Rick E. Cooley, Team Leader
Measurement Technology
Eli Lilly and Company

Utilizing PAT to Monitor and Control Bulk Biotech Processes

University of Michigan
Pharmaceutical Engineering Seminars
March 4, 2003

Lilly
Answers That Matter.

Presentation Preview

1. What is and isn't PAT?
2. Implementing PAT in Manufacturing: *What does it take?*
3. Characteristics of bulk, biotech API processes
4. Why PAT?
5. Review of PAT technologies utilized
6. PAT application examples

Copyright © 2003 Eli Lilly and Company

PAT Isn't.....

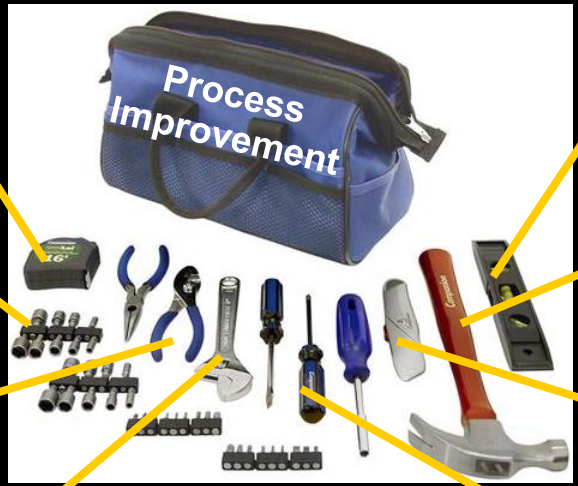
PAT isn't the universal tool to fix all processes problems

PAT isn't a new idea

- Used extensively in the chemical industry since WW II

Copyright © 2003 Eli Lilly and Company

PAT Is Only One Tool In The Process Improvement "Tool Box"



- Strategy Plan
- Process Knowledge
- Training
- Procedures
- Process Sensors "PAT"
- Process Control
- Process Automation
- Statistical Tools

Copyright © 2003 Eli Lilly and Company

PAT Implementation in Manufacturing

Expertise required in multiple areas:

- Process Engineer, Tech Service Chemist, Process Analytical Chemist, Process Control Engineer, Instrument Engineer, Metrologist

Successful applications utilize a team approach:

- *Process Quality Measurement Systems: An Integrated Approach To A Successful Program In Analytical Instrumentation*, Stephen M. Jacobs & Satish M. Mehta, Am. Lab., 12/87, 15-22.

Oversight of PAT after installation by a specialized, dedicated PAT support group

- The key to our long term success in applying PAT in manufacturing

Copyright © 2003 Eli Lilly and Company

PAT Implementation Philosophy

Keep it simple

- Utilize the simplest technology that fulfills its *intended use*

Analyzers should automatically perform routine checks

- Calibration
- System suitability checks
- Verification of proper sample system operations
- Monitor other analyzer critical operations

Copyright © 2003 Eli Lilly and Company

Bioprocess Characteristics

Feedstocks are more difficult to control:

- Complexity and variability tends to be higher than chemical synthesis

High resolution analytical techniques required for QC

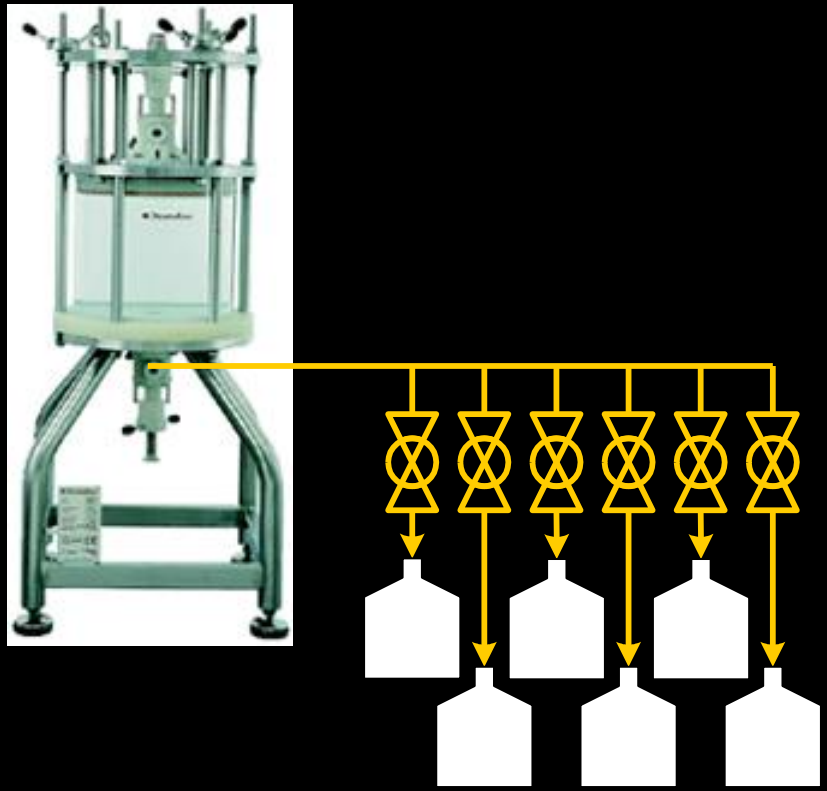
- HPLC, CZE, mass spectroscopy are common tools

Chromatography is a common unit operation

- Process variability closely related to eluent variability
- Typically involves a large number of manual manipulations

Copyright © 2003 Eli Lilly and Company

Typical Process Scale Chromatography



Copyright © 2003 Eli Lilly and Company

Why PAT? Our Major Driver:

Increase operating efficiency

- Cycle time reduction
  - Days cut from process cycle time by eliminating off-line analysis
- Close coupling of batch steps to produce semi-continuous operations
- Enable use of larger scale processing equipment
  - Elimination of fraction collection enabled larger scale purification columns
- Greater utilization of production equipment
  - Reduction of cycle time minimizes equipment down time
- Minimize storage space required for WIP

Copyright © 2003 Eli Lilly and Company

Why PAT? Other Benefits Realized

Reduce the possibility of processing errors

- Eliminate manual handling of fractions and samples

Reduce the opportunities for product contamination

- Eliminate open fraction containers
  - Product streams never leaving process piping

Minimize variability using on-line measurements

- Enable feedback control of critical process parameters
- Enable automatic sequencing of process

Copyright © 2003 Eli Lilly and Company

PAT's Utilized in Our Biotech Processes

Spectroscopy

- Optical: UV, VIS, NIR, turbidity, suspended solids, refractive index
- Mass spec

Chromatography

- HPLC
- GC (at-line)

Electrochemical

- pH, DO_2, ORP, conductivity

Wet chemistry

- Continuous flow and flow injection analysis

Copyright © 2003 Eli Lilly and Company

Optical Sensor Applications

Over 120 sensors utilized in multiple applications:

- Automatic collection of product eluting from chromatography columns
- Feedback control of elution gradients containing organic solvents
- Monitor/control of centrifuges
- Monitor/control of filtration unit ops

Copyright © 2003 Eli Lilly and Company

Optical Sensor Characteristics

Fixed wavelength

- No moving parts
- Stable
- High energy throughput (wide linear range)

Simple, NIST traceable calibration

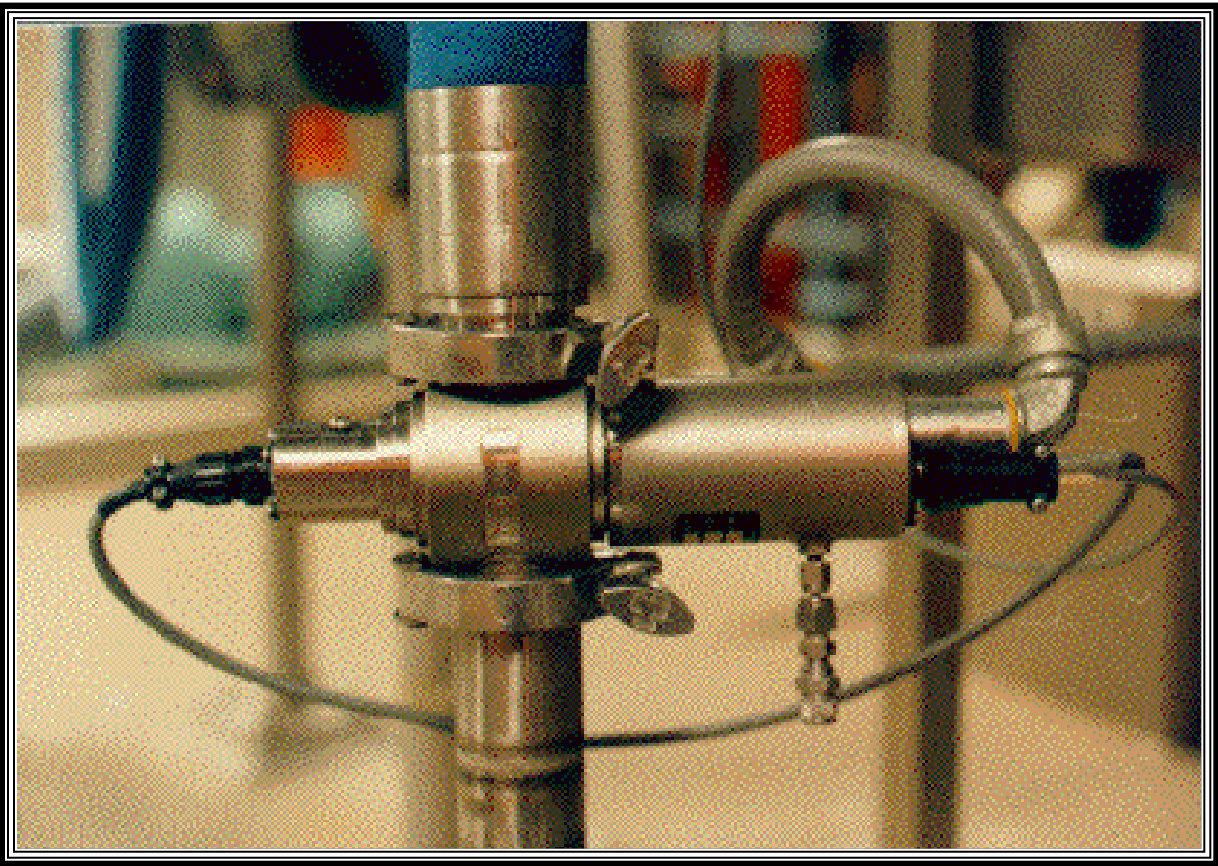
- Pathlength adjusted using “feeler gauge”
- Optical response adjusted using ND filter
- Interference filter characterized in lab

