Optimizing Solvent Management in Bio-Pharma

Common Sense Sustainability

David March
Process Capital Productivity Specialist

ALLEN-BRADLEY • ROCKWELL SOFTWARE

Rockwell Automation

Agenda

- Some Startling Statistics: A Warm Up
- The Economics of Solvent reuse and Recovery
- A new way of looking at solvent contamination
- Solvents and Sustainability
- Suggested Next Steps

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)
  - Synthetic Pharma Average Ratio is 200 to 1
  - BioPharma: Ratio is 3,000 to 100,000
  - By comparison Refineries operate at approx. 97.3% atom efficiency

- Pharmaceutical Plant Site Waste is 80% Solvent

- Solvent cost is often the largest manufacturing cost and dominates most operational activities.

- Solvents Represent:
  - 75-80% of energy usage
  - 75-80% of the environmental impact
  - 80-90% of the mass balance

- Most traditional API solvents are not recovered because of their thermal value. Comparable fuel.
  - 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

- Biopharma solvent mixtures (gradient elution) reduces BTU often difficult to use as comparable fuel.

- Most BioPharma Plants do not consume enough solvent(s) to justify on-site recovery.

- For BioPharma Plants that utilize a high percentage of organic solvents, about 80% of the plant's mass balance is going up the smokestack as carbon dioxide.

An Example: Solvent Recovery Distillation

- Large Bio-molecule oncology drug.
- 3 sequential column process. (all gradient programs)
- 200 liters of solvent per day.
- Production is 0.6 grams per day.
- Atom economy of the process 333,000 to 1; waste to product.
- Number of Solvents Utilized: 6
- Largest Single Solvent Consumption: 20,000 liters per year
- On Site Distillation Breakeven Point: 900,000 liters per year
- Conclusion:
  - On site recovery not economically feasible
  - Stripped to improve BTU content and sold / paid for off-site incineration.

Solvent Reuse (no distillation): ROI

Using the previous example: What are the savings and ROI?

Average solvent price: $ 2.20 per liter

Solvent usage: 200 liters per day

Yearly solvent usage: $ 110,000

Recovery Percentage: 90%

Make Up Solvent: 5,000 liters ($ 11,000)

Net Solvent Savings: $ 99,000

Investment: $ 62,000

Payback Period: 8 Months

ROI: 158%

Simple Solvent Reuse Concepts

- Chromatography Solvent Contamination is Temporal. Unlike batch synthesis, where the entire solvent volume is contaminated. In chromatography, only that portion which co-elutes is contaminated.

- Fractionating the eluent and directing to waste only that volume with contaminated elution allows us to recovery a large portion of the solvent, with minimal risk and expense.

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

Total Solvent: 80 Liters

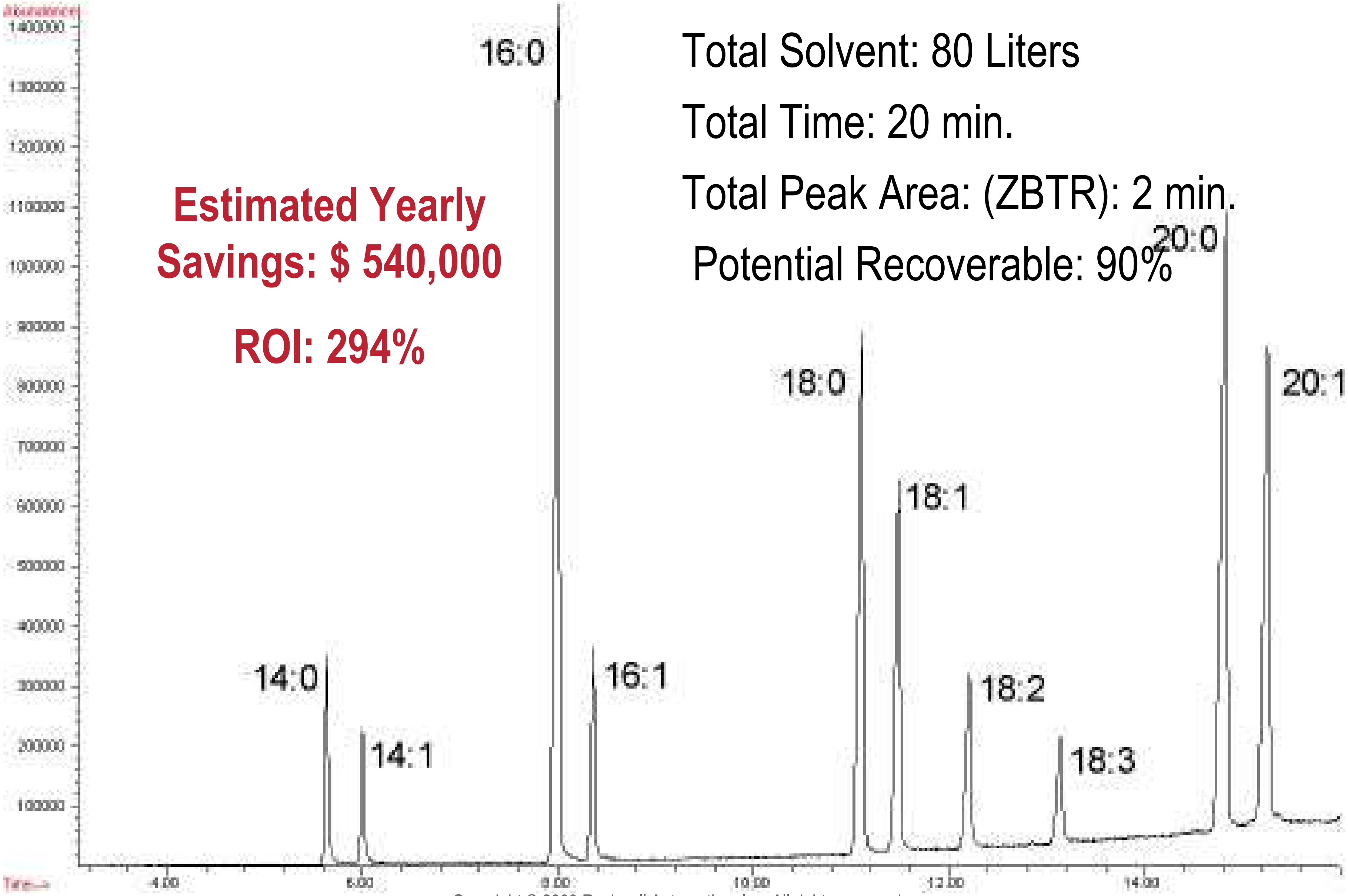
Total Time: 20 min.

