

Dichloromethane, CH_2Cl_2, (CAS No. 75-09-2) is used to dissolve the PEG-co-poly(lactic acid) copolymers and other reactants during the PEG-co-poly(lactic acid) diacrylate macromer synthesis step in Med Dev's hydrogel synthesis.

Flammability Dichloromethane is not a significant flammability risk as it must be heated before it may combust. The lower and upper explosion limits for dichloromethane are 12 (% by volume) and 19 (% by volume) [xxiii] respectively.

Possible Adverse Health Effects Dichloromethane is classified as a Carcinogenic, Mutagenic, and Reproductive Toxin (CMR) category 3 in the European Union, meaning it has probable CMR characteristics but they have not been proven definitively yet. The US Environmental Protection Agency (EPA), under the 1986 Guidelines for Carcinogenic Risk Assessment, list dichloromethane as category B2, a "probable human carcinogen". The International Agency for Research on Cancer (IARC), lists dichloromethane as category 2B, "possibly carcinogenic to humans", while OSHA lists it as a "potential human carcinogen"[x]. Dichloromethane exposure has been implicated in an increased incidence of lung and liver cancers in laboratory tests performed in mice, however similar exposures have not increased these cancer incidences in hamsters or rats[xxiv]. The metabolic pathways used by rats, hamsters, and humans metabolize dichloromethane to a lesser extent than do those responsible for tumor formation in rats, and it is therefore unlikely that dichloromethane will promote cancer in humans. Dichloromethane is a skin and eye irritant. Vapor over exposure may cause depression of the central nervous system (anesthesia) and may irritate the skin, eyes, mucuous membranes, and respiratory tract. Within the body, dichloromethane is metabolized to carbon monoxide and raises levels of carboxyhaemoglobin in the blood stream. The carboxyhaemoglobin concentrations in the blood resulting from dichloromethane inhalation remain higher, for a longer period of time than those resulting from inhalation of carbon monoxide. In people with coronary artery disease, carbon monoxide poisoning is particularly serious, where only marginal increases in carboxyhaemoglobin may result in ischaemia.[xxv]

Use Guidelines and Limitations The oral LD50 (rat) for dichloromethane is 1600 mg/kg, while the inhalation LC50 (rat) is 52 g/m^3.

The permissible exposure limit (PEL) prescribed by OSHA for dichloromethane, based on an eight hour time weighted average, is 25 ppm[xxvi].

Dichloromethane is a class 2 solvent according to the FDA classification and has a PDE of 6.0 mg/day (or, in terms of concentration, 600 ppm)[x]. Due to its potential role as an animal carcinogen and the potential threats it poses to human health, the use of dichloromethane in cosmetics products is prohibited[xxvii]. In addition, the use of dichloromethane as a food additive is regulated by the FDA, residual dichloromethane concentrations should not exceed: <30 ppm in spice oleoresins (21CFR 173.255), <10 ppm in decaffeinated roasted coffee and decaffeinated soluble (instant) coffee, <2.2% in hop extract, and <5 ppm in modified hop extract for beer (21CFR 172.560)[xxviii].

The US EPA has classified dichloromethane as a hazardous air pollutant (HAP) under section 112 of the Clean Air Act[x]. In 2007 the EPA moved to prohibit the use of dichloromethane in foam adhesives, while in 2008 the EPA moved to require dichloromethane containing paint strippers to implement management practices that would reduce solvent evaporation.

III.3 Diethyl ether

Diethyl ether, $C_4H_{10}O$, (CAS No. 60-29-7) is used as an extraction agent in the PEG-co-poly(lactic acid) diacrylate macromer synthesis portion of Med Dev's hydrogel production.

Flammability Diethyl ether is extremely flammable in the presence of open flames or heat, while it is flammable in the presence of oxidizing agents and acids. Its auto ignition temperature is 180°C and its flash point is -45°C. Diethyl ether ignites or otherwise creates a violent reaction on contact with halogens, interhalogens, oxidants, sulfur, and sulfur compounds. In addition, diethyl ether tends to form explosive peroxides upon exposure to light and air. The upper and lower flammability limits for diethyl ether are 1.9% and 36% respectively.

Possible Adverse Health Effects Diethyl ether is a skin and eye irritant, and may cause reversible eye injury on contact. In addition, diethyl ether is rapidly adsorbed by the lungs upon inhalation and may result in excitement, drowsiness, headache, nausea, vomiting, increased respiration rate, decreased pulse/temperature, irregular respiration, coughing, bronchodilation, increased heart rate, excessive salvation, muscle relaxation, anesthetic affects, kidney irritation/injury, and temporarily abnormal liver function. Diethyl ether ingestion may result in gastrointestinal tract irritation accompanied by nausea and vomiting.

Use Guidelines and Limitations The oral LD50 (rat) for diethyl ether is 1215 mg/kg, while the inhalation LC50 (rat) is 73,000 ppm over 2 hours. OSHA's PEL for diethyl ether on an 8 hour time weighted average basis is 400 ppm. Diethyl ether is a class 3 solvent according to the FDA classification and has a PDE of 50 mg/day (or, in terms of concentration, 5000 ppm)[x].

III.4 Summary of Hazardous Solvents

Chemical	Chemical formula	CAS No.	Boiling point	Flash point	LEL	UEL	LD50 (rat, ingestion)	LC50 (rat,inhalation)	OSHA PEL	FDA PDE
n-hexane	C_6H_{14}	110-54-3	69°C	-23°C	1.2%	7.7%	28,700 mg/kg	48,000 ppm/4hrs	500 ppm	2.9 mg/kg 290 ppm
Dichloromethane	CH_2Cl_2	75-09-2	40°C	None	12%	19%	1,600 mg/kg	52 g/m^3	25 ppm	6.0 mg/kg 600 ppm
Diethyl ether	$C_4H_{10}O$	60-29-7	34.6°C	-45°C	1.9%	36%	1,215 mg/kg	73,000 ppm/2hrs	400 ppm	50 mg/kg 5000 ppm

UEL, LEL: upper, lower explosive limits, lowest and highest concentrations supportive of combustion in air
LD50, LC50: lethal dose (inhalation) or concentration (ingestion) that will kill 50% of exposed specimens
OSHA PEL: permissible exposure limit, legal limit on the concentration of a substance an employee may be exposed to on an 8hr time weighted average
FDA PDE: permitted daily exposure, pharmaceutically acceptable residual solvent intake

Table 1: Summary of Hazardous Solvents. Summary of key characteristics and limits for each of the chemicals used in Med Dev's synthesis.

III.5 Stannous 2-ethylhexanoate

In addition to toxic solvents, Med Dev's hydrogel synthesis route utilizes a catalyst, stannous 2-ethylhexanoate (also known as stannous octoate, $C_{16}H_{30}O_4Sn$, CAS No. 301-10-0) that may have neurodegenerative properties. Today, stannous 2-ethylhexanoate is widely used as a catalyst in ring opening polymerization of poly(lactic acid) and its co-polymers and is FDA approved as a food additive[xxix]. The toxicity of stannous 2-ethylhexanoate has been investigated both in vivo and in vitro in conjunction with its use as a food additive, these studies however, surmise the toxicity profile of stannous 2-ethylhexanoate from its dissociation products (stannous 2-ethylhexanoate is completely dissociated at the pH of the digestive tract (pH 1.2)) stannous and 2-ethylhexanoic acid[xxx]. The acceptable daily intake

(ADI) of 2-ethylhexanoic acid is 0.5 mg/kg BW/day, while for tin the provisional tolerable weekly intake (PTWI) is 14 mg/kg BW/week (or 2 mg/kg BW/day)[xix].

Very little is known about stannous 2-ethylhexanoate's toxicological profile today. Worried about the safety profile of medical devices, produced with stannous 2-ethylhexanoate, directed for use in the brain or central nervous system where they may break the blood-brain barrier, Yamada et al[xxxi] launched an exploration of the effects of stannous 2-ethylhexanoate on the central nervous system. Yamada et al investigated both the in vitro cell viability of normal human astrocytes (NHA) in response to various concentrations of stannous 2-ethylhexanoate, and the in vivo neurotransmitter and behavioral effects on rat brains directly injected with stannous 2-ethylhexanoate.

The effects of stannous 2-ethylhexanoate on NHAs were investigated using an Astrocyte Microtiter Terazolium Assay in which 1 x 10^4 NHAs were cultured for a week with 2.5, 5, or 10 μg/mL of stannous 2-ethylhexanoate. After incubating for one week with the stannous 2-ethylhexanoate, the culture media was replaced, substituted by fresh media, TetraColor One reagent was added to each astrocyte sample and the samples allowed to sit for two hours prior to reading the absorbance at 450/360 nm. The viability of normal human astrocytes exposed to 2.5 and 5 μg/mL of stannous 2-ethylhexanoate marginally decreased (a decrease of 10% and 20% compared to the control, respectively), while the decrease in viability witnessed for NHAs exposed to 10 μg/mL of stannous 2-ethylhexanoate was significant (80% compared to the control), as shown in figure 4.

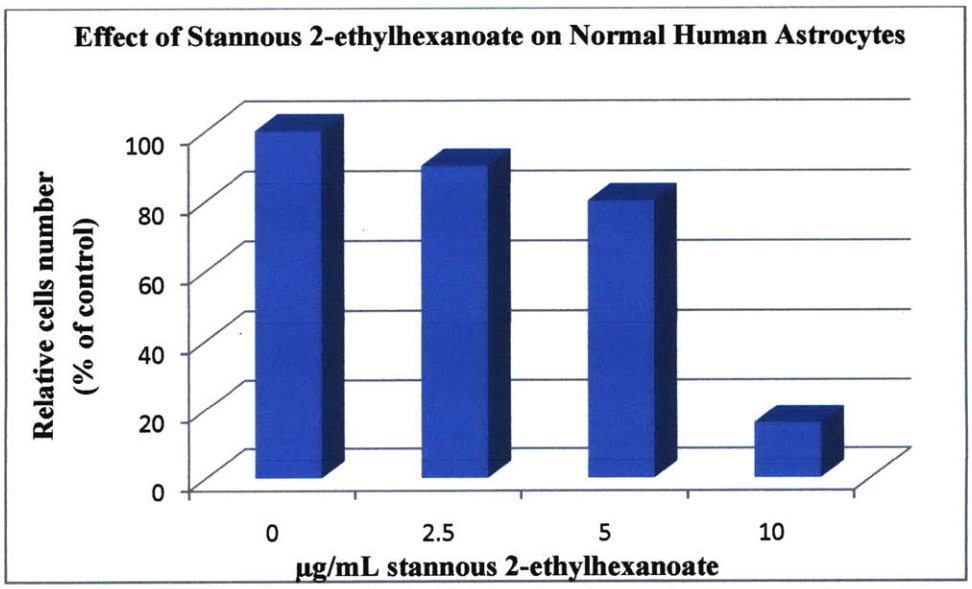


Figure 4: Summary of the effect of various stannous 2-ethylhexanoate concentrations on viability of normal human astrocytes. From this plot, it is clear that cells treated with 10 μg/mL of stannous 2-ethylhexanoate are only 20% as viable as those untreated, or alternatively, NHAs treated with 10 μg/mL of stannous 2-ethylhexanoate demonstrate an 80% decrease in viability compared to those untreated. Adapted from Yamada et al.

Decreased viability in normal human astrocytes in response to incubation with stannous 2-ethylhexanoate suggests that the mitochondrial activity in these cells was suppressed. Suppression of mitochondrial

activity decreases adenosine triphosphate (ATP) production within the cell, thereby disrupting important processes of energy storage/transport as well as CNS signaling. Yamada et al contest that the decreased mitochondrial activity witnessed in response to incubation with stannous 2-ethylhexanoate indicates that the catalyst is cytotoxic to cells in the central nervous system.

Stannous 2-ethylhexanoate was injected intra-cerebrally at a concentration of 6.28 mg/kg BW (corresponding to 2 mg/kg BW tin (the ADI of tin)). Open field tests were performed on the rats 1, 7, and 30 days post injection to determine the effect stannous 2-ethylhexanoate had on their motor activities (total locomotion distance, average locomotion speed, number of sections crossed, and beginning latency). In field studies, the total locomotion distance and the average locomotion speed of the rats injected with stannous 2-ethylhexanoate decreased and beginning latency increased 1 day post injection. Seven days post injection there were no differences in the field study test results of the injected and the control rats. Thirty days post injection, the total locomotion distance and average locomotion speed of the rats injected with stannous 2-ethylhexanoate increased, while their beginning latency decreased. Open field tests typically indicate decreased locomotion distance on repeated testing, and Yamada et al point to the fact that the rats increased their locomotion distance thirty days post injection as evidence of possible chronic neurotoxicity.

After 30 days the rats were sacrificed and their brain tissue were processed so that neurotransmitters could be detected using an HPLC fitted with a reverse phase column and an electrochemical detector. The neurotransmitters measured included dopamine (DA), serotonin (5-HT), and norepinephrine (NE). Dopamine metabolites, 3,4-dihydroxyphenyl-acetic acid (DOPAC) and homovanillic acid (HVA), and serotonin metabolites, 5-hydroxyindole-3-methoxyphenylacetic acid (5HIAA) were also measured. Neurotransmission of dopamine (DA) promotes ambulation and decreases anxiety in rats. Depression may result from dysfunctional neurotransmission of dopamine, while Parkinson's disease is associated with decreased dopamine levels. Dopamine concentrations in the cerebral cortex decreased in response to intracrainal injection of stannous 2-ethylhexanoate, while the concentration of dopamine metabolites DOPAC and HVA increased. This increased dopamine turnover is consistent with the results of the open field test, and may account for the rats increasing (rather than decreasing their locomotion distance with repeated testing). Norepinephrine and serotonin are two neurotransmitters related to emotion, emotional behavior, stress, and hormone secretion. Serotonin levels increased while norepinephrine levels decreased post intracranial injection with stannous 2-ethylhexanoate; such disturbances in these neurotransmitters may cause dystrophy or depression.

Yamada et al, held that the neurodegenerative qualities of stannous 2-ethylhexanoate should prevent its use as a catalyst in the synthesis of PLA and its copolymers intended for use in drug delivery. Large manufacturers of PLA and its copolymers have used and continue to use stannous 2-ethylhexanoate as a catalyst and it is unlikely they will remove stannous 2-ethylhexanoate from their process without definitive proof of its toxicity.

IV What Environmental Legislation Exists that Might Apply to Med Dev?

A plethora of environmental legislation exists today, most of which describes hazardous chemical reporting requirements. The legislation most pertinent in proving the utility of designing for the environment impose reduction demands on the use of the most hazardous chemicals, two examples of this type of legislation are the Massachusetts Toxics Use Reduction Act (TURA) and the European Union's Registration Evaluation Authorization and Restriction of Chemicals (REACH).

IV.1 Massachusetts Toxics Use Reduction Act

The Massachusetts Toxics Use Reduction Act[xxxii] was enacted to promote pollution prevention in businesses within the Commonwealth of Massachusetts. The Massachusetts Legislature first passed the Massachusetts Toxics Use Reduction Act (TURA) in 1989, and most recently amended it in 2006 (Chapter 188 of the Acts of 2006). The Toxics Use Reduction Act requires large quantity toxics users (those using 25,000 lbs/year or more of a toxic substance) to perform two tasks: 1.) to report the manufacture, processing, or use of toxic chemicals and 2.) to prepare and follow a toxics use reduction plan. Massachusetts businesses have reduced their toxics use by 41% and have curtailed their toxic by product production by 65% through compliance with TURA.

The TURA covers the toxic chemicals detailed in the lists established through the following pieces of federal legislation:

Section 313 of *Emergency Planning and Community Right to Know Act* (EPCRA) [42 U.S.C. S1101 et seq]
Sections 101 (14) and 102 of *Comprehensive Environmental Response, Compensation, and Liability Act* (CERCLA) [42 U.S.C. S9601 et seq]

The administrative council on toxics use reduction may further classify the substances found in these lists as higher or lower hazardous substances (with Persistant, Bioaccumulative, and Toxic Substances being automatically classified as higher hazardous substances).

The first task required by the TURA in regards to the listed toxic or hazardous substances entails reporting the manufacture, processing, and use of toxic chemicals. Large quantity toxics users (using 25,000 lbs/year or more of a toxic substance) with more than ten full time employees operating under SIC codes 10-14, 20-39, 40, 44-51, 72, 73, 75, or 76 must file reports with the United States Environmental Protection Agency (EPA) and the Massachusetts Department of Environmental Protection (DEP) detailing each toxic or hazardous substance manufactured, processed, or used at a given facility. Even when a facility is exempt from reporting, reports should be completed for each toxic substance used and kept on record. A full toxics use report includes:

Form S cover sheet
Form R (for each toxic chemical)
Form S (for each toxic chemical)
Fee worksheet

Reporting Requirements [xxxiii]

These reports identify the large quantity toxics user, the facility, the production unit, and the toxic or hazardous substance manufactured, processed, or used. The reports are maintained both by the appropriate agencies (the US EPA and the MA DEP) and the facility filing them.

The Toxics Use Fee (MGL Chapter 21.I, Section 19) is based on the number of employees a facility employs and is comprised of a base fee supplemented by a $300 fee per toxic or hazardous substance up to a prescribed maximum fee level:

Number of Employees	Base Fee	Maximum Fee
10< employees <50	$500	$1,500
50< employees <100	$750	$2,000
100< employees <500	$1,250	$4,000
500< employees	$2,500	$8,000

Table 2: Toxics Use Fee Schedule[xxxiv]

These fees are not exorbitant, nor are they intended to be, they are meant to call attention to toxic chemical use and not to penalize it, the proceeds from the fees are used to fund toxics use reduction research and programs conducted by the Toxics Use Reduction Institute and the Office of Technical Assistance.

The second task required by the TURA for listed toxic or hazardous substances is the preparation and completion of a toxics use reduction plan. Toxics use reduction refers to the mitigation or elimination of toxic or hazardous substances in a production process through the implementation of process or raw materials changes. These changes should reduce risks for employees, citizens, and the environment in a manner that does not redistribute those risks. A number of toxic use reduction techniques exist and include:

Toxic Use Reduction Techniques
Raw material substitution
Product reformulation
Production unit redesign/modification
Production unit modernization
Improved operation and maintenance of production unit equipment and methods
Recycling, reuse, extended use of toxics

Table 3: Toxic Use Reduction Techniques

Each of the toxic use reduction techniques capitalize on substitution, process efficiency improvements, or recycling to affect toxic use reduction. Raw material substitution implies replacement of a toxic or hazardous substance with its non-toxic, non-hazardous counterpart, while product

reformulation implies replacement of a toxic or hazardous end product with an innocuous one, in order to reduce toxics use. Production unit redesign/modification and production unit modernization both rely on design improvements and the resultant efficiency benefits to curtail toxics use. Improved operation and maintenance of production unit equipment and methods implies toxics use reduction through efficiency improvements made using existing equipment (either by cleaning the equipment more frequently, better or operating under more preferable conditions). Finally, recycling, reuse, and extended use of toxics implies introduction of less naive toxic substances into the production process as the process approximates a closed loop system.

The toxics use reduction plan required by TURA outlines measures a facility will take to lessen their use of toxic substances and should include (according to Massachusetts General Laws, Chapter 21.I: Section 11. Toxics Use Reduction Plan):

a.) An economic/technical assessment of each proposed technique for toxics use reduction, including cost of implementation and any anticipated cost savings
b.) An analysis of current/projected toxics use, by products, and emissions
c.) An assessment of the types/amounts of toxic or hazardous substances in use
d.) A schedule for implementation

Each toxic use reduction plan must be certified by a toxics use reduction planner and the plan must be updated and recertified after 2 years. Once a company has filed 1 toxic use reduction plan and 2 plan updates, it may file: a.) another update, b.) an alternative resource conservation plan, or c.) implement an Environmental Management System (EMS).

The DEP may further impose a performance standard on large quantity toxic users within a particular user segment, under Massachusetts General Laws, Chapter 21.I: Section 15. Performance Standards, which will require said users to achieve a prescribed level of by-products generated per unit of product within a reasonable time (not to exceed 3 years).

The toxics use reduction plan is meant to facilitate compliance with various environmental legislation, but as its implementation requires time, it can also delay compliance. A large quantity toxics user may, under Massachusetts General Laws, Chapter 21.I: Section 16, petition the DEP for a temporary waiver of laws/regulations administered by the DEP, if said user intends to achieve compliance with those laws/regulations through the implementation of their toxics use reduction plan.

IV.1.1 Implications of Massachusetts Toxics Use Reduction Act on Med Dev

Presently, Med Dev has fewer than 10 employees and does not use 25,000 lbs of toxic or hazardous substances, nor is it likely that Med Dev will use 25,000 lbs of these substances in the future. Med Dev does however use two of the toxic or hazardous substances covered by this legislation, namely dichloromethane and n-hexane. If the producers of dichloromethane and n-hexane were to discontinue manufacturing these substances, it would disrupt Med Dev's supply chain of raw materials which would in turn hinder Med Dev's ability to produce its hydrogel until such a time as it could find a suitable alternative. The Massachusetts Toxics Use Reduction Act highlights the important role that Design for the

Environment has in ensuring Med Dev's supply chain is secure: by designing toxic substances out of the process from the beginning Med Dev will not succumb to production stoppage when a toxic or hazardous substance is pulled off the market.

Furthermore, while Med Dev may not produce a large enough quantity of material to be subject to TURA today, complying with TURA is an intelligent strategy, as future legislation may extend TURA's applicability to small quantity generators (SQG) or very small quantity generators (VSQG). Even without TURA's applicability being extended to SQG, and VSQG, though, the type of environmental stewardship highlighted in this legislation will aid Med Dev in conducting more cost effective operations, by reducing the amount of hazardous waste generated.

IV.2 European Union's Registration Evaluation Authorization and Restriction of Chemicals (REACH)

The European Union's Registration Evaluation Authorization and Restriction of Chemicals (REACH)[xxxv] legislation went into effect on June 1, 2007 and is currently being implemented in a phased manner. This legislation serves to consolidate the fragmented laws and regulations concerning safe chemical use within the European Union and places the onus on the chemical manufacture or user to identify and assess risks, rather than on public authorities.

A company's first obligation under REACH is Registration, all substances manufactured or imported in quantities of 1 ton or more must be registered with the European Chemicals Agency (ECHA). Failure to register a substance will nullify a company's right to manufacture or import that substance.