Low cost

- Less than $10K/point

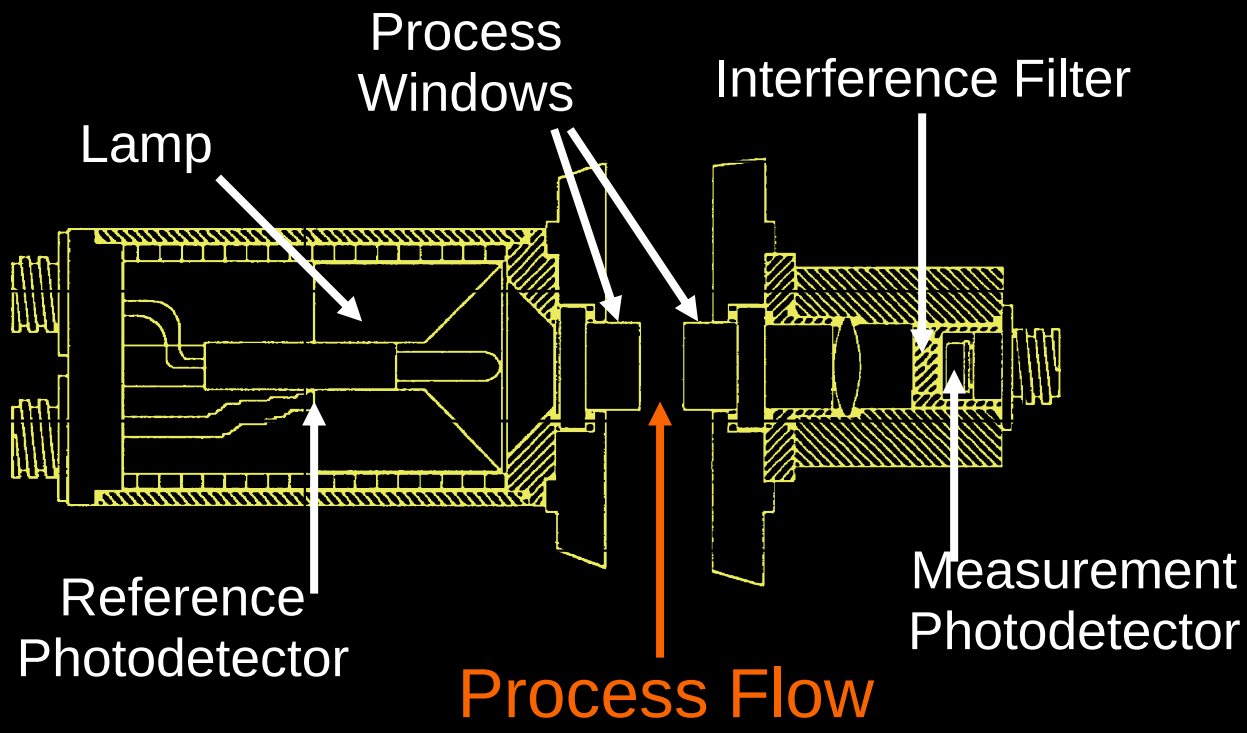
Copyright © 2003 Eli Lilly and Company

Typical Installed UV Sensor



Copyright © 2003 Eli Lilly and Company

Cut Away View of Wedgewood UV Sensor



Copyright © 2003 Eli Lilly and Company

On-Line HPLC at Lilly

Over 30 systems installed world-wide since 1981

Utilized in applications requiring high selectivity

- Automatic mainstream collection from purification columns
- Automatic quenching of enzymatic reactions

Custom (in-house built) and commercial systems utilized

- Transitioning to commercially available analyzers
  - Dionex DX800

Copyright © 2003 Eli Lilly and Company

Lilly and Dionex DX800 On-Line HPLCs

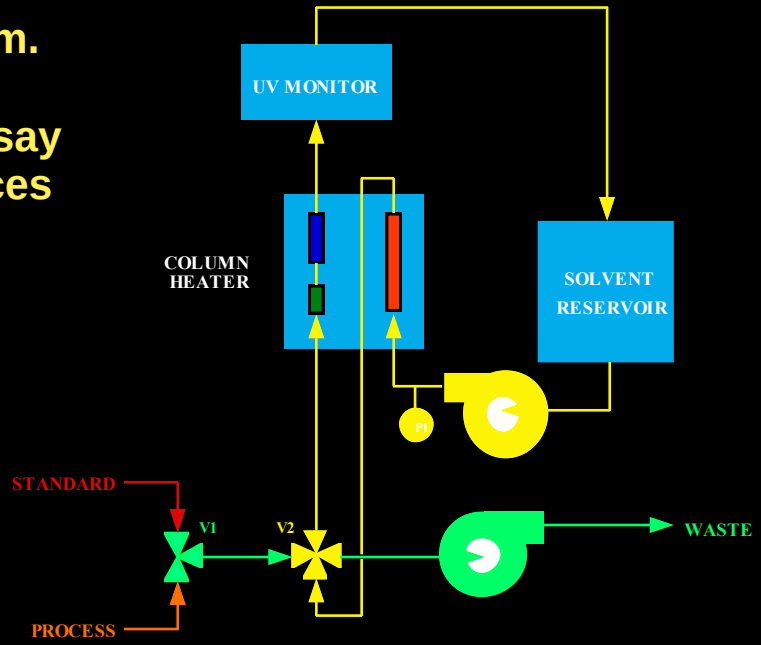
Lilly

Dionex

Copyright © 2003 Eli Lilly and Company

Lilly On-Line HPLC Flow Diagram

*** Note closed system. Recycling mobile phase increases assay precision and reduces maintenance**



R. E. Cooley and C. E. Stevenson, Process Control and Quality, 2, 1 (1992) 43-53.

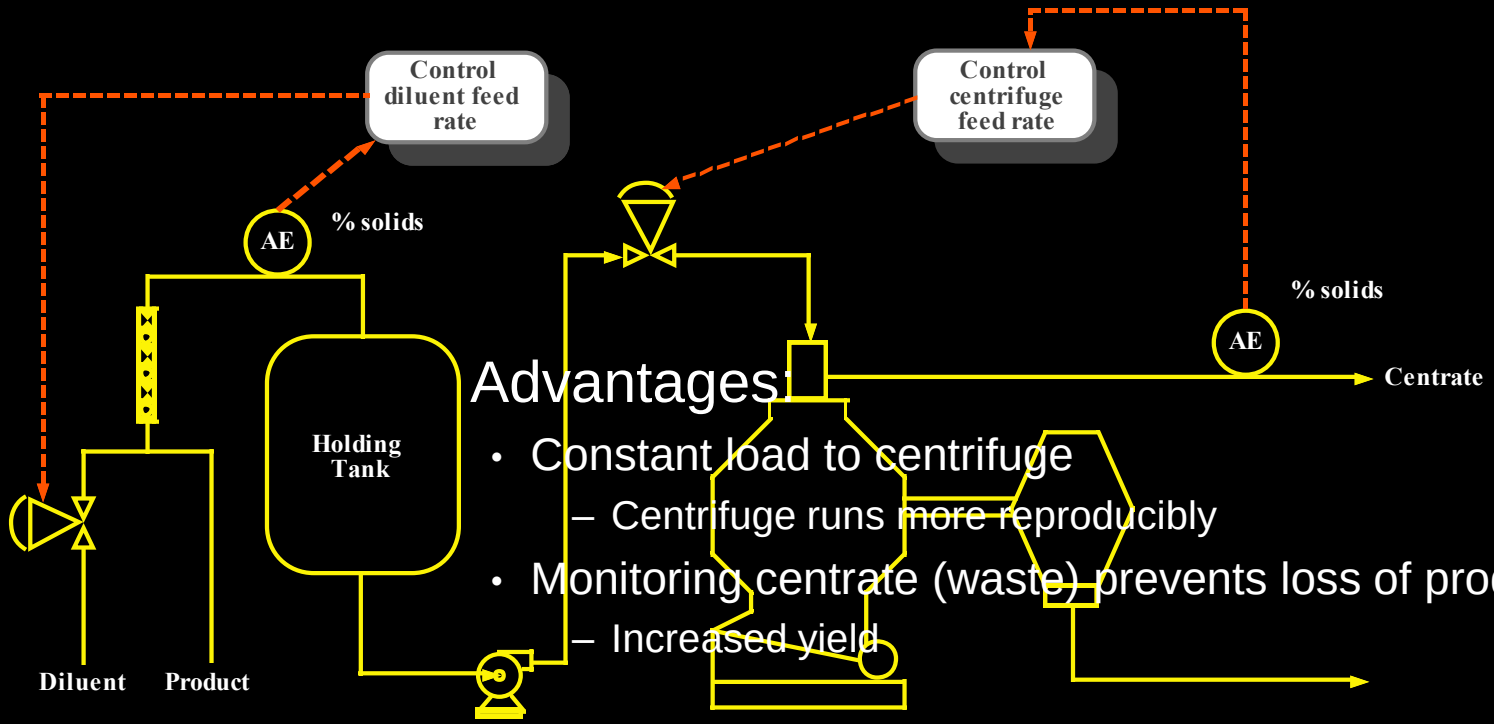
Copyright © 2003 Eli Lilly and Company

PAT Examples

1. Control of feed concentration to a centrifuge
2. Control of gradient generation for chromatography columns
3. Control of tangential flow filtration
4. Automation of gel permeation chromatography operation
5. Determination of the end point of an enzymatic reaction
6. “Close Coupling” of 2 batch ion exchange chromatography steps

Copyright © 2003 Eli Lilly and Company

Example #1: Centrifuge Monitoring and Control



Advantages:

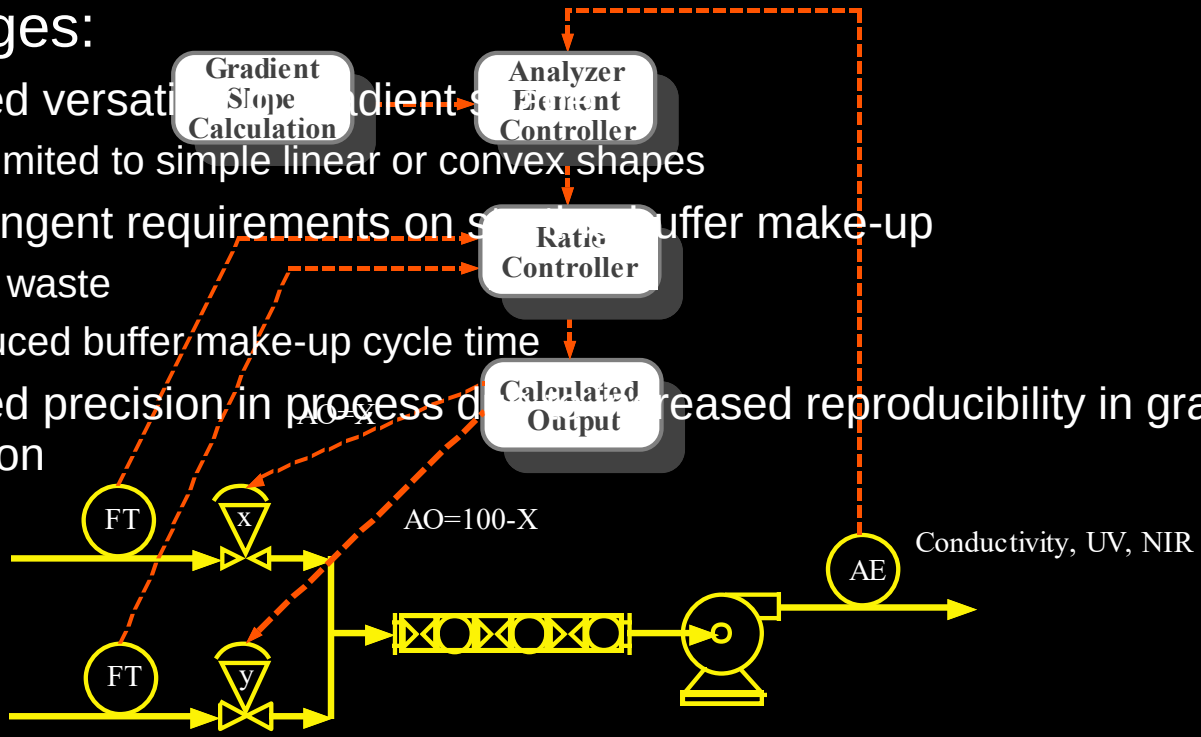
- Constant load to centrifuge
  - Centrifuge runs more reproducibly
- Monitoring centrate (waste) prevents loss of product
  - Increased yield

Copyright © 2003 Eli Lilly and Company

Example #2: Gradient Monitoring and Control

Advantages:

- Increased versati dient s
  - Not limited to simple linear or convex shapes
- Less stringent requirements on s uffer make-up
  - Less waste
  - Reduced buffer make-up cycle time
- Increased precision in process d reased reproducibility in gradient generation

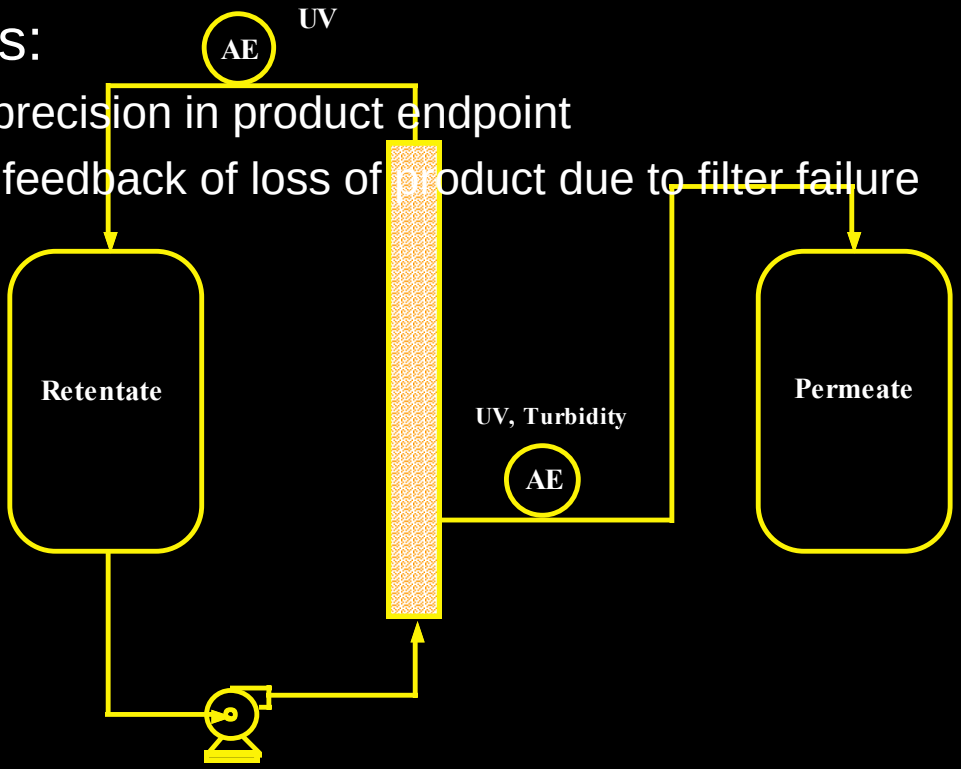


Copyright © 2003 Eli Lilly and Company

Example #3: Filtration Monitoring and Control

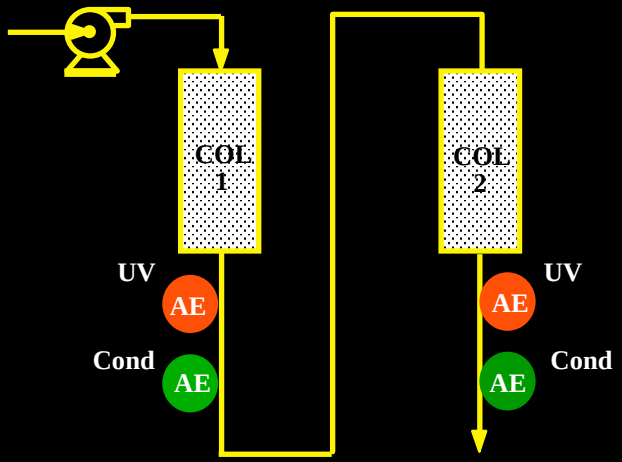
Advantages:

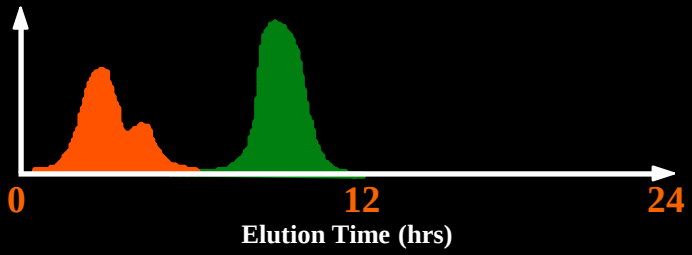
- Increased precision in product endpoint
- Immediate feedback of loss of product due to filter failure



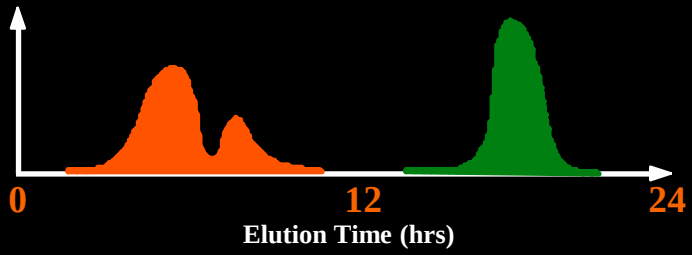
Copyright © 2003 Eli Lilly and Company

Example #4:
Column Cycle Time Reduction





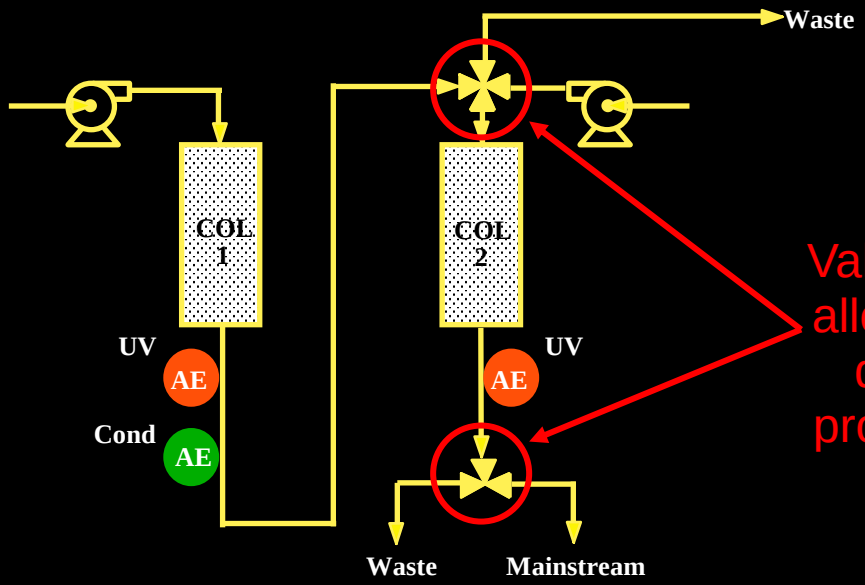
Column 1 Elution Profile



Column 2 Elution Profile

Copyright © 2003 Eli Lilly and Company

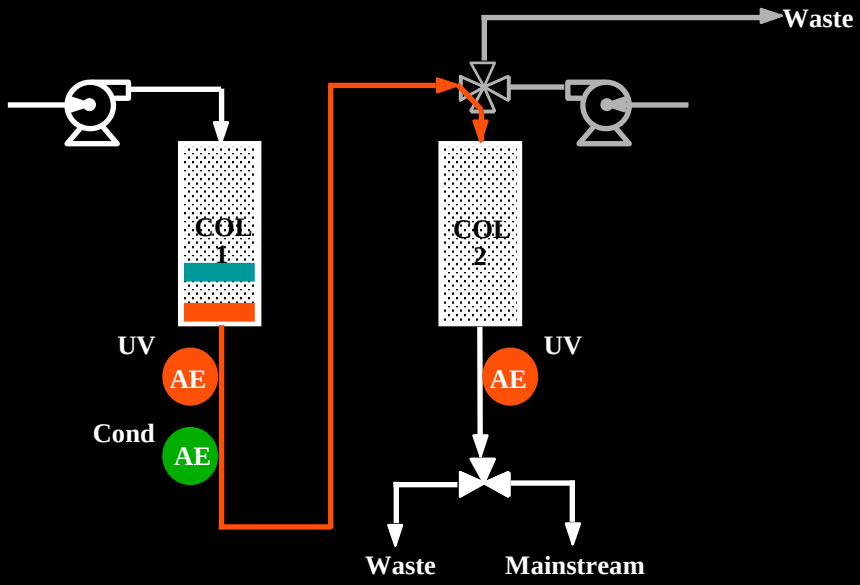
Modify For Parallel/Series Operation



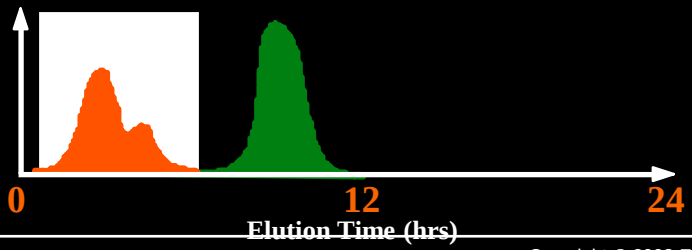
Valves added to allow automatic diversion of process stream