Total Peak Area: (ZBTR): 2 min.

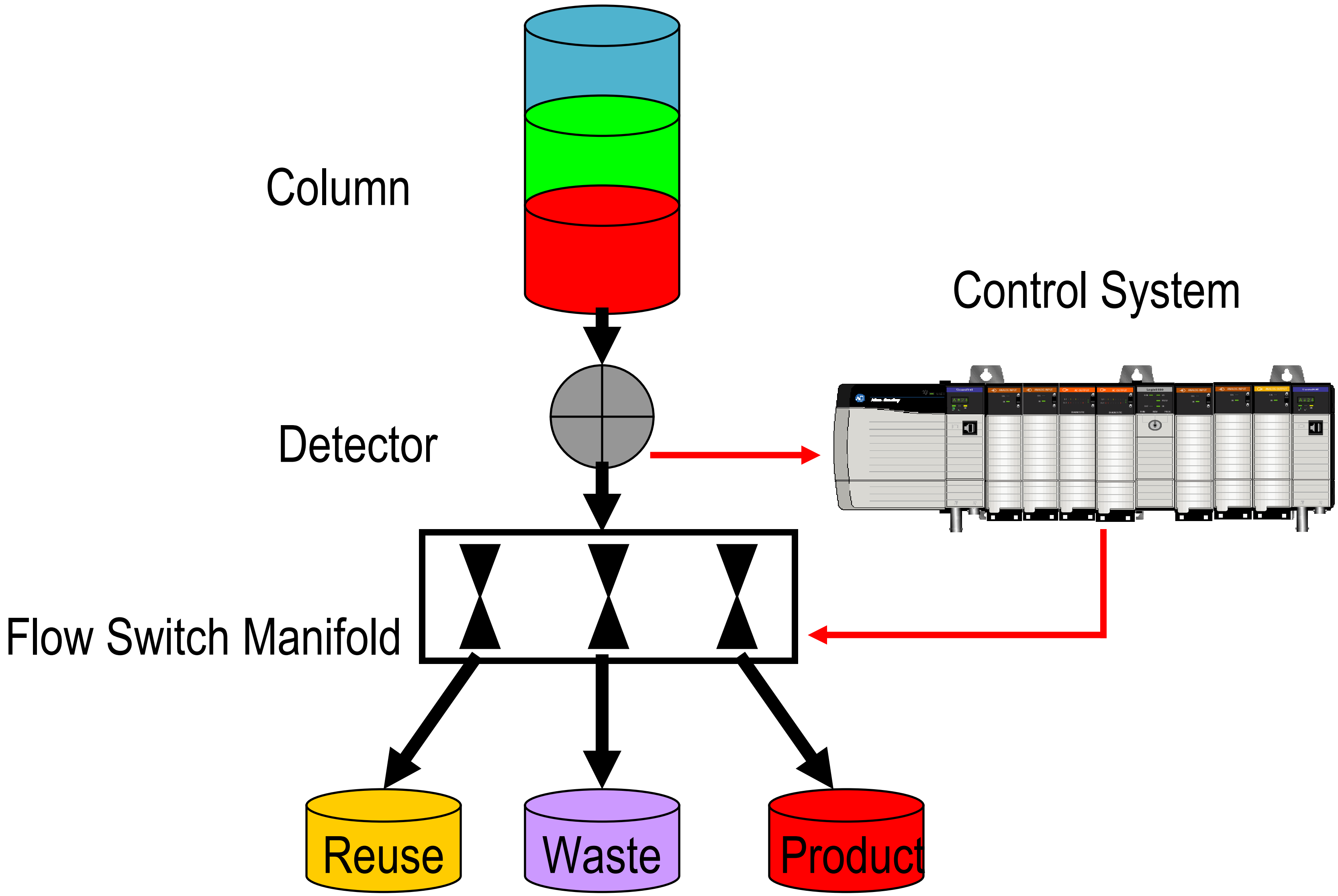
Potential Recoverable: 90%

Estimated Yearly Savings: $ 540,000

ROI: 294%



Simple Control System Process

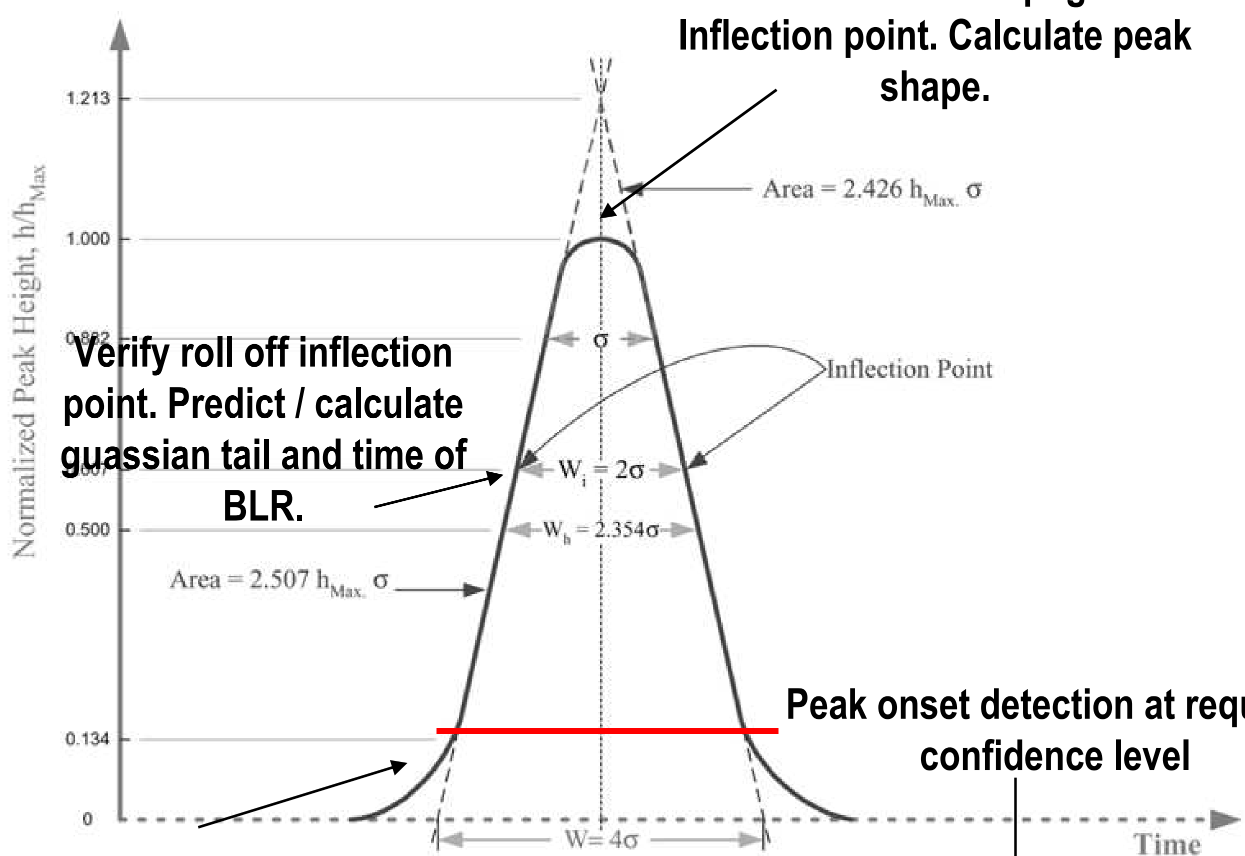


Considerations and Concerns

- 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

Getting More Aggressive:

- Chromatography systems separate so it is not necessary to dispose of all contaminated fractions: provided:
  - The contaminant concentrations do not reach break-through
  - The increased contaminate concentration does not change reaction equilibrium and reduce yield.

Therefore, we can improve the recovery percentage and reduce waste cost by reusing even "contaminated" solvents.

Same Example: Aggressive Strategy

Total Solvent: 80 Liters

Total Time: 20 min.

