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Reduce Cost and Waste of Solvent in Pharmaceutical Manufacturing

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A Warm Up: Did You Know…….

- Pharmaceutical manufacturing is the least efficient of all chemical industries in terms of **Atom Economy** (kg waste / kg product)
  - Pharma Average Ratio is 200 to 1 (waste generated to product) some products as high as 800 X
  - BioPharma is worse. Typical solvent waste to product ratios between 3,000 to 10,000 to 1
- Pharmaceutical Plant Site Waste is 80% Solvent
- Pharmaceuticals reported 530 Million Tons of Waste to EPA.
- Of the 170 chemicals reported to the EPA for Pharmaceuticals, the top 20 solvents represent 90% of the mass of waste generated.
- Solvent cost is one of the largest components of overall product cost.
- Solvents Represent:
  - 75-80% of energy usage
  - 75-80% of the environmental impact
  - 80-90% of the mass balance
- Most solvents are not recovered because of their thermal value (similar to coal). Incinerated for power at plant, or sold to others for incineration.
  - Natural Gas: 54.3 MJ/kg
  - Coal 30.3 MJ/kg (48% of US Energy Generation)
  - THF 32.2 MJ/kg (40% lower than Natural Gas)
  - MEK 34.0 MJ/kg
  - Ethanol 30.0 MJ/kg

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New Events That Will Alter the Landscape

- EPA has been authorized to regulate Carbon Dioxide Emission
- France has passed a carbon tax.
- Other European countries are likely to pass a carbon tax this year.
- China is trying to be the world leader. (embarrassing all others)
- The US will probably do something this year.
  - China impact. (negotiation)
  - EPA Ruling. Very cunning. Business rather work with carbon tax than EPA regs.
- Expect a "global carbon harmonizing tax" part of WTO deliberations.
  - US will not want this either.
- Estimated that Cap and Trade legislation will impose a "tax" of approximately $ 28 per ton of carbon dioxide emitted.
  - Update: Independent Report Advising Congress Suggests Tax must be between $40 and $90 per ton in order to be effective.

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HOLD ON….Things are going to change

Pharmaceutical Manufacturers, especially Generics, could be significantly impacted by a carbon tax:

because of the very high mass leverage (inverse atom economy):

<u>Almost 90% of the mass balance ends up as Carbon Dioxide.</u>

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Basic Factors in Evaluating Solvent Recovery

- Capital Cost of the Equipment. (declines as a percentage of cash flow as volume increases)
- Operating Cost of Recovery (energy, labor)
- Price of Virgin Solvent
- Price (or cost) to dispose of waste solvent
- Volume of solvent waste generated.
- Depreciation (tax benefit of capital purchase)
- Percent of Solvent Recovered.
- Purity Requirements
- Required Rate of Return.
- Difficulty of Separation (Aezotrope)
- Tax Incentives (tax credits, low cost financing, energy credits/rebates)
- Brand and Sustainability Positions.

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The Current State:

Because of the high Calorific Value of Most Pharmaceutical Solvents are incinerated for energy and not recycled because at current prices:

(comparable fuel compliance)

the difference in price between virgin solvent and its energy value at moderate consumption volumes does not meet most ROI targets.

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Comparison of Ethanol Recovery from IDA

Item	Recovered Energy	Hazardous Waste Disposal
Virgin IDA Used	728,000 gallons / year	728,000 gallons / year
Price of Virgin Solvent	$ 2.50 per gallon	$ 2.50 per gallon
Sell Price of Waste	$ 0.42 per gallon	- $ 0.52 per gallon
Solvent Recovery %	92%	92%
Labor Operating Costs	$ 55,500 per year	$ 55,500 per year
Energy and Consumables	$ 39,800	$ 39,800
Initial Investment	$ 3,080,000	$ 3,080,000
Savings Per Year	$ 1,393,000	$ 4,498,000
ROI / Payback (months)	22% and 27 month payback	80% and 8 month payback

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Basic Solvent Recovery Finance Model

Savings= $$\sum (Ps-(Fv-LCc*Ct))*Ys*Vs$$

Costs:

Heat=(Emvap*Vts*te*$he*Ct*Ac)

Cool=((Vts-Vbs)*(E2vap-Elvap)*te*$ce*Ct*LCc)

Labor=((Vts/Vphr)*0.42*Lc/hr)+ 0.025*LcE/yr

Capital:

$$Investment = Fixed*(1+Cf^{(\#S/A)}) + X*Vt^{(-bVt)}$$

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Most Important from a Carbon Dioxide Perspective

If we differentiate the preceding equations for carbon dioxide (ie dCost / dCarbon Dioxide) the following are the most important factors regarding the impact of greenhouse gas legislation.