Exemptions from this legislation include polymers and substances adequately regulated under other legislation, such as medical products covered by the following two pieces of legislation[xxxvi]:

EC No 726/2004 *Community procedures for authorization/supervision of medicinal products for human use* Establishing a European Medicines Agency

Directive 2001/83/EC *Community Code for medicinal products for human use*

Manufacturers and importers of substances which may be used in medicinal products, as active, inactive, or excipient ingredients do not have to register under REACH. This exemption only applies to the manufacturer or importer of a substance used in medicinal products, to the extent that that substance is used for that particular use, quantities of the substance used for other uses must be registered under REACH.

Registration is comprised of two documents which provide information on substances, risks arising from their use, and measures used to ensure risks are managed: the technical dossier and the chemical safety report (CSR). The technical dossier[xxxvii] is filed for substances manufactured or imported in quantities of 1 ton or more and identifies the manufacturer/importer, the substance, uses of the substance, guidance on safe use, study summaries of Annexes VII to XI testing, indication that the dossier was

reviewed by an assessor, proposals for testing, and exposure information. The chemical safety report[xxxviii] (CSR) is filed for substances manufactured or imported in quantities of 10 tons or more and documents hazards associated with the substance as well as exposure scenarios. The exposure scenarios included in the CSR describe how the substances are manufactured or used during their life cycle, and how environmental/human exposures are controlled.

Registration is a lengthy process and in order to prevent redundancy and redoubled efforts the European Chemicals Agency (ECHA) allows joint submission of registrations for a particular substance. When joint submission is used, a lead registrant compiles the majority of the information for the technical dossier and CSR, while the others individually submit their company details and production volumes. The ECHA has set up a forum, called the Substance Information Exchange Forum (SIEF) to help registrants find one another. This is particularly important in light of the downstream user requirement of the REACH legislation, as it requires coordination between the industrial user of a chemical and its manufacturer. The downstream user (i.e. industrial user of a chemical) is required to consider their safe use of the substance, ensuring their use is covered in the manufacturer's registration. Based on the information downstream users obtain from their supplier, they must apply appropriate risk management techniques.

Evaluation is the second piece of the REACH legislation and entails both dossier evaluation and substance evaluation.

1.) **Dossier evaluation**

Compliance check: 5% of dossiers subject to check, ECHA checks compliance of registration dossier against regulation requirements

Checking of testing proposals: all testing proposals subject to check, performed by ECHA to prevent unnecessary animal testing

2.) **Substance evaluation**

Agency and competent member state Authorities request additional info on a substance to clarify suspicions of risk

Evaluations performed by the ECHA may lead to the conclusion that further control of a substance is necessary under the Authorization or Restriction provisions of REACH.

The authorization provision of the REACH legislation is provided as a central mechanism to regulate substances of very high concern through a process where risks are vigorously assessed, considered, and decided upon by the Community. Substances that constitute the very high concern category warranting authorization include:

Carcinogenic, Mutagenic, Reproductive Hazards (CMR) category 1 or 2
Persistent Bioaccumulative and Toxic (PBT)
Very Persistent, very Bioaccumulative (vPvB)
Substances with similar effects as identified on a case by case basis

The use of authorized substances will not be banned by default. Authorization applications must include an analysis of possible substitutes, measures being taken to research/develop possible substitutes, and if a substitute exists, a substitution plan. An authorization will be granted if risk from the use of the substance can be controlled, or that its socio economic benefits outweigh the risks and no suitable alternatives exist. Authorizations are reviewed on a schedule and if suitable substitutes arise prior to a review, the authorization may be amended or withdrawn. A downstream user may apply for their own authorization for use of a substance of very high concern or may use the substance from an authorized manufacturer provided their use is within the use scenarios covered in the manufacturer's application.

The restriction provision of the REACH legislation may prohibit the manufacture, marketing, and use of substances that pose an unacceptable risk to human health and the environment. The member states in conjunction with the ECHA on behalf of the European Commission prepare the proposals for restrictions in the form of a structured dossier.

IV.2.1 Implications of REACH on Med Dev

REACH currently has an explicit exemption for medicinal products and therefore does not pose an imminent concern for Med Dev. Furthermore the chemicals used in Med Dev's synthesis are not classified as substances of very high concern (none are CMR category 1 or 2, PBT, or vPvB), only dichloromethane (otherwise known as methylene chloride) is classified as a CMR category 3, where its carginogenic and mutagenic behaviors are only probable not proven. However, the regulation is fairly new and may be amended or otherwise subject to change, thus it should be monitored.

Furthermore, while the exemption dismisses manufacturers from reporting on substances used for medicinal products, they are still obligated to report on the same substance used in different applications; the exemption is only partial. The partial nature of the exemption may leave Med Dev vulnerable to possible supply chain disruptions, where manufacturers finding it too expensive or difficult to comply with legislation may discontinue producing a substance. A prime example of this is the impending European Community ban on dichloromethane in paint strippers (this ban was prompted by carbon monoxide poisoning deaths associated with using dichloromethane based paint strippers in improperly ventilated areas, of which there had been 3 in the 5 years preceding 2007 according to the European Chlorinated Solvents Association (ECSA)[xxxix]). The graph in Table (X) demonstrates the breakdown of sales of dichloromethane in the European Union's 25 member states plus Norway, Switzerland, and Turkey by application for 2005. According to this graph, pharmaceuticals account for 51% of dichloromethane sales, while paint stripping accounts for 13%, and solvents or auxiliary agents account for 18%.

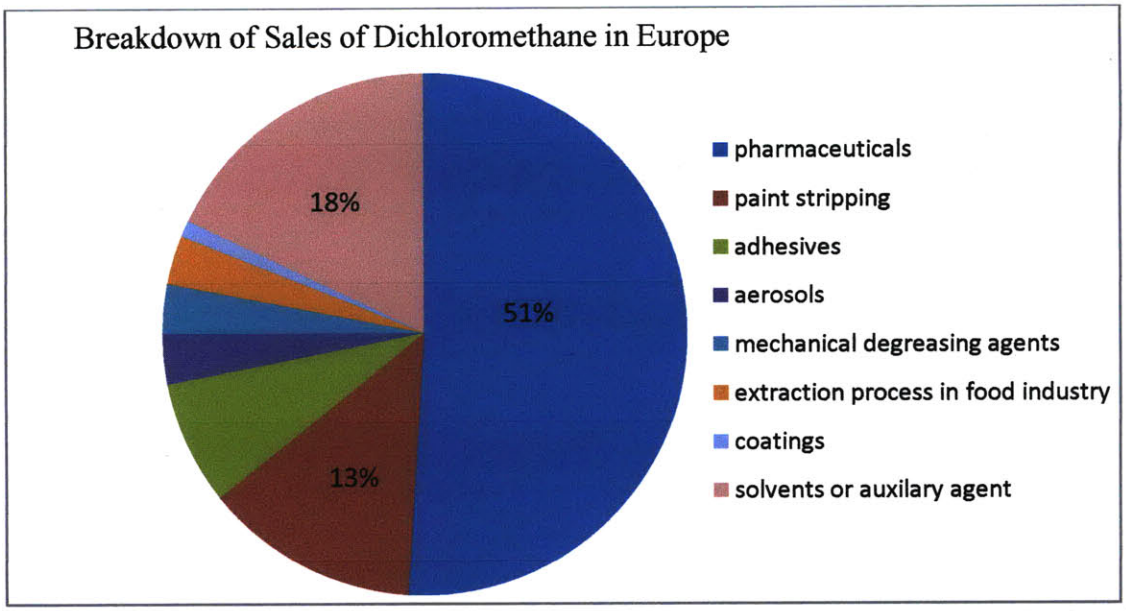


Figure 5: Breakdown of Sales of dichloromethane in the EU25 plus Norway, Switzerland, and Turkey; the data was adapted from a report to the European Commission Directorate-General Enterprise and Industry by Risk and Policy Analyst, Limited entitled: *Impact Assessment of Potential Restrictions on marketing and use of DCM in paint strippers*[xi] to prepare this chart.

In dollar and cents terms (based on a dichloromethane price of $750/ton), an outright ban on dichloromethane would account for a $9,750,000 loss in revenues to dichloromethane manufacturers whose sales are approximately $82,500,000.

Application Category	Tonnage Sold in Europe	Revenue based on $750/ton of DCM
Pharmaceuticals	50,000	$37,500,000
Paint strippers	13,000	$9,750,000
Adhesives	5,000-10,000	$3,750,000-$7,500,000
Aerosols	1,000-5,000	$750,000-$3,750,000
Mechanical/Electrical Degreasing Agents	1,000-5,000	$750,000-$3,750,000
Extraction in food industry	1,000-5,000	$750,000-$3,750,000
Coating	1,000	$750,000
Solvents or auxiliary agents in:	10,000-25,000	$7,500,000-$18,750,000
Foam blowing (polyurethane)	*1,000-5,000*	*$750,000-$3,750,000*
Polycarbonate production	*1,000-5,000*	*$750,000-$3,750,000*
Triacetate production	*1,000*	*$750,000*
Degreasing	*1,000*	*$750,000*
Other	*5,000-10,000*	*$3,750,000-$7,500,000*
Total	**110,000**	**$82,500,000**

Table 4: Breakdown of sales of dichloromethane in EU25 plus Norway, Switzerland, and Turkey as well as estimation of revenues based on a price per ton of DCM of $750, this data is exactly as it appears in the report to the European Comission Directorate-General Enterprise and Industry by Risk and Policy Analyst, Limited entitled: *Impact Assessment of Potential Restrictions on marketing and use of DCM in paint strippers*[viii].

Such a loss (13% or $9,750,000 out of $82,500,000) is probably insufficient to end dichloromethane production altogether, especially where it is produced as a byproduct in chloroform manufacture, however it may serve to drive prices of dichloromethane down due to oversupply.

Table 5 summarizes the scenarios that could arise from a ban on DCM use in paint strippers. The first scenario assumes that the price of DCM would not change as a result of the ban and total revenues would only fall by the amount of revenues accounted for by paint strippers. The second scenario assumes that not only would total revenues reduce by paint strippers revenues, but that the ban would result in an over capacity of dichloromethane forcing the price per ton down to $675 (10% less than $750). The third scenario assumes that over capacity resulting from the ban would decrease the dichloromethane price by 50%, as in scenario two not only would the amount of dichloromethane sold be less, but the cost per ton would also be less ($375/ton).

Scenarios if DCM were banned in paint strippers	**Total Revenue from sales of DCM**
Total DCM revenue without paint strippers *($750/ton)*	$72,750,000
Total DCM revenue without paint strippers with 10% price drop *($675/ton)*	$65,475,000
Total DCM revenue without paint strippers with 50% price drop *($375/ton)*	$36,375,000

Table 5: Summarizes the effects of banning paint strippers on overall sales of DCM, the first scenario assumes that the price of DCM is unaffected by the DCM ban, the second scenario assumes that due to over capacity (and therefore oversupply) of DCM its price will drop by 10%, while the third scenario assumes that DCM price will drop by 50% due to oversupply. The idea for these scenarios was again adopted from the report to the European Committee Directorate-General Enterprise and Industry by Risk and Policy Analyst, Limited, entitled: *Impact Assessment of Potential Restrictions on Marketing and use of DCM in paint strippers*[viii].

Considering that dichloromethane accounts for 13% of the European market share, it is unlikely its ban would drive prices down 50% due to overcapacity, it is more likely that prices would not be driven down at all or by 10%. With prices driven down 10% (to $675/ton) by overcapacity, the total revenue from DCM sales would be $65,475,000, which represents a fall of ~21% from the total sales of DCM without a paint stripper ban ($82,500,000). Even a 21% drop in revenues is probably not enough to destroy the DCM industry, however this analysis shows the detrimental affects restrictions and bans can have on revenue streams. Even if a restriction or ban is imposed on a chemical for use outside the pharmaceutical industry, that same ban can have repercussions within the pharmaceutical industry. If stiff enough or far reaching enough, a ban may cause a manufacture to discontinue manufacturing a product that is critical to a pharmaceutical company's supply chain, forcing the pharmaceutical company to scramble to find alternatives, undergoing costly recertification with the FDA and production stoppages in the process.

The graph in Figure 6 demonstrates the breakdown of sales of dichloromethane in the United States by application in 2006[xli]. According to this graph, pharmaceuticals account for 12% of dichloromethane

sales, while paint stripping accounts for 40%, chemical processing accounts for 10%, and formulated products account for 20%.

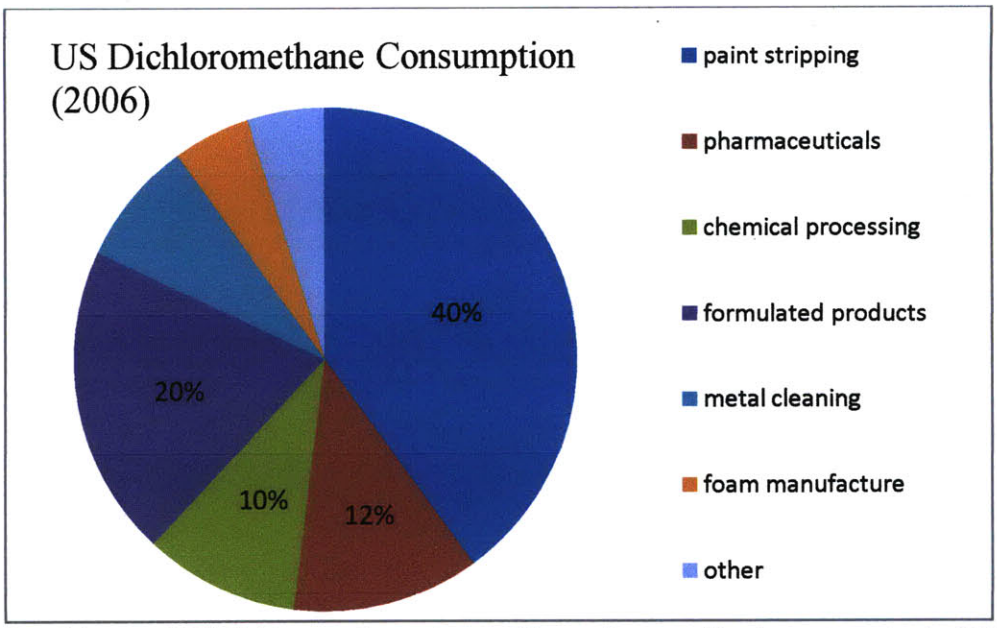


Figure 6: Breakdown of US dichloromethane demand for various application categories in 2006 data was adapted from a Halogenated Solvents Industry Alliance, Inc, White Paper on Methylene Chloride[xlii].

Paint strippers represent a much larger percentage of dichloromethane sales in the United States as compared to in the EU (40% vs 12%). The US pharmaceutical industry and the EU paint stripper industry account for an identical percentage of dichloromethane demand (12%) in their respective markets. While the US paint stripper industry and the EU pharmaceutical industry account for similarly higher percentages of dichloromethane demand (40% and 51% respectively) in their respective markets. The fact that the percentage of dichloromethane demand is higher for paint strippers as compared to pharmaceuticals, whereas in the EU the opposite is true, indicates that the effect of a paint stripper ban in the US would be much more pronounced on the overall dichloromethane market.

	Paint Stripping	**Pharmaceuticals**
% of US DCM demand	40%	12%
% of EU DCM demand	12%	51%
US industry demand	33,560	10,068
EU industry related demand	13,000	50,000
US industry related revenues	$25,170,000	$7,551,000
EU industry related revenues	$9,750,000	$37,500,000

Table 6: Comparison of % of total DCM demand, industry (i.e. paint stripping, pharmaceutical) related demand, and industry (i.e. paint stripping, pharmaceutical) related revenues for the US and EU. All data were compiled from ECSA and HSIA sources, previously identified.

In dollar and cents terms (based on a dichloromethane price of $750/ton), an outright ban on dichloromethane would account for a $25,170,000 loss in revenues to dichloromethane manufacturers whose sales are approximately $62,925,000.

Application Category	Tonnage Sold in US	Revenue based on $750/ton of DCM
Pharmaceuticals	10,068	$7,551,000
Paint strippers	33,560	$25,170,000
Chemical processing	8,390	$6,292,500
Formulated products	16,780	$12,585,000
Metal cleaning	6,712	$5,034,000
Foam manufacture	4,195	$3,146,250
Other	4,195	$3,146,250
Total	**83,900**	**$62,925,000**

Table 7: Breakdown of sales of dichloromethane in the US as well as estimation of revenues based on a price per ton of DCM of $750 (adopting the ECSA's price for DCM) adapted from a Halogenated Solvents Industry Alliance, Inc, White Paper on Methylene Chloride[xliii].

Such a loss (40% or $25,170,000 out of $62,925,000) is probably insufficient to end dichloromethane production altogether, especially where it is produced as a byproduct in chloroform manufacture, however it may serve to drive prices of dichloromethane down dramatically due to oversupply.

Table 8 summarizes the scenarios that could arise from a ban on DCM use in paint strippers. As in the European Union analysis, the first scenario assumes that the price of DCM would not change as a result of the ban and total revenues would only fall by the amount of revenues accounted for by paint strippers. The second scenario assumes that not only would total revenues reduce by paint strippers revenues, but that the ban would result in an over capacity of dichloromethane forcing the price per ton down to $675 (10% less than $750). The third scenario assumes that over capacity resulting from the ban would decrease the dichloromethane price by 50%, as in scenario two not only would the amount of dichloromethane sold be less, but the cost per ton would also be less ($375/ton).

Scenarios if DCM were banned in paint strippers	Total Revenue from sales of DCM
Total DCM revenue without paint strippers *($750/ton)*	$25,170,000
Total DCM revenue without paint strippers with 10% price drop *($675/ton)*	$33,979,500
Total DCM revenue without paint strippers with 50% price drop *($375/ton)*	$18,877,500

Table 8: Summarizes the effects of banning paint strippers on overall sales of DCM, the first scenario assumes that the price of DCM is unaffected by the DCM ban, the second scenario assumes that due to over capacity (and therefore oversupply) of DCM its price will drop by 10%, while the third scenario assumes that DCM price will drop by 50% due to oversupply. The idea for these scenarios was again adopted from the report to the European Committee Directorate-General Enterprise and Industry by Risk and Policy Analyst, Limited, entitled: *Impact Assessment of Potential Restrictions on Marketing and use of DCM in paint strippers*[viii] and information from the HSIA *White Paper on Methylene Chloride* was used[xliv]

Considering that dichloromethane accounts for 40% of the US market, its ban may drive prices down 50% due to overcapacity, though it is almost certain that prices would be driven down by 10%. With prices driven down 10% (to $675/ton) by overcapacity, the total revenue from DCM sales would be $33,979,500, which represents a fall of ~46% from the total sales of DCM without a paint stripper ban ($62,925,000). A 46% drop in revenues may be enough to destroy the DCM industry, if it foresees continued bans and restrictions on DCM use. Even if a restriction or ban is imposed on a chemical for use outside the pharmaceutical industry, that same ban can have repercussions within the pharmaceutical industry. Again, if stiff enough or far reaching enough, a ban may cause a manufacture to discontinue manufacturing a product that is critical to a pharmaceutical company's supply chain, forcing the pharmaceutical company to scramble to find alternatives, undergoing costly recertification with the FDA and production stoppages in the process. If a ban on dichloromethane based paint strippers were to be invoked in the United States as opposed to Europe, it could have a more crippling effect on the overall dichloromethane market (since paint strippers account for 40% of the overall demand in the US as compared to 12% in the EU) and might force pharmaceutical companies to scramble to find suitable substitutes against a backdrop of costly FDA re-validation and production stoppages.

IV.3 An Act for a Competitive Economy through Safer Alternatives to Toxic Chemicals

The Massachusetts state legislature is currently working on an Act for a Competitive Economy through Safer Alternatives to Toxic Chemicals[xlv]. This legislation seeks to augment the environmental gains made through compliance with the Toxics Use Reduction Act, by encouraging companies to explore safer alternatives in addition to reducing their toxics use. Furthermore, this legislation echoes the provisions calling for solvent substitution under the Authorization portion of REACH, in an attempt to ensure that the 37% of Massachusetts business which export to the EU remain competitive under REACH. The legislators and stakeholders in favor of this legislation hope chemical substitution will result in a cleaner environment and a safer work place with reduced health care costs, worker illnesses, and turnover.

Under the safer alternatives legislation, the administrative council will identify 2 to 5 priority toxic substances from a list of chemicals of high concern and the Toxics Use Reduction Institute will prepare safer alternative assessment reports analyzing whether safer alternatives exist for those substances[xlvi]. The list of chemicals of high concern is comprised of CMR category 1 and 2, PBT, and vPvB substances and relies on government lists of chemical categorization for its composition. The safer alternatives assessment report prepared by the TURI will:

Safer Alternatives Assessment Report

1.) Identify the use and function of a priority toxic substance, select a subset of uses for further study
2.) Identify whether alternatives exist for these uses and functions
3.) Identify whether any existing use is unnecessary
4.) Research relevant factors to characterize feasible alternatives
5.) Provide a qualitative assessment of economic viability, opportunity, and cost associated with adopting or implementing safer alternatives
6.) Identify the uses of the priority toxic substance which do not have suitable safer alternatives, and recommend possible R&D initiatives
7.) Use chemical categorization lists to identify potential safer alternatives

*This information is provided in An Act for a Competitive Economy through Safer Alternatives to Toxic Chemicals, redraft in progress to Senate no. 2481 (January 12, 2009), MGL Chapter 21I.Section 5, 24(b)

A company manufacturing a priority toxic substance in MA must file a notice with the DEP within 120 days of learning of its designation. This notice will identify the substance, its distribution within MA (amount and concentration), the uses of the substance, the name and address of the manufacturer.

In addition to the safer alternatives assessment report, the TURI will work in conjunction with the MA DEP and OTA to complete a chemical action plan which shall set out specific actions a company must take in regards to their priority toxic substance and the schedule for actions. The actions covered by the action plan include implementing safer alternatives when feasible or when infeasible ensuring tight control over human and environmental exposure. In addition, where substitution is costly this legislation has created an "Assist Businesses to Compete" Fund (ABC Fund) overseen by the OTA to facilitate the transition[xlvii]. Each chemical action plan will be presented to the administrative council on toxics use reduction by the DEP and shall then be reviewed by the public, prior to adoption. The DEP may compile regulations to restrict the use of a priority toxic substance covered by the chemical action plan subject to a substitution deadline and the specification of a suitable alternative by the DEP.