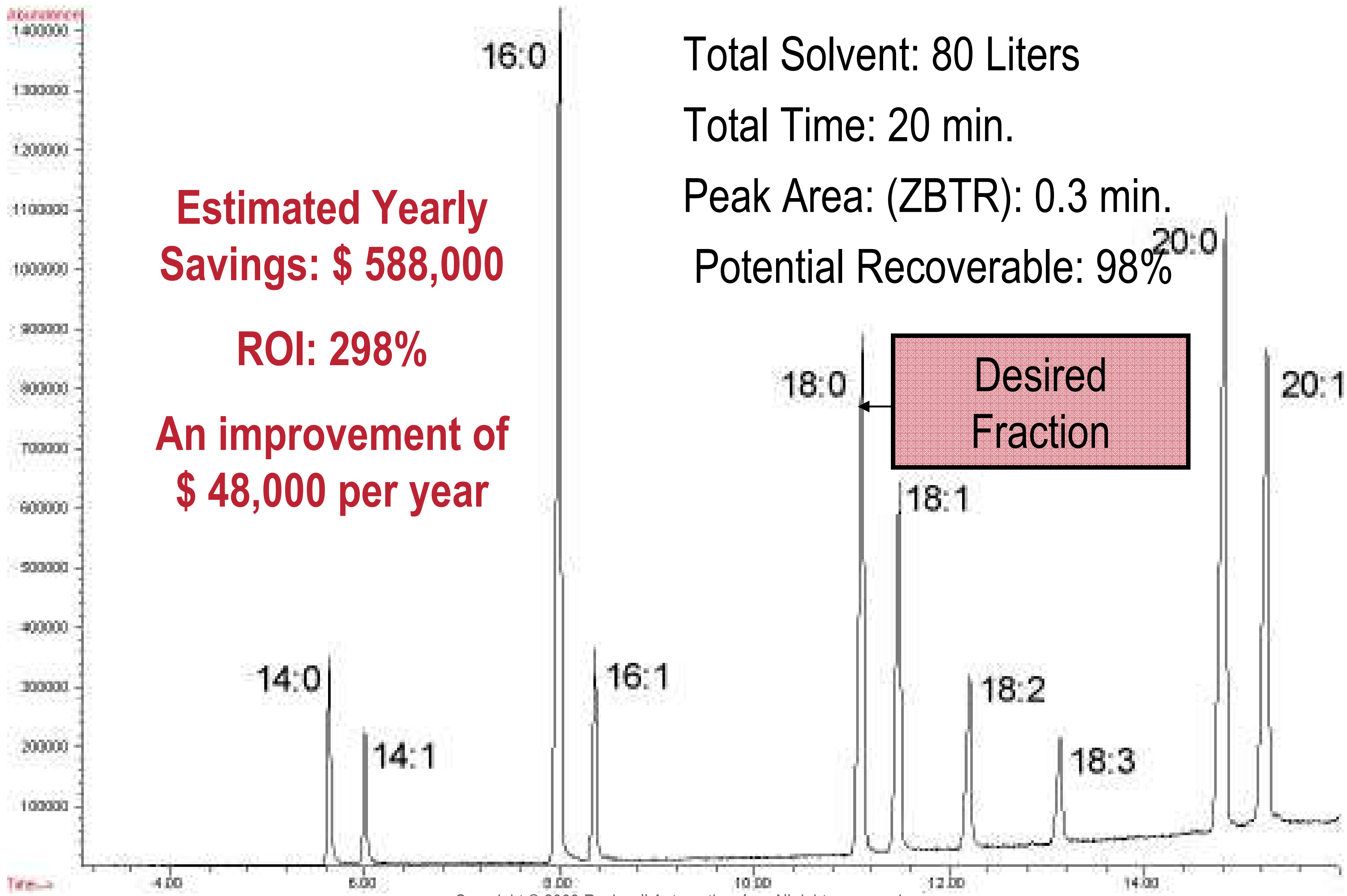
Peak Area: (ZBTR): 0.3 min.