1. **Life Cycle Carbon Dioxide Generated ("LCc")**
2. **Carbon Tax ("Ct")**
3. **Total Solvent Volume ("Vts")**
4. **Recovery Yield ("Ys")**
5. **Energy Conversion Efficiency ("te")**

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The Current State:

Because of the high Calorific Value of Most Pharmaceutical Solvents, Solvents are incinerated for energy and not recycled because at current prices, the difference in price between virgin solvent and its energy value at moderate consumption volumes does not meet most ROI targets.

That is about to change.

1. The required ROI is overstated for solvent recovery investments.
2. Greenhouse gas legislation is going to dramatically increase the effective cost of not recycling solvents, especially for pharmaceutical companies because of their high solvent usage.

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Simple ROI Calculations Are Inappropriate

ROI and NPV was originally devised for financial investments. Here price does represent the underlying value equation. However, in other investments, especially solvent recovery; current or spot prices may not be an efficient representation of underlying economics.

- Required Rate of Return is an average of investor perception of the risks of the company's primary business. Not necessarily same as a single investment.
- Ignores protection / insurance aspects since they are not explicitly part of cash flow. (reduction in sensitivity to supply disruption)
- Assume that prices efficiently reflect all life cycle costs of the product.
- All factors are assumed statistically independent (supply and demand).

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What Other Factors Should Be Considered?

Factor	Impact on Required Rate of Return (+/-)
Business Risk (additional mitigation through modular and multi-solvent, not classical fixed asset)	-
Supply Chain Risk	-
Fossil Cumulative Energy Content of final product. (capped supply)	-
Cumulative Carbon Dioxide Generation (we will eventually need to deal with it)	-
Legislative Risk	-
Co-variant Risk (are prices artificially low due to by/co-product) Acetonitrile	-
Atom Economy (overall process efficiency)	-

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Modular Distillation System

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Looking Beyond Plant Boundaries

One of the problems that solvent recovery investments face is the perception of the environmental advantage for recycling the solvent is limited to plant boundaries. Often the analysis focused solely on:

- Cost Accounting
- Environmental Regulation
- In plant total waste.

To truly understand the real economics (and what will eventually be represented in realized costs with greenhouse gas taxes) is to consider the entire life cycle analysis of the solvent.

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Prices and Costs Are Simplified Abstractions

BE AN ENGINEER!

Develop the atom efficiency of the entire process from raw material (extraction) to finished product. In a supply constrained world, the economics (prices) should eventually reflect the atom efficiency.

To understand the potential return and the risk of a process or investment.

1. Work out the entire process flow from initial raw material to finished product.
2. Understand all the energy requirements at each process step.
   - Transportation
   - Feedstock
   - Yields
3. Calculate "carbon dioxide" generation of each step.
4. Understand the interdependences, yield and value chain of all materials.
5. Then assign an adjustment (+/-) factor to the required rate of return. Do not assume prices reflect true costs (statistically independent)

Don't Forget The Lesson of Acetonitrile.

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A Life Cycle Analysis: THF

A plant boundary view distorts the impact of incineration vs recovery. As a result most THF is incinerated rather than recovered. (higher energy than coal)

Incineration creates energy and generates waste (carbon dioxide)

Distillation uses energy which creates waste (carbon dioxide and un-recoverable bottom stills)

Incineration: 0.573 kg waste/kg THF
Recovery 0.368 kg waste/kg THF

Solvent	Heat Released MJ/kg	Carbon content kgC/kg solvent
Ethyl Acetate	**12.1**	**0.64**
Ethanol	**13.85**	**0.52**
Methanol	**9.99**	**0.37**
Toluene	**23.15**	**0.91**
THF	**17.99**	**0.67**
Acetic Acid	**5.87**	**0.40**
Hexane	**23.66**	**0.84**
Ether	**17.89**	**0.65**
IPA	**15.70**	**0.60**

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Life Cycle Analysis of THF

Broaden our perspective from plant boundary to entire life cycle.

When we recover a solvent, emissions are being avoided because there is no need to produce that kilogram of solvent.

We need to consider not only the production of THF itself, but all the intermediaries required throughout the process, all the way back to the original fossil extractive source.

We must consider the entire **Chemical Tree.**

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Chemical Tree (LCA) THF

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			

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THF Life Cycle and Carbon Dioxide

The Difference in Carbon Dioxide generation between recovery and incineration at the plant boundary is only 0.205 kg/kg solvent (0.573-0.368)

However, 78 kg of carbon dioxide was generated in producing the 1 kg of THF.

This is a 380 times difference. **(78 kg / 0.205 kg)**

What will a carbon tax or cap and trade do to the economics of solvent recovery?

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Impact of Carbon Tax

- Current Legislation is expected to result in a tax of $ 28 per ton Carbon Dioxide
- That equals $ 0.0063 per kg Carbon Dioxide
- 1 kg THF requires 78kg of Carbon Dioxide in its production

    A tax of $0.496 per kg of THF (22% price increase)
    A tax of $ 0.56 per liter of THF

    A tax of $ 2.11 per gallon THF

The carbon tax will negate the fuel value of incinerating THF!