Massachusetts General Law Chapter 21.I Section 26 (3) of an Act for a Competitive Economy through Safer Alternatives to Toxic Chemicals indicates that a priority toxic substance user may apply to the DEP for a waiver from a substitution deadline if no economically or technically feasible safer alternative exists. The waiver application will include:

Waiver Application for Safer Alternatives to Toxic Chemicals substitution deadline

1.) Identify the specific use of the priority toxic substance for which the waiver is sought
2.) Identify all the alternatives considered and their costs
3.) Identify the basis for finding no suitable alternatives
4.) Provide documentation of minimization efforts to be made in regards to the use/exposure of the priority toxic substance until a suitable alternative is found
5.) Comment on steps the applicant will make to determine a safer alternative in 3 years

*This information is provided in An Act for a Competitive Economy through Safer Alternatives to Toxic Chemicals, redraft in progress to Senate no. 2481 (January 12, 2009), MGL Chapter 21I.Section 26(3)

Violation of this legislation shall result in punishment by fines of up to $25,000/day for each day a company is out of compliance. In addition a Safer Alternatives in Products Fee is under consideration, this fee shall apply to Massachusetts wholesalers and distributors of products containing priority toxic substances exceeding a *de minimis* threshold. These fines should not be very large as the legislation in its draft form describes raising $2 million from all manufacturers/users in the first year escalating up to $6 million plus in years after year 3 (each year new priority toxic substances will be introduced, thus the burden will be shared).

IV.3.1 Implications of an Act for a Competitive Economy through Safer Alternatives to Toxic Chemicals on Med Dev

Massachusett's Act for a Competitive Economy through Safer Alternatives to Toxic Chemicals is much more restrictive and more comprehensive than the European Union's REACH regulations. Where REACH has provisions for the exemption of materials used in medicinal products, the Massachusetts legislation only provides for *de minimis* thresholds and waivers to substitution deadlines. The Authorization provision under the REACH legislation, which calls for phased in substitution, probably has broader applicability as it encompasses all manufacturers/importers/users of substances of very high concern (CMR category 1 and 2, PBT, and vPvB substances) whereas the Massachusetts legislation only applies to 2-5 priority toxic substances (i.e. a subset of the substances of very high concern) per year. The risk associated with the Massachusetts legislation is significantly reduced thanks to the limited number of substances it covers, however a vast amount of uncertainty exists over which priority toxic substances will be identified for substitution next. Due to the severity of the restrictions (essentially substitute or bust) and the few provisions the legislation provides for avoiding substitution and substitution deadlines, especially the fact that there is no provision for medicinal products, this legislation is very worrisome.

Med Dev would probably not have to make safer alternative substitutions under this legislation in the sense that the amount raw materials they use would probably not exceed the *de minimis* threshold. Furthermore the hazardous raw materials that Med Dev does use: n-hexane, diethyl ether, and dichloromethane, would not be considered substances of very high concern (and therefore probably would not be designated as priority toxic substances). Dichloromethane is the closest to a substance of very high concern that Med Dev uses in its manufacturing facility and it is only a CMR category 3. If the DEP, TURA, and the OTA were to force substitution of dichloromethane through this legislation (without the provision for its use in medicinal products), it is probable that dichloromethane manufacturers would cease to provide dichloromethane to Massachusetts. Though Massachusetts is small and would not effectively put a dichloromethane manufacturer out of business altogether, the cost of doing business in Massachusetts would become prohibitive and distributors would discontinue supplying DCM to Massachusetts. Without a supplier of dichloromethane in the state, Med Dev would be forced to make the costly post market substitution of DCM incurring costs of FDA re-registration/re-testing and production stoppage along the way, not to mention an inability to provide their product to patients who desperately need it. In light of such legislation it is wise to design for the environment and avoid having to make costly substitutions in the future.

IV.4 Legislation Overview

Although none of the legislation discussed (TURA, REACH, or the Safer Alternatives Legislation) pose a direct and imminent threat to Med Dev's ability to pursue its manufacturing plan in its current form, it should raise awareness of potential future supply chain disruptions. Solvent substitution and designing for the environment could aid Med Dev in avoiding potentially costly re-validation and production stoppages due to supply chain disruptions, by eliminating toxic or hazardous substances from the outset. Foresight and environmental action will not only lead to a better, more robust process, but will also result in a reputation of environmental stewardship.

V. What are other Pharmaceutical Companies Doing?

Med Dev is a medical device manufacturer, however where their medical device is a polymeric material many parallels may be drawn between Med Dev's process and those of more traditional pharmaceutical companies producing complex organic molecules. The vast scale differences between Med Dev and large pharmaceutical companies, pharmaceutical companies being substantially larger than Med Dev, may drive pharmaceutical company's decisions to pursue green manufacturing, as the regulations described above have a more direct effect and significant cost savings (on permitting as well as raw materials) may result. Pfizer, Merck, and many other large pharmaceutical companies have realized significant waste reduction and therefore cost savings through implementing green chemistry initiatives; these initiatives have also been recognized with awards as shown in table 9.

	Product	Improvement	Award
Pfizer	LIPITOR atorvastatin calcium	65% reduction in organic waste	IChemE Crystal Faraday Award for Green Chemical Technology
	VIAGRA (sildenafil citrate) tablets	93% reduction in organic waste	
MERCK Research Laboratories	EMEND (aprepitant)	2nd generation 80% less raw materials 85% reduction in waste	US EPA Presidential Green Chemistry Award
	Januvia (sitagliptin) tablets	2nd generation 50% reduction raw materials 80% reduction in waste	US EPA Presidential Green Chemistry Award IChemE Excellence in Green Chemistry and Engineering

Table 9: Description of green chemistry improvements and awards received by Pfizer and Merck.[xlviii]

The synthetic organic chemistry methods used by Med Dev and other pharmaceutical companies generate emissions, effluents, and waste that are potentially adverse to human health and the environment, this piece of analysis describes the steps pharmaceutical companies have taken to minimize their environmental impact. Below is a plot of hazardous waste generated by the major pharmaceutical companies over a six year period (normalized by millions of $ of sales in order to facilitate comparison), from this plot it is evident that pharmaceutical companies are beginning to decrease their hazardous waste generation through green chemistry initiatives.

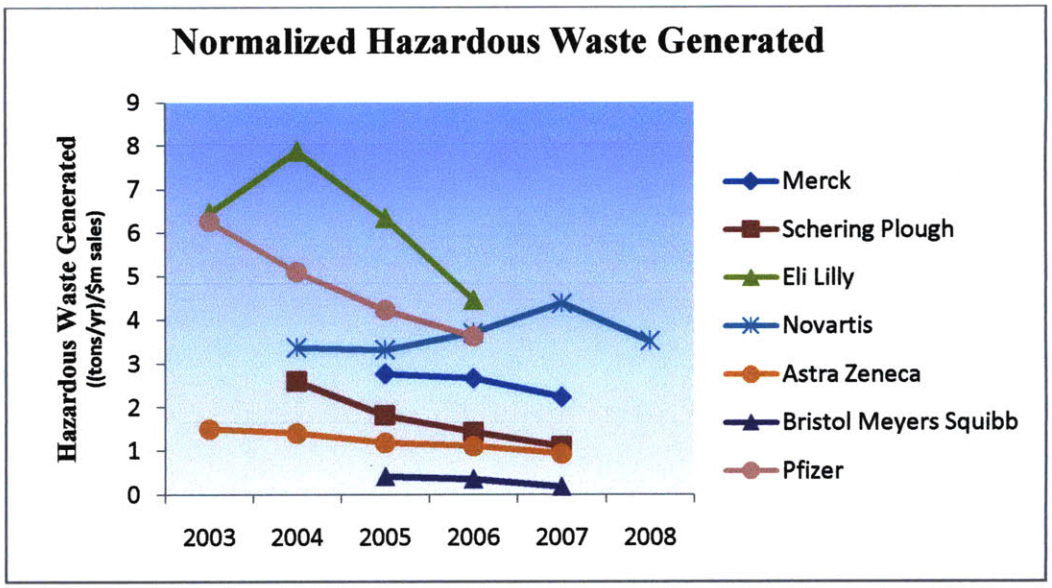


Figure 7: Normalized (by $m sales) Hazardous Waste generated by each of the major pharmaceutical companies over a 6 year period. The information for this plot was obtained from each company's corporate responsibility report and their annual financial reports.[xlix]

In addition to achieving overall reductions in the amount of hazardous waste generated, the pharmaceutical industry is directing special attention toward reducing their dichloromethane consumption in view of intensifying regulation concerning its use. Glaxo Smith Kline has decreased its dichloromethane use by 50% while Merck plans to begin a campaign to eliminate the use of the solvent, and Pfizer has reduced its dichloromethane use by more than 50% (as shown in the figure below).

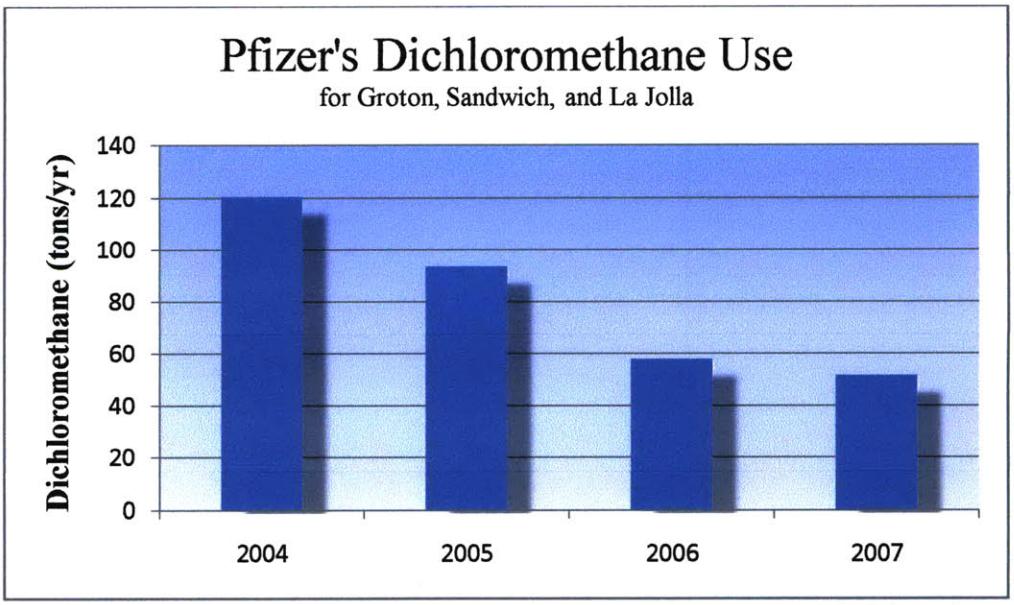


Figure 8: Pfizer's Dichloromethane use from 2004 to 2007 for their Groton, Sandwich, and La Jolla facilities has decreased by more than 50%.[l]

While the cost savings and regulatory avoidance issues may not be as compelling for Med Dev, Med Dev can use this analysis to benchmark which steps it can take to operate in an environmentally more favorable way. Also, since Med Dev may aspire toward acquisition, building green chemistry into their manufacturing processes early may make them a more appealing acquisition target.

V.1 Merck

Merck and Co. published its first environmental report and announced its first set of environmental improvement goals in 1990 and have been committed to assessing their environmental footprint ever since. Merck evaluates its environmental footprint on the basis of the following dimensions: energy and water use, greenhouse gas and pollutant emissions to air and water, and waste generation and recycling rates. This discussion will focus on emissions, effluents, and waste as green house gas generation and energy and water use are outside the scope of this analysis.

Pharmaceuticals are comprised of complex organic molecules and the processes used to synthesize these molecules are often multi-step batch operations that require numerous solvent changes and extensive solvent based cleaning between batches. Merck had revenues of $24 billion in 2007 and purchases approximately 30 million kg of solvent/year. Solvents are an integral part of pharmaceutical synthesis and formulation and constitute a majority of Merck's effluents, emissions, and wastes.

Through a program to track their effluents, emissions, and waste, Merck is able: to identify areas where their environmental footprint can improve, to evaluate the impact of new projects, and to understand their progress against environmental goals. Beginning with the original design of their manufacturing processes, Merck tries to incorporate green chemistry techniques that will prevent pollution. The green chemistry techniques applied to new product development include using alternate, less toxic synthesis routes, designing efficient processes that significantly reduce the amount of raw materials used, substituting toxic solvents with their innocuous counterparts, replacing solvent based cleaning methods with water based ones, reusing and/or recycling spent solvents, and employing in-process as well as end of pipe treatment technologies and controls for solvent emissions. Each of these methodologies reduce or prevent emissions, effluents, and wastes, resulting in decreased costs associated with new solvent purchase and waste treatment. In 2007, Merck generated 54,000 metric tons of hazardous waste, 56% of which was reused in the manufacturing process. Of the solvent streams Merck is incapable of reusing 23% are reused by industries with less strict purity standards, 32% are burned for energy generations, 44% are treated and disposed of (of which less than 4% are landfilled)[li]. Merck also reports their emissions of volatile organic compounds (VOCs) and toxics reduction inventory (TRI) substances, this number has remained relatively flat (around 400 metric tons of VOC/yr, and approximately 120 metric tons of TRI substances/yr) over the five years, 2003 to 2007, reported in their Corporate Social Responsibility Report[lii].

Merck also participates in promoting green chemistry initiatives in the broader pharmaceutical industry by belonging to the American Chemical Society's (ACS) Green Chemistry Institute (GCI) Pharmaceutical Roundtable and Pharmaceutical Industry Principles for Responsible Supply Chain Management (PhRMA) which aims to ensure suppliers practice environmental responsibility. Merck also

takes additional measures to understand the effects of the final products on the environment (Pharmaceuticals in the Environment (PIE) testing).

A few case studies on Merck's environmental performance serve to demonstrate Merck's commitment to green chemistry. Interestingly, both the EMEND and Januvia processes were changed post clinical trials. Large pharmaceutical companies may be able to afford post approval changes, especially in light of the long term return on environmental process improvements (both from a legislative and efficiency perspective), however the best strategy for green chemistry implementation remains: design for the environment.

Merck Case Studies

EMEND (Aprepitant)

EMEND is a novel therapeutic for chemotherapy induced nausea and vomiting. Merck was rewarded the US EPA's Presidential Green Chemistry Challenge Award in 2005 for cutting the number of steps in EMEND's synthesis in half, while doubling the process yield and eliminating a costly, energy intensive cryogenic step. The resulting process required 80% less raw materials resources and 80% less water, while producing 85% less waste (approximately 340,000 L of waste/kg of product were eliminated). Merck's Vice President of Process Research, R.P. "Skip" Volante said:

"We used the first generation process in clinical trials, but it involved hazardous materials. It also involved cryogenics- very low temperatures- and had very significant waste issues. It actually could have been scaled up, but lots of aspects didn't make it green efficient."[xxv]

1st Generation Synthesis: Used in clinical trials
6 synthesis steps adapted from the discovery process
An expensive, complex chiral acid was required in stoichiometric amounts to set stereogenic center of the resultant molecule

2nd Generation Synthesis: 3 highly atom economical steps
Used a molecule as a stereogenic center to set the new stereocenters with high selectivity

In Merck's instance replacing a reactant and altering the synthesis route had significant results, the 2nd generation synthesis was implemented in the first year of EMEND production and demonstrated huge

[liii]

Januvia (Sitagliptin phospate)

Januvia is an active ingredient in type 2 diabetes treatment, manufactured by Merck in conjunction with Solvias. Merck and Solvias were awarded the US EPA's Presidential Green Chemistry Challenge Award in 2006 and the Astra Zeneca Award for Excellence in Green Chemistry and Engineering by the Institute of Chemical Engineers (IChemE) in 2005 for their novel β-Amino acid based synthesis. The resulting process reduced the number of processing steps from 8 to 3 and decreased the amount of waste by 80% (approximately 220lbs waste/lb product were eliminated.

1st Generation Synthesis: Used in clinical trials
- 8 step synthesis
- Numerous aqueous work-ups were involved as were several high molecular weight reagents that did not contribute to the final molecule

2nd Generation Synthesis: 3 step synthesis, improves process yield by almost 50%
- Novel asymmetric catalytic hydrogenation of unprotected enamines
- Catalyst: rhodium salt of ferrocenyl based ligand
- The catalyst was used in the final synthetic step to allow recovery/recycling
- Protective groups are unnecessary as the reactive amino group is not revealed until the last step

Dr. Viviane Massonneau, Merck's director of Global Science, Technology, and Commercialization leading Chemical Small Scale Synthesis Pilot Plants discussed her impression of Merck's green chemistry initiatives in a phone interview[liv]. Merck is making strides to improve their environmental track record, however their progress is slow and they lag behind other pharmaceutical companies like Pfizer and GSK. Presently, the Environmental and Process Safety Engineering group (which Dr. Massonneau formerly led) assesses a process for viability and safety when it is transitioning from Process Research to Scale Up, an assessment which typically is characterized by a significant amount of paperwork. A reagent assessment, that would use a color coded system to signify the environmental implications of reagents used in a particular synthesis (red would indicate a reagent is bad for the environment, yellow a reagent is tolerable, and green a reagent is not a concern) is slowly being added to the overall safety assessment, however it lacks coordinated alternative suggestions. The reagent assessment system Merck is implementing will allow them to identify environmental hazards in their process, but it will not help them to replace those hazards with more benign alternatives.

In addition, Merck has yet to create many of the web based green chemistry tools that could help facilitate their employees use of green chemistry principles, for instance Pfizer has electronic laboratory notebooks that suggest alternative chemicals when a protocol contains a hazardous one. Merck also has not performed many of the lifecycle analysis on nor has it taken a holistic approach to its operations, thereby leaving many of the opportunities for environmental improvement undiscovered. Merck is slowly beginning to track the atom efficiency ((molecular weight of desired products/molecular weight of all products) x 100%) and the process mass intensity (quantity of raw materials input (kg)/quantity of bulk active pharmaceutical ingredient (API) output (kg)) of its reactions in an effort to identify their inefficiencies. Their major focus is on promoting efficiency, which can lead to reductions in solvent consumption resulting in cost savings both from the purchasing and disposal perspectives.

A number of the decisions Merck makes regarding purchasing, outsourcing, and even acquisition hinge on environmental performance. If a start-up would like to be acquired by a large pharmaceutical company, Dr. Massonneau argues, their environmental track record will be one of the factors integrated into the decision making process. Furthermore, Dr. Massoneau stressed there are chemicals Merck already avoids using today due to their toxicity, including: ethylene oxide, chloroform, and benzene. Merck is presently evaluating the potential of eliminating the use of dichloromethane in their operations as well.

Dr Massonneau felt green chemistry's greatest impact on Merck as an organization would result from instituting green thinking from the beginning; if the scientists in Medicinal Chemistry were well versed in green chemistry, they could help make syntheses green by design. While processes can be changed further along in development cycle, often times later stage changes are associated with costly process benchmarking or re-validations, even when repeat clinical trials are unnecessary there is a considerable expense involved in changing the process.

Merck believes that implementing green chemistry is not only a mechanism for improving their environmental footprint, but also for ensuring they remain competitive in the future. And while being competitive is paramount, a positive public perception is also important, Dr. Massonneau quoted one source as saying that the allied chemical industry had an approval rating of 26%, placing them just ahead of the nuclear and tobacco industries in the public's perception, surely something has to be done.

V.2 Astra Zeneca

Astra Zeneca is trying to integrate health, safety, and environmental concerns across its organization and throughout the life cycle of its products. Their goals for promoting environmental sustainability include: considering environmental implications through the process, product, and packaging development processes, reducing waste and emissions generation, and avoiding the use of hazardous substances wherever relevant. To achieve these goals, Astra Zeneca has employed a number of strategies to promote green chemistry.

One strategy, called the "SHE Triggers" model is used in the early stages of manufacturing process development for new active pharmaceutical ingredients (API) and aids in the identification and elimination of potential safety, health, and environmental issues. The "SHE Triggers" model has been incorporated into secondary manufacturing process development as well as pharmaceutical products development (including packaging and devices).

Another strategy employed by Astra Zeneca is a Green Chemistry Network linking chemists and engineers within process development with environmental specialists, who aid them in integrating principles of green chemistry. The Green Chemistry Network's environmental specialist use a tool kit that incorporates: a solvent selection guide, acid/base, alkylating agent, and amide formation reagent selection guides, a substance avoidance database, and an active pharmaceuticals ingredient removal technology selection tool, to aid them in teaching green chemistry to process development. The solvent selection guide gives the process development scientist/engineer assistance in selecting the most environmentally friendly solvents. The acid/base, alkylating agent, and amide formation reagent selection it enables

intelligent selection of reagents based on their environmental considerations. The substance avoidance database chronicles substances on all the relevant environmental regulation lists (UK, Europe, Sweden, US), highlighting substances to be avoided and offering alternatives in their stead. The API removal technology selection tool provides assistance in identifying the most appropriate effluent treatment technology.

In 2007, a training session was held to educate Astra Zeneca's Global Process Research and Development employees about their role in minimizing the environmental impact of the manufacturing processes they were responsible for designing. Astra Zeneca is also working with more than 30 of their outsourcing partners to ensure the environmental impacts of their manufacturing processes are tracked and understood, through measuring waste production for instance. On a broader scale, Astra Zeneca works to promote the implementation of green chemistry principles through its membership in the American Chemistry Society Green Chemistry Institute's Pharmaceutical Roundtable. Astra Zeneca also promotes green chemistry education through its Green Chemistry Summer School and its AZ Green Chemistry and Engineering Grant.

Astra Zeneca's stance on waste minimization is one of prevention through continual improvement of existing processes, improved design of new processes, improved purchasing processes, and internal waste awareness programs. Whenever possible solvents are recycled and reused to minimize fresh solvent requirements and emissions abatement equipment is installed to prevent release of hazardous chemicals (i.e. volatile organic chemicals) to the environment.