Potential Recoverable: 98%

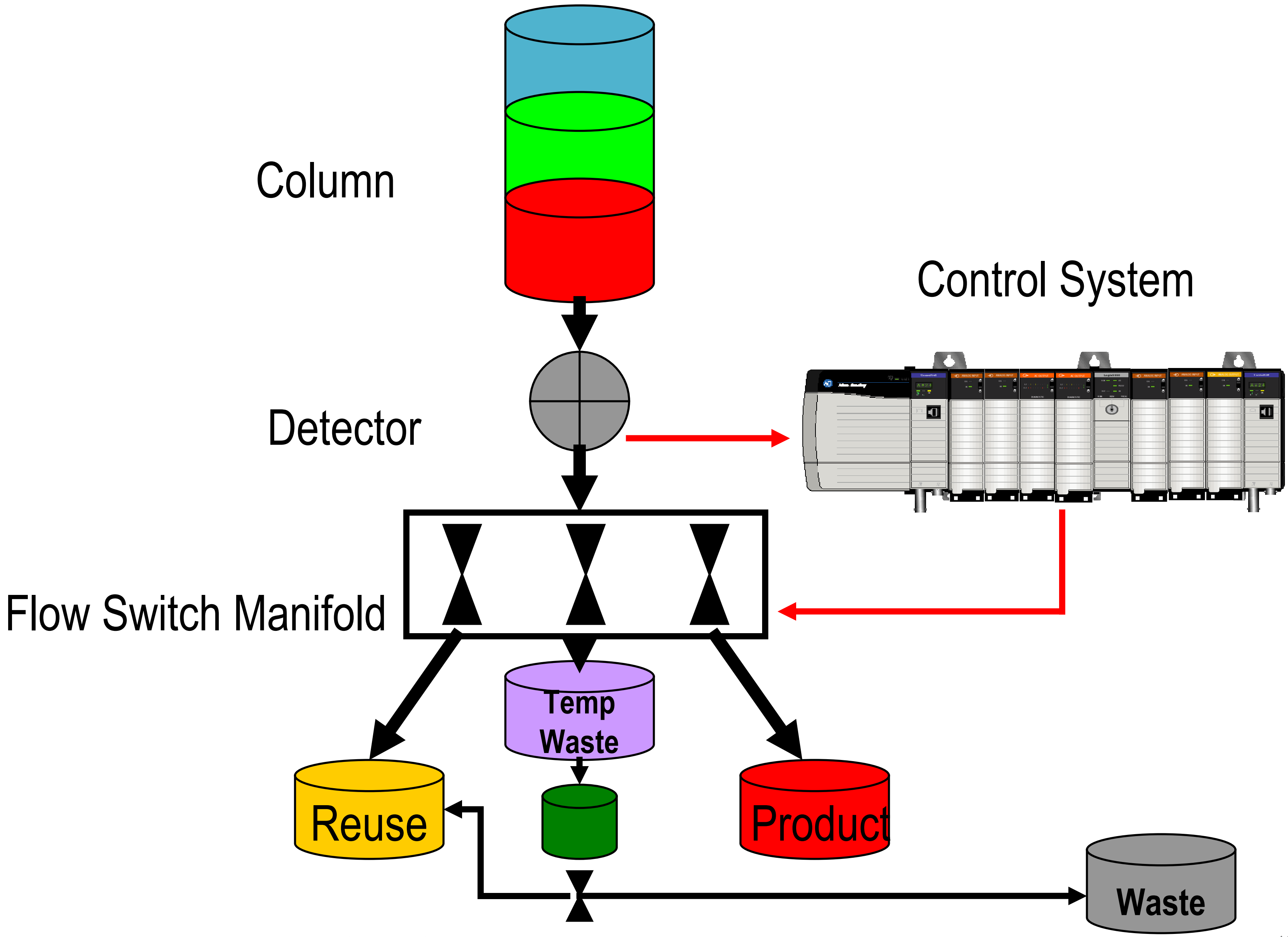
Estimated Yearly Savings: $ 588,000

ROI: 298%

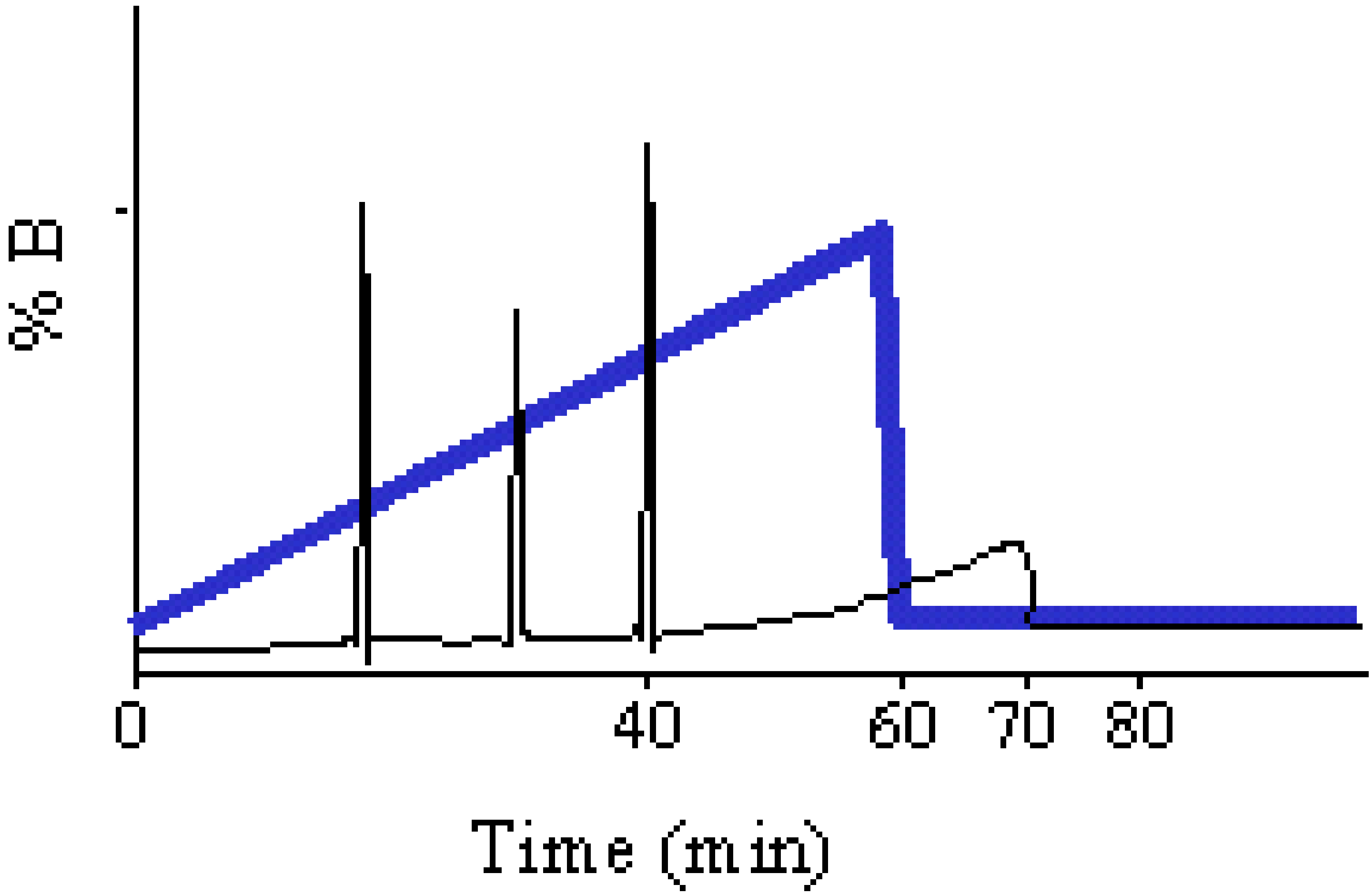
An improvement of $ 48,000 per year



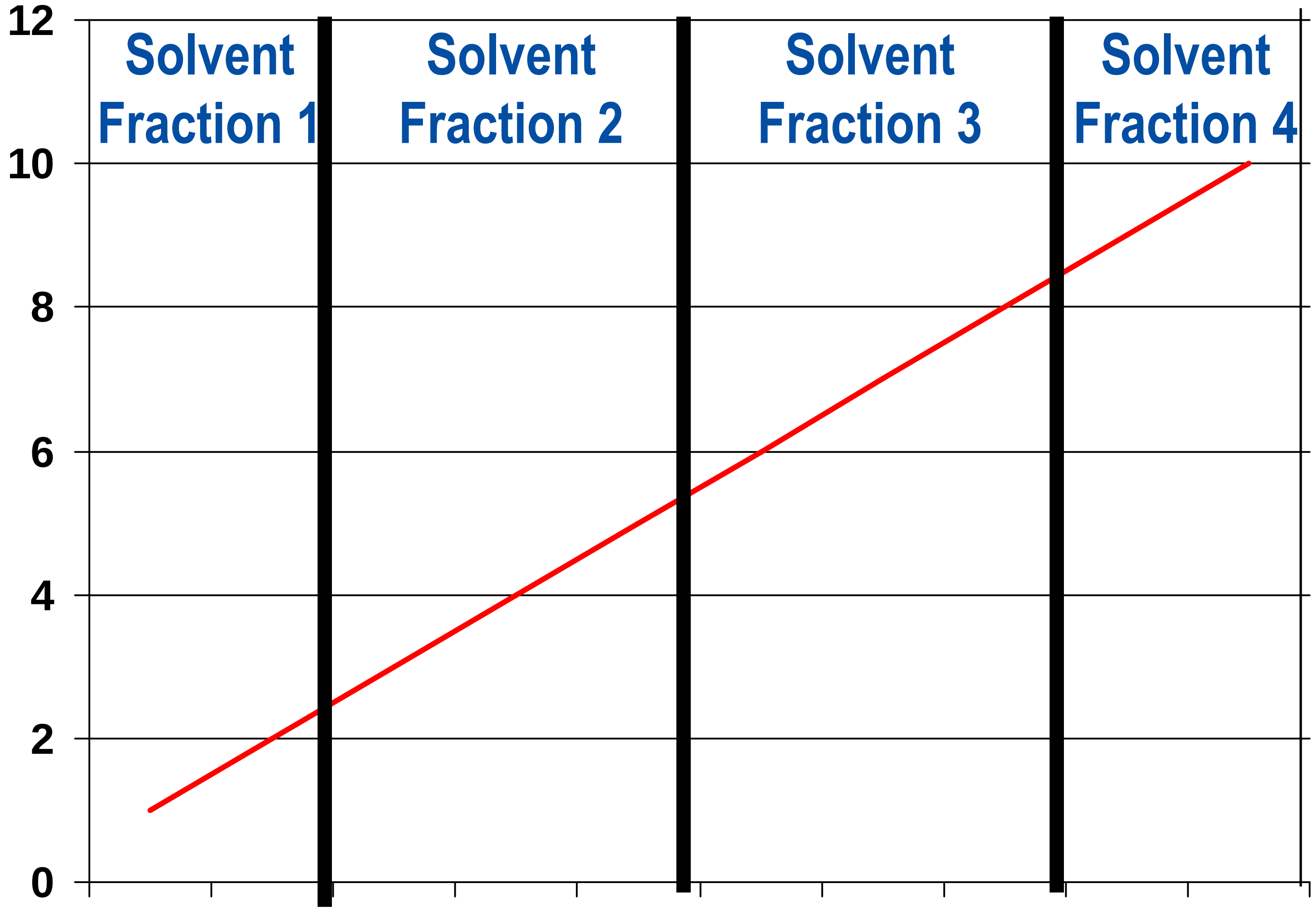
Best of Both Worlds: Stripper Column



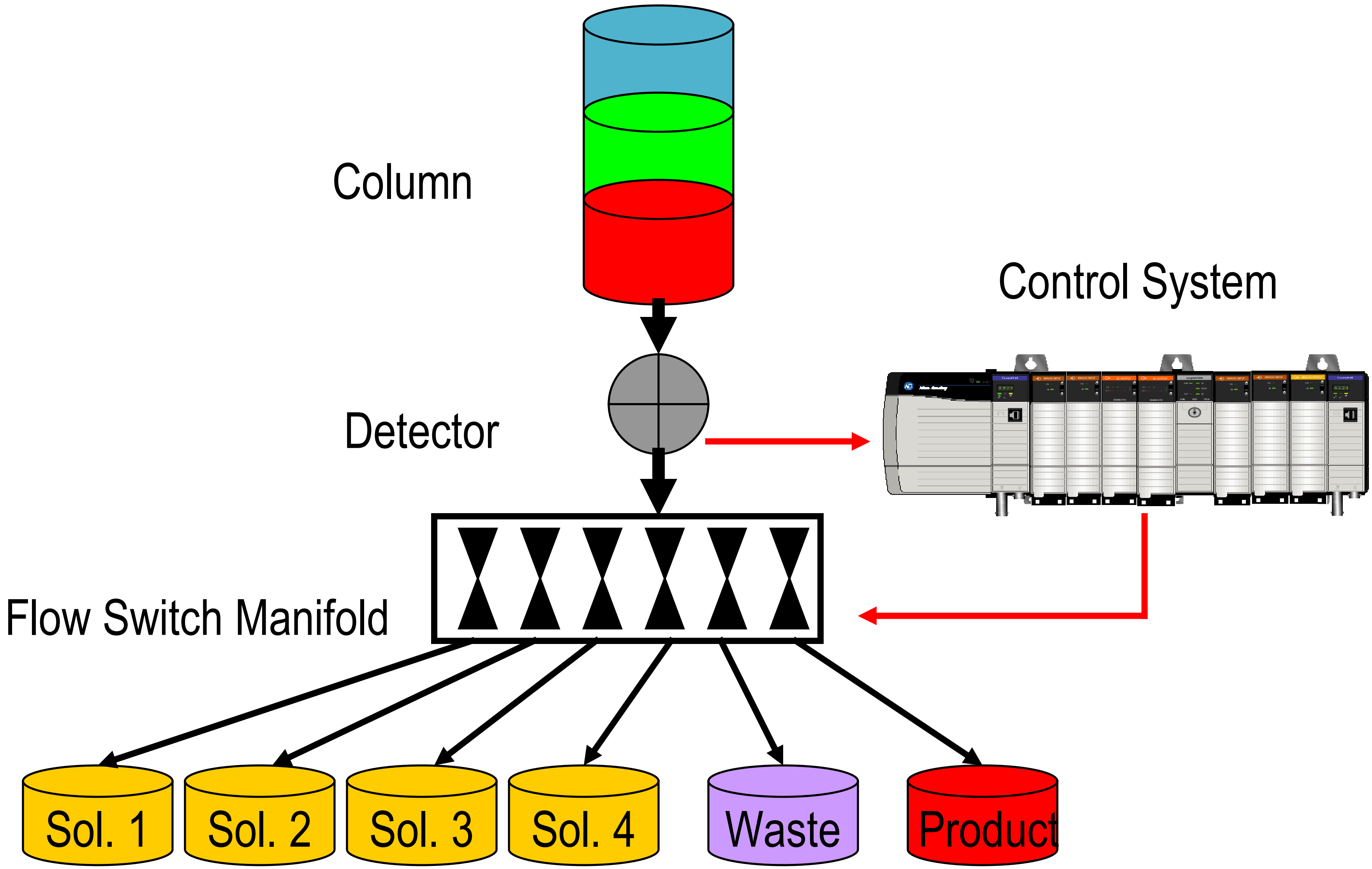
Dealing With Gradient Programs



Collecting Solvent Gradient Fractions

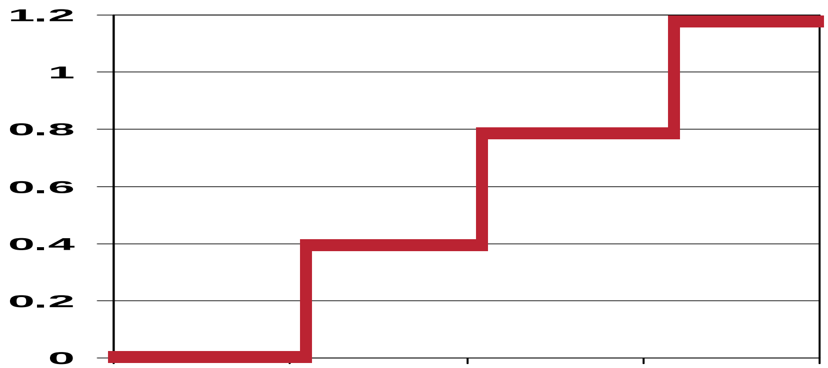


Gradient Solvent Recovery

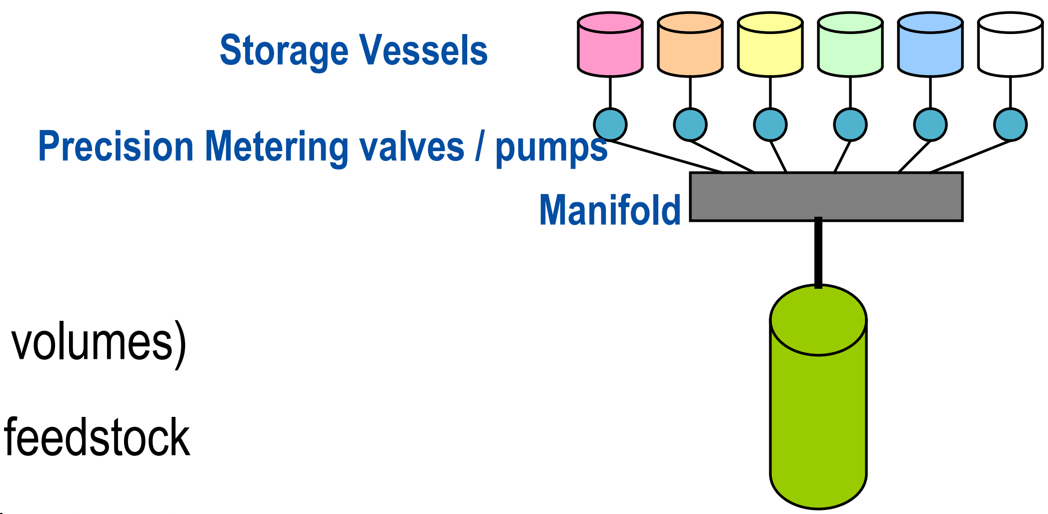


Using Recovered Gradient Solvents

- 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



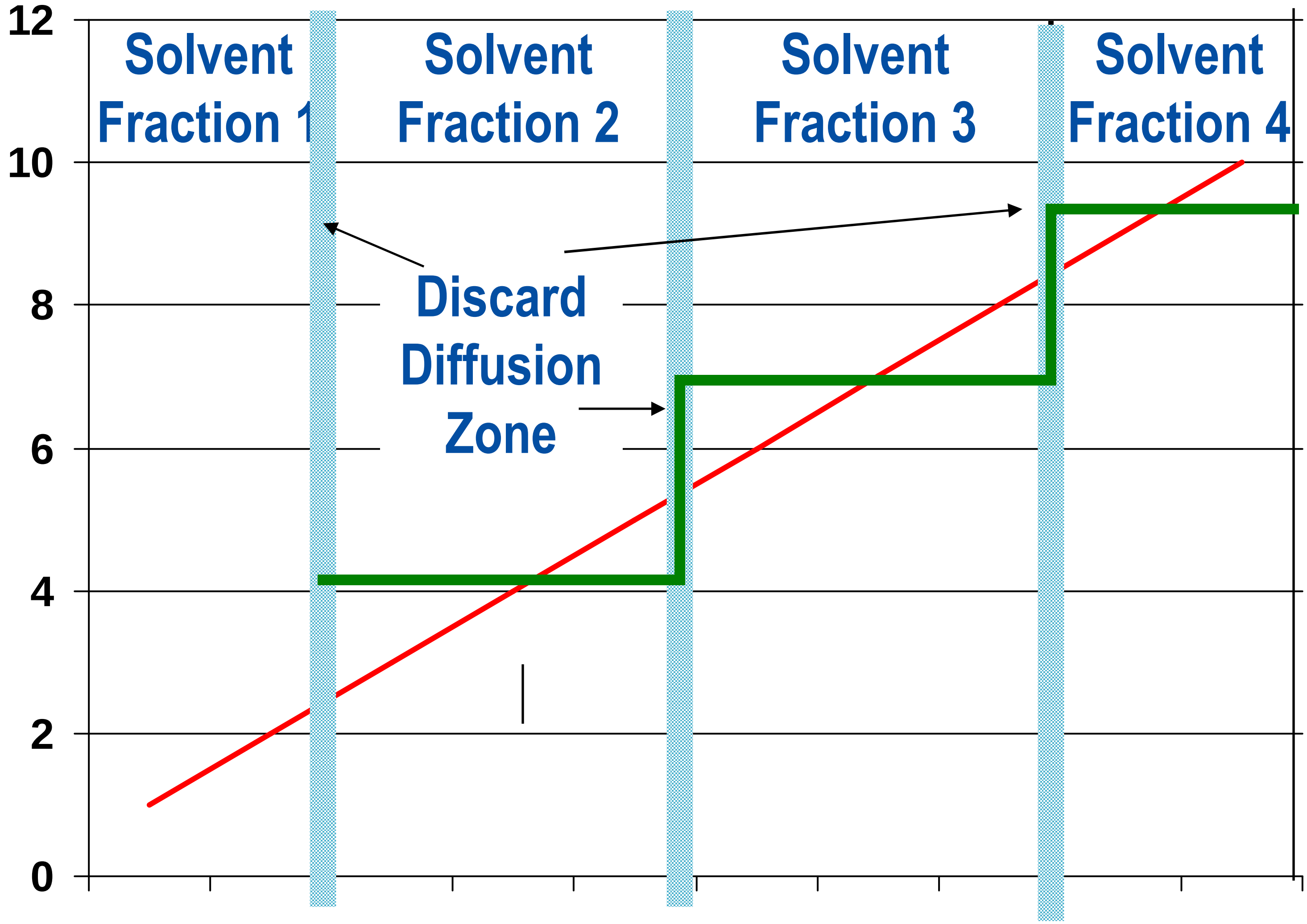
Considerations and Implications

- Blending for linear or continuous programs will eventually lead to an accumulation at average concentration.
