An Executive Guide to Pharmaceutical Manufacturing Efficiency and the Effect of Environmental Legislation

This paper describes the use and waste of organic solvents in pharmaceutical manufacturing and the possible impact that greenhouse gas legislation, in the form of a carbon tax, may have on solvent usage and pharmaceutical manufacturing costs. It also will review a financial model for solvent recovery in light of the appropriate rate of return on capital and sensitivity to greenhouse gas legislation, as well as the implications on U.S. Food and Drug Adminstration validation.

Executive Summary

Pharmaceutical manufacturing is the most solvent-intensive of all chemical processes. Instead of recycling spent solvents, manufacturers incinerate a vast majority of the solvents on-site as a means to generate energy. The decision to burn rather than recycle has been driven by simple financial analysis and return on investment (ROI). At current prices, the cost difference between the heat energy value of burning spent solvents and the replacement cost of those solvents with virgin material has not been sufficient to meet the industry's required rate of return. At closer look, however, these calculations are flawed. Applying the same ROI rules for production capital expenditures to investments in solvent recovery can be overly simplistic and inconsistent with financial theory.

As the U.S. government looks to establish mandates for greenhouse gas emissions, companies may change their approach to how they use spent solvents. Because pending legislation could dramatically increase the cost of spent solvent incineration, manufacturers may determine that recovering these solvents may have the best impact on the company's bottom line. As time progresses, solvent recovery will likely become a "must-invest" decision for the majority of pharmaceutical manufacturers.

Pharmaceutical Manufacturing Efficiency

The pharmaceutical industry is the least efficient of all chemical industries in terms of waste generated per unit of product. Statistics compiled across the industry point to an average waste-to-product ratio of 200 times. In other words, factories generate 200 pounds of waste for every pound of active pharmaceutical ingredient produced.

According to the U.S. Environmental Protection Agency (EPA), pharmaceutical companies generated 530 million tons of toxic waste in 2005; 90 percent of which was produced by the 20 solvents listed below:

- Methanol
- Dichloromethane (DCM)
- Formaldehyde
- Toluene
- Acetonitile (ACN)
- Hexane
- Isopropanol Alcohol (IPA)
- n-Butyl Alcohol
- Methyl tert-butyl ether (MTBE)
- Xylene
- Trichloroethane (TCE)
- Ethanol
- Tetrahydrofuran (THF)

Pharmaceutical plants also produce a variety of wastes that are not reported to the EPA. If we consider spent solvents as a percentage of all pharmaceutical plant waste, solvents still represent 80 percent of total waste generation. Clearly, pharmaceutical manufacturing is not only highly solvent-intensive, but the entire operation is dominated by the management, use and disposal of solvents. Solvents constitute the primary cost drivers for pharmaceutical manufacturing gross margins. Even though a solvent comprises 80 to 90 percent of the mass balance and the bulk of the operational management costs, it is used just once in the manufacturing process with 99 percent of it being incinerated for power. Consider the impact solvents have on operations:

Plant Energy Usage: 75-80 percent attributed to solvents
Environmental Impact: 75-80 percent attributed to solvents
Percentage of Overall Mass Balance: 80-90 percent attributed to solvents

Expressed differently, 80-90 percent of a pharmaceutical plant's mass balance is going up the smokestack as Carbon Dioxide.

Value Equation

In today's sustainability-focused environment, it's important to keep in mind that pharmaceutical processes are developed on sound economic principals. These processes may appear wasteful and unsustainable when one takes too narrow of a view of the value equation. Economic decisions are based on maximizing the return on invested capital, which requires manufacturers to optimize valuable process resources. In the case of pharmaceuticals, the scarcest resources are not solvents, but rather investment capital and cash flow.

Pharmaceutical business models are dominated by three primary factors:

- Price or value the product creates in improving the health of the patient
- Market or size of the reachable patient population
- Cost of development and certification of the product

Investment capital and cash flow are the scarcest resources due to the length of time and level of risk that occurs between the investment period (new drug discovery and validation) and market sales. Therefore, alternative uses of capital, such as manufacturing projects, must earn the required rate of return demanded of drug discovery, according to traditional economic theory.

In general, solvent recovery investments have failed to meet the ROI hurdle.

During the patent period, drug prices are high and manufacturing margins are robust. So even though pharmaceutical manufacturing costs and operations are dominated by solvents, the high margins and alternative capital demands reduce the incentive for recovery and recycle investments. In general, solvent recovery investments have failed to meet the ROI hurdle.