V.3 Schering Plough

Schering Plough has a Sustainable Chemistry Initiative that aims to promote the use of renewable reagents and the consideration of safety and the environment in the design of manufacturing processes. A Green Chemistry Kick-off meeting was held in their Werthenstein Operations in Switzerland to initiate their green chemistry commitment. Presently, Schering Plough hosts bimonthly Green Chemistry Forums in their Chemical and Physical Sciences unit, in addition to giving external presentations to educate a broader audience about Green Chemistry.

Schering Plough has developed and updated (as of 2007) a Chemical Selection Guide which uses a color coded system to indicate the environmental impact of the chemicals listed: green (environmentally acceptable), yellow (conditionally acceptable), and red (use caution, consider alternatives), so that those with the least environmental impact may be chosen. In addition, a "Pathways to Greener Solvents" poster was distributed within the Chemical Development and Discovery division. Schering Plough also launched a web-based Process Sustainability Index (PSI) database that captures the sustainability of new products in development. In 2007 Schering Plough used the following green chemistry principles in its operations: solvent substitution and recycling, atom efficiency, in situ elimination of cyanide waste, continuous distillation, use of supercritical fluid chromatography, and enzymatic approaches.

V.4 Novartis

Novartis was named a super sector leader in healthcare for the Dow Jones Sustainability Index which tracks the economic, environmental, and social performance of sustainable companies worldwide. Novartis waste management strategy like that of most pharmaceutical companies emphasizes waste prevention followed by reduction, recycling, and reuse.

V.5 Eli Lilly

Eli Lilly is diligently pursuing green chemistry in its new production processes to ensure safer, environmentally more sound operations. Lilly has used a number of innovations to integrate green chemistry into the thought processes of their scientists and engineers.

Chemists at Lilly use electronic lab notebooks equipped with green chemistry tools that indicate when less hazardous alternatives exist and that give feedback on the efficiency of the process. Process development scientists and engineers use a system of check points to ensure efficiency and hazardous material use are within set boundaries. At each of the check points the efficiency factor (raw material input/unit of active pharmaceutical ingredient produced) is calculated, where it does not meet the efficiency factor standard a management review is triggered. The use of these new technologies (for instance replacing conventional batch reactors with coiled tube reactors) has enable Lilly to realize a 100 fold reduction in raw materials use.

In addition to monitoring and improving their own processes, Lilly assesses their third party suppliers during the selection and implementation processes to ensure they have sufficient health, safety, and environmental standards. Lilly uses a 5 step process to conduct an assessment on a 3rd party supplier, the first step is to build an understanding of the 3rd party's EHS program, then to perform a material risk review, followed by an on-site assessment, and finally to provide Lilly EHS materials to the company and assist them in meeting the necessary EHS standards.

V.6 Bayer

Bayer has made a number of operational improvements in their pursuit of green chemistry, most notably BaySIS which is an internet based tool for capturing health, safety, and environmental data (HSE). When on-site reporting mangers enter their data into BaySIS, the system cross and plausibility checks it and then incorporates it into a five year trend map. Another operational improvement Bayer has made is the integration of health, safety, environment, and quality (HSEQ) into a single high quality management system.

V.7 Bristol Meyers Squibb

Bristol Meyers Squibb intends to manufacture sustainable products that have as little effect on the environment as possible through initiatives that promote green chemistry, packaging reductions, and process safety. To meet these goals, Bristol Meyers Squibb has established specific programs to improve the EHS profiles of its key suppliers, sustainability awards to acknowledge their employees' sustainable

behaviors, and leadership development programs to help integrate EHS throughout the company. Bristol Meyers Squibb has been aggressively targeting packaging use reduction through innovative packaging design, increased recycled content, and the use of environmentally sound materials. Within their pharmaceuticals processes, Bristol Meyers Squibb aims to use renewable materials whenever possible.

A specific example of Bristol Meyers Squibb's efforts to use renewable materials is in the manufacture of Taxol. The active ingredient in Taxol, paclitaxel, is derived from the bark of yew trees found in the the Pacific Northwest. The yew trees were being killed when their bark was harvested, endangering the habitat of the spotted owl and threatening the sustainability of paclitaxel production, thus scientists investigated alternatives and found that twigs and needles from yew shrubs would also yield paclitaxel.

Bristol Meyers Squibb has set a goal of reducing their off-site emissions of chemicals it lists as priority reduction chemicals by 50% (from 2002 levels) by 2010. In classifying chemicals as priority reduction chemicals, Bristol Meyers Squibb considers the level of regulation applicable to the chemical and whether the chemical contributes to process hazards/health hazards. Presently their priority reduction chemicals include: acetonitrile, benzene, alkyl acetate, methyl isobutyl ketone, methanol, methyl-t-butyl ether, n-butyl acetate, tetrahydrofuran, toluene, and most notably methylene chloride (i.e. dichloromethane).

V.8 Pfizer

As the first pharmaceutical company to hire a full time green chemistry lead responsible cross functional teams spanning the globe, Pfizer has a strong commitment to green chemistry. Pfizer incorporates environmental, health, and safety (EHS) considerations throughout the lifecycle of its products, from raw material sourcing, to research and development, to manufacturing, and through to end use and recycling/disposal. A quote from Kuzemko et al in their article in *Organic Process Research and Development* summarizes Pfizer's role in promoting green chemistry best:

"The industry gold standard for a pharmaceutical process in which solvent usage and recycling scenarios are considered would be the Viagra (sildenafil) process...The details of this manufacturing process were disclosed, and more importantly, significant development efforts were undertaken to set this benchmark for the pharmaceutical industry."[lv]

Pfizer's green chemistry initiatives revolve around discovering innovative ways to enhance process robustness, reduce emissions and hazardous materials use, and increase recycling. Thus far Pfizer has worked to identify and replace hazardous solvents, to reduce its overall solvent usage, to perform reagent change out, and to minimize waste. Such green initiatives have helped Pfizer conserve energy, realize cost savings on new and established products, and gain public recognition for their green efforts.

In order to facilitate Pfizer's green chemistry initiatives multi-disciplinary teams composed of chemists, engineers, and EHS professionals work collaboratively to first identify opportunities for EHS process improvements and then implement those improvements. These chemists, engineers, and EHS professionals use internally developed guides to aid them in the selection of environmentally responsible

solvents and reagents. In addition, Pfizer participates in a number of community outreach programs to educate the populous about green chemistry. Pfizer sponsors on-site workshops and site visits for undergraduate and graduate students highlighting their use of green chemistry in achieving sustainable product development. Pfizer is also developing green chemistry curriculum for middle and high school students and actively participates in national and international conferences, seminars, and workshops focused on green chemistry.

A number of specific examples of the inroads Pfizer has made in implementing green chemistry in its campaigns exist. Pfizer was able to achieve a 65% reduction in the total organic waste (3.5 million L/year of methanol and tetrahydrofuran) and eliminate liquid nitrogen use in one step of the synthesis of Lipitor, their blockbuster high cholesterol drug. Process improvements in the third generation synthesis of Lyrica (a drug used for neuropathic pain associated with diabetes or shingles) resulted in the elimination of 5 million gallons of solvent per year and more than 150 tons of nickel catalyst. Pfizer won the top European Green Chemistry award, the Excellence in Green Chemistry and Engineering Award for their accomplishments in Lyrica process improvement. Pfizer utilized novel process innovations including a highly selective coupling reaction and a ultra efficient intermediate synthesis to design away 25,000 metric tons of waste per year in its Vfend (an antifungal medication) campaign. In 2003, Pfizer won the UK's IChemE award (the Crystal Faraday Award for Green Chemical Technology) by significantly reducing the annual organic process waste burden (from 4,300 to 300 tons/yr) associated with the production of Viagra. Pfizer won the US EPA's 2002 Presidential Green Chemistry Award for green chemistry improvements in the synthesis of Zoloft that doubled process yield and significantly reduced the process's environmental burden.

Pfizer's commitments to green chemistry extend beyond their processes to those of their suppliers and contract manufacturers, in 2007, Pfizer conducted 140 EHS audits of its suppliers, 27 follow up reviews, and provided coaching on EHS standards to 19 of its suppliers. In addition Pfizer helped develop the Pharmaceutical Supply Chain Initiative which attempts to standardize EHS competencies across suppliers to the pharmaceutical industry.

V.9 Glaxo Smith Kline (GSK)

Glaxo Smith Kline (GSK) has identified five priority areas of focus to ensure the environmental, health, and safety profiles of the chemicals it uses and produces are as innocuous as possible: 1.) hazard assessment and communication, 2.) substitution of hazardous chemicals, 3.) transparency, 4.) supply chain management, and 5.) sustainable chemistry.

Hazard assessment and communication requires that GSK identify the hazards intrinsic in its process through an EHS assessment. Where information regarding a hazard is unavailable within GSK methods to obtain information from suppliers and the literature should exist. Once adequate information is gathered about process hazards it should be shared with relevant stakeholders including employees, contract manufacturers, and suppliers to enable them to manage the hazards properly.

Substitution of hazardous chemicals involves categorizing certain chemicals as having priority for substitution, then assessing whether feasible, less hazardous alternatives for those chemicals exist. When

developing new products emphasis should be placed on identifying instances where a less hazardous alternative exists and making the appropriate substitution. In existing manufacturing processes, "priority chemicals" replacement should be pursued if it is technically and economically feasible, otherwise appropriate risk management measures should be employed to ensure adverse effects are minimized. GSK realizes that implementing substitution in an existing process requires considerable effort to ensure that the substitute does not affect the overall chemistry of the process and that the efficacy and/or patient safety profile has not been altered, therefore substitution is primarily pursued in new process development.

Transparency, whenever competitive advantage is not lost in the process is pursued by GSK to ensure that their stakeholders understand what constitutes a "priority chemical" and what progress is being made in terms of eliminating or otherwise substituting "priority chemicals". Furthermore, GSK shares their risk management practices for the continued use of "priority chemicals" and the EHS data on its products, to ensure adverse environmental impacts are minimized.

Supply chain management helps GSK ensure that its internal EHS standards are met throughout its supply chain from contract manufacturers to suppliers. GSK conducts pre-contract EHS evaluations and periodic EHS audits of their suppliers and contract manufacturer to ensure that consistent EHS standards are maintained. GSK selection criteria for suppliers or contract manufacturers, requires that robust EHS management systems and responsible care programs are maintained.

Sustainable chemistry initiatives at GSK aim to minimize chemical use (and therefore waste) through implementation of process design and process efficiency innovations. Wherever possible GSK strives to use safer alternatives to hazardous chemicals, where that is impossible GSK seeks to manage their EHS risks effectively. Furthermore, GSK explores opportunities to use renewables, biotransformations, and inherently safer chemistry; while optimizing recycling and reuse.

GSK has designed an Eco Design tool kit to aid their employees in addressing the 5 priority areas outlined above. This tool kit includes a Green Chemistry and Technology guide, Materials guide, Green Packaging Guide, a Fast Lifecycle Assessment for Synthetic Chemistry (FLASC) tool, and Chemicals Legislation Guide. The Green Chemistry and Technology guide provides information on how to improve efficiency, reduce environmental impacts, and minimize costs through green chemistry. The Materials guide summarizes the environmental impacts of solvents and reagents. The Green Packaging guide aids in the selection of environmentally sound packaging materials. The Fast Lifecycle Assessment for Synthetic Chemistry (FLASC) is a web-based tool to help identify the environmental impacts of a synthesis and offer greener alternatives, it is used to compile a environmental scorecard for each campaign. The Chemicals Legislation Guide (CLG) provides a quick reference on hazardous substance legislation. Green chemistry metrics are collected for each potential new drug in development to determine whether raw materials are being used efficiently, what hazardous chemicals are being employed and their possible environmental impacts, this information is then used to determine whether a new drug should be promoted or not.

In light of the fact that pharmaceutical companies typically use approximately 100 tons of raw material for every ton of active pharmaceutical ingredient produced, GSK has committed to a goal of doubling the material efficiency of its manufacturing processes for new products from 2006 by 2010.

One relatively simple example of where GSK has made strides in improving its environmental footprint can be found in their replacement of batch manufacturing with continuous manufacturing in their production of toothpaste. In switching from batch to continuous manufacturing GSK was able to reduce their annual costs by forty five thousand pounds, reduce raw material consumption by 24.5 tons/year, and reduce water consumption by 20 million L/year.

V.10 Big Pharma considerations weigh on Med Dev

All of the major pharmaceutical companies are actively investigating ways to make their processes, and those of their suppliers, more environmentally friendly on the grounds of reputational as well as economic gains. These companies are placing increasing environmental scrutiny on not only their suppliers, but also their acquisitions, thus if Med Dev wishes to pursue acquisition as a growth strategy, the environment should be factored into their process design.

VI. Hurdles to Green Chemistry? How do they affect Med Dev?

Product designers face constant pressure to devise new products in a faster, cheaper manner and it is against this backdrop that green chemistry must attempt to vie for their time and attention. Time to market considerations are particularly crucial in a start-up environment, like Med Dev's, where the company's operations are essentially cash flow negative until its first product successfully enters the market. A staged approach to implementing green chemistry practices in manufacturing may be appropriate for companies where time is of the essence, where the changes which are quickest/involve the least amount of change or are projected to be costly to change in the future (i.e. requiring FDA re-validation) could be implemented first, with other incremental improvements being made according to a schedule.

Another method of facilitating design for the environment is through the creation of a green chemistry team which identifies areas in the design which could be improved with green chemistry techniques. Admittedly a green chemistry task force would be difficult to establish within a start-up employing 7 people, however a start-up may look toward external sources, such as the Massachusetts Office of Technology Assistance (OTA), to assist them in identifying green opportunities.

Yet another method of ensuring green principles are designed into a process is the use of a design checklist/framework, which would direct a designer to consider the environment at various stages in the design process. Comprehensive checklists are not generally part of a start-up, like Med Dev's modus operandi, however implementing such a systemic approach to designing for the environment may ensure that considerations that would otherwise be ignored would be included in the design.

Certainly green chemistry initiatives aid in cutting costs, but those cost cutting provisions are not always inherently obvious up front, such savings are often long term rather than near term. Start-ups with

funding limitations often do not have the luxury of expending in the short term to see long term benefits; their focus is the present. In fact, a start-up may argue against incurring the expense of designing for the environment upfront while funds are tight, when deferring such decisions until a larger company acquires them or they became a publicly traded entity would be less financially cumbersome. The large company acquisition scenario, would transfer the responsibility for environmentally responsible operations to the acquirer. With environmental standards becoming more and more stringent today and companies focusing on their environmental performance from cradle to grave, there is a strong possibility that a company's environmental report card may become a determining factor in its ability to be acquired. In the publicly traded scenario, the company maintains responsibility over its early environmental choices, which may have legacy implications on process efficiency and waste generation. Furthermore, with indexes like the Dow Jones Sustainability Index and the FTSE4 Good Index gaining ground, it is likely that investors of the future may invest contingent upon a company's environmental performance. In the end, designing for the environment may be more costly (though it might also cost the same or less) in the short term, the only true way to identify its impact on a company's bottom line is through a holistic view of the process using Life Cycle Assessment techniques.

One of the greatest concerns medical device companies have in regards to making environmentally driven post-approval process changes is whether they'll have to conduct a revalidation for the FDA. Such a concern is valid, since the FDA rigorously regulates process changes and since revalidation would undoubtedly involve additional, costly clinical trials. Designing a robust quality management systems (QMS) when filing with the FDA may ensure that post approval changes may be made without the necessity of a FDA review and validation. According to "An Environmental Guide for the Medical Device Industry in Massachusetts"[lvi] many medical device companies make environmentally driven process changes without seeking revalidation from the FDA.

VII. What possible avenues can Med Dev pursue to Green their manufacturing process?

Med Dev has limited influence over the environmental performance of its first generation product as they rely on a supplier (Boehringer Ingelheim) to provide them a synthesized polymer (PLGA). The PLGA synthesis represents the least environmentally favorable portion of Med Dev's first generation production process. Although Boehringer Ingelheim largely dictates how PLGA is produced, Med Dev could attempt to educate them about possible greener alternatives, like solvent substitution. Boehringer Ingelheim's production method was discussed in the section detailing Med Dev's first generation production process and is considered the industry standard, however another greener methodology is emerging and Med Dev may attempt to source their materials from this alternate source.

A limited liability corporation between Cargill and Teijin Limited of Japan called NatureWorks, LLC[lvii] has devised a method to ferment lactic acid from corn, using an estimated 65% less fossil fuel and reducing their green house gas emissions by 80-90% compared to producing traditional petroleum based polymers[lviii]. Deriving polymers from natural annually renewable materials, represents a huge environmental gain as compared to their synthetic derivation. Their process consists of the following steps[iv]:

1.) Farmers harvest corn and it is sent to a milling plant

2.) The corn is cooked for 30-40 hrs at 122°F at the milling plant causing it to swell and soften, the resultant water is used later in the process and in the production of animal feed
3.) The corn mixture is machine ground and screened to isolate starch, which is then converted into sugar
4.) The sugar is converted into lactic acid by microorganisms in the fermentation process
5.) The lactic acid molecules combine to form oligomeric lactide rings
6.) The oligomeric lactide rings are opened through a condensation reaction to form a long chain polylactic acid polymer

The final polymerization step described above (ring opening polymerization through condensation) typically results in low molecular weight polylactic acid polymers, thus for NatureWork's polymer to be used for Med Dev's purposes, in medical devices, the polymerization methodology would have to change. Unfortunately, even a polymerization method change would not suffice to make sourcing NatureWork's polylactic acid a possibility, as they do not allow the use of their polymer for medical purposes. An inquiry[lix] to NatureWorks, LLC to determine whether they were currently partnering with any pharmaceutical/medical device companies to supply PLA as a feedstock for polymer synthesis garnered the following response:

"NatureWorks LLC customer agrees that, unless permitted by NatureWorks LLC in writing, customer will not use or allow others, including their customers, to use Ingeo™ biopolymer or products made from NatureWorks' biopolymer, in the following:

(i) Components of or packaging for tobacco products.
(ii) Components of products intended for human or animal consumption.
(iii) In any application that is intended for any internal contact with human body fluids or body tissues.
(iv) As a critical component in any medical device that supports or sustains human life.
(v) In any product that is designed specifically for ingestion or internal use by pregnant women.
(vi) In any application designed specifically to promote or interfere with human reproduction."[v]

While NatureWorks' nature based plastic is not presently available for Med Dev's use, more naturally synthesized polymers may be available in the future and could become an important part of Med Dev's green manufacturing strategy for its first generation product.

Med Dev is more directly responsible for the environmental performance of its second generation product, as it performs the polymer hydrogel synthesis itself. In the second generation polymer synthesis, the substances of greatest environmental concern include: dichloromethane, diethyl ether, hexane, and stannous 2-ethyl hexanoate. Environmentally benign alternatives to each of these toxic or hazardous substances have been identified and the discussion that follows is a proposal for designing for the environment. In this proposal, dichloromethane will be substituted by a less toxic solvent, while diethyl ether, hexane extraction will be replaced with supercritical carbon dioxide extraction.

Solvent substitution requires the least modification to an existent synthetic process of any approach to green manufacturing, however easy substitutes do not always exists and care must be taken not to replace a highly toxic substance with a marginally less toxic substance. When evaluating possible solvents for substitution three things must be considered: 1.) the physical and chemical properties of the

original solvent, 2.) the EHS profile desired, and 3.) the reagent (i.e. solute) solvent interactions. Dichloromethane is capable of dissolving many organic molecules, has favorable physical properties (it is a weak Lewis Base), is inert toward reagents and reaction conditions, and can be used in oxidations, organometallic reactions, Lewis Acid reactions, and functional group interconversions[lx]. The major impediments to continued use of dichloromethane include its toxicity and its low boiling point (39°C). Water or phosphate buffered saline (PBS) should be not be considered when choosing possible substitutes for dichloromethane in the synthesis of PEG-co-poly(lactic acid) diacrylate, as the reagent acryoyl chloride is hydrolysable.

Ogawa et al[lxi] identified benzotrifluoride ($C_6H_5CF_3$) as an attractive alternative for dichloromethane, as it has a relatively low toxicity and price, is slightly less polar than dichloromethane, but more polar than ethyl acetate. Benzotrifluoride has not been used extensively as an organic solvent, however it is capable of dissolving a number of organic solutes. Ogawa et al conducted head to head (dichloromethane to benzotrifluoride) reactions to determine the suitability of benzotrifluoride as a substitute for dichloromethane. The reactions demonstrated included: derivatization of alcohols, oxidation of alcohols, and carbon-carbon bond formation. Through these reactions Ogawa et al showed that benzotrifluoride was a appropriate substitute for dichloromethane, though its freezing point may be too high for certain applications, it is susceptible to reduction, and it may be hydrolyzed by aqueous acids a high temperatures.

Gani et al[lxii] devised a 4 step solvent selection process for solvent substitution using a computer aided molecular design (CAMD) technique. In step 1 the functions of the solvent to be substituted are identified from the process description, functions include: the ability maintain inertness while dissolving a reactant, the ability to isolate the product, or the ability to serve as a intermediate wash. In the second step, search criteria are devised, these search criteria are called R-indices and indicate the physical and chemical properties, EHS characteristics, and operational properties of a solvent. Target alternatives may be identified by setting upper and lower bounds on the values of the search criteria, where all solvents falling within the bounds are considered. In the third step, the search is performed, where a list of solvent candidates that fall within the R index bounds outlined in the search criteria step is generated and then assigned RS indices according to the rules laid out in table 10. In step 4, those solvent candidates with RS indices are assigned scores (S) according to the following scale:

RS Index	Corresponding S score
1	10
2	8
3	6
4	4
5	1

Table 10: Definition of S scores. Given the RS index, the corresponding S score is shown.

Any solvent receiving an S score of 1 will be eliminated from contention. Once the list of solvent alternatives has been generated, then each solvent on the list must be investigated for substitution through laboratory experiments. Head to head comparisons between the solvent to be substituted and the

substitute are conducted, and successful candidates will demonstrate behavior identical to that of the original solvent.