  - Additional virgin solvent will need to be blended to maintain gradient profile.
  - Eventually accumulated average concentration solvent will need to be recovered
    - Distillation
    - Extraction
    - Original Virgin Purity is not required in the recovery. (Azeotrope)
      - Simpler and less costly.

- Stepwise Gradient Programs are more efficient in solvent reuse because trend toward average is mitigated by about 95%. Link

- Gradient program can be optimized for economic return while maintaining purity and resolution.

Collecting Solvent Gradient Fractions



Review Point

- Solvent Reuse in Chromatography
  - Reasonably Simple:
    - Conceptually easy to understand
    - Diffusion and residual volume models exist
    - Diffusion and residual volume empirical data is easy to acquire.
    - Optimized Valve Switching Algorithms exist
    - Blending Control Programs Exist (Rockwell's Digital Blending)
      - Manage Inventory
      - Understand concentrations
      - Dynamically meet target profile concentrations
    - Minimal impact on operations and infrastructure.
  - Low cost and risk to implement.
  - Very High ROI. Fast Payback.
  - Yes You Will Need to Validate!

Review Point

- Important Point about Solvent Reuse:

It's Green.

And that's going to become increasing more important.

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

New Events That Will Alter the Landscape

- EPA has been authorized to regulate Carbon Dioxide Emissions
- Carbon Tax (Cap and Trade) legislation likely to pass. Global political pressure. France has already passed a carbon tax.
- New international treaty on Global Warming and Carbon Dioxide Emissions will likely get agreement soon.
- 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.

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.**

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, $Ca(C_2H_3O_2)_2$-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			

THF Life Cycle and Carbon Dioxide

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

Reusing solvents can have a significant impact on the greenness of your process!

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!

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

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.

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.

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

Solvent Sustainability: Avg 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

Next Steps
How To Get Started

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)

Acknowledgements

Our Thanks To:

• C. Jimenez-Gonzalez:	North Carolina State University
• M. Overcash:	North Carolina State University
• S. Slater;	Rowan University
• M. Savelski	Rowan University

- US EPA
- Bristol Myers Squibb
- Pfizer
- GlaxoSmithKline
- European-Science-News
- Lyondell Corporation
- Wikkipedia
- www.engineeringtoolbox.com
- National Physical Laboratory

Thank You
And
Good Luck

For more information please contact:

David March

704-559-5348

damarch@ra.rockwell.com