Generic drug manufacturers face a different price and market environment. Their much slimmer manufacturing margins provide stronger incentives for continuously improving manufacturing efficiency. Even here, solvent recovery investments have been timid due to the high fuel value of the solvents.

It is interesting to note that almost all pharmaceutical organic solvents have a thermal energy value (calorific value) greater than coal, which provides 48 percent of the U.S. energy requirements. However, pharmaceutical organic solvents only provide approximately 60 percent of the thermal capacity of natural gas. The table below compares the thermal energy capacity of three common pharmaceutical solvents to both coal and natural gas.

Substance	Calorific Value
Natural Gas	54.3 MJ/kg
Coal	30.3 MJ/kg
THF	32.2 MJ/kg
MEK	34.0 MJ/kg
Ethanol	30.0 MJ/kg

The high calorific values of the solvents coupled with substantially reduced EPA regulatory costs for on-site incineration has resulted in virtually all solvents being incinerated.

The financial return on a solvent recovery investment is determined by four primary factors:

- Price of virgin solvent
- Fuel value of burning the spent solvent
- Volume of solvent used
- Capital cost of the recovery unit

Recent energy prices have driven up the fuel value of the solvents by a greater margin than the percentage increase in the price of replacement virgin solvent, thus reducing the "recovery margin." At the same time, solvents that are incinerated rather than shipped off-site can substantially reduce the EPA regulatory costs. As a result, manufacturers are incinerating virtually all solvents.

Atom Economy

The atom economy looks at the overall efficiency of output creation regardless of price abstractions. It is simply an equation of resources in versus resources out. In its simplest form, it is just a counting exercise, counting all the "atoms" that go into making the product as compared to the total number of atoms in the product. This is important because it is believed that over time the value equation and the atom economy will converge as the price of the product falls to its marginal cost to manufacture, when the product becomes generic. Both views are important in determing the sustainability of a process. They simply answer different economic questions. The value equation answers the question, "Does it make money?" while the atom economy asks "Does it make sense?"

The value equation is easy to determine because it is just the difference between cost and sale price while a detailed engineering analysis is required to determine the atom economy. When each process consituent is considered from cradle to use, the average pharmaceutical synthesis often contains thousands of process steps.

Each process step is accompanied by some yield loss resulting in a low cumulative yield propagation. More over, virtually every step creates spent solvent where consumption is many times greater than the cumulative yield losses. Applying industry averages, for each kg of tetralone produced, 200 kg of waste is created. This generates an atom economy index of 0.005 (1/200), which is a measure of efficiency or lack thereof. Contrast that to the average atom efficiency of basic petrochemical production of propane with an atom index of approximately 0.97. This results from high yield in the synthesis, as well as the reuse or selling of all byproduct.

The atom economy of a process is important because proposed carbon tax legislation will be applied to the atom economy and act similar to a value-added tax. Each process step that utilizes energy, vents carbon dioxide or creates organic waste added to the tax on the product. Basically, a carbon tax is a penalty on the inefficient use of carbon.

The Economics of Solvent Recovery

Before we can ascertain the economic impacts of a greenhouse gas tax on pharmaceutical solvents, it is instructive to understand and analyze the economics of solvent recovery prior to any legislation. Let's begin by looking at the recovery of THF.

Item	Value
Virgin THF used	166,320 gallons/year
Price of virgin solvent	$9.46 per gallon
Thermal energy value of incineration	$0.60 per gallon
Solvent recovery percentage	90 percent
Labor operating costs	$25,500 per year
Energy and consumables	$37,600 per year
Initial investment - 10 percent carbon tax credit	$4,000,000
Savings per year	$1,157,000
IRR/payback	15 percent and 44-month payback

This project has been reviewed and rejected several times by one pharmaceutical manufacturer because it fails to meet the payback hurdle of 24 months. There are three factors working against this investment:

- **High thermal capacity** – Burning THF is 6.3 percent more efficient than burning coal, so its thermal value is relatively high.
- **High capital costs** –THF forms an azeotrope with water at a ratio of 88 percent. In order to get the THF purity level to the required 93 percent, manufacturers must apply simple distillation in addition to other separation steps.
- **Limited volume** – The ROI of solvent recovery is very sensitive to solvent volume. This is because the cost savings increase with volume. The costs of the equipment increase are directly proportional to the area of material used (a square function). The volume (amount of solvent generating savings) is a cube function of the geometric size of the tanks. The cost of engineering and project management are mainly fixed and do not increase substantially with increased recovery volume.