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Comparison of THF Recovery: Carbon Tax

Item	Recovered Energy	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
Sell Price of Waste	$ 0.60 per gallon	($ 2.10) per gallon
Solvent Recovery %	90%	90%
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% carbon tax credit	$ 4,000,000	$ 3,600,000
Savings Per Year	$ 1,157,000	$ 1,800,000
IRR / Payback (10 yr/month)	15% and 44 month payback	28% and 24 month payback

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Investment Recap

- Factors Influencing Solvent Recovery Investment Decision
  - Price Solvent
  - Energy Content of Solvent or Disposal Cost
  - Atom Economy of Solvent (life cycle carbon dioxide)
  - Complexity of Recovery (determines capital investment)
  - Volume of solvent
  - Required Purity
  - Discount Rate (Required Rate of Return)

In General, when considering the Life Cycle Atom Economy and the Solvent Mass Balance Leverage:

Only Solvent Volume Determines The Financial Viability of Solvent Recovery in Light of a Carbon Tax.

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Terminology

Distillation: *"separation of a mixture of liquids into separate components based on differences in boiling point, using energy (steam) input"*

"Batch" or "Continuous" ?

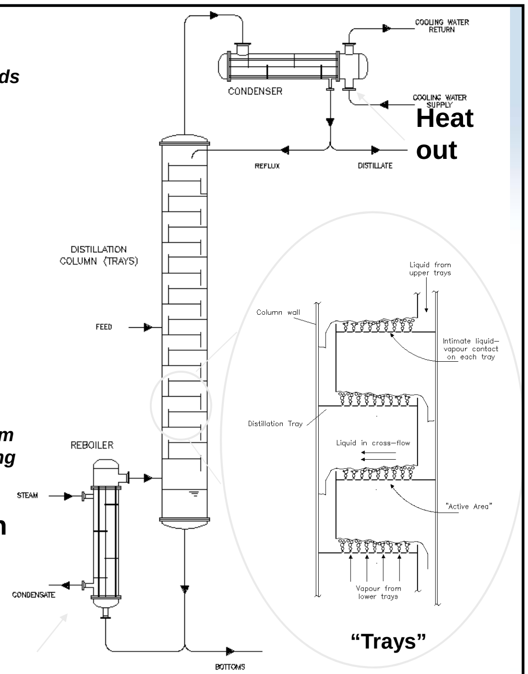
Equipment:

- **Column (or "tower")**
- **"Reboiler" (boils liquid)**
- **"Condenser" (condenses vapour)**
- **Product coolers / feed-preheaters**
- **Pumps & instrumentation**

Design Problem:

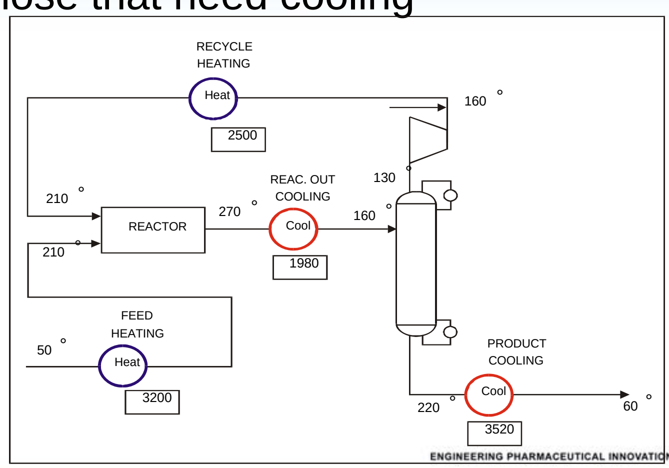
"Given a mixture of solvents, design a system to separate them into pure components, using minimum energy, at minimum capital cost"

Water
Methanol
Toluene
Dichloromethane
Ethyl Acetate
Also: Crude oil, Air Separation



Distillation is Energy Inefficient! What is a Pinch Analysis?

- Linking streams that need heating to those that need cooling



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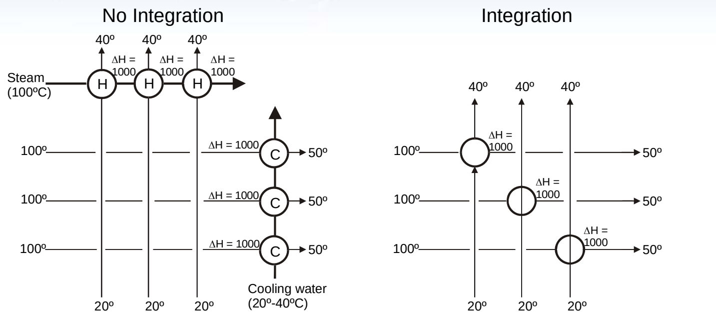
Why carry out Process Integration?