Copyright © 2003 Eli Lilly and Company

Series Operation: Charge Protein Onto Column 2



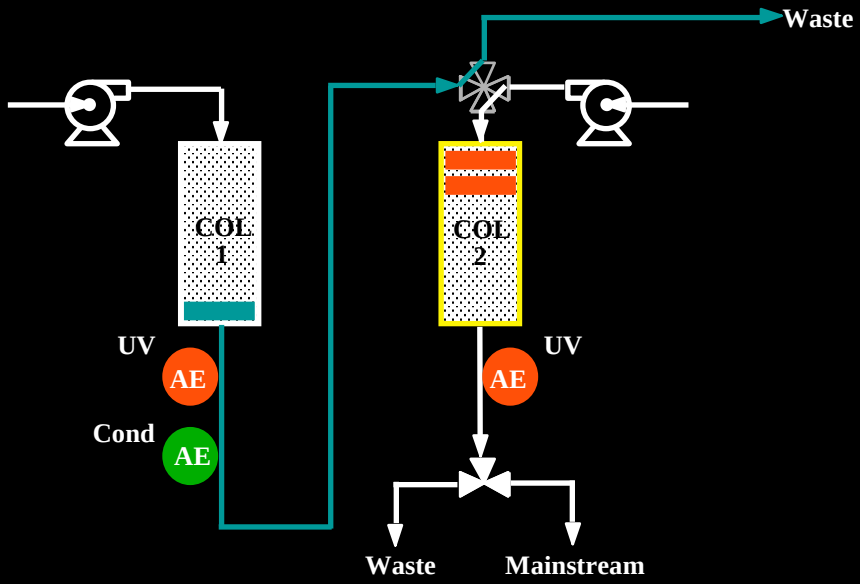
Charge this area to Column 2

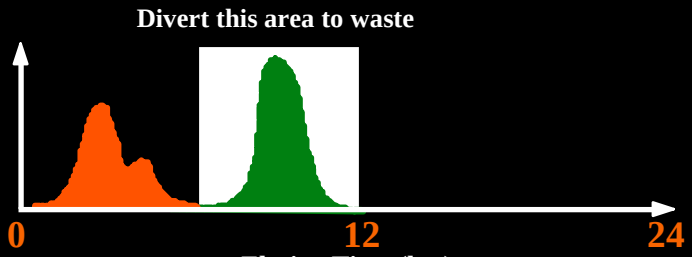


Column 1 Elution Profile

Copyright © 2003 Eli Lilly and Company

Parallel Operation: Divert Salt to Waste

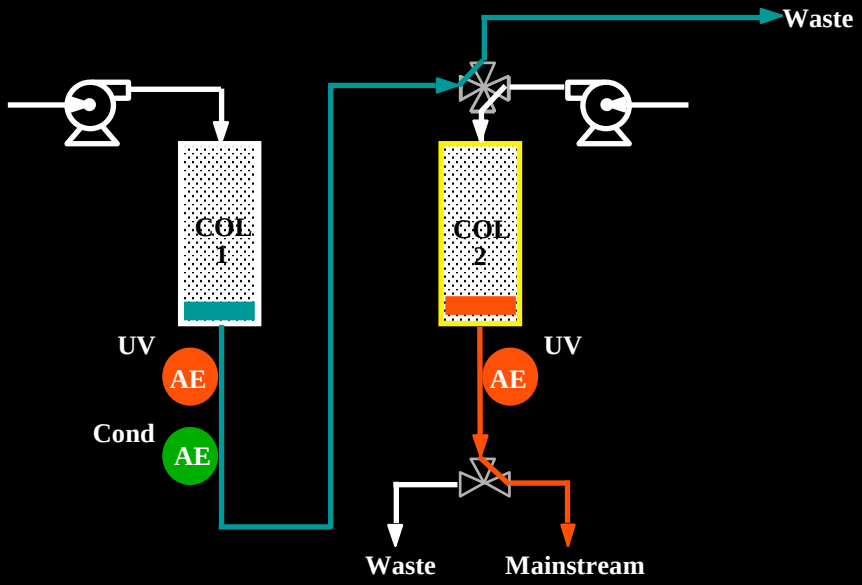


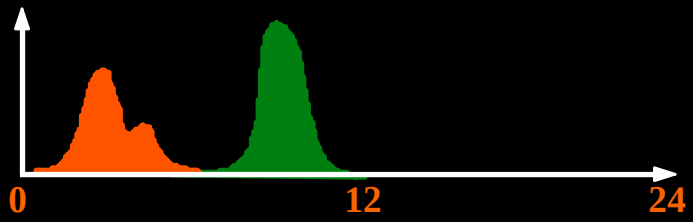


Column 1 Elution Profile

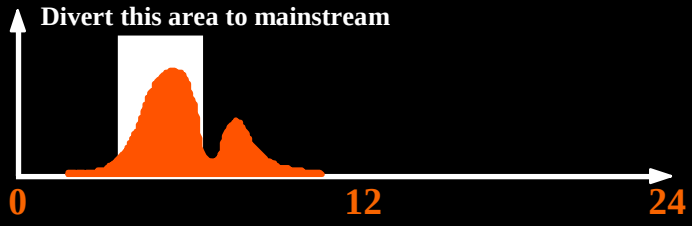
Copyright © 2003 Eli Lilly and Company

Parallel Operation: Collect Protein Product





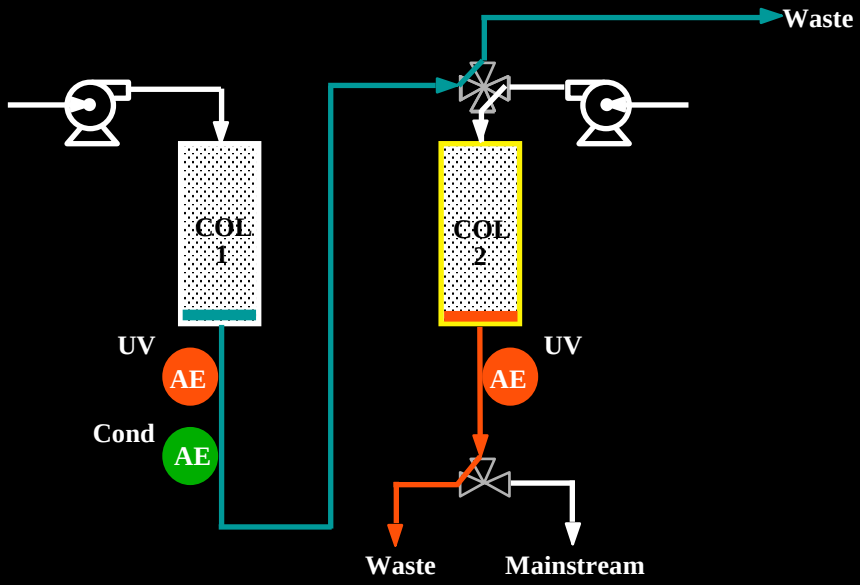
Column 1 Elution Profile

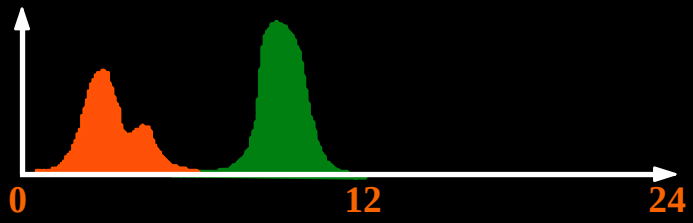


Column 2 Elution Profile

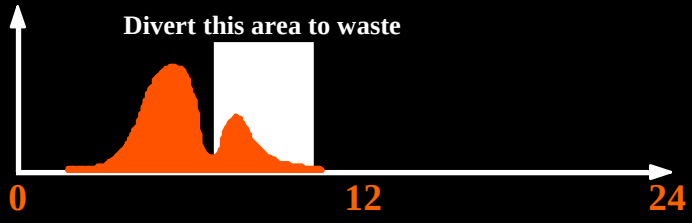
Copyright © 2003 Eli Lilly and Company

Parallel Operation: Divert Impurity to Waste