The Appropriate ROI

The required rate of return on an investment is typically an average of investment classes ranging from high-risk to moderate- to low- or no-risk investments. In the case of solvent recovery, the typical investment class and context would typically be considered moderate-risk manufacturing equipment. Most manufacturing equipment is considered moderate risk, because its return is a direct function of the demand for the product in the market and can change rapidly due to a variety of factors. However, we contend that solvent recovery investments are misclassified for the following reasons:

Limited Market Risk: There are only a small number of organic solvents that are used in pharmaceutical manufacturing. As mentioned previously, of the 530 million tons of waste reported to the EPA, 90 percent of the mass was the result of just 20 solvents. Solvents are chosen for the combination of their unique properties, and their health and safety aspects. As such, the same solvents tend to be used repeatedly. Manufacturers often use a solvent in many different preparations and at widely varying locations. So, while solvent demand for a specific active pharmaceutical ingredient (API) is subject to external forces, the overall demand for a specific solvent tends to be relatively stable, both across the company and often at a single location, since most locations produce more than one API. Therefore, solvent recovery investments should have a lower market risk premium than otherr, less flexible manufacturing investments.

Minimal Location Risk: While a company's overall demand for a specific solvent tends to be quite stable, there are highly unlikely scenarios where a plant's manufacturing volume is either solely or highly dominated by a single API that is the only user of a solvent at that site. In the case of a radical decline in market demand, the local demand utilization of the solvent recovery system could plummet. However, the overall consumption of that solvent across the company is likely to be insignificantly changed.

The ROI in solvent recovery can still be realized through two alternatives. First, other production sites could ship their spent solvent to an underutilized location for recovery. Alternately, since solvent recovery systems are often built as transportable modules, the solvent recovery system could simply be relocated to another location that has solvent demand. When conducting a solvent recovery financial analysis, rather than the investment bearing the burden of market and location risk for the entire investment amount, it should only bear the potential transportation cost of relocation, which is approximately 10 to 15 percent of the capital cost.

Reducing Supply-Chain Risk: Organic solvents used in pharmaceutical manufacturing are often complex derivatives of petrochemicals or sometimes, waste byproducts of some other high-volume synthesis. There can be considerable risk in the supply chain with any petrochemically derived product. Considering that 80 to 90 percent of the mass balance of a pharmaceutical plant is solvents, the amount of supply-chain risk is considerable and unnecessary. On average, pharmaceutical plants can recover about 90 percent of their spent solvents, which can provide a substantial reduction in supply-chain risk.

A recent example illustrates the point. The following is a quotation from a major acetonitrile (ACN) supplier's correspondence to its customers in May 2009:

"Although the availability of acetonitrile has improved, there is still a global shortage of material. This may last into the third quarter of 2009, especially for higher-quality grades. We have a reliable supply chain based on multiple sources from a number of our business partners manufacturing the raw materials. Nevertheless, the production of these raw materials is affected by factors driven by market and economic conditions outside our direct control."

While there were a number of factors contributing to the reduction in supply, it is important to remember that acetonitrile is a byproduct of acrylonitrile production, which is used in the manufacture of car parts, electronic housings, and other products severely hurt by a weakened economy. As incredible as it may seem, ACN suppliers have had to ration their customers. Image a life-saving medication potentially unavailable due to a slow down in automotive manufacturing. Supply was not the only thing affected. Prices for ACN increased between 800 and 1,000 percent.

A solvent recovery investment actually reduces a company's supply chain, thus revenue and profit risk. Solvent recovery also should be considered an insurance policy against future supply-chain disruptions.

Environmental and Legislative Risk

Organic solvents are derived from petrochemicals, a limited resource. Its use has been directly tied to environmental impacts and global warming. Future U.S. and global environmental regulations likely will increase the cost of organic solvents. In addition, some solvents are byproducts or waste streams from another process. If that process is no longer deemed profitable in light of new environmental legislation, the supply of a particular solvent may be severely impacted.

Based on these considerations, it's clear that the investment risk of solvent recovery is considerably lower than that of typical production capital investments. Therefore, the required ROI should be substantially lower than what is currently applied to these projects. Companies have limited capital, so even though an investment in solvent recovery may pass the ROI hurdle, this begs the question – should a company apportion some of its limited capital to such an investment?