Gani et al applied this search methodology to identify substitutes for dichloromethane. The dichloromethane being substituted was used to inertly dissolve reactants in a reaction (the exact purpose Med Dev uses dichloromethane for). The R indices formulated during the search criteria identification included:

R index	Value	Meaning
R0	1	Solvent addition required to improve reactants miscibility
R1	1	Reaction occurs in liquid phase
R2	278 K	Reaction temperature is 278 K
R3	1	Solvent must dissolve reactants
R4	0	Solvent does not need to dissolve products
R5	1	Solvent must have phase split with water
R6	1	Solubility parameters for DCM are known
R7	1	Solvent must be inert toward reactants/products
R8	1	Solvent should not associate/dissociate
R9	1	Solvent should have desirable EHS properties

Table 11: R-indices identified for dichloromethane in Gani et al's study[lxiii]

Once the R-indices were identified, they were used as criteria to perform a search of a solvent database for possible candidates. Ethyl acetate, isopropyl acetate, ethyl propionate, toluene, and methylcyclopentane were identified as possible candidates and assigned the following RS indices according to the rules laid out in table 12:

Solvent	RS2	RS3	RS5	RS6	RS7	RS8	RS91	RS92
Ethyl acetate	1	1	1	2	N/A	1	3	2
Isopropyl acetate	1	1	1	3	N/A	1	2	3
Ethyl propionate	1	1	1	2	N/A	1	2	3
Toluene	1	1	1	3	N/A	1	2	2
Methylcyclopentane	1	1	1	3	N/A	1	2	2

Table 12: RS indice for possible dichloromethane substitutes, generated by Gani et al[lxiv]

The RS values were then assigned their corresponding S scores, and any solvent receiving an S score of 1 was eliminated from consideration.

Solvent	S2	S3	S5	S6	S7	S8	S91	S92	Score
Ethyl acetate	10	10	10	8	N/A	10	6	8	62
Isopropyl acetate	10	10	10	6	N/A	10	8	6	60
Ethyl propionate	10	10	10	8	N/A	10	8	6	62
Toluene	10	10	10	6	N/A	10	8	8	62
Methylcyclopentane	10	10	10	6	N/A	10	8	8	62

Table 13: S scores corresponding to the RS indices for possible dichloromethane substitutes, generated by Gani et al[lxv]

Ethyl acetate, isopropyl acetate, ethyl propionate, toluene, and methylcyclopentane were all identified as suitable substitutes for dichloromethane using Gani et al's 4 step computer aided molecular design methodology. The true test for whether these proposed substitutes will be truly suitable is a head to head laboratory comparison between a process performed using dichloromethane and the same process being performed with the proposed substitute. A successful substitute will demonstrate identical behavior to dichloromethane and will not affect the resultant products characteristics in any way.

Rule	Reaction index calculation (R_i)	Reaction–solvent indices calculation (RS_i)
Rule A: Establish need for solvents	$R_0 = 1$	N/A
Rule B: Liquid-phase reactions	If $R_0 = 1$, and if the reaction must be occurring in the liquid phase, set $R_1 = 1$. Otherwise, set $R_1 = 0$	N/A
Rule C: The solvent must be liquid at the reaction temperature	R_2 = specified reaction temperature	Remove the solvents from the candidates list that are not likely to be liquid at $R_2 \pm 20$ K, where R_2 is the specified reaction temperature. That is to say, the melting point of the solvent must be lower, and the boiling point must be higher, than the reaction temperature. Note that values for RS_2 are needed only if $R_1 = 1$
Rule D: Need the solvent as a carrier	If one or more reactants are solids (or large molecules) set $R_3 = 1$. Otherwise, set $R_3 = 0$	If $R_3 = 1$, solvent is needed as a carrier for the reactant in the liquid phase. Assign RS values according to the following rules: $RS_3 = 1$, if reactants are totally miscible; $RS_3 = 2$, if reactants are highly soluble; $RS_3 = 3$, if reactants are soluble; $RS_3 = 4$, if reactants are slightly soluble; $RS_3 = 5$, if reactants are not soluble
Rule E: Need solvent to remove products	If one or more of the products are solid (or large molecules), set $R_4 = 1$. Otherwise, set $R_4 = 0$	If $R_4 = 1$, solvent is needed to remove the product from the reacting phase. Assign RS values for solvents according to the following rules: $RS_4 = 1$, if products are totally miscible; $RS_4 = 2$, if products are highly soluble; $RS_4 = 3$, if products are soluble; $RS_4 = 4$, if products are slightly soluble; $RS_4 = 5$, if products are not soluble
Rule F: Need for phase split	If phase split is necessary, set $R_5 = 1$. Otherwise, set $R_5 = 0$	Create a LLE or a SLE diagram where the phase split can be seen and according to this assign the RS indices
Rule G: Matching of solubility parameters of solute and solvent	If $R_3 = 1$ or $R_4 = 1$, then $R_6 = 1$. Otherwise, $R_6 = 0$	Create a graph with Hansen hydrogen solubility parameter values on *X*-axis and Hansen polar solubility parameter values on *Y*-axis. In this way this index has been assigned
Rule H: Neutrality of the solvent	If $R_3 = 1$ or $R_4 = 1$, set $R_7 = 1$ if the solvent must be neutral to all the compounds present in the reacting system. Otherwise, set $R_7 = 0$	If $R_7 = 1$, check for the solvent pK_a value for the feasible solvents and assign RS_7 values based on the following rules: $RS_7 = 1$, if $pK_a > 3$; $RS_7 = 2$, if $2 < pK_a > 3$; $RS_7 = 3$, if $1 < pK_a > 2$; $RS_7 = 4$, if $0 < pK_a > 1$; $RS_7 = 5$, if $pK_a < 0$
Rule I: Association/dissociation properties of the solvent	If the solvent must not associate or dissociate, set $R_8 = 1$. Otherwise, set $R_8 = 0$	If $R_8 = 1$, check for the solvent molecule type data for the feasible solvents and assign RS_8 values based on the following rules: $RS_8 = 1$, if solvent is non-polar; $RS_8 = 2$ or 3, if solvent is polar non-associating; $RS_8 = 4$, if solvent is associating; $RS_8 = 5$, if solvent is ionic
Rule J: EHS property constraints	If EHS properties are to be used as constraints, set $R_9 = 1$. Otherwise, set $R_9 = 0$. Since there are a number of EHS properties, each R_9 and its corresponding RS_9 index has a second subscript to identify the specific EHS property. RS_{91} correspond to LC_{50} and RS_{92} corresponds to $\log K_{ow}$	If $R_9 = 1$, then set the goal values for LC_{50} and $\log K_{ow}$ and retrieve the solvent values for the corresponding properties and assign the RS_9 values according to the following rules: $RS_9 = 1$, if $G_s = G \pm 5\%$; $RS_9 = 2$, if $G_s = G \pm 10\%$; $RS_9 = 3$, if $G_s = G \pm 15\%$; $RS_9 = 4$, if $G_s = G \pm 20\%$; $RS_9 = 5$, if $G_s > G \pm 20\%$, where G is the goal value of a specific EHS property G_s is the corresponding solvent property

Table 14: Appendix A Rules for calculating the Reaction Index (R_i) and the Reaction-Solvent (RS_i), copied verbatim from Rafiqul Gani, Paola Arenas Gomez, Milica Folic Concepcion Jimenez-Gonzalez, David J C Constable, *Solvents in Organic Synthesis: Replacement and Multi-Step Reaction Systems,"* Computers and Chemical Engineering, 32, 2008, pg 2420-2444.

While simply replacing a toxic solvent with another, less noxious solvent seems like a logical and easy approach toward producing environmental benefit, the resultant outcome may not be the best.

According to Fages et al[lxvi] two thirds of pharmaceutical products are particulates, the majority of which are generated via crystallization or precipitation. Supercritical processes serve as an environmentally friendly alternative to precipitation for compounds which are susceptible to thermal stress, producing highly pure micro/nano particles with narrow size distributions in a single step. A supercritical fluid is any substance whose temperature and pressure are both higher than their corresponding critical point values (Tc and Pc). The supercritical phase replaces distinct liquid and gas phase and the thermophysical properties of supercritical fluids are unique from those of the liquids and gases.

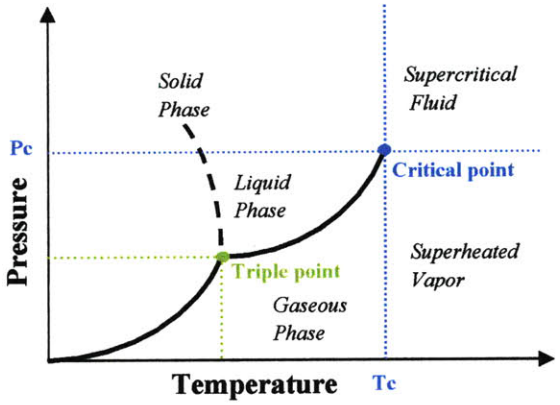


Figure 9: Phase diagram demonstrating critical temperature and pressure, as well as supercritical fluid (adapted from http://en.wikipedia.org/wiki/Critical_point_(thermodynamics))[lxvii]

Supercritical fluids have liquid like densitities, high compressibilities, intermediate viscosities, and substantially higher binary solute diffusion coefficients compared to liquids[lxviii]. Supercritical fluids are capable of dissolving many nonvolatile, thermally labile substances; manipulation of this solvency over a range of temperatures and pressures allows these fluids to be used as effective extraction agents. Supercritical carbon dioxide, in particular, has been used extensively as an extraction agent in the pharmaceutical, food processing, and other allied chemicals industries due to its innocuous nature: it has a relatively low supercritical temperature (Tc= 31.04) and pressure (Pc= 72.8 atm), it is non-toxic and nonflammable, and it will not leave a toxic residue. Three families of supercritical fluid processes exists: Rapid Expansion of Supercritical Solutions (RESS), Supercritical Antisolvent (SAS), and Particles from Gas Saturated Solutions (PGSS).

The RESS process is comprised of two steps, in the first the substance of interest is dissolved in a supercritical fluid, while in the second the supercritical fluid/substance mixture is rapidly depressurized through a nozzle. The rapid depressurization results in particle nucleation and generation. Figure 10 shows the process, liquid CO2 is pumped through a pressure regulating pump to a heat exchanger where it is superheated, then it is fed into the extraction autoclave where it mixes with the solute prior to being expanded through a nozzle at the top of the expansion chamber.

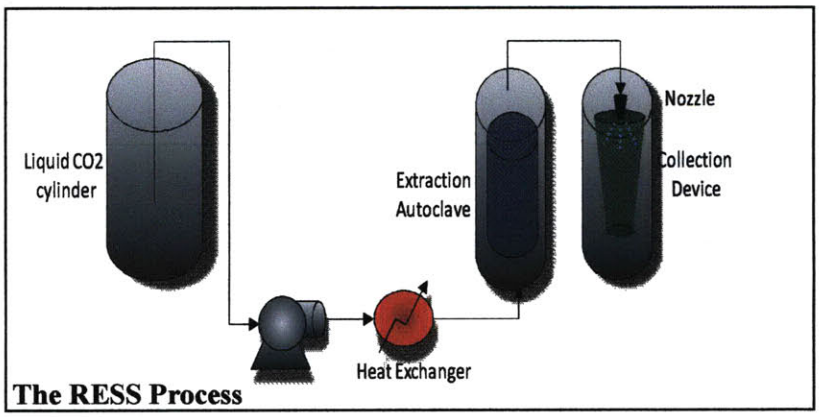


Figure 10: Schematic of the RESS Process, adapted from Fages et al[lxix]

Expansion is an isenthalpic process in the single (vapor) phase zone of a pressure-enthalpy phase diagram and occurs with a simultaneous drop in temperature.

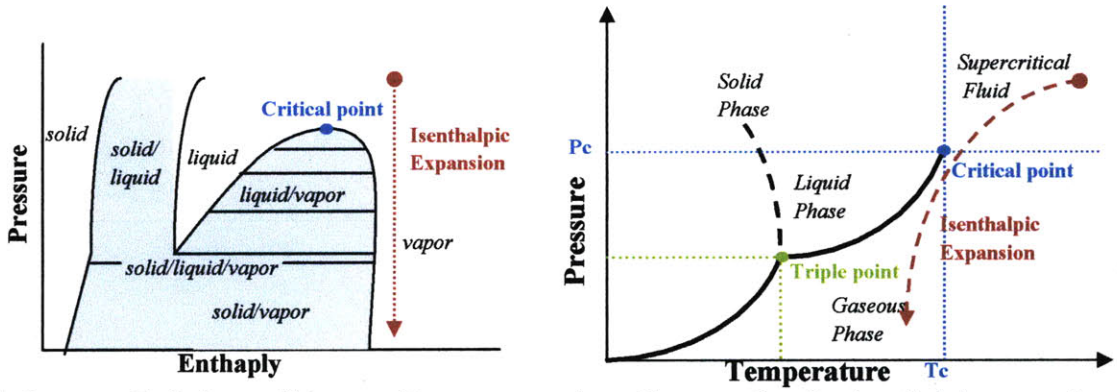


Figure 11: Pressure-Enthalpy and Pressure-Temperature phase diagram, showing isenthalpic expansion. Notice that as the pressure decreases, the temperature also decreases. Adapted from Fages et al[lxx]

The starting temperature must be sufficiently high (360 K = 87°C) to avoid condensation/freezing of the supercritical fluid post expansion, however thermo-labile solutes may be adversely affected. To counteract the temperature drop upon expansion and avoid clogging of the nozzle, a heated nozzle or a heating device upstream of the nozzle may be used. Solute nucleation is initiated by mechanical perturbation upon sudden expansion and is predicated by operating conditions, the nature of the fluid, and the length of the nozzle. During solute nucleation solute solubility falls several orders of magnitude on a time scale of 10^{-4} to 10^{-6} s, leading to high super saturation ratios.

The super saturation ratio (S) is defined as the concentration of the solute divided by its solubility (i.e. its concentration at saturation). Supercritical fluids are often capable of dissolving a particular solute much more effectively than their ideal gas counterparts, as much as 10^5 or 10^6 times as effectively, this phenomenon is captured in a parameter called the enhancement factor. The enhancement factor is the ratio of the solute solubility in a supercritical fluid divided by the theoretical solute solubility in the corresponding ideal gas. The enhancement factor phenomenon, implies that large supersaturation ratios

can be obtained, when the supercritical fluid is expanded to an ideal gas. Large supersaturation ratios will result in the formation of a large number of small particles, in fact particle size is dictated by manipulating the pressure drop at the nozzle and/or the solute concentration (i.e. the supersaturation ratio). A balance must be struck between generating very small particles with a high supersaturation ratio and maintaining some pressure in the expansion vessel to facilitate recycling. The less a supercritical fluid is perturbed from its initial pressure, the easier it will be to recycle.

The RESS process is not universally applicable, as some solutes are insoluble in supercritical carbon dioxide. The solubility issue may be solved by using a different supercritical fluid, though other supercritical fluids may be more hazardous than supercritical CO_2 and may require harsher supercritical conditions. Entraining a co-solvent, such as ethanol or acetone, in supercritical CO_2 may also facilitate better solute solubility, but at the cost of employing a less environmentally friendly solvent. RESS has been used encapsulate naproxen in poly(lactic acid)[lxxi], where poly(lactic acid) is soluble in CO_2; PEG on the other hand is insoluble in CO_2 and a co-solvent must be used in the RESS process to affect PEG encapsulation of proteins like lysozyme and lipase[lxxii]. The RESS process has been used in the pharmaceutical industry for production of single constituent particles (aspirin and ibuprofen), encapsulation, and coating of pre-existing particles. In addition, RESS has replaced traditional organic solvent precipitation as the extraction method for decaffeination of coffee. Jung et al[lxxiii] have performed an extensive literature review on the use of RESS across various industries and their findings can be found in appendix X.

The supercritical antisolvent (SAS) process overcomes the solute solubility limitations associated with the RESS process, by using the supercritical fluid as an antisolvent. The solute is dissolved in a solvent (ethanol, acetone, ethyl acetate, dichloromethane) and co-injected with a supercritical fluid through a nozzle into an extraction vessel pre-charged with antisolvent (to achieve a specific pressure), as shown in Figure 12. When a solute is added to a solvent/antisolvent system, there is less miscibility between the solvent and antisolvent (i.e. a smaller antisolvent effect) as the solute competes with the antisolvent for interaction with the solvent. Particle formation is facilitated by the collision of drops of solute solution with the supercritical fluid phase, the supercritical fluid dissolves and then evaporates the solvent lowering its solvent power forcing the solute to precipitate. Once particles are formed it is often necessary to strip any entrained solvent by flowing fresh antisolvent (i.e. supercritical fluid) over them.

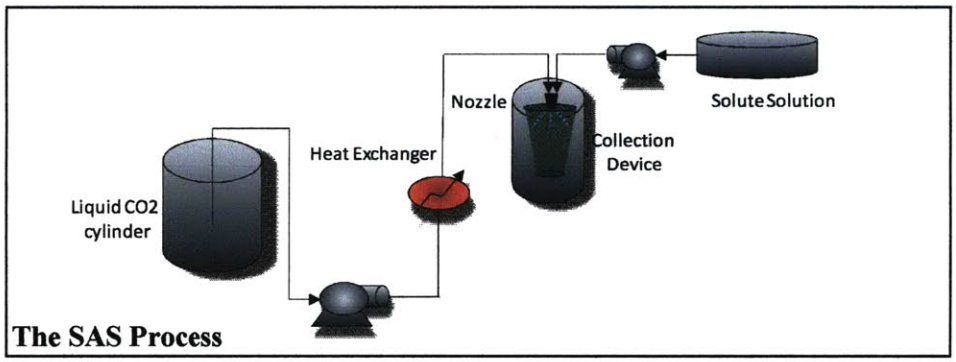


Figure 12: Schematic of the SAS process. Adapted from Fages et al[lxxiv]

The solvent should be chosen based on its miscibility with the antisolvent, ability to dissolve the solute, and its non-toxic nature. The optimal solvent-antisolvent miscibility can be determined by looking at the phase behavior of the mixture, as postulated by Scott and Van Konynenburg and discussed in Lora et al[lxxv], solvent-antisolvent systems with type I phase behavior (a single liquid-gas critical point, and no liquid-liquid immiscibility) should be selected. Selection between type I solvent-antisolvent systems should be dictated by the volatility of the solvent, as a more volatile solvent will be easier to remove from the final particles.

The nozzle plays an important role in solute solution-antisolvent mixing and particle formation, as it serves to increase the interfacial area and mass transfer rate of the solvent with the antisolvent by uniformly injecting small liquid droplets into the continous supercritical fluid. Once the solute solution-antisolvent droplets leave the nozzle, they are subjected to three forces: cohesive forces (i.e. surface tension) that resist break up, velocity dependent friction between the droplets and the continuous supercritical fluid in the extraction vessel, and turbulence within the droplets whose radial components are no longer constricted once through the nozzle. Atomization, or immediate generation of very fine particles upon nozzle clearance, is achieved when friction and turbulence forces are very large and can be manipulated through choosing a low nozzle length to diameter ratio, pressurizing the extraction vessel, and choosing a solvent with a low viscosity and surface tension.

Operating temperature and pressure are rather important, while a higher temperature might be desired to promote solvent evaporation, it requires a simultaneous increase in pressure to ensure the anti-solvent effect is still strong enough to affect precipitation. The pressure may be increased to the critical point of the solvent/anti-solvent mixture, thereby creating two fully miscible components, enabling faster mass transfer. The presence of the solute, however, raises the critical point and the associated critical pressure may be too high for operation.

In the RESS process particulates are formed in the gas phase, while in the SAS process particulate formation occurs in the supercritical CO_2-solvent mixture. A solute's residence time in the supercritical mixture should be minimized in order to avoid such phenomenon as dissolution-recrystalization and solid-solid transition which may cause polymorphs (different morphological forms of the particle to form). Polymorphs are a particular issue in the pharmaceutical industry because of their potential to perturb compound activity and shelf life. Kordikowski et al[lxxvi] have demonstrated, through the choice of the appropriate flowrate and operating temperature that polymorphs may be avoided. SAS has been used with a wide variety of molecules such as antibiotics, proteins, and biopolymers owing to the fact that it does not require solubility in supercritical CO_2. Furthermore SAS allows for the co-precipitation of two different compounds simultaneously resulting improved dissolution rates or drug release systems. Jung et al[lxxvii] have also performed an extensive literature review on the use of SAS across various industries and their findings can be found in appendix X.

The Particles from Gas Saturated Solutions (PGSS) process utilizes the fact that dense gases can be dissolved in large quantities of liquids. Typically gaseous CO_2 is dissolved to the point of saturation in a solution-suspension of solute or a melted solid, then expanded through a nozzle into an expansion chamber where particles are formed. The PGSS is widely used in polymer process where it has been shown to modify glass transition and melting temperatures, as well as densitites.

VII.1 Economics of supercritical CO2 for Med Dev

The laboratory process for generation of PEG-co-poly(lactic acid) diacrylate macromer requires three diethyl ether precipitations and a hexane precipitation. The precipitations use large amounts of costly, toxic solvents and result in the generation of polydisperse particles which lack reproduciblitity, so not only are they terrible for the environment but they are also not very defensible against FDA regulations, which require reproducibility. Approximately 9 L (6 L of diethyl ether and 3 L of hexane[lxxviii]) of solvent are used to generate 30 g of PEG-co-poly(lactic acid) diacrylate macromer in the second synthesis step, in mass terms:

Solvent	Volume (mL)	Density (g/mL)	Mass (g)	Cost (based on $64.50/L diethyl ether, and $67.40/L hexane)[lxxix]
Hexane	3000	0.6548	1964.4	$202
Diethyl Ether	6000	0.7134	4280.4	$387
Total Solvent	9000		6244.8	$589
$\left(\frac{\text{Mass Macromer}}{\text{Total Mass Solvent}}\right)100\%$			0.48%	

Table 15: Summary of hexane and diethyl ether use in the second synthesis step for production of 30 g of PEG-co-poly(lactic acid) diacrylate macromer. Densities obtained from Wikipedia[lxxx]

Table 15 summarizes the amount of hexane and diethyl ether used in production of 30 g of PEG-co-poly(lactic acid) diacrylate macromer, put in another way 200 times the mass of solvent is required to make the final mass of macromer (6244.8 g solvent divided by 30 g of macromer), pointing to the excesses inherent in precipitation processes.