Column 1 Elution Profile

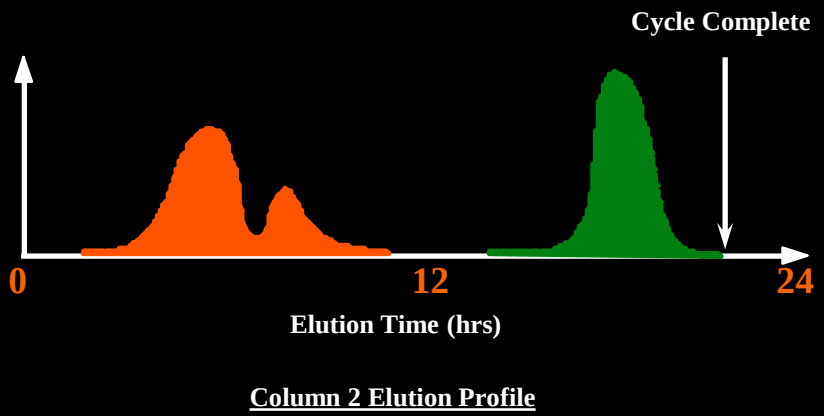


Column 2 Elution Profile

Copyright © 2003 Eli Lilly and Company

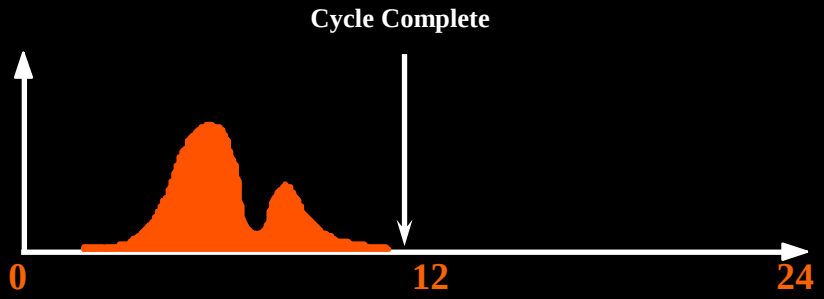
Overall Cycle Time Reduced by 50%

Before process change enabled by PAT



Column 2 Elution Profile

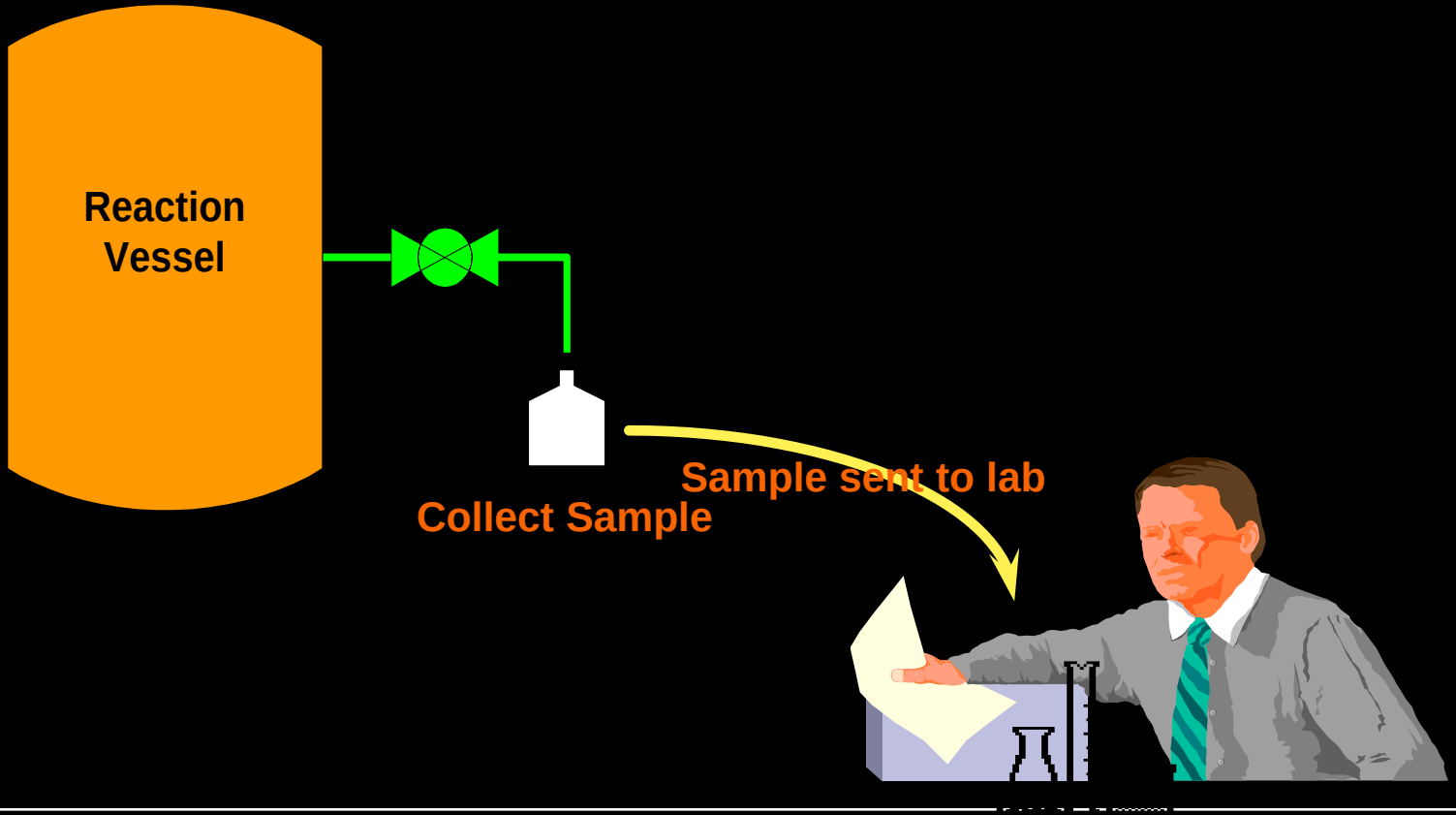
After process change enabled by PAT



Column 2 Elution Profile

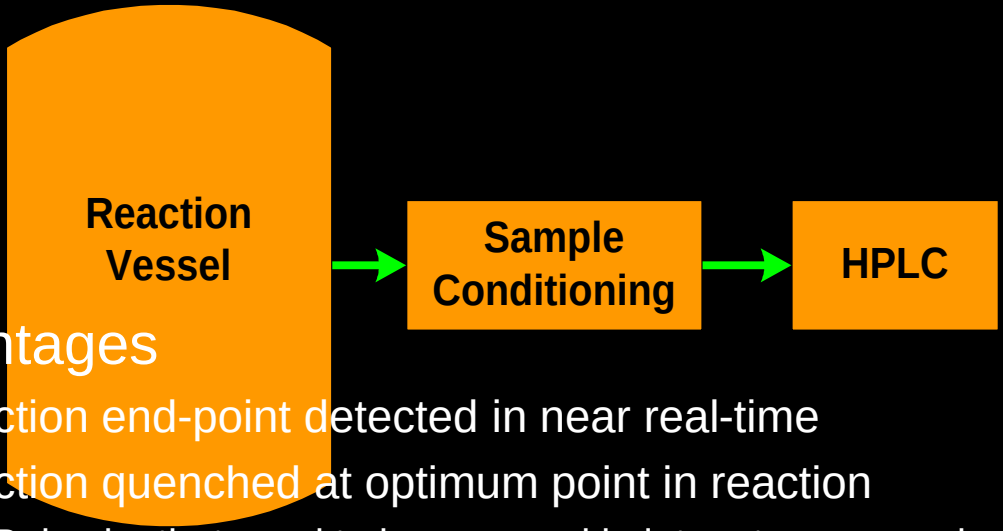
Copyright © 2003 Eli Lilly and Company

Example #5:
Enzymatic Reaction End Point Detection



Copyright © 2003 Eli Lilly and Company

Example #5: Enzymatic Reaction End Point Detection

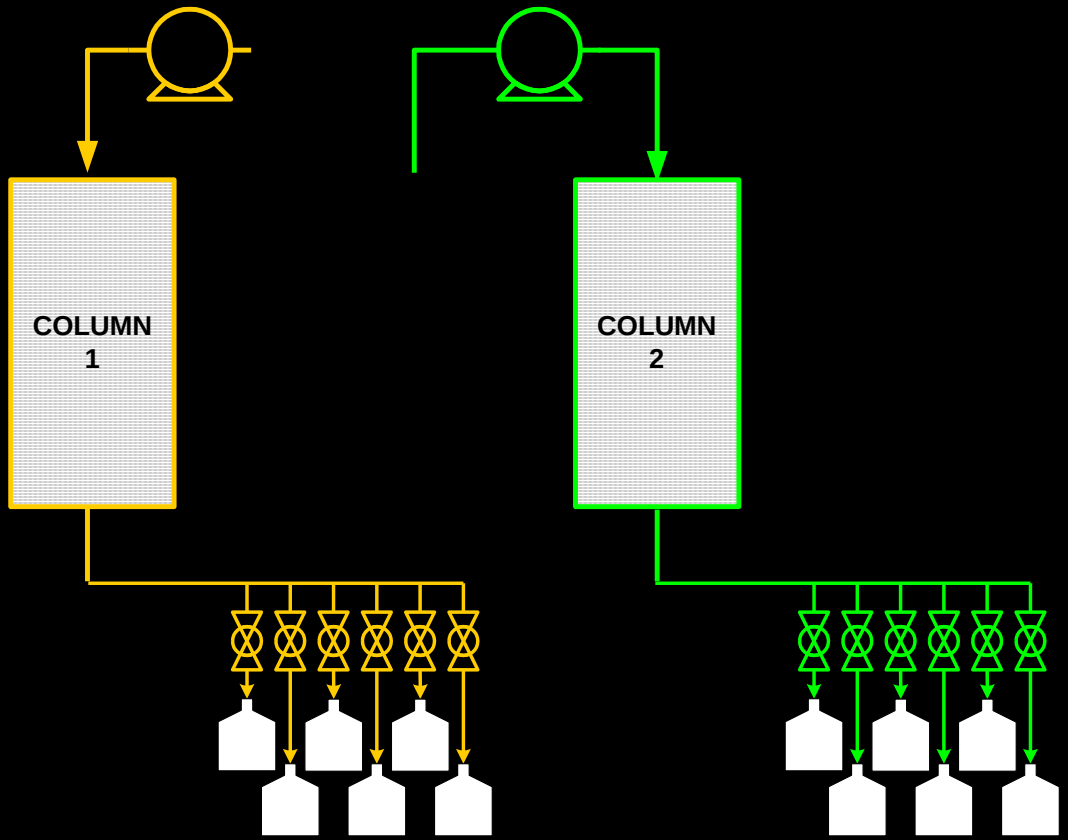


Advantages

- Reaction end-point detected in near real-time
- Reaction quenched at optimum point in reaction
  - Rel subs that need to be removed in later steps are reduced
- Yield increased