Process Costs Reduced



Total Heat Transferred = 6000kW	Total Heat Transferred = 3000kW
ΣArea = 112m²	ΣArea = 69m²

Savings of 50% in Plant Services

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Composite Curves

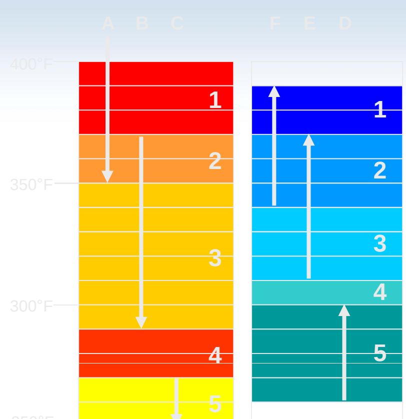
Prepare the composite curves, distinguishing interval of temperature where streams influent/effluent temperatures begin/end

hot streams

A	B	C
410	370	270
350	290	250

cold streams

D	E	F
260	310	340
300	370	390



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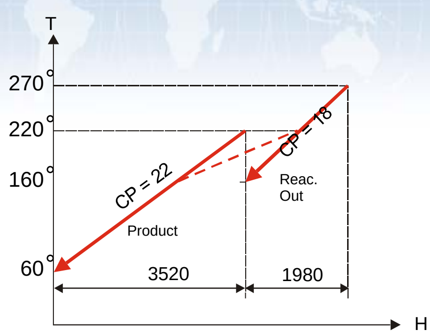
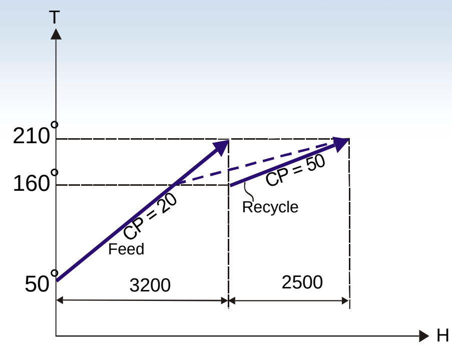
The Composite Curve





No	Name	T_{supply}	T_{target}	ΔH
1	Product	220	60	3520
2	Reac. Out	270	160	1980

No	Name	T_{supply}	T_{target}	ΔH
3	Feed	50	210	3200
4	Recycle	160	210	2500

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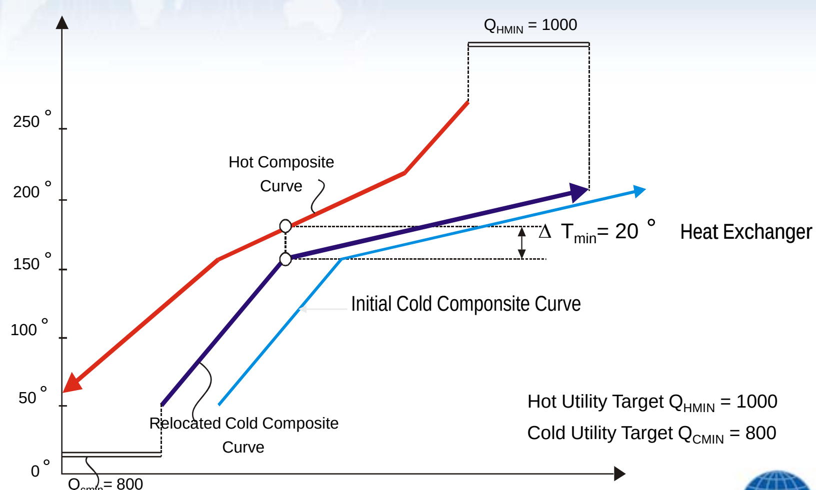
The Composite Curve



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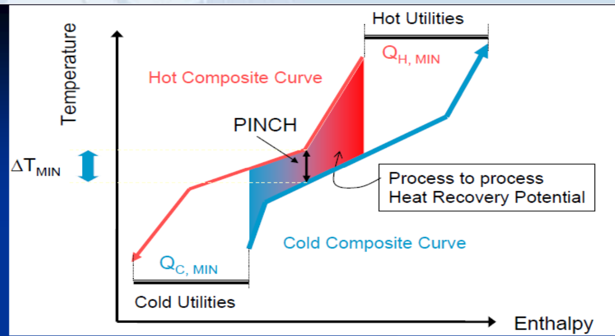
Graphical Heat Recovery



- At a particular ΔTMIN value, the overlap shows the maximum possible scope for heat recovery within the process. The hot end and cold end overshoots indicate minimum hot utility requirement (QH,MIN) and minimum cold utility requirement (QC,MIN), of the process for the chosen ΔTMIN.
- Thus, the energy requirement for a process is supplied via process to process heat exchange and/or exchange with several utility levels (steam levels, refrigeration levels, hot oil circuit, furnace flue gas, etc.)