Thar SFC, a division of Waters Corporation, manufactures supercritical CO_2 systems for particle extraction, including supercritical antisolvent (SAS) and rapid expansion of supercrical solutions (RESS) systems. Since PEG-co-poly(lactic acid) diacrylate macromer is polar and likely insoluble in carbon dioxide, thus a SAS system is appropriate for Med Dev's needs. Thar SFC's SAS system is fully integrated and is delivered ready to operate; the system includes a chilled pump head (to ensure liquid CO_2 is delivered to the preheater), a preheater, a back pressure regulator to ensure critical pressure is maintained within the particle formation vessel, a particle formation vessel, and a collection basket and two 0.5 μm stainless steel filters to ensure capture of particulates. The system is completely computer automated and can be operated and monitored through a software interface. Thar SFC's SAS50 system is capable of operating at CO_2 flowrates of 5-50 g/min and solution flowrates of 1-20 mL/min and its particle formation vessel has a capacity of 500 mL, according to its product spec sheet[lxxxi].

Solute solution flowrate (mL/min)	Time required for 3000 mL solute solution (min)	Total process time *(with additional 120 min wash)* (min)	Carbon Dioxide flowrate (g/min)	Amount of CO2 required (g)	Number of bottles of CO_2 required *(based on 20000 g/bottle)*	Cost of CO_2 *(based on $20/bottle[lxxxii])*
1	3000	3120	50	156000	7.8	$ 187.2
5	600	720	50	36000	1.8	$ 43.2
10	300	420	50	21000	1.05	$ 25.2
15	200	320	50	16000	0.8	$ 19.2
20	150	270	50	13500	0.675	$ 16.2

Table 16: Tabulation of the amount of carbon dioxide required for SAS extraction of PEG-co-poly(lactic acid) diacrylate for various solute solution flowrates, based on the second synthesis step in the 30 g synthesis.

The table above summarizes the amount of carbon dioxide required for the SAS extraction of PEG-co-poly(lactic acid) diacrylate for various solute solution flowrates for the second synthesis step for a 30 g synthesis. Antisolvent use is much higher than diethyl ether and hexane (for instance for a solute flowrate of 20 mL/min 13500 g of CO_2 are required to affect the precipitation of the product, whereas only 6244.8 g of diethyl ether and hexane would be required to affect the same precipitation (nearly 2.2 times more solvent is needed for the SAS process over the diethyl ether and hexane process). Assuming a solute flowrate of 20 mL/min, approximately 450 times the mass of solvent is required to make the final mass of macromer using supercritical CO_2,(mass of CO_2 required (assuming 20 mL/min solute flowrate) divided by mass of macromer produced (13500 g/30 g)). The cost of materials is significantly less for carbon dioxide (ranging from $43.20 to $16.20 for a 30 g synthesis depending on SAS solute flowrates between 5 and 20 mL/min respectively versus $589). The whole economic story however is only evident when the cost of the Thar SFC SAS 50 system is taken into account, the system was quoted to Med Dev for $68,115.00[lxxxiii]. A breakeven analysis shows that an investment in the SAS50 system will pay off in 2.3 years for a solute flowrate of 20 mL/min and 2.4 years for a solute flowrate of 5 mL/min. These calculations were based on 40,000 patients a year, with a market penetration of 40% (16,000 patients a year), 0.3 mL hydrogel/patient, where the hydrogel is 30% (wt/vol) PEG-co-poly(lactic acid) diacrylate in PBS. To meet this forecasted demand 1460 g of PEG-co-poly(lactic acid) diacrylate would have to be produced each year.

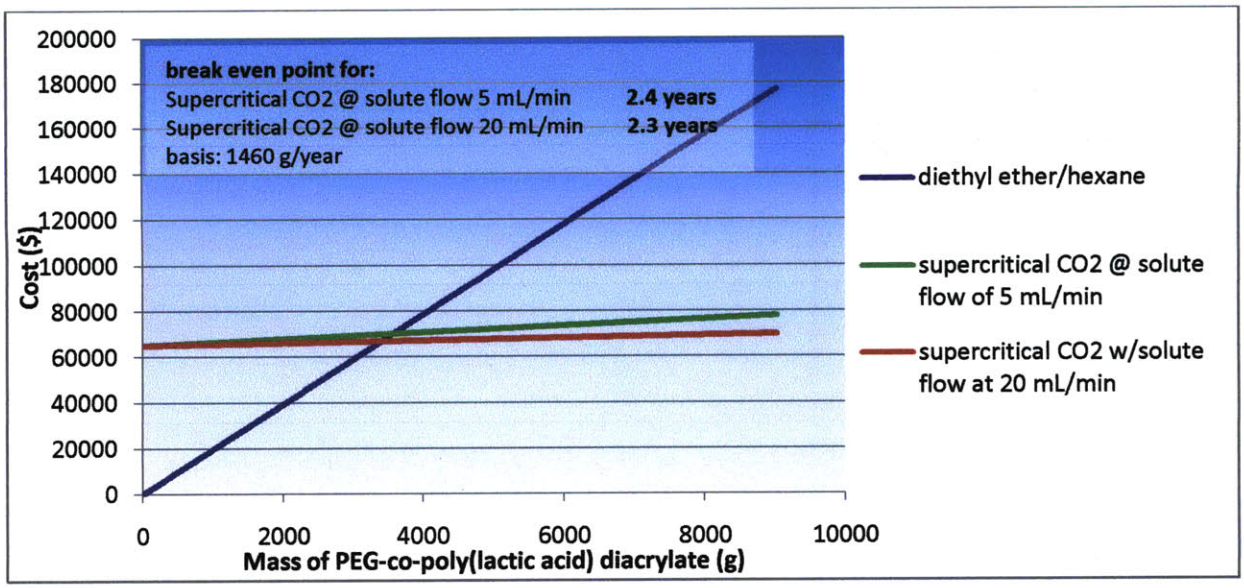


Figure 13: Break Even plot for supercritical CO_2, showing that approximately 2.35 years are required to achieve return on the SAS50 investment.

The calculations for this analysis can be found in the appendix and the results are illustrated in Figure 13, above.

The catalyst stannous 2-ethyl hexanoate was found to be a neurodegenerative agent and although used in very small quantities, its replacement might be beneficial. Stannous 2-ethyl hexanoate utilizes a coordination-insertion mechanism to catalyze reactions and other possible catalysts employing this mechanism included: aluminum alkoxides, and zinc derivatives. Aluminum alkoxides are not suitable alternatives to stannous 2-ethyl hexanoate as aluminum has been found to promote Alzhiemer's disease. Zinc derivatives, like zinc (II) lactate are nontoxic and commercially available, however laboratory scale tests have demonstrated that zinc (II) lactate is less efficient than stannous 2-ethyl hexanoate. Another class of catalysts that could work as possible substitutes for stannous 2-ethyl hexanoate include metal free catalysts, which are both economical and environmentally friendly. The enzyme lipase is an excellent example of such a metal free catalyst, it benefits from easy removal post processing, however it promotes very low yields, making it less desirable as a substitute for stannous 2-ethyl hexanoate. Since stannous 2-ethyl hexanoate is used in such minor quantities and a suitable efficient substitute does not exist for it, it may be best to continue its use and carefully monitor so that excessive residues of the catalyst do not go undetected.

VII.2 Cost Analysis of proposed solutions

A cost sensitivity analysis on the replacement of dichloromethane with ethyl acetate, isopropyl acetate, ethyl propionate, toluene, methyl cyclopentane, or benzotrifluoride shows that the % change in cost resulting from substitution ranges from -42% to 12%. The cost per liter of each of the substitutes and dichloromethane are given in table 17 below as well as the cost of manufacturing 30 g of PEG-co-poly(lactic acid) diacrylate (using 600 mL of dichloromethane (or substitute)).

Possible substitutes	Cost/L	Cost of 600 mL	% change
Ethyl acetate	$55.70/L	$33.42	-24.6%
Isopropyl acetate	$63.50/L	$38.10	-42.0%
Ethyl propionate	$39.40/L	$23.64	11.9%
Toluene	$40.90/L	$24.54	8.5%
Methyl cyclopentane	$253.00/L	$151.80	-466%
Benzotrifluoride	$44.60/L	$26.76	0.22%
Dichloromethane	$44.70/L	$26.82	

Table 17: Summary of the cost for each substitute on a per L basis, per 30 g synthesis basis (600 mL), and the % change in cost involved in substitution.

Where % change in cost is calculated from:

$$\% \text{ change in cost} = \frac{\text{cost of dichloromethane} - \text{cost of substitute}}{\text{cost of dichloromethane}} \times 100\%$$

Methyl cyclopentane will not be included in any substitution investigations, as it is too costly for consideration.

The cost sensitivity analysis on the replacement of diethyl ether and n-hexane with supercritical CO_2 extraction was performed on the basis of a 30g synthesis to facilitate comparison. Table 18 describes the cost of diethyl ether and n-hexane for a 30 g synthesis.

	Volume used in 30g synthesis (mL)	Cost/L	Cost
Diethyl ether	6000 mL	$64.50/L	$387
Hexane	3000 mL	$67.40/L	$202.20
Total	9000 mL		$589.20

Table 18: The cost of diethyl ether and hexane on a per L basis, and per 30 g synthesis basis

Substituting diethyl ether and hexane with the SAS process using the SAS50 system, would require a 2.3 to 2.4 years depending on the solute flowrate used, according to the above analysis. Once the breakeven point has been reached and the investment in SAS becomes cash flow positive, a cost sensitivity analysis on SAS versus diethyl ether and hexane extraction (on the basis of a 30 g synthesis) reveals that SAS process results in an 93 to 97% cost reduction.

	Cost for 30 g synthesis	% change in cost
SAS extraction (5 mL/min)	$43.20	93%
SAS extraction (20 mL/min)	$16.20	97%
Diethyl ether/ Hexane extraction	$589.00	

Table 19: The cost of SAS extraction (for solute solution flowrates of 5 mL/min and 20 mL/min, in order to bracket the entire data set) for a 30 g synthesis basis, compared to that of diethyl ether/hexane extraction.

Where the % change in cost is given by:

$$\% \text{ change in cost} = \frac{\text{Cost of diethyl ether/hexane extraction} - \text{Cost of SAS extraction (5 or 20 mL/min)}}{\text{Cost of diethyl ether/hexane extraction}}$$

A cost sensitivity analysis was also performed for the simultaneous substitution of dichloromethane and replacement of diethyl ether/hexane extraction with the SAS process, to reflect cost savings after the 2.3/2.4 year SAS process breakeven point. This analysis includes two factors (dichloromethane substitute, SAS process solute solution flowrate) each at two levels (ethyl propionate and isopropyl acetate, and 5 mL/min and 20 mL/min solute solution flowrate), where the levels were chosen to bracket the possible costs (with one representing the high end of the cost spectrum, and the other representing the low end of the cost spectrum). Effective comparison of these two factors at two levels requires the creation of a cost matrix:

Cost Matrix: (hi, hi) isopropyl acetate, SAS 5
(hi, lo) isopropyl acetate, SAS 20
(lo, hi) ethyl propionate, SAS 5
(lo, lo) ethyl propionate, SAS 20

Table 20: Cost Matrix for cost sensitivity analysis of dichloromethane substitution and replacement of diethyl ether/hexane extraction. For dichloromethane substitution- low: ethyl propionate ($23.64), high: isopropyl acetate ($38.10). For SAS process solute solution flowrate- low: 20 mL/min ($16.20), high: 5 mL/min ($43.20).

Once the cost matrix is created the total cost (for dichloromethane substitution and SAS extraction) for each bracketing scenario can be calculated and in this way the lowest and highest total costs (and therefore cost savings) can be identified.

	Isopropyl acetate, SAS extraction (5 mL/min)	Isopropyl acetate, SAS extraction (20 mL/min)	Ethyl propionate, SAS extraction (5 mL/min)	Ethyl propionate, SAS extraction (20 mL/min)	Dichloromethane, diethyl ether/ hexane extraction
Substitute cost	$38.10	$38.10	$23.10	$23.10	$26.82
Extractant cost	$86.40	$32.40	$86.40	$32.40	$589.20
Total cost	$124.50	$70.50	$110.04	$56.04	$616.02
% change in cost	79%	89%	82%	91%	-

Table 21: The costs associated with dichloromethane substitution and SAS extraction for each of the bracketing scenarios developed in the cost matrix: isopropyl acetate, SAS5; isopropyl acetate, SAS20, ethyl propionate, SAS5; ethyl propionate, SAS20. As well as the % change in cost as compared to using dichloromethane and diethyl ether/hexane extraction.

Depending on the dichloromethane substitute and SAS extraction solute solution flowrate chosen, the percent reduction in cost from instituting these changes ranges from 79 to 91%. Figure 14 shows this result graphically.

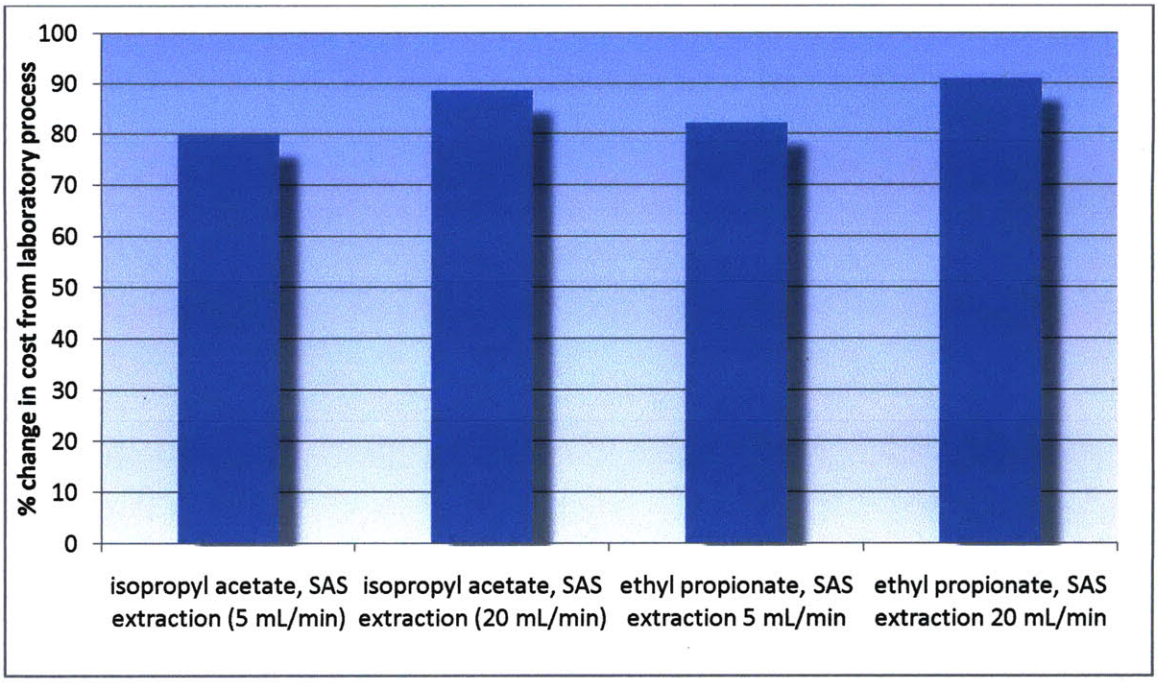


Figure 14: Percent change (reduction) in cost associated with substituting dichloromethane and implementing the SAS extraction process (after the 2.4 year break-even point).

While significant cost savings are not realized through substituting dichloromethane with a less toxic solvent (anywhere from a 43% increase to a 12% decrease in cost are associated with such substitutions), this substitution is required to avoid the possibility of costly supply chain disruptions in the future. The disposal cost of dichloromethane as opposed to that of its substitutes was not taken into account for a couple of reasons: the transportation costs are actually the largest costs associated with disposal and do not vary with the type of substance disposed (for instance: disposal of a 55 gallon drum of chlorinated solvents costs $300, while disposal of a 55 gallon drum of nonhalogenated organic solvents costs $150-200; the transportation cost irrespective of the type of waste ranges from $200-300) and Med Dev does not generate enough waste for waste disposal costs to be relevant.

The cost savings involved in replacing diethyl ether/hexane extraction with the SAS process are considerable (ranging from 93 to 97% after breaking even in 2.3 to 2.4 years). The cost analysis was again performed without consideration of disposal costs for the reasons mentioned above, inclusion of disposal costs would result in even higher cost savings.

Considering both dichloromethane substitution and the replacement of diethyl ether/hexane extraction with SAS process (after breaking even in 2.3 to 2.4 years), the cost savings can range from 79-91% depending on the solute solution flowrate used for the SAS process and the dichloromethane substitute chosen.

VIII. Conclusion

Med Dev is about to embark on designing its first manufacturing process and is investigating whether designing for the environment will provide positive returns. The above analysis laid out the laboratory

process currently used and its associated environmental problems, then offered some solutions and their possible implementation benefits. The larger context suggesting these changes was also developed in terms of present and future chemicals legislation and strides large pharmaceutical companies are presently taking to green up and down their supply chains.

On the contextual front, much of the chemical legislation today does not apply to Med Dev since they are such a small toxic substance user/hazardous waste generator. While the legislation may not directly apply to Med Dev, Med Dev must be cognizant of it because of the possible implications it could have on its supply chain (for instance if a particular chemical in Med Dev's synthesis were banned from production, Med Dev would suffer a serious supply chain disruption). Also future legislation may become even stricter abandoning *de minimus* requirements and medicinal product exemptions, directly affecting Med Dev. Designing a robust process from the beginning is of the utmost importance in the medical device industry so as to avoid costly revalidation and re-approval from the FDA.

Pharmaceutical companies are becoming increasingly aware of their environmental footprint and are making strides toward reducing their use of toxic solvents, partially in response to chemical legislation, but also due to a desire to gain a more positive public perception and to maintain cost competitiveness. Large pharmaceutical companies have experienced firsthand the cost savings that can be involved in invoking green chemistry and in an age where generics undercut their ability to gross high profit margins continually, these cost savings are essential to remaining competitive. Pharmaceutical companies are not looking within their confines alone to evaluate their environmental performance, rather they are investigating the environmental performance of their suppliers and their possible acquisitions and making decisions based on those environmental performances.

Given these contextual drivers, it makes sense that Med Dev would investigate green manufacturing early. In this thesis, possible green alternatives are offered for investigation and their costs are evaluated. In the case of dichloromethane substitution with benzotrifluoride, ethyl acetate, isopropyl acetate, ethyl propionate, or toluene the associated cost savings are not particularly compelling, but the fact that most major pharmaceuticals are moving away from its use is.

Supercritical carbon dioxide extraction presents significant cost savings (93-97% after allowing 2.3-2.4 years for capital expenditures to break even) over diethyl ether/hexane extraction, and produce reproducibly sized particles that will enhance manufacturing control and therefore lead to easier FDA approval. Overall, instituting both the dichloromethane substitution and the supercritical carbon dioxide extraction process changes would represent an 80-90% cost savings over doing nothing.

The largest concern that remains is the time required to actually implement these changes, its estimated that an investigation of the dichloromethane substitutes should take approximately a month, as should the supercritical carbon dioxide extraction process, these evaluations could be performed simultaneously, so as to ensure no additional lags. It is still unclear whether a month's wait will significantly dissuade Med Dev from these valuable process changes, but even if it did, the solutions are presented here and may be instituted in the future.

Med Dev intends to conduct human clinical trials within the next six months and delaying one month to make significant process changes could jeopardize this goal. Med Dev is a start-up, and as such there are two factors that further dissuade it from pursuing process changes that could lead to substantial future savings: 1.) start-ups have less up-front cash to burn, thus the capital expenditure involved in purchasing the supercritical extraction equipment may be prohibitive, 2.) Med Dev aims to have an initial public offering or be acquired within the next year, thus capital expenditures aimed at process improvements and future cost savings are not immediately salient. Acquisitions and cash burn considerations aside, another factor dissuading Med Dev from pursuing a more environmentally, economically beneficial process is the large initial margins associated with their devices. Pharmaceutical companies have long benefitted from large margins that reward the arduous FDA approval process and as a result have largely ignored process costs, today this indifference to costs is beginning to change in response to increased competition and patent expiration that has introduced generics to the market. Med Dev's aspirations towards acquisition, makes them indifferent toward future cost savings and the possibility of margin erosion due to competition and patent expiration.

The major incentives to Med Dev adopting the greener manufacturing process presented herein given their stage in development and their future plans are mostly altruistic: ensuring the health and wellbeing of their employees and the environment at large, while building a positive environmental reputation. In addition, implementing environmentally friendly manufacturing processes may attract possible investors/acquirers, as process changes will be unnecessary to ensure Med Dev is sufficiently in line with their environmental health and safety regulations.

APPENDIX

A. Licensing and Permitting required for toxic or hazardous substances

Flammable Substance Storage

Flammable substance storage in Massachusetts is covered under 527 Code of Massachusetts Regulations 14.00 (527 CMR 14.00) [lxxxiv]. In these regulations a flammable liquid is defined as a liquid having a flash point below 100°F and a vapor pressure below 40 psia at 100°F. The flash point of a liquid is the lowest temperature at which a liquid effervesce enough vapor to achieve ignition, though not sustained combustion. 527 CMR 14.03(1) provides that any entity wishing to keep, store, manufacture, or sell flammable or combustible liquids or flammable gases must obtain a permit from the head of the fire department in their locality. The application for the flammable substance storage permit will include the amounts of flammable substances to be kept and stored and the conditions in which these substances will be held, and the head of the fire department may require an inspection of the premises prior to issuing a permit to ensure compliance with 527 CMR 14.00, MGL Chapter 148, and 29 CFR 1910.119 (Process Safety Management of Highly Hazardous Chemicals). The head of the fire department retains the right to limit the quantity of flammable substance that can be held at any particular site. The local fire Department oversees the restrictions in each town/city.
Fines for violation of permitting include:

Permitting Violation Fines[lxxxv]
$100 -failure to store flammables in prescribed manner
$100 -failure to obtain a permit to store flammables/combustibles
$100 -failure to obtain a permit for underground storage tanks

Wastewater

Wastewater discharge prohibitions and regulatory requirements are largely decided by local authorities. Wastewater discharge permitting is required under 314 CMR 17.00. For facilities discharging under 300 gallons/day, a Low Flow/Low Pollutant General Permit must be filed with the Massachusetts Water Resources Authority and should include: discharge flow volume (on a daily basis), a sample of existing discharge, whether a pH adjustment system is in place, a current chemical inventory, and a chemical management plan. Call 617-305-5950 for the MWRA or The Industrial Coordinator for Toxics Reduction and Control 617-305-5627 for further information.