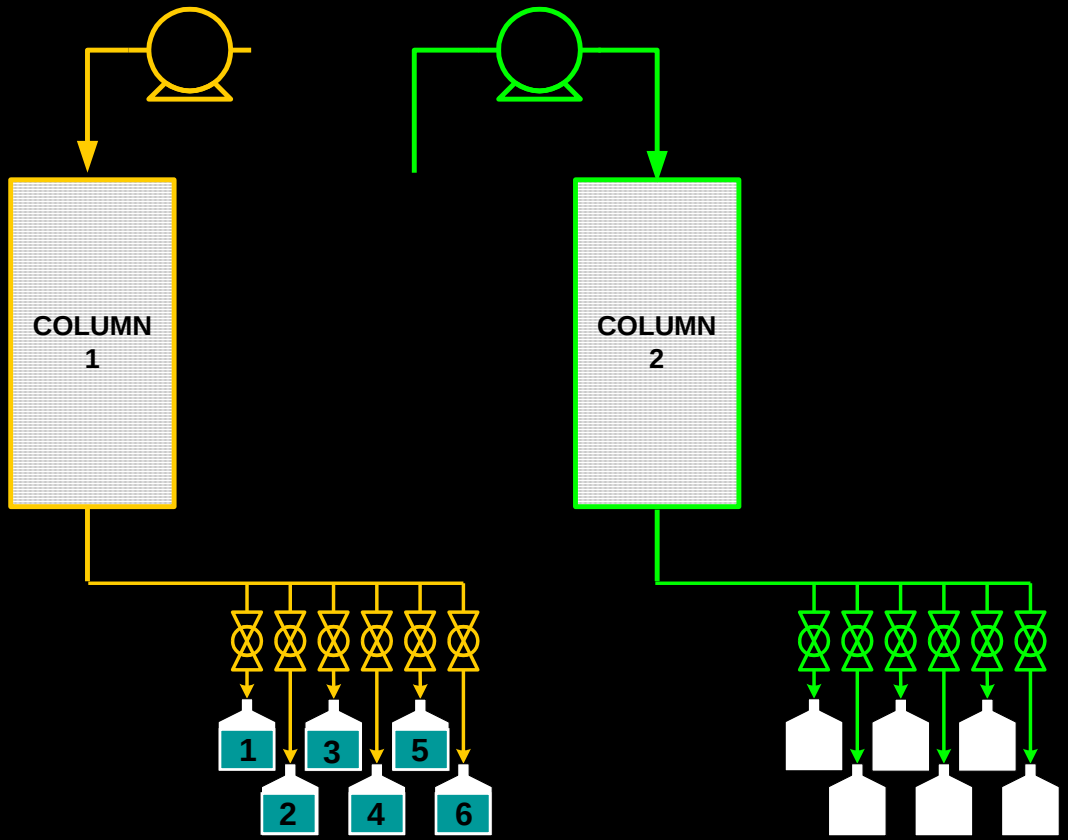
Copyright © 2003 Eli Lilly and Company

Example #6:
“Close Coupling” of 2 Batch Operation



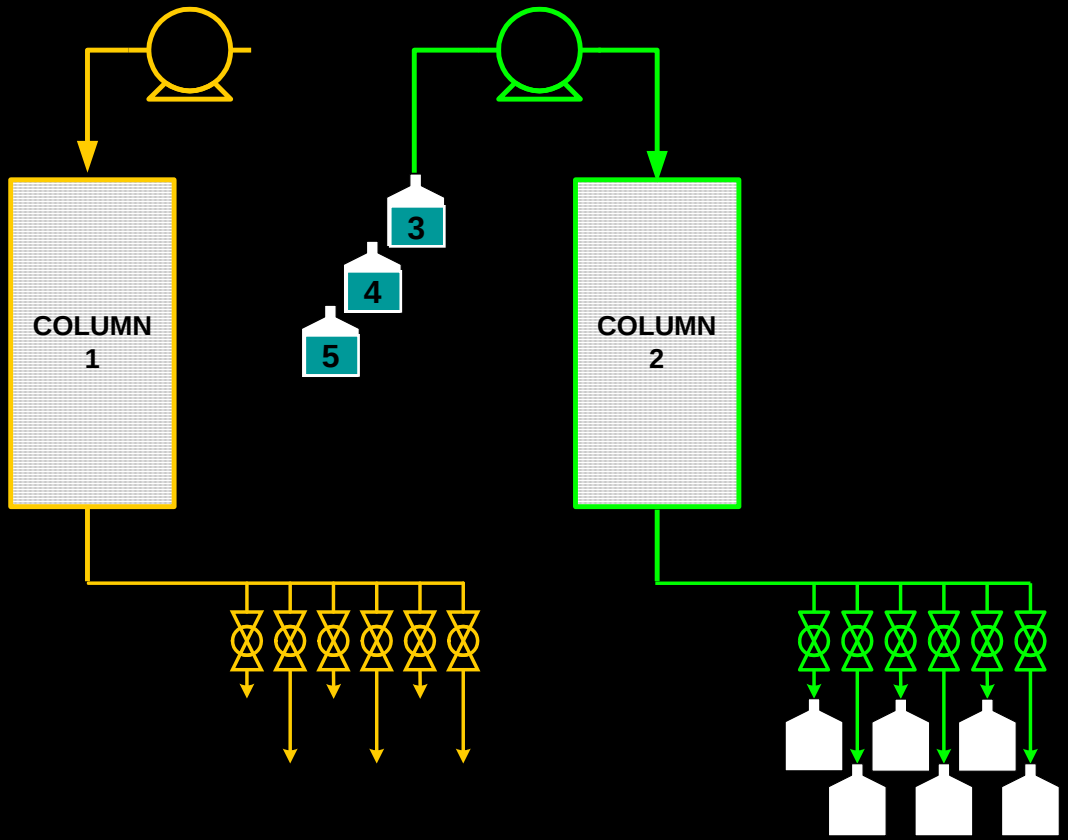
Copyright © 2003 Eli Lilly and Company

Example #6: Manual Operation
Elute Column #1 While Collecting Fractions



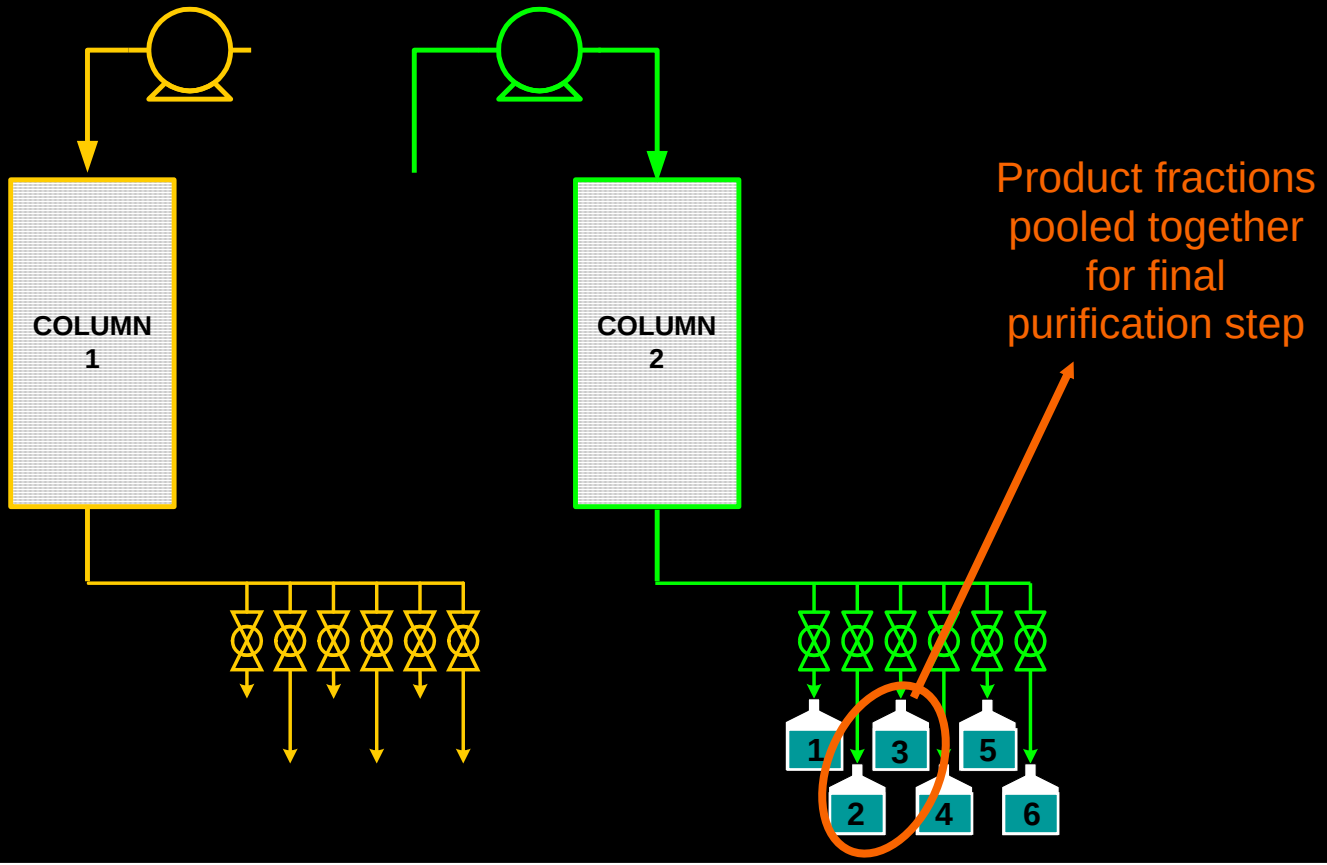
Copyright © 2003 Eli Lilly and Company

Example #6: Manual Operation Charge Fractions Onto Column #2



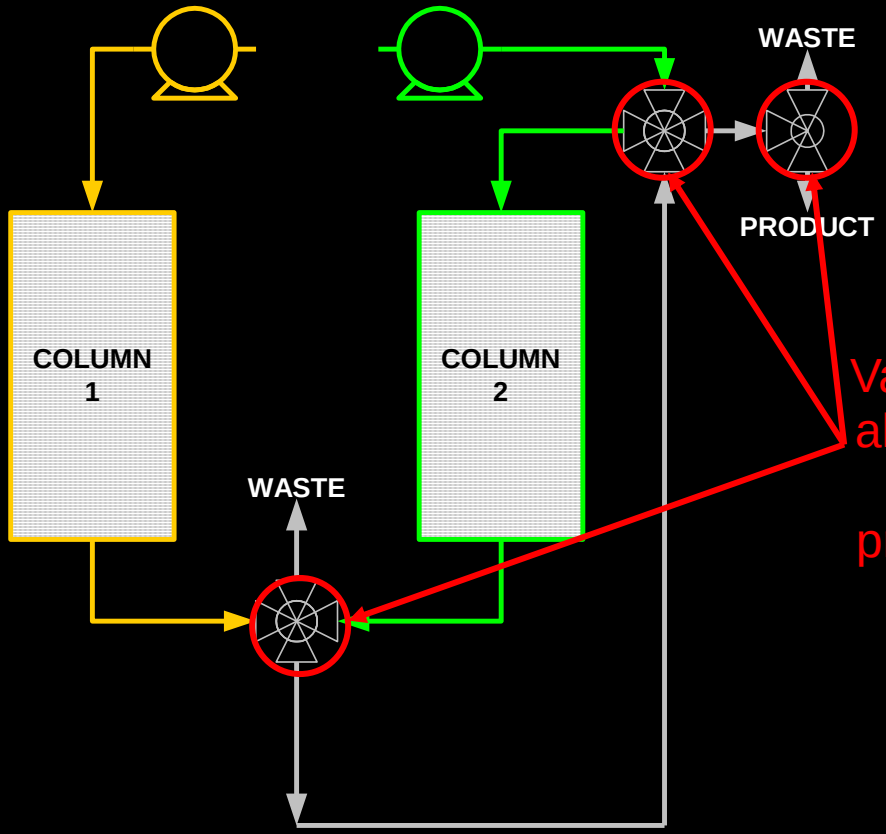
Copyright © 2003 Eli Lilly and Company

Example #6: Manual Operation
Elute Column #2 While Collecting Fractions



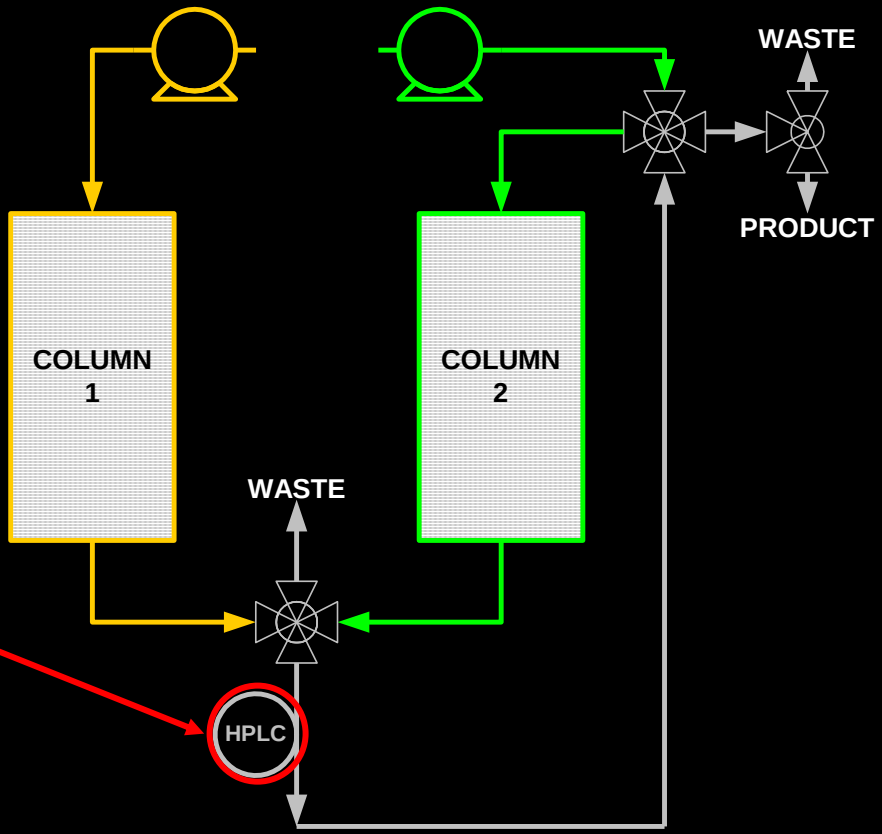
Copyright © 2003 Eli Lilly and Company

Modify for Parallel/Series Operation



Copyright © 2003 Eli Lilly and Company

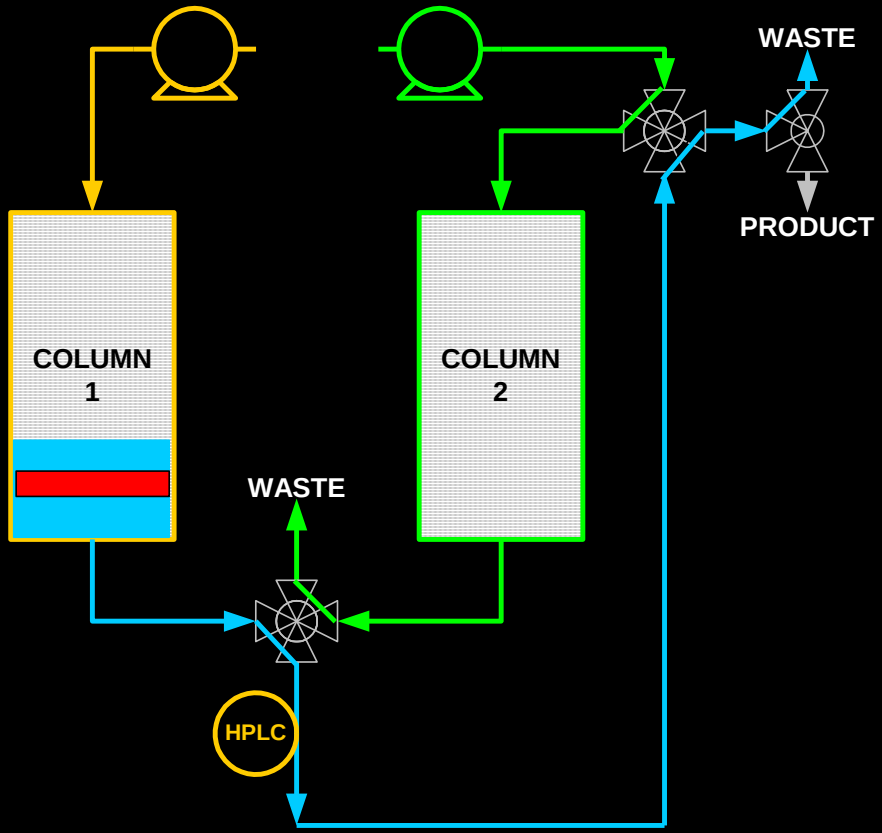
Add PAT To Enable Automation



On-line HPLC added to enable automatically detecting product

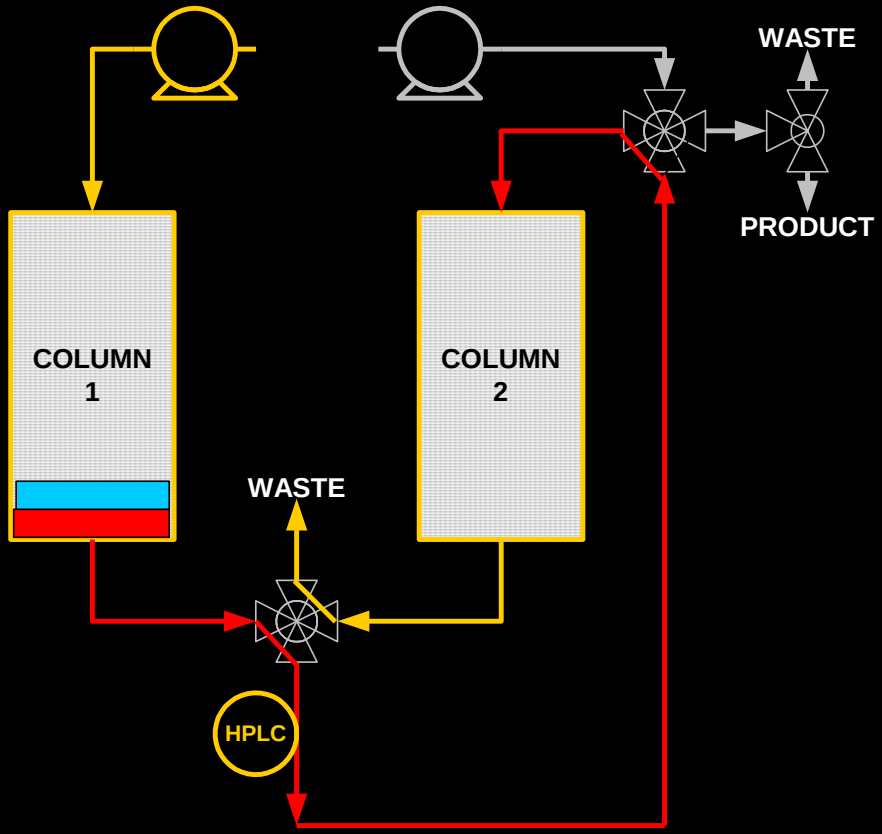
Copyright © 2003 Eli Lilly and Company