The fundamental question centers on whether viable investment alternatives are available to mitigate the strategic and tactical risks to the company. The essential value of a solvent-recovery investment is business risk reduction in the form of reducing supply-chain, legislative and product-margin risk. Given the implications of such risks, most pharmaceutical executives believe it is not a question of whether to do solvent recovery, but how.

There are three ways a pharmaceutical company can implement a solvent-recovery operation. If the facility has the technical expertise and space, then the most cost-effective solution is to acquire and operate the assets directly. If the site lacks the operational expertise, the company should either in-source the project by purchasing or leasing the equipment and contracting the operation to a company experienced in the technology; or contract with a third-party recycler to provide the service.

The decision between in-sourcing and outsourcing is a function of the solvent volume. In-sourcing is more advantageous for larger volumes because of the reduction in transportation costs and administrative costs related to hazardous-waste shipping.

Implications of Environmental Legislation

Many expect that the passage of some form of environmental legislation will reduce the generation of greenhouse gases and help mitigate the rate of global warming. While several schemes have been discussed, the most likely appears to be a cap-and-trade system modeled after the successful sulfur program of the 1990s. A carbon cap-and-trade tax will impact the prices of all goods that require energy for their manufacture or delivery. Since carbon dioxide is generated from virtually all activity, prices of products will increase by the amount of carbon dioxide that is generated throughout the entire product life cycle. The impact of a carbon tax on a pharmaceutical manufacturing plant requires us to understand the plant's overall carbon footprint.

Life-Cycle Costs

A carbon-dioxide tax will behave like a value-added tax, except it will track the release of carbon dioxide at every stage of the value chain. When solvent recovery investments were analyzed in the past, the analysis context boundary was limited to the plant site known as gate-to-dock. Now, the investment becomes a function of the entire carbon dioxide life cycle of the product. Since a pharmaceutical company's mass balance is dominated by solvents, the implications on the API plant's gross margin is the impact on its solvents.

To illustrate the implications, let's go back to our previous example of the recovery of THF, which had an internal rate of return of 15 percent and a simple payback period of 44 months. We need to determine the generation of carbon dioxide throughout the entire life cycle of THF. Accumulating all the carbon dioxide generated from the first raw-material extraction from the ground, i.e. crude oil to the truck's carbon dioxide emissions delivering the final THF to the plant site.

The image below is the chemical tree for THF. It depicts each chemical process step in the synthesis, starting from the initial extraction on the right to the final product on the left.

Tetrahydrofuran, C_4H_8O	Hydrogen, H_2	Natural Gas					
	Furan, C_4H_4O	Furfural, $C_5H_4O_2$	Corncobs				
			Water, H_2O				
			Sulfuric acid, H_2SO_4	Sulfur trioxide, SO_3	Sulfur, S	Naphtha Refinery	Petroleum Reserve
					Air		
				Water, H_2O			
		Calcium acetate monohydrate, $Ca(C_2H_3O_2)_2 \cdot H_2O$	Calcium Hydroxide, $Ca(OH)_2$	Limestone			
				Carbon Dioxide, CO_2	Natural Gas		
					Air		
					Water, H_2O		
				Water, H_2O			
			Acetic Acid, $C_2H_4O_2$	Carbon Monoxide, CO	Natural Gas		
					Water, H_2O		
					Carbon Dioxide, CO_2	Natural Gas	
						Air	
						Water, H_2O	
				Methanol, CH_3OH	Natural Gas		
					Water, H_2O		
				Water, H_2O			

The energy, waste and byproducts for each process step have been determined. The chemical tree takes into account all process steps, materials and yields. Unfortunately, it ignores ancillary energy expenditures, such as transportation of raw, intermediary and final delivery of the materials. We account for this additional carbon-dioxide generation by applying industry-average transportation studies for the materials in question. The life-cycle analysis results in 78 kg of imputed carbon dioxide for every kilogram of THF delivered to a pharmaceutical plant. This imputed carbon-dioxode content is 136 times greater than the carbon dixode liberated when THF is incinerated at the plant. This carbon-dioxode leverage factor will multiply the impact of a carbon tax on the cost of THF usage.

The high solvent mass leverage of pharmaceutical plants makes determining manufacturing gross margin exposure important. To assist in the determination of the imputed carbon-dioxide content within solvents there are a number of life-cycle analysis and life-cycle inventory resources available. These resources are listed in the appendix.