Hazardous Waste

Hazardous waste disposal is covered under the 310 CMR 30 regulations in Massachusetts and Federally by the Resource Conservation and Recovery Act (RCRA) of 1976. Hazardous waste disposal is becoming more and more costly as fewer hazardous waste disposal sites exist and those that do have limited capacity. A hazardous waste generator has responsibility, under the Superfund law, for the wastes they generate from cradle to grave, they must know where their wastes are going and ensure their wastes are properly handled both during transport and once they reach their final destination. Waste generators are segmented according to the quantities of hazardous waste they generate:

Segmentation of Hazardous Waste Generators[lxxxvi]

Segment	Quantities Generated
Very Small Quantity Generators (VSQG)	100 kg/month (~25 gallons/month)
Small Quantity Generators (SQG)	1000 kg/month (~250 gallons/month)
Large Quantity Generators (LQG)	<1000 kg/month (<~250 gallons/month)

A waste generator must register with the MA DEP and the US EPA as a generator of hazardous waste, failure to get a registration ID will result in fines of up to $1,000/day, while failure to use an ID on a manifest could result in additional fines of up to $1,000/day. In addition both hazardous waste transporters and property/casualty insurers may refuse service to a waste generator who cannot produce a valid ID.[lxxxvii] The Massachusetts regulations are stricter than the federal regulations, thus compliance with Massachusetts regulations automatically indicates compliance with federal regulations.

In Massachusetts every shipment of hazardous waste from a SQG or LQG must be accompanied by a Uniform Hazardous Waste Manifest and be transported by a licensed hauler to a licensed treatment, storage, or disposal facility (TSDF) or a permitted recycling center. Waste manifests accompany the shipment and are returned to the waste generator by the TSDF or recycling center where they should be kept on file for at least 3 years. A small quantity generator, like Med Dev, pays an annual compliance fee of $525 to the DEP to cover the costs of their services. Wastes are classified as hazardous by 310 CMR 30.133 and for Med Dev Therapeutics, Inc include: ethyl ether (US EPA hazardous waste number U117) and dichloromethane (US EPA hazardous waste number U080)[xv]. The MA DEP's website has a list of licensed transporters and TSDFs (www.mass.gov/dep), also call the Bureau of Waste Prevention at the DEP 617-292-5576.

B. Use of RESS and SAS for particle extraction

For RESS

Table 22: Summary of solutes extracted using the RESS process, copied from: Jung, Jennifer, Michel Perrut, "Review: Particle design using supercritical fluids: Literature and patent survey," *Journal of Supercritical Fluids*, 20, 179-219 (from pages 183-185)

Table 1
Compounds atomized with the RESS process[a]

Substrates	Supercritical fluid	Results and observations	References
Benzoic Acid	CO_2	Particle size: 2–7 μm	Kröher, 2000 [57]
Caffeine + anthracene	CO_2	Tablet-like core with sprouting needles	Subra, 1998 [48]
$Cr(acac)_3$	Acetone	Formation of a chromium film after reaction at 800°C	Hansen, 1992 [21]
$Cr(hfa)_3$	N_2O	Formation of a Cr_2O_3 film after reaction at 100°C	Hansen, 1992 [21]
$Cu(oleate)_2$	Pentane	Formation of a copper film after reaction at 740°C	Hansen, 1992 [21]
$Cu(thd)_2$	N_2O	Formation of a copper film after reaction at 700°C	Hansen, 1992 [21]
	N_2O	Formation of a CuO film after reaction at 100°C	Hansen, 1992 [21]
GeO_2	Water	5 μm agglomerates or 0.5–0.3 μm-diameter spheres depending on preexpansion temperature	Matson, 1987 [7]
$In(acac)_3$	CO_2	Formation of an indium film after reaction at 600°C	Hansen, 1992 [21]
Naphtalene	CO_2	45°C 220 bar ➡ particle size: 30–135 μm 55°C 350 bar ➡ Particle size: 4–38 μm Particle size: 0.5–3 μm	Mohamed, 1989 [13,14] Matson, 1987 [7]
$Ni(thd)_2$	Pentane	Formation of a nickel film after reaction at 600°C	Hansen, 1992 [21]
Oil Blue N (organic dye)	CO_2	Particle size: 0.3–1 μm	Sievers, 1993 [28]
PbS	Ammonia	A supercritical ammonia/$Pb(NO_3)_2$ solution is expanded in a solution of NaS in ethanol to produce PbS nanoparticles with an average particle size of 4 nm	Sun, 2000 [60]
$Pd(tod)_2$	Pentane	Formation of a palladium film after reaction at 600°C	Hansen, 1992 [21] Hybertson, 1991 [17]
Phenanthrene	CO_2	Particle size: 5 μm	Shaub, 1991 [20]
	CO_2	Particle size: 10–25 μm	Nagahama, 1997 [42]
	CO_2	Particle size: 1–5 μm	Domingo, 1997 [39]
Phenanthrene + Anthracene	CO_2	Particle composed of homogeneous crystals	Nagahama, 1997 [42]
SiO_2	Water	Product morphology: >1.0-μm thick film and 0.1–0.5 μm diameter spheres	Matson, 1987 [7]
$Si(OC_2H_5)_4$	N_2O	Formation of a SiO_2 film after reaction at 100°C	Hansen, 1992 [21]
SiO_2, KI	Water	20-μm agglomerates	Matson, 1987 [7]
$Y(thd)_3$	N_2O	Formation of an yttrium film after reaction at 687°C	Hansen, 1992 [21]
$Y(thd)_3 + Cu(thd)_2$ + $Ba_6(thd)_6(H_2O)_2OH$	Pentane	Formation of a $(YBa_2Cu_3O_{7-x})$ film after reaction at 800°C	Hansen, 1992 [21]
$ZrO(NO_3)_2$	Ethanol	Particle size: 0.1 μm	Matson, 1987 [7]
$Zr(tfa)_4$	Diethyl ether	Formation of a zyrconium film after reaction at 600°C	Hansen, 1992 [21]
Pharmaceutical compounds			
Aspirin	CO_2	Capillary nozzle: 2–5 μm	Domingo, 1997 [39]
Caffeine	CO_2	Needles of size: 3–5 μm	Subra, 1998 [48]
Cholesterol	CO_2	Particle size: 0.3–0.5 μm Particle size: 2–3 μm	Kröher, 1999/2000 [49,57] Sievers, 1993 [28]
Dipalmitoylphosphatidyl-Choline (DPPC)	CO_2 + EtOH		Sievers, 1993 [28]
β-estradiol	CO_2	Particle size: less than 1 μm	Krukonis, 1984 [4]

Table 1 (*continued*)

Substrates	Supercritical fluid	Results and observations	References
Polymers and biopolymers			
Krytoxdiamide of hexamethylene (KRYTOX)	CO_2	Droplet size from 0.6 to 4.5 μm with an average size of 2.8 μm	Chernyak, 2000 [54]
Polycaprolactone	Chlorodifluoro-methane	Powder or fibers depending on the conditions	Lele, 1992 [24]
Poly(carbosilane)	Pentane	<0.1-μm-diameter particles or 1-μm-diameter fibers of 80–160 μm length	Matson, 1987 [7,8]
Poly(2-ethylhexyl acrylate)	CO_2	Formation of a stable aqueous latex with particles of diameter 2–5 μm	Shim, 2000 [59]
Poly(heptadecafluorodecyl-acrylate)	CO_2	Particle size 0.1–5 μm	Blasig, 2000 [52]
Poly-l-lactic acid (l-PLA)	CO_2	Spherical and 'cornflakes' particles with a length of 4–10 μm	Tom, 1991 [19]
	CO_2 + 1 wt% acetone	Variety of morphology: microparticles of 10–25 μm (T = 15–37°C), dendrites of up to 100 μm (50°C)	Tom, 1991 [19]
Poly(methylmethacrylate)	Propane	0.5–1.0 μm-diameter particles or 1-μm diameter fibers of 100–1000 μm length	Matson, 1987 [7,8]
	Chlorodifluoro-methane	Powder or fibers depending on the conditions	Lele, 1992 [24]
Poly(phenyl sulfone)	Propane	Agglomerated spheres (each sphere of 0.5 μm diameter)	Matson, 1987 [7,8]
Polypropylene	CO_2	Small fibers of diameter 1–5 μm	Krukonis, 1984 [4]
	Pentane	0.5–1.0 μm-diameter spheres or 1 μm-diameter fibers of 100–1000 μm length	Matson, 1987 [8]
	Pentane		Petersen, 1987 [9]
Polystyrene	Pentane		Petersen, 1987 [9]
	Pentane	20-μm diameter spheres or 1-μm diameter fibers of 100–1000 μm length	Matson, 1987 [8]
	Pentane + 2% cyclohexanol	Particle size 0.3 μm with extremely narrow size distribution	Smith, 1983 [6]
Poly(vinyl chloride), K1	Ethanol	7 μm diameter spheres	Matson, 1987 [7]
Inorganic and organic materials			
AgI	Acetone	Formation of a silver film after reaction at 600°C	Hansen, 1992 [21]
Ag triflate	Diethyl ether	Formation of a silver film after reaction at 600°C	Hansen, 1992 [21]
$Al(hfa)_3$	Pentane	Formation of an aluminium film after reaction at 680°C	Hansen, 1992 [21]
	N_2O	Formation of a Al_2O_3 film after reaction at 100°C	Hansen, 1992 [21]
Anthracene	CO_2	Change in morphology from 20-μm hexagonal particles to 45-μm dendritic particles with an increase in the dilution	Nagahama, 1997 [42]
	CO_2	Tablets of size 5–20 μm	Subra, 1998 [48]
Benzoic acid	CO_2	Particle size with a capillary nozzle 2–8 μm With a sintered nozzle 0.2–0.3 μm	Domingo, 1997 [39]
	CO_2	Spherical particles with diameter 20–40 μm	Peirigo, 1998 [47]
	CO_2	Particle size 0.5–1.1 μm	Türk, 1999 [50]
	Trifluoro-methane	Particle size 0.4–1.4 μm	Türk, 1999 [50]

Table 1 (*continued*)

Substrates	Supercritical fluid	Results and observations	References
Flavone and 3-Hydroxyflavone + PEG	CO_2 + ethanol	Polymeric microspheres with flavone cores Particle size: 10 μm	Mishima, 1997 [41]
Griseofulvin	CHF_3		Reverchon, 1995 [33]
Hydrogenated palm oil	CO_2		Peiriço, 1998 [47]
3-Hydroxyflavone + Eudragit E-100	CO_2 + Ethanol	The 3-hydroxyflavone is coated thoroughly by the polymer	Mishima, 2000 [58]
Ibuprofen	CO_2	Capillary nozzle: less than 2 μm	Charoenchaitrakool 1999-2000, [51,53]
Lazaroid compound U-74389F	CO_2 + EtOH		Sievers, 1993 [28]
Lecithin	CO_2	Particle size: 1 μm	Krukonis, 1984 [4]
Lidocaine	CO_2	Particle size around 100 nm with spherical shape	Frank, 2000 [55]
Mevinolin	CO_2	Particle size: 0.1–1 μm	Mohammed, 1989 [14]
	CO_2 + 5 wt.% MeOH	Particle size: 10–50 μm	Larson, 1986 [5]
Nifedipin	CO_2	Particle size: 1–3 μm	Stahl, 1988 [12]
PLA + lovastatin	CO_2	Microspheres containing needles of lovastatin	Debenedetti, 1993 [22]
PLA + naproxen	CO_2		Kim, 1996 [34]
PLA + pyrene	CO_2		Debenedetti, 1994 [30]
Progesterone	CO_2	Particle size: 2–5 μm	Coffey, 1988 [10]
Salicylic acid	CO_2	Varying conditions, a wide range of particles were obtained: particles with diameters from 1 to 5 μm and length from 1 to 170 μm	Reverchon, 1993 [26,27]
	CO_2	Capillary nozzle: 2–5 μm Sintered nozzle: 1–2 μm	Domingo, 1997 [39]
Stigmasterol	CO_2	Whisker-like crystals	Ohgaki, 1990 [15]
Testosterone	CO_2	Particle size: 2–5 μm	Coffey, 1988 [10]
Theophyllin	CO_2	Needles of length 4–12 μm and diameter: 0.9 μm	Subra, 1996 [37]
α-tocopherol	CO_2	Particle size: 1–2 μm	Hybertson,1993 [23] Sievers, 1993 [28,32]
Tropic acid ester	CO_2	Particle size: 5–50 μm	Peiriço, 1998 [47]

For SAS

Table 23: Summary of solutes extracted using the SAS process, copied from: Jung, Jennifer, Michel Perrut, "Review: Particle design using supercritical fluids: Literature and patent survey," *Journal of Supercritical Fluids*, 20, 179-219 (from Table 2, pages 193-197)

Table 2:
Solutes extracted with the SAS process[a]

Substrates (solvent)	Supercritical fluid	Process	Results and observations	References
Explosives				
Cyclotrimethylenetri-nitramine (RDX) (*acetone or cyclohexanone*)	CO_2	GAS	Production of void-free particles Particle sizes depending on the conditions: from 200 to 1 μm	Gallagher, 1992 [9,10]
β-HMX (*acetone*)	CO_2	GAS	Particle size: 2–5 μm	Cai, 1997 [24]
β-HMX (acetone)	CO_2	GAS	Particle size: 65 μm	Förter-Barth, 1999 [56]
β-HMX (g-butyrolactone)	CO_2	GAS	Particle size: 90 μm	Förter-Barth, 1999 [56]
Nitroguanidine (NMP or DMF)	CO_2	GAS	Particle size: a few microns Different shapes were obtained during the tests	Gallagher, 1989 [6]
NTO (DMF or DMSO or methanol)	CO_2	GAS	Variety of shapes (sphere, cube, spherical agglomerate) of sizes 0.5–20 μm depending upon the conditions	Lim, 1998 [38]
Polymers and biopolymers				
ALAFF (ester of alginic acid) (DMSO)	CO_2	GAS	Particle size: 0.8 μm	Pallado, 1996 [23]
Dextran (DMSO)	CO_2	ASES	Particle size: 0.1–0.2 μm	Reverchon, 1999 [54]
Ester of pectinic acid (DMSO)	CO_2	GAS	Particle size: 0.7 μm	Pallado, 1996 [23]
HPMA (poly(hydroxypropyl methacrylamide)) (DMSO)	CO_2	ASES	Spherical microparticles of diameter 0.1–0.2 μm	Reverchon, 1999 [61]
HYAFF 7 (ethyl ester of hyaluronic acid) (DMSO)	CO_2	GAS	Particle size: 1 μm	Pallado, 1996 [23]
HYAFF 11 (hyaluronic acid ethyl ester) (DMSO)	CO_2	ASES	Particle size: 0.3–10 μm	Benedetti, 1993 [11] Reverchon, 1999 [54]
		GAS	Particle size: 0.6 μm	Pallado, 1996 [23]
HYAFF 11 p75 (DMSO)	CO_2	GAS	Particle size: 0.8 μm	Pallado, 1996 [23]
Inulin (DMSO)	CO_2	ASES	Spherical particles with a maximum diameter of 5 μm	Reverchon, 1999 [54,61]
PLA (acetone)	CO_2	ASES	Brittle solid similar to the starting material	Chou, 1997 [25]
PLA (methylene chloride)	CO_2		Particle size: 1–10 μm Particle size: 1–2 μm	Bleich, 1993 [13] Reverchon, 1999 [61]
DL-PLA (n.a.)	CO_2+N_2	SEDS	Particle size: 10 μm	Ghaderi, 1999 [68]
DL-PLG (n.a.)	CO_2+N_2	SEDS	Particle size: 10 μm	Ghaderi, 1999 [68]
PLGA (acetone)	CO_2	GAS	Particle size: 50 nm	Dillow, 1997 [26]
Polyacrylonitrile (DMF)	CO_2	ASES	Formation of microfibrilles	Johnston, 1994 [19]
Polycaprolactone (n.a.)	CO_2+N_2	SEDS	Particle size: 25–85 μm	Ghaderi, 1999 [68]
Poly(methacrylated sebacic anhydride) (methylene chloride)	CO_2	ASES	A high powered ultraviolet source allows photopolymerisation. Particle size: 1–5 μm	Owens, 1999 [67]

Table 2 (*continued*)

Substrates (solvent)	Supercritical fluid	Process	Results and observations	References
Polystyrene (toluene)	CO_2	ASES	Particle size: 0.1–20 μm	Dixon, 1993 [14]
Polystyrene (toluene)	CO_2	SEDS	Particle size: 0.5 μm	Hanna, 1998 [36]
Inorganic and organic materials: coloring matters, catalysts, superconductors...				
Ammonium Chloride (DMSO)	CO_2	GAS	Particle size: 1–5 μm	Yeo, 2000 [84]
Barium Chloride (DMSO)	CO_2	GAS	Particle size: 7–9 μm with cubic shape or needle-like crystals depending on the conditions	Yeo, 2000 [84]
Bronze Red (ethanol)	CO_2	ASES	Spheres of diameter between 1 and 10 μm depending on experimental conditions	Hong, 2000 [76]
Bronze Red (acetone)	CO_2	ASES	Spheres or needles of diameter between 3 and 15 μm depending on the conditions	Hong, 2000 [76]
Buckminster-fullerene (toluene)	CO_2	ASES	Particle size: 100–300 nm	Chattopadhyay, 2000 [71]
Cobaltous nitrate (acetone)	CO_2	SEDS	Free-flowing pink powder	Hanna, 1994 [18]
Epoxy powder (acetone or methyl ethyl ketone)	CO_2	ASES	Without surfactant: agglomerates with pluronic R-17: separated particles with uniform spherical morphology	Heater, 1998 [37]
Hydroquinone (acetone)	CO_2	GAS and ASES	GAS: agglomerates of size 500 μm ASES: needle and prismatic shaped particles of size 50–100 μm	Wubbolts, 1997 [32]
Nickel Chloride hexahydrate (absolute ethanol)	CO_2	SEDS	Very fine free-flowing powder	Hanna, 1994 [18]
Phenanthrene (toluene)	CO_2	GAS	Particle size: 160–540 μm	Berends, 1994 [16]
Red Lake C pigment Pigment Yellow 1 Pigment Blue 15 (acetone)	CO_2	GAS	Particle size: down to 0.6 μm	Gao, 1997 [27]
Samarium acetate (DMSO)	CO_2	ASES	Particle size: 0.1–0.3 μm	Reverchon, 1997 [29,44]
Samarium acetate (water+methanol)	CO_2	SEDS	Particle size: 0.2 μm	Hanna, 1998 [36]
Silver nitrate (methanol)	CO_2	SEDS	Particle size: 0.3 μm	Hanna, 1998 [36]
Superconductor precursors	CO_2	ASES		Reverchon, 1998 [42]
Yttrium acetate (DMSO)	CO_2	ASES	Ballons formed by submicronic elements	Reverchon, 1997 [29,43] Muhrer, 2000 [78]
Zinc acetate (DMSO)	CO_2	ASES	Particle size: 0.08–0.13 μm	Reverchon, 1997 [30,63]
Pharmaceutical compounds				
Acetaminophen (ethanol)	CO_2	SEDS	Particle size: 6–8 μm	Gilbert, 2000 [75]
Albumin (water)	CO_2+Ethanol	SEDS	Particle size: 50–500 nm	Bustami, 2000 [70]
7-aminocephalo-sporanic acid (acetone and water)	CO_2	GAS	n.a.	Liang, 2000 [77]
Amoxicillin (NMP)	CO_2	ASES	Particle size: 0.2–0.8 μm	Reverchon, 1999 [57,64]
Antibody Fab fragment (water)	CO_2+ethanol	SEDS	Activity of processed antibody: 45%	Sloan, 1999 [58]
Antibody Fv fragment (water)	CO_2+ethanol	SEDS	Activity of processed antibody: 3%	Sloan, 1999 [58]
Ascorbic acid (ethanol)	CO_2	ASES	Particle size: 1–10 μm	Weber, 1999 [55]

Table 2 (*continued*)

Substrates (solvent)	Supercritical fluid	Process	Results and observations	References
β-carotene (ethyl acetate)	CO_2	GAS	Particle size: platelet morphology of 2–10 μm size	Cocero, 2000 [72]
Catalase (ethanol-water 90:10)	CO_2	ASES	Particle size: 1 μm	Debenedetti, 1992 [8]
Substrates (solvent)	Supercritical fluid	Process	Results and observations	References
Chloramphenicol (ethanol)	CO_2	ASES	Particle size: 1–10 μm	Weber, 1999 [55]
Cu_2(indomethacin)$_4$ (DMF)$_2$ (DMF)	CO_2	GAS	Slow expansion: rhombic crystals of 50 μm size Fast expansion: crystals of 20 μm size	Warwick, 2000 [83]
p-HBA (methanol)	CO_2	GAS ASES	GAS: Particle size: 1–2 μm ASES: 0.1–1.0 μm	Thiering, 1998 [49]
Hydrocortisone acetate (DMF)	CO_2	ASES	Particle size: 5 μm	Schmitt, 1995 [22]
Insulin (ethanol-water 90:10)	CO_2	ASES	Particle size: 1 μm	Debenedetti, 1992 [8]
Insulin (water)	CO_2 + Ethanol	SEDS	Particle size: 50–500 nm	Bustami, 2000 [70]
Insulin (DMSO or DMF)	CO_2	ASES	Particle size [15]: <4 μm Particle size [80,81,82]: 1.4–1.8 μm	Yeo, 1993 [15] Thiering, 2000 [80, 1,82]
Insulin (Methanol)	CO_2	GAS	Particle size: 0.2–0.7 μm	Thiering, 2000 [80,81,82]
Insulin (Ethyl acetate)	CO_2	GAS	Particle size: 0.3–0.7 μm	Thiering, 2000 [80,81,82]
Insulin (Ethanol)	CO_2	GAS	Particle size: 0.05–0.3 μm	Thiering, 2000 [80,81,82]
Insulin (water)	NH_3	GAS	Particle size: 0.2–0.3 μm	Thiering, 2000 [80,81,82]
β-lactamase (water)	CO_2 + ethanol	SEDS		Hanna, 1994 [18]
Lactose (water)	CO_2 and methanol	SEDS	Particle morphology depends on the nozzle Particle size: 3.0–10.5 μm	Hanna, 1995 [21] Palakodaty, 1998 [40]
Lecithin (ethanol or hexane)	CO_2	ASES		Weber, 1999 [59]
Lobenzarit disodium (water)	CO_2 + Ethanol	ASES	Particle size: 0.2–0.6 μm	D. Amaro-Gonzalez, 2000 [69]
Lysozyme (water)	CO_2 + ethanol	SEDS	Particle size [46]: 0.78 μm Activity of processed enzyme: 95% Particle size [70]: 500 nm Particle size [75]: 0.5–5 μm	Sloan, 1998 [46] Bustami, 2000 [70] Gilbert, 2000 [75]
Lysozyme (DMSO)	CO_2	GAS	Particle size: 0.05–0.2 μm	Thiering, 2000 [80,81,82]
Lysozyme (DMSO)	CO_2 + DMF (30% vol.)	GAS	Particle size: 0.1 μm	Thiering, 2000 [80,81,82]
Lysozyme (DMSO)	CO_2 + Ethanol (30% vol.)	GAS	Particle size: 0.02–0.04 μm	Thiering, 2000 [80,81,82]
Lysozyme (DMSO)	CO_2 + acetic acid (8% vol.)	GAS	Particle size: 0.05 width × 0.25 length	Thiering, 2000 [80,81,82]
Lysozyme (Ethanol)	CO_2 + water	GAS	Particle size: 0.05–0.07	Thiering, 2000 [80,81,82]
Lysozyme (Methanol)	CO_2	GAS	Particle size: 0.01–0.05 μm	Thiering, 2000 [80,81,82]
Lysozyme (Water)	NH_3	GAS	Particle size: 0.05–0.2 μm	Thiering, 2000 [80,81,82]
Maltose (water)	CO_2 + absolute ethanol	SEDS	Result: free-flowing white powder	Hanna, 1995 [21]
Mefenamic acid (methanol or ethanol or acetone)	CO_2	ASES	Particle size: 10–50 μm	Bustami, 1999 [66]