Parallel Operation: Elute Column 1 to Waste



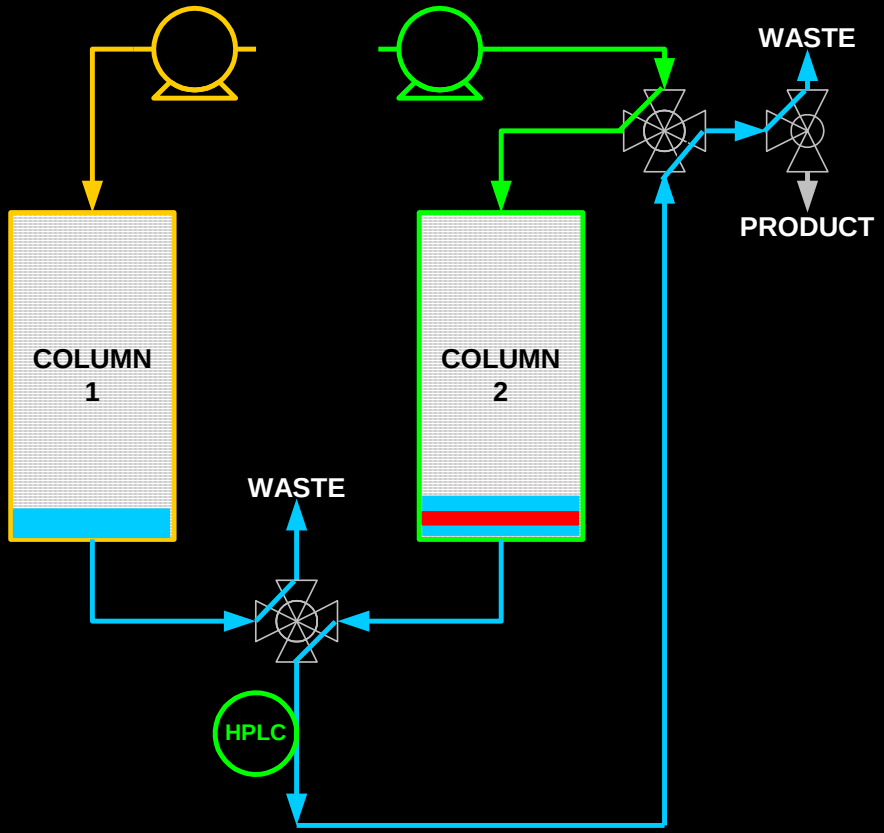
Copyright © 2003 Eli Lilly and Company

Series Operation:
Charge Column 1 Heart Cut to Column 2



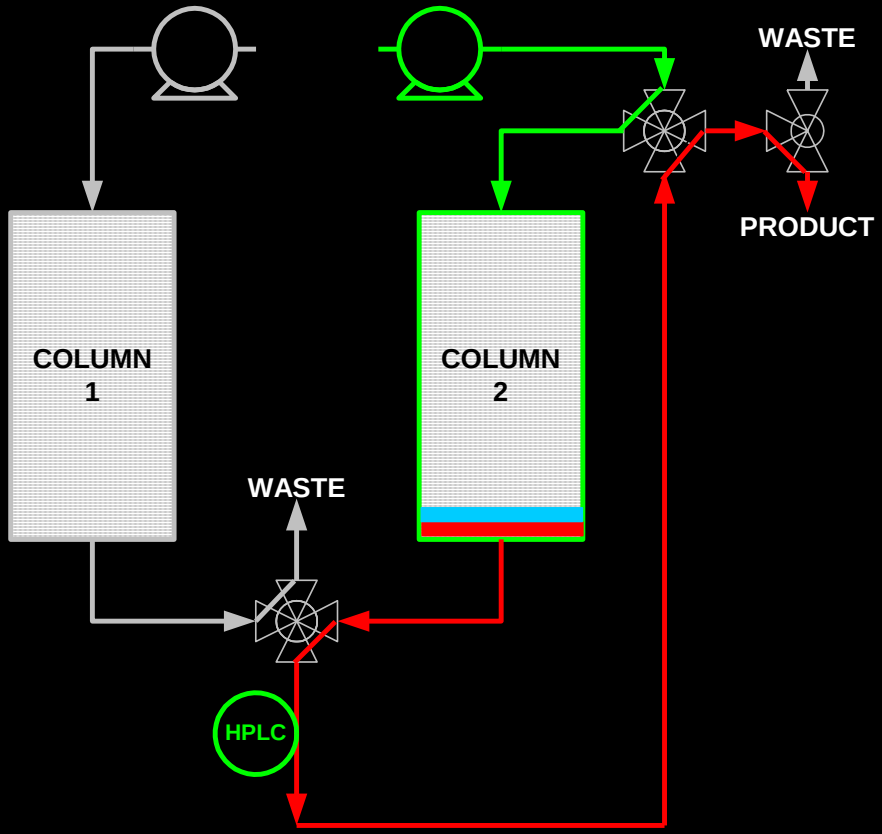
Copyright © 2003 Eli Lilly and Company

Parallel Operation:
Elute Column 2 to Waste, Regen Column 1



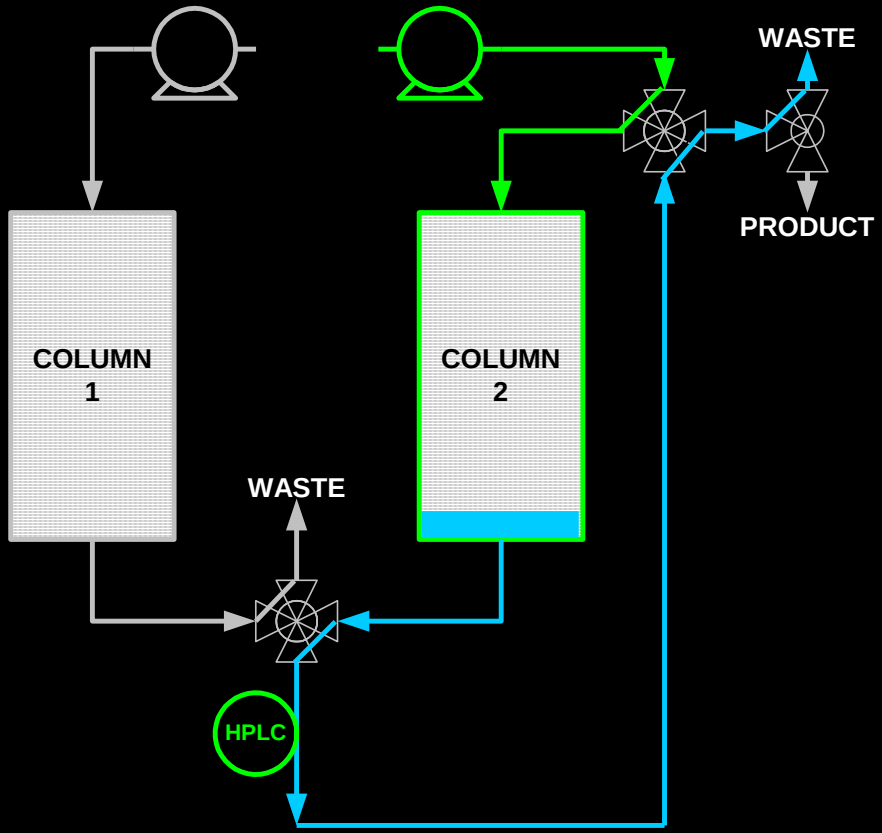
Copyright © 2003 Eli Lilly and Company

Parallel Operation: Elute Column 2 to Product



Copyright © 2003 Eli Lilly and Company

Parallel Operation: Regenerate Column 2

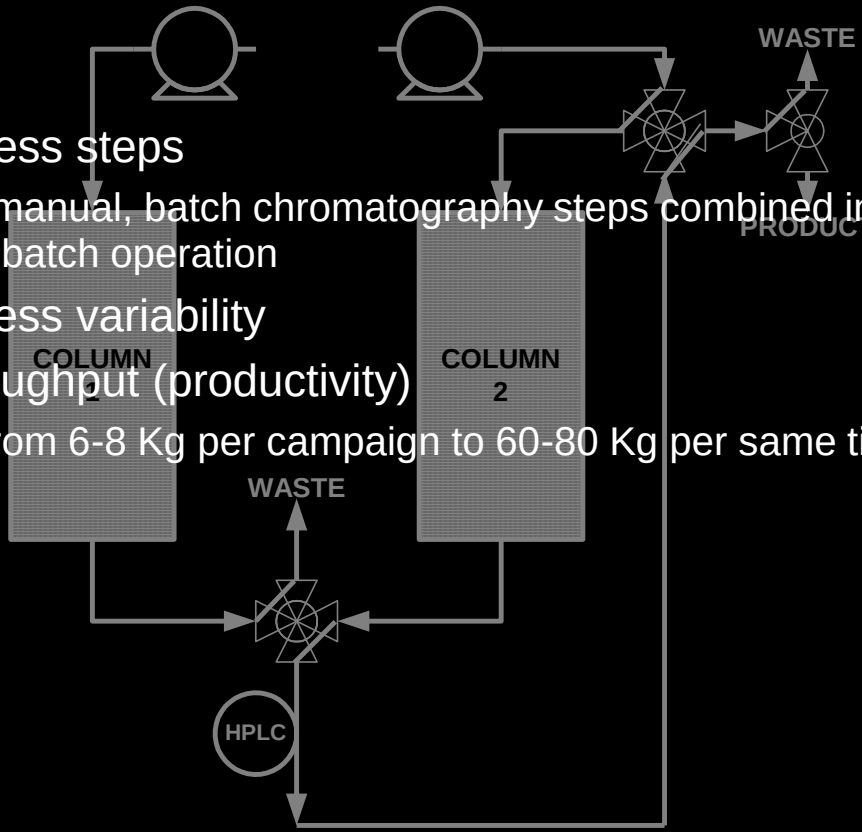


Copyright © 2003 Eli Lilly and Company

Overall Throughput Increased 10 Fold

Advantages:

- Reduced process steps
  - 2 separate manual, batch chromatography steps combined into single automated, batch operation
- Reduced process variability
- Increased throughput (productivity)
  - Increased from 6-8 Kg per campaign to 60-80 Kg per same time period



Copyright © 2003 Eli Lilly and Company