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Material: Pinch is Not Limited to Heat

Pinch analysis can be supplied to any material that has multiple uses in the process with each use having different compositional requirements.

Examples	Water
	Ethanol
	ACN
	THF
	IPA
	Other
Difference:	Heat Pinch is: Temperature vs Enthalpy
	Resource Pinch is: Volume vs Requisite Purity

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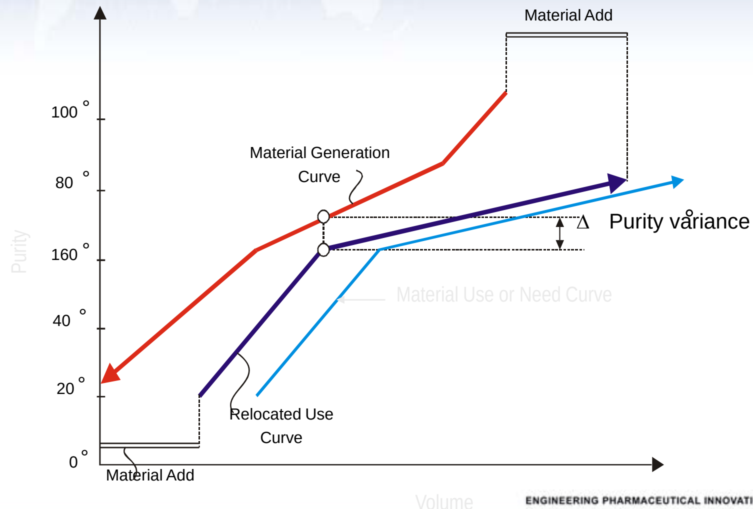
Material Pinch



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Intermediate Solvent Rejuvenation

- Often a solvent is contaminated by only one species that posses a problem.
- Other contaminates are at too low a concentration or do not effect the reaction.
- Consider, reducing the problem contaminant only and reusing:
  - Faster
  - Less expensive
  - Can often be done at line (in process)
- Example:
  - Water is reaction product and contaminant.
  - Water contamination will reduce shift equilibrium and reduce yield
  - Consider simple “dehydration” for solvent reuse rather than full distillation and recovery. Save a lot. Distillation when other contaminant concentrations become problematic.

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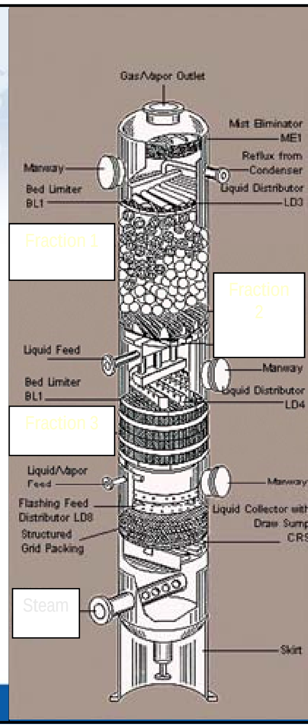

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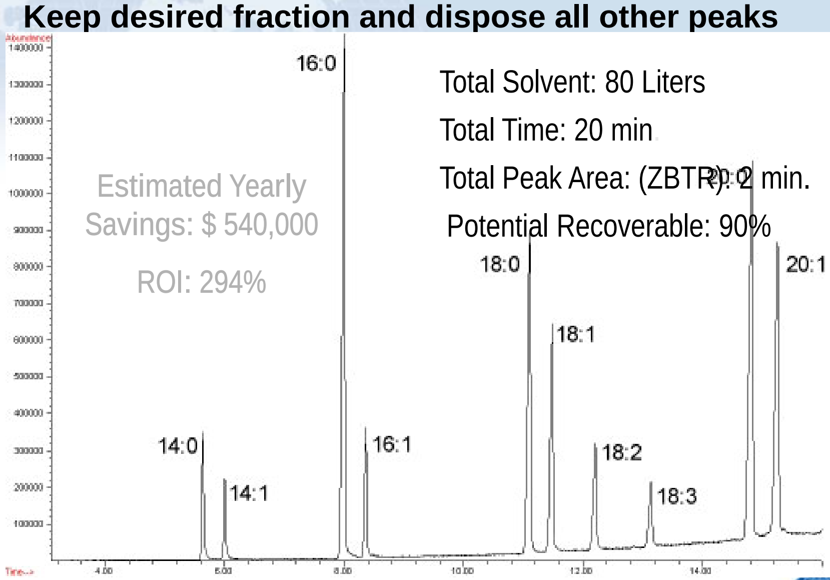
Solvent Recovery: Simple Fractioning:
Keep desired fraction and dispose all other peaks



Total Solvent: 80 Liters

Total Time: 20 min

Total Peak Area: (ZBTR): 2 min.