Table 2: (*continued*)

Substrates (solvent)	Supercritical fluid	Process	Results and observations	References
Methylprednisolone (tetrahydrofuran)	CO_2 or ethane	ASES	Particle size: 5 μm	Schmitt, 1995 [22] Muhrer, 2000 [78]
Myoglobin (DMSO)	CO_2	GAS	Particle size: 0.03–0.4 μm	Thiering, 2000 [80,81,82]
Myoglobin (Methanol)	CO_2	GAS	Particle size: 0.05–0.3 μm	Thiering, 2000 [80,81,82]
Naproxen (acetone)	CO_2	ASES	Needles-like crystals with diameter 1 μm and length 1 mm	Chou, 1997 [25]
Nicotinic acid (absolute ethanol)	CO_2	SEDS	Particle size: 0.4–0.75 μm	Hanna, 1998 [36]
Paracetamol (ethanol)	CO_2	ASES	Particle size: 1–10 μm	Weber, 1999 [55]
Phospholipids (chloroform or ethanol)	CO_2	ASES	Spherical particles of size: 1–40 μm	Magnan, 1999 [53,60]
Plasmid DNA pSVb with no protectant (water)	CO_2 + ethanol	SEDS	Activity of processed plasmids: 10%	Sloan, 1999 [58]
Plasmid DNA pSVb with protectant (water)	CO_2 + ethanol	SEDS	Activity of processed plasmids: 75%	Sloan, 1999 [58]
Prednisolone acetate (acetone)	CO_2	ASES	Particle size: 1 μm	Anderson, 1998 [33]
RhDNase (water)	CO_2 + ethanol	SEDS	Particle size: 50–500 nm	Bustami, 2000 [70]
Salbutamol(methanol + acetone)	CO_2	SEDS	Particle size: 0.5 μm	Hanna, 1998 [36]
Salmeterol xinafoate (methanol or acetone)	CO_2	ASES	Particle size: 1–10 μm	Hanna, 1994 [18] Hanna, 1998 [35]
Salmeterol xinafoate (acetone or methanol)	CO_2	SEDS	With acetone: platelet particles with methanol: needles-like particles	Hanna, 1998 [36]
Sodium cromoglicate (methanol)	CO_2	ASES	Particle size: 0.1–20 μm	Jaarmo, 1997 [28]
Sucrose (water)	CO_2 + absolute ethanol	SEDS	Result: free-flowing white powder	Hanna, 1995 [21]
Tetracycline (NMP)	CO_2	ASES	Particle size: 0.6–0.8 μm	Reverchon, 1999 [57,64], 2000 [79]
Trehalose (water)	CO_2 + absolute ethanol	SEDS	Result: free-flowing white powder	Hanna, 1995 [21]
Trypsin (HCl 1mM)	CO_2 + ethanol	SEDS	Particles size: 1.53 μm Activity of processed enzyme: 36%	Sloan, 1998 [46]
Urea (ethanol)	CO_2	ASES	Particle size: 1–10 μm	Weber, 1999 [55]
Microcomposites				
Calcitonin + HYAFF (DMSO)	CO_2	GAS	Particle size: 0.5–1 μm	Pallado, 1996 [23]
Chimotrypsin-AOT + PLA (methylene chloride)	CO_2	ASES	Particle size: 1–2 μm	Elvassore, 2000 [73]
Chloramphenicol and urea (ethanol)	CO_2	GAS		Weber, 1998 [50]
Copper-, Barium- and Yttrium acetate (ethanol)	CO_2	ASES	Composite particles of 50–150 nm with a unique homogeneous distribution of each of the elements	Weber, 1999 [55]
GMCSF + HYAFF (DMSO)	CO_2	GAS	Particle size: 0.5–1 μm	Pallado, 1996 [23]
p-HBA (methanol) + PLGA (acetone)	CO_2	SEDS	Crystals of p-HBA coated with a layer of PLGA microspheres	Sze Tu, 1998 [48]
p-HBA (methanol) + PLA (methylene chloride)	CO_2	SEDS	Fibrous network of drug and polymer mixture	Sze Tu, 1998 [48]

Table 2 (*continued*)

Substrates (solvent)	Supercritical fluid	Process	Results and observations	References
Hydrocortisone + Poly(DL-lactide-co-glycolide):copolymer composition 50:50 (n.a.)	$CO_2 + N_2$	SEDS	Particle size: 10–60 μm	Ghaderi, 1999 [68]
Insulin + HYAFF (DMSO)	CO_2	GAS	Particle size: 0.4 μm	Pallado, 1996 [23]
Insulin-lauric acid conjugate + PLA (methylene chloride)	CO_2	ASES	Particle size: 1–5 μm	Elvassore, 2000 [73]
Insulin + PLA (methylene chloride + DMSO 50%)	CO_2	ASES	Particle size: 1–5 μm	Elvassore, 2000 [73]
Lysozyme + PLA (methylene chloride + DMSO 50%)	CO_2	ASES	Particle size:1–2 μm	Elvassore, 2000 [73]
Naproxen + PLA (acetone)	CO_2	ASES	Particle size: 5 μm	Chou, 1997 [25]
Paracetamol and ascorbic acid (ethanol)	CO_2	GAS	By variation of the composition, the product changed from needle-like crystals (10 μm) to large tubes (length 30–100 μm, diameter 2 μm) covered with prismatic crystals (<1 μm)	Weber, 1998 [50]
PLA + clonidine HCl (dichloromethane)	CO_2	ASES	Hollow spheres of diameter: 100 μm	Schwarz Pharma, 1987 [4]
PLA + hyoscine (butylbromide)	CO_2	ASES	Particle size < 20 μm	Bleich, 1994 [17]
Salmeterol xinafoate + hydroxypropyl-cellulose (acetone)	CO_2	SEDS	Fine white powder	Hanna, 1994 [18]

C. Sample Calculation for Dichloromethane Consumption in Europe

DCM paint stripping (tons)	13000	
revenue DCM paint stripping ($750/ton)	9750000	DCM paint stripping (tons) x ($750/ton)
total DCM (tons)	110000	
revenue for total DCM ($750/ton)	82500000	total DCM (tons) x ($750/ton)
revenue for total DCM ($750/ton)-revenue DCM paint stripping ($750/ton)	72750000	
10% of (revenue for total DCM ($750/ton)-revenue DCM paint stripping ($750/ton))	7275000	
revenue for total DCM($750/ton)-revenue DCM paint stripping ($750/ton)-10% of" "	65475000	
50% of (revenue for total DCM($750/ton)-revenue DCM paint stripping ($750/ton))	36375000	
revenue for total DCM($750/ton)-revenue DCM paint stripping ($750/ton)-50% of" "	36375000	
$750/ton less 10%	675	
$750/ton less 50%	375	
DCM pharma (tons)	50000	
revenue DCM pharma ($675/ton)	33750000	DCM pharma (tons) x ($675/ton)
revenue DCM pharma ($375/ton)	18750000	DCM pharma (tons) X ($375/ton)
(revenue for total DCM($750/ton)-revenue DCM paint stripping ($750/ton)-10% of" "/revenue for total DCM ($750/ton))*100	20.63636364	

D. Synthesis Costs

For the original process:

The following calculations are based on the assumptions:

0.3 mL of hydrogel/patient

PEG-co-poly(lactic acid) diacrylate 30% (wt/vol) in PBS

Market (contusion patients and off label): 10k in the US, 30k in Europe (say 40% of this overall market is captured: 16k)

1440 g of PEG-co-poly(lactic acid) diacrylate

Ring opening polymerization of lactide

Original process	MW (g/mol)	amount used	price/unit	cost ($)	amount used/year
PEG 6k	6009.09	30 g	$54.10/kg	1.623	1440 g
d,l-lactide	146.14	3.60 g	$19.10/100g	0.6876	172.8 g
dichloromethane	84.93	300 mL	$44.70/L	13.41	14.4 L
diethyl ether	74.12	3000 mL	$64.50/L	193.5	144 L
stannous octoate	405.1	0.0150 g	$19.10/100g	0.002865	0.72 g
PEG-co-poly(lactic acid)	*6729.71*	*33.2 g*			
total				209.223465	
for synthesis of 1,440 g (48 times the 30 g synthesis)				10042.7263	

Acrylation

Original process	MW (g/mol)	amount used	price/unit	cost ($)	amount used/year
PEG-co-poly(lactic acid)	6729.71	30 g		209.2235	1440 g
dichloromethane	84.93	300 mL	$44.70/L	13.41	14.4 L
triethylamine	149.188	1.31 mL	$61.90/L	0.081089	62.88 mL
acryloyl chloride	90.5	1.77 g	$38.80/5g	13.7352	84.96 g
diethyl ether	74.12	3000 mL	$64.50/L	193.5	144 L
hexane	86.18	3000 mL	$67.40/L	202.2	144 L
PEG-co-poly(lactic acid) diacrylate	6821.8	30.4 g			
Triethylamine hydrochloride	185.65	1.66 g			
total				632.149789	
for synthesis of 1,440 g (48 times the 30 g synthesis)				30343.1899	

thus the overall cost for the synthesis: $30,343.19

For benzotrifluoride substitution:

Ring opening polymerization of lactide

Benzotrifluoride substitution	MW (g/mol)	amount used	price/unit	cost ($)	amount used/year
PEG 6k	6009.09	30 g	$54.10/kg	1.623	1440 g
d,l-lactide	146.14	3.60 g	$19.10/100g	0.6876	172.8 g
benzotrifluoride	146.11	300 mL	$44.60/L	13.38	14.4 L
ethyl acetate	88.105	3000 mL	$55.70/L	167.1	144 L
stannous octoate	405.1	0.0150 g	$19.10/100 g	0.002865	0.72 g
PEG-co-poly(lactic acid)	*6729.71*	*33.2 g*			
total				182.793465	
for synthesis of 1,440 g (48 times the 30 g synthesis)				8774.08632	

Acrylation

Benzotrifluoride substitution	MW(g/mol)	amount used	price/unit	cost ($)	amount used/year
PEG-co-poly(lactic acid)	6729.71	30 g		209.2235	1440 g
benzotrifluoride	146.11	300 mL	$44.60/L	13.38	14.4 L
triethylamine	149.188	1.31 mL	$61.90/L	0.081089	62.88 mL
acryloyl chloride	90.5	1.77 g	$38.80/5g	13.7352	84.96 g
ethyl acetate	88.105	3000 mL	$55.70/L	167.1	144 L
heptane	100.21	3000 mL	$56.70/L	170.1	144 L
PEG-co-poly(lactic acid) diacrylate	6821.8	30.4 g			
Triethylamine hydrochloride	185.65	1.66 g			
total				573.619789	
for synthesis of 1,440 g (48 times the 30 g synthesis)				27533.7499	

E. SAS process Economics

assumption: 30 g synthesis

Solute solution Flowrate (mL/min)	time required for 3000 mL solute solution (min)	total time (with additional 120 minutes wash) (min)	CO2 flowrate (g/min)	Amount of CO2 required (g)	number of bottles of CO2 required	CO2 Cost
1	3000	3120	50	156000	7.8	187.2
5	600	720	50	36000	1.8	43.2
10	300	420	50	21000	1.05	25.2
15	200	320	50	16000	0.8	19.2
20	150	270	50	13500	0.675	16.2

CO2: 20000 g/bottle
$24/bottle

Cost of SAS system: ~$65,000.

Amount of polymer	cost of diethyl ether/hexane	cost of supercritical CO2 @ solute flow of 5 mL/min	cost of supercritical CO2 @ solute flow of 20 mL/min
30	589.2	65043.2	65016.2
60	1178.4	65086.4	65032.4
90	1767.6	65129.6	65048.6
120	2356.8	65172.8	65064.8
150	2946	65216	65081
180	3535.2	65259.2	65097.2
210	4124.4	65302.4	65113.4

These calculations were performed until sufficiently many points were calculated to allow a break-even point to emerge, then the results were plotted to help facilitate identification of the break-even point.

break even point for:	g	g/year	years to break even
Supercritical CO2 @ solute flow 5 mL/min	3570	1460	2.445205479
supercritical CO2 @ solute flow 20 mL/min	3390	1460	2.321917808

	Cost/ 1L	cost for 30 g sysnthesis	% change in cost due to dichloromethane substitution
possible substitutes			
ethyl acetate	$55.70	$33.42	-25%
isopropyl acetate	**$63.50**	$38.10	-42%
ethyl propionate	**$39.40**	$23.64	12%
toluene	$40.90	$24.54	9%
methyl cyclopentane	$253.00	$151.80	-466%
benzotrifluoride	$44.60	$26.76	0%
laboratory process			
dichloromethane	**$44.70**	**$26.82**	

	MW (g/mol)	amount used	price/unit	cost ($)	amount used/year	replace dichloromethane w/isopropyl acetate, SAS extraction (5 mL/min)	replace dichloromethane w/isopropyl acetate, SAS extraction (20 mL/min)	replace dichloromethane with ethyl propionate, SAS extraction 5 mL/min	replace dichloromethane with ethyl propionate, SAS extraction 20 mL/min
PEG 6k	6009.09	30 g	$54.10/kg	1.623	1440 g	1.623	1.623	1.623	1.623
d,l-lactide	146.14	3.60 g	$19.10/100g	0.6876	172.8 g	0.6876	0.6876	0.6876	0.6876
dichloromethane	84.93	300 mL	$44.70/L	13.41	14.4 L	19.05	19.05	11.82	11.82
diethyl ether	74.12	3000 mL	$64.50/L	193.5	144 L	43.2	16.2	43.2	16.2
stannous octoate	405.1	0.0150 g	$19.10/100g	0.002865	0.72 g				
PEG-co-poly(lactic acid)	*6729.71*	*33.2 g*	Solvent total	206.91		62.25	35.25	55.02	28.02
total				209.223465		64.5606	37.5606	57.3306	30.3306
for synthesis of 1,440 g/year (48 times the 30 g synthesis)				10042.72632		69.14275366	82.04761593	72.598389	85.50325127

Acrylation

	MW (g/mol)	amount used	price/unit	cost ($)	amount used/year	isopropyl acetate, SAS extraction (5 mL/min)	isopropyl acetate, SAS extraction (20 mL/min)	ethyl propionate, SAS extraction 5 mL/min	ethyl propionate, SAS extraction 20 mL/min
PEG-co-poly(lactic acid)	6729.71	30 g		209.2235	1440 g	209.2235	209.2235	209.2235	209.2235
dichloromethane	84.93	300 mL	$44.70/L	13.41	14.4 L	19.05	19.05	11.82	11.82
triethylamine	149.188	1.31 mL	$61.90/L	0.081089	62.88 mL	0.081089	0.081089	0.081089	0.081089
acryloyl chloride	90.5	1.77 g	$38.80/5g	13.7352	84.96 g	13.7352	13.7352	13.7352	13.7352
diethyl ether	74.12	3000 mL	$64.50/L	193.5	144 L	43.2	16.2	43.2	16.2
hexane	86.18	3000 mL	$67.40/L	202.2	144 L				
PEG-co-poly(lactic acid) diacrylate	6821.8	30.4 g							
Triethylamine hydrochloride	185.65	1.66 g	Solvent total	409.4352		62.25	35.25	55.02	28.02
total				632.149789		285.289789	258.289789	278.059789	251.059789
						54.86990679	59.1410464	56.01362306	60.28476267

	MW (g/mol)	amount used	price/unit	cost ($)	replace dichloromethane w/isopropyl acetate, SAS extraction (5 mL/min)	replace dichloromethane w/isopropyl acetate, SAS extraction (20 mL/min)	replace dichloromethane with ethyl propionate, SAS extraction 5 mL/min	ethyl propionate, SAS extraction 20 mL/min
dichloromethane	84.93	600 mL	$44.70/L	26.82	38.1	38.1	23.64	23.64
diethyl ether	74.12	6000 mL	$64.50/L	387	86.4	32.4	86.4	32.4
hexane	86.18	3000 mL	$67.40/L	202.2				

			dichloromethane, diethyl et	isopropyl acetate, SAS extraction (5 mL/min)	isopropyl acetate, SAS extraction (20 mL/min)	ethyl propionate, SAS extraction 5 mL/min	ethyl propionate, SAS extraction 20 mL/min
		Solvent total	616.02	124.5	70.5	110.04	56.04
total		total	616.02	124.5	70.5	110.04	56.04
				79.78961722	88.55556638	82.13694361	90.90289276

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[lix] Below you will find our response to your recent inquiry. We appreciate your interest and hope we have been of assistance.

Please do not reply to this email. To respond to this email, please click here.
http://natureworks.custhelp.com/cgi-bin/natureworks.cfg/php/enduser/acct_login.php?p_userid=leighg@mit.edu&p_next_page=myq_upd.php&p_iid=12472&p_created=1233862908

Subject

Is NatureWorks currently partnering with any pharmaceutical/medical device co...

Discussion Thread

Response (Anita Castanier) - 02/09/2009 03:34 PM
Dear Miss Leigh Gautreau,

Thank you for contacting NatureWorks LLC, home of Ingeo™ Innovations. NatureWorks' biopolymer represents a new family of products derived entirely from annually renewable resources. This new, revolutionary polymer bridges the gap between natural and synthetic materials.

NatureWorks LLC customer agrees that, unless permitted by NatureWorks LLC in writing, customer will not use or allow others, including their customers, to use Ingeo™ biopolymer or products made from NatureWorks' biopolymer, in the following:

(i) Components of or packaging for tobacco products.
(ii) Components of products intended for human or animal consumption.
(iii) In any application that is intended for any internal contact with human body fluids or body tissues.
(iv) As a critical component in any medical device that supports or sustains human life.
(v) In any product that is designed specifically for ingestion or internal use by pregnant women.
(vi) In any application designed specifically to promote or interfere with human reproduction.

For more information please review the following:

Title: Will Ingeo™ biopolymer be used in medical applications?
URL: http://natureworks.custhelp.com/cgi-

bin/natureworks.cfg/php/enduser/std_adp.php?p_faqid=292&p_created=1072213052

All of the technical data the business is prepared to disclose is available on our website: http://www.natureworksllc.com.

Regards,
Anita C.
Customer Service
NatureWorks LLC, home of Ingeo Innovations
www.natureworksllc.com

Customer (Leigh Gautreau) - 02/05/2009 02:41 PM
Is NatureWorks currently partnering with any pharmaceutical/medical device companies to supply PLA as a feed stock for polymer synthesis? Many pharmaceutical/medical device manufacturers use ring opening polymerization of PLA as a process step and as environmental awareness grows they will undoubtedly look to green their processes including their PLA feed stock. Is there a reason NatureWorks doesn't currently offer PLA for post processing in the pharmaceutical/medical device industries? Is the PLA made using NatureWorks technology reproducible enough to stand up to FDA regulations? Could NatureWorks PLA be produced in a c-GMP fashion?

Auto-Response - 02/05/2009 02:41 PM
*** YOUR QUESTION HAS NOT YET BEEN SUBMITTED, PLEASE CLICK "FINISH SUBMITTING QUESTION" AFTER READING THE INFORMATION BELOW *** .

Title: What corn options do you offer your customers?
Link: http://natureworks.custhelp.com/cgi-bin/natureworks.cfg/php/enduser/popup_adp.php?p_faqid=532&p_created=1177086458

Title: What is the difference between biodegradable and compostable?
Link: http://natureworks.custhelp.com/cgi-bin/natureworks.cfg/php/enduser/popup_adp.php?p_faqid=539&p_created=1177096983

Title: Why is Ingeo™ biopolymer a more sustainable product?
Link: http://natureworks.custhelp.com/cgi-bin/natureworks.cfg/php/enduser/popup_adp.php?p_faqid=75&p_created=1059664815

Title: What is the technical process for producing Ingeo™ biopolymer today? In the future?
Link: http://natureworks.custhelp.com/cgi-bin/natureworks.cfg/php/enduser/popup_adp.php?p_faqid=72&p_created=1059664474

Title: How is NatureWorks® PLA made?
Link: http://natureworks.custhelp.com/cgi-bin/natureworks.cfg/php/enduser/popup_adp.php?p_faqid=533&p_created=1177096236

Question Reference #090205-000004

Application:: Other Applications

Sub-product: : Other Applications
Topic:: Medical
Date Created: 02/05/2009 02:41 PM
Last Updated: 02/09/2009 03:34 PM
Status: Solved

[---001:003736:28236---]

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