The Impact of a Carbon-Dioxide Tax on the ROI of Solvent Recovery

The current cap-and-trade legislation is expected to result in a tax of $28 per ton of carbon dioxide. That equates to:

• $ 0.0063 per kg of carbon dioxide

Since 1 kg THF requires 78 kg of carbon dioxide in its production, the legislation will result in:

• A tax of $0.496 per kg of THF (22% price increase)
• A price increase of $2.11 per gallon THF

To illustrate the impact of this legislation on investment in solvent recovery, let us review the ROI analysis of THF we completed earlier.

Item	No Carbon Tax	Carbon Tax
Virgin THF used	166,320 gallons/year	166,320 gallons/year
Price of virgin solvent	$9.46 per gallon	$11.57 per gallon
Thermal energy value of incineration	$0.60 per gallon	($2.10) per gallon
Solvent recovery percentage	90 percent	90 percent
Labor operating costs	$25,500 per year	$25,500 per year
Energy and consumables	$37,600 per year	$37,600 per year
Initial investment - 10 percent carbon tax credit	$4,000,000	$3,600,000
Savings per year	$1,157,000	$1,800,000
IRR/payback	15% and 44-month payback	28% and 24-month payback

The table above compares the investment analysis of recovery versus incineration with and without a carbon tax. As can be easily seen, a carbon tax doubles the investment return and reduces the payback period by half. Under the scenario of a carbon tax, the investment in recovery of THF meets most pharmaceutical moderate-risk capital investment hurdle rates. However, as we contend from the earlier discussion, investments in solvent recovery should be considered lower risk, as well as an investment in sustainability and business continuity.

Validation

Changing from virgin to recovered solvents will likely require revalidation. How extensive this effort will be depends on the exact wording of the original validation documentation. In general, validation batches will need to be completed to demonstrate that the quality of product can be mantained using recovered solvents. Many firms use the material data sheets provided by the solvent manufacturer to document validation purity levels, even if those purity levels are not required. This can make solvent recovery needlessly more expensive. It is important therefore that during R&D and process scale up, solvent specifications are kept as broad as possible and the term “recovered” or “recycled” is used in the documentation.

Conclusion and Next Steps

Impending global-warming legislation offers an economic incentive to reduce carbon-dioxide generation. If approved, new cap-and-trade regulations will dramatically improve the ROI in solvent recovery for pharmaceutical companies and, more importantly, change the investment analysis context from one of cost savings to one more directly focused on sustainability and business continuity. Bottom line: solvent recovery offers a simple, low-risk method to reduce your carbon footprint and help shield your company from significant adverse effects of environmental legislation.

Because of their extensive use of solvents and high mass leverage, pharmaceutical companies should determine the impact of a carbon-dioxide tax and start preparing action plans now. In the short run, investing in solvent recovery offers companies an effective profit-protection strategy. In the long term, reducing reliance on solvents with high imputed carbon dioxide will be necessary. We recommend that pharmaceutical companies consider the following actions:

- Collect data on solvent usage
  - Volume of each solvent used
  - Composition of “waste solvent streams”
  - Volume of each “waste solvent stream”
  - Purity requirement for each solvent (with and without re-validation)

- Establish appropriate rate of return
  - Identify personnel responsible for sustainability and green initiatives
  - Discuss investment with responsible parties, get support and sponsorship
  - Determine “appropriate” rate of return for this type of investment

- Complete funding and tax homework
  - Global warming incentives
    - Tax credits
    - Low-interest financing
    - Energy credits, rebates (state and local utilities)
    - Determine position on carbon tax or cap and trade
  - Structure of investment (capital, service contract, outsource)

- Determine life-cycle impact of each solvent

- Work with experienced technology partner like Rockwell Automation for help in calculating ROI (capital investment requirements, ROI tools, and project strategy, planning and implementation)

References and Acknowledgements

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- www.engineeringtoolbox.com
- National Physical Laboratory

Life Cycle Assessment Tools and Sources

- National Renewable Energy Laboratory: US Life-Cycle Inventory Database
  - http://www.nrel.gov/lci/

- LCI@CPM: Industrial Environmental Informatics at Chalmers University of Technology
  - www.cpm.chalmers.se/CPMDatabase

- Danish LCA Center
  - www.lca-center.dk

- Center for Environmental Science Lieden University Netherlands
  - www.leidenuniv.nl/cml/ssp/software/cmlca/index.html

- The Society for the Promotion of Life Cycle Assessement
  - http://lca-net.com/spold/

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Publication – SSB-WP001A-EN-E – December 2009