Potential Recoverable: 90%

Estimated Yearly Savings: $ 540,000

ROI: 294%

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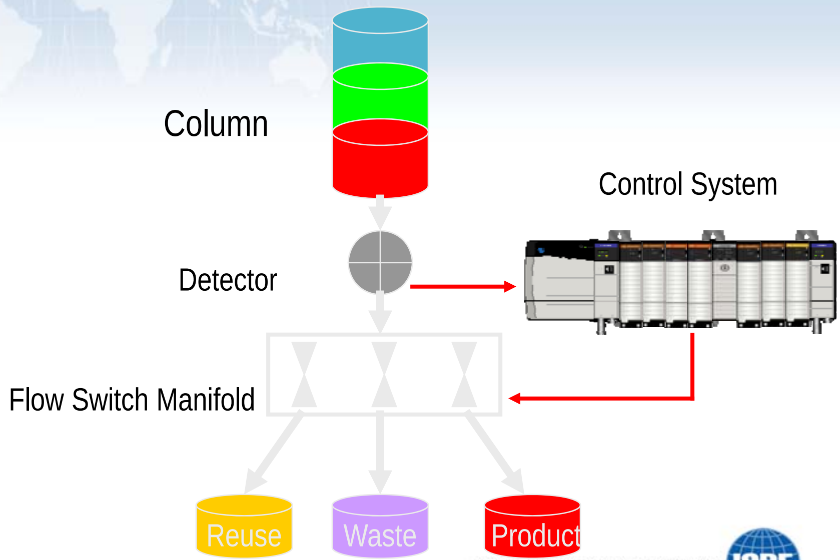
Simple Control System Process



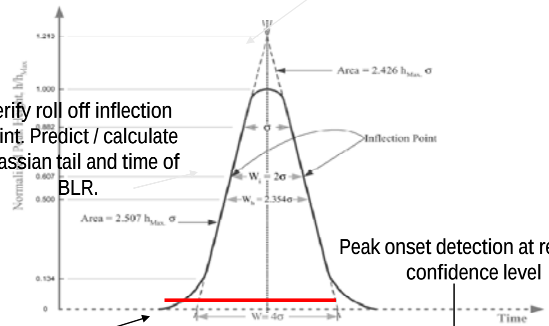
Considerations and Concerns

- Peak Detection Feed Forward (time between peak detection confidence level and switching valve)
  - Short as possible
  - No bounce, jitter or oscillation.
- Post Column Diffusion.
- Peak shape modeling
- Fluid flow velocity calculation.
- Fluid Delay Circuit

- It's all a game of math and statistics
- Beauty is:
  - Empirical data (a priori information)
  - Repeatable
  - Modeled

Anatomy of A Peak for Solvent Reuse

Determine Peak Apogee / Inflection point. Calculate peak shape.



Verify roll off inflection point. Predict / calculate guassian tail and time of BLR.

Peak onset detection at required confidence level

Verify gaussian tail and feedforward

Feed forward. Timed delay for fluid flow rate to valve, based on calculation of pressure and pump rate

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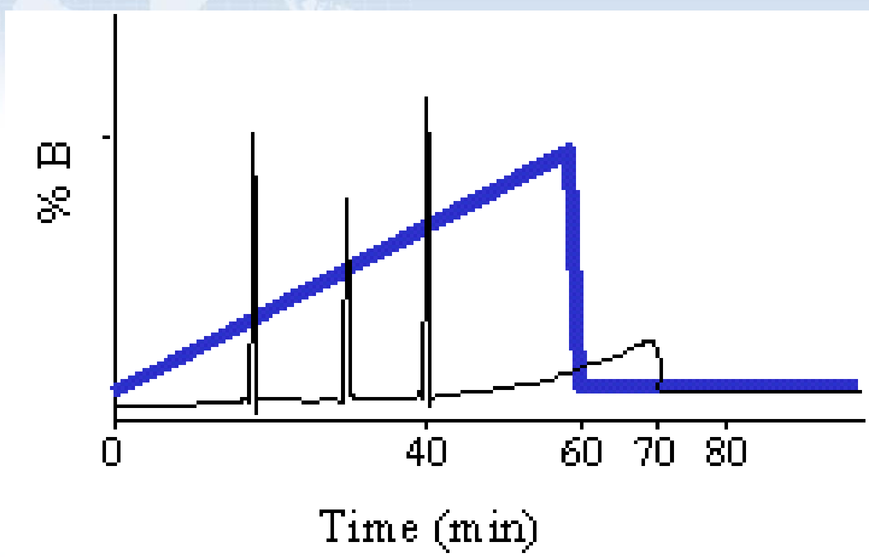
Dealing With Gradient Programs



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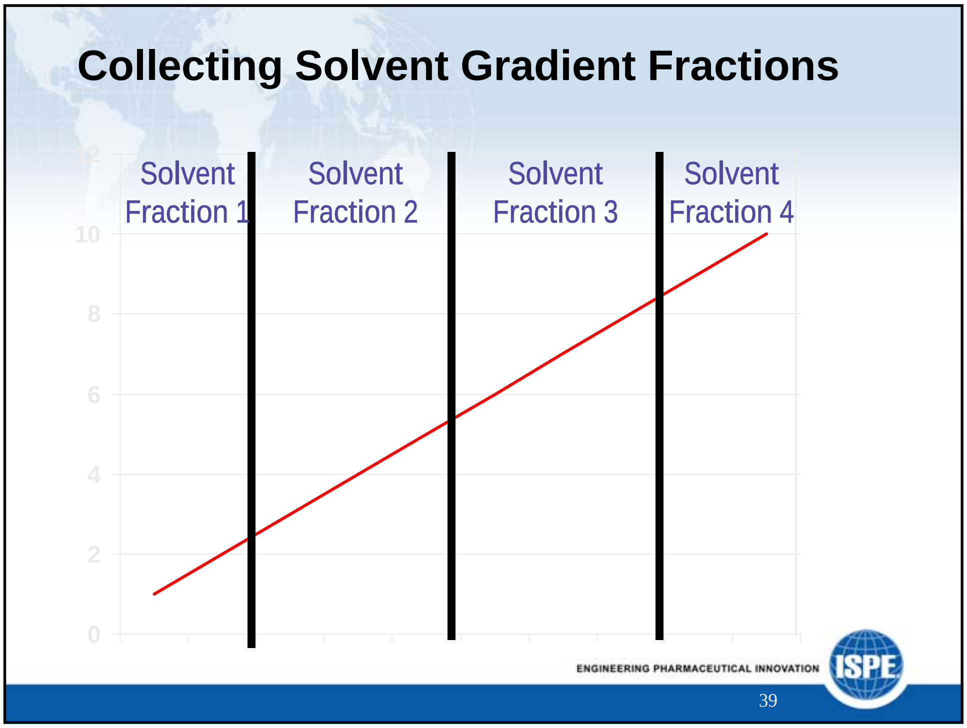

Collecting Solvent Gradient Fractions
Solvent Fraction 1
Solvent Fraction 2
Solvent Fraction 3
Solvent Fraction 4
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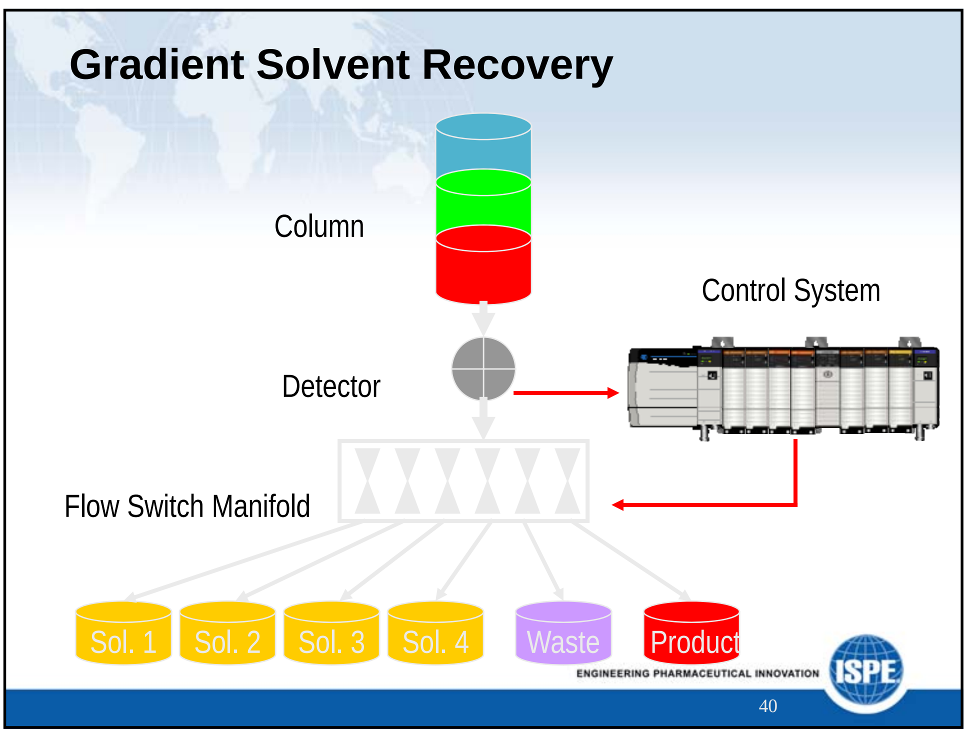

Gradient Solvent Recovery
Column
Control System
Detector
Flow Switch Manifold
Sol. 1
Sol. 2
Sol. 3
Sol. 4
Waste
Product
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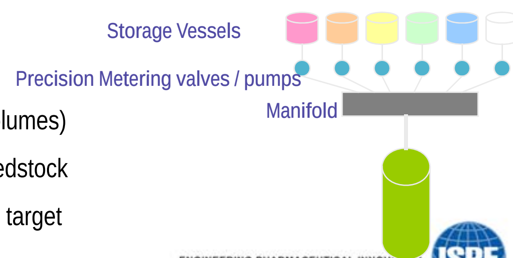
Using Recovered Gradient Solvents

- Consider changing to stepwise gradient Program if possible. Easier, lower capital cost and greater reuse:

- Digital Blending ™
  - Real time precision "mixing"
    - Knows:
      - Inventory (fraction volumes)
      - Concentrations of feedstock
      - Output concentration target



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SO WHAT? I'm a big molecule Bio Person

This is all fine, good and interesting but doesn't apply to me because we use an aqueous process. Our solvents are all buffers.

Sure aqueous buffers are inexpensive and easily neutralized and disposed of…..BUT it is wasteful and does have an environmental impact.

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Sustainability Issues of Aqueous Solvents

- Energy required to create the purified water (12-18 megohm)
- Energy required to treat the waste water discharge.
- Energy Required to create buffer components (acids, ionic compounds)
- Carbon Dioxide generated in buffer component process.

** These maybe minor in comparison to organic solvents, but they represent waste and environmental stress.

Let's look at the sustainability costs and implications of aqueous buffers.

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Life Cycle Analysis of Aqueous Buffers

Item	Unit	Energy	Carbon Dioxide
High Purity Water	Liters	0.32 KWh/L	0.42 lbs/L
Waste Water	Liters	0.001 KWh/L	0.001 lbs/L
Acid / Bases	Kg	1.042 KWh/Kg	1.41 lbs/Kg
Ionic Buffers	Kg	0.843 KWh/Kg	1.22 lbs/Kg
Transportation	Kg/Mile	NA	0.0376 lbs/Kg-mile

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Solvent Sustainability: BioPharma Plant

- Avg Solvent Usage 40 liters/min
- Avg Lines 4
- Yearly Solvent Consumption: 4,800,000 liters
- KWh consumed: 1,630,000 KWH
- Electricity Cost: $ 146,480 (at $0.09 KWH)
- Carbon Dioxide Generation: 2,275 Tons
- Carbon Tax: $ 63,706 (at current $ 28 per ton)

- Estimated Capital Investment: $ 250,000
- IRR (5 years): 79%
- Payback period: 1.25 years

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Validation

Every company has its own Validation Guidelines and Procedures which may conflict those presented here. Check with your validation department.

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Validation Implications

- What to consider
  - Has the drug filing been submitted with option to use recovered solvents?
    - If not then validation batches will need to be completed to demonstrate that quality of product can be achieved using recovered solvent
  - During R&D ensure that solvent specifications are kept as broad as possible – for example if a solvent <5% Water will achieve the desired effect, do not document <1% Water due to the lab using virgin solvents, it can have a big impact on the capital and operational cost of future recoveries. If water content is not critical to the process then do not include in the filing
  - Try and engage with EHS department (Solvent Recovery Group) to review potential for recoveries during product development, some small adjustments can mean recovery being feasible saving the company $MM
  - A solvent recovery system will require some level of validation either the towers can be validated or if there is the likelihood of various recoveries – then the recovery is validated by use test and 3 validation batches and then go into full scale production
  - Consider the separation of solvents gathered from different process steps to avoid risk of cross contamination!

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Available Resources

If you would like any of these materials, please just drop me a note.

1. This presentation. (PowerPoint)
2. The accompanying White Paper.
3. Article Reprint: “A method to characterize the greenness of solvents used in pharmaceutical manufacturing” (Slater and Savelski)
4. Ph’d Dissertation: Jimenez-Gonzalez; “Life Cycle Assessment in Pharmaceutical Applications”

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Next Steps

How To Get Started

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Next Steps

1. 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)
2. Establish Appropriate Rate of Return (Hurdle)
   - Identify the executive responsible for sustainability and green initiatives.
   - Discuss investment with the above person. Get support and sponsorship
   - Determine "appropriate" rate of return for these types of investment.
3. 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)
4. Determine Life Cycle Impact of Each Solvent (Chemical Tree: LCA)
5. Call Rockwell for help in calculating ROI (cap investment, ROI Tools etc)

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Thank You

And

Good Luck

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