Summary

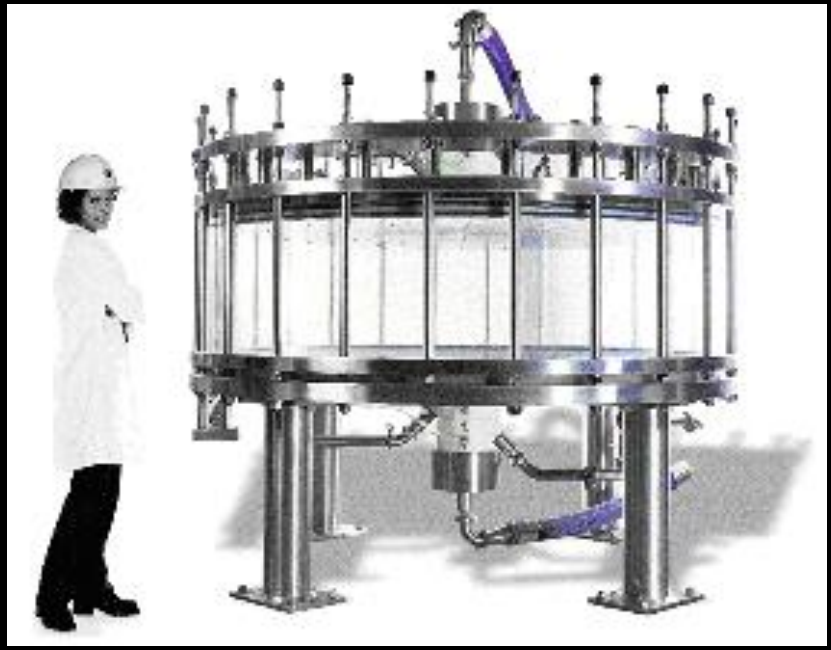
With *proper support*, we have found PAT to:

- Increase process efficiency
  - Example: cycle time reduced by 1/2
  - Example: throughput increased 10 fold
- Increase yields
  - Example: increase reaction yield by reducing rel subs
- Improve process control
- Enable new processing technologies
  - Example: Computerized, feedback controlled gradient generation
  - Example: Close coupling of batch operations

Copyright © 2003 Eli Lilly and Company

Enable New Technology: Process Scale Chromatography Post PAT

Pre-PAT Scale
100 - 400 liter



Post-PAT Scale
2000 liter

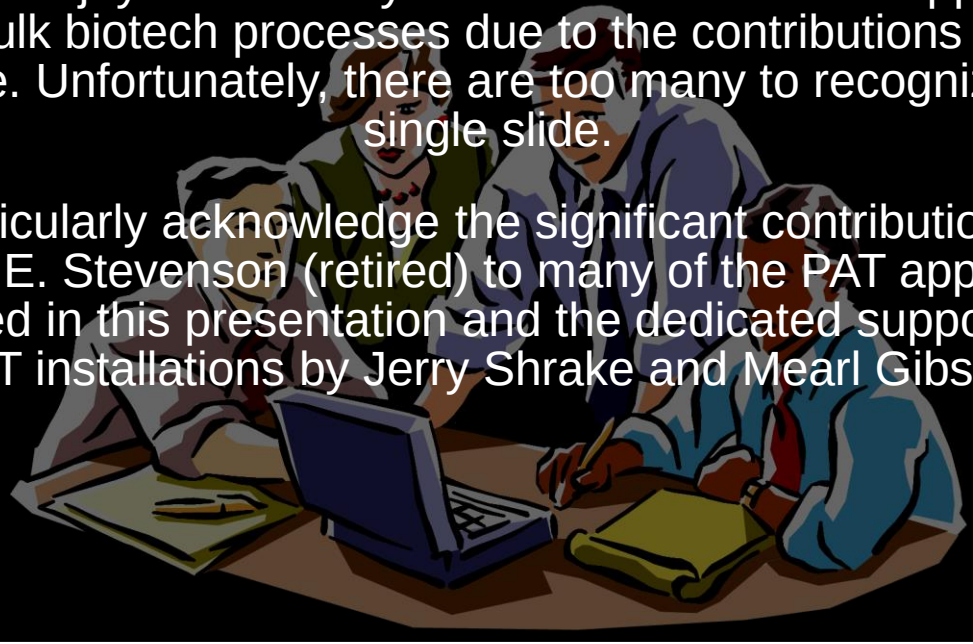
Copyright © 2003 Eli Lilly and Company

Acknowledgements

Amersham Biosciences for their process column photos

We have enjoyed over 20 years of successful PAT applications in our bulk biotech processes due to the contributions of many people. Unfortunately, there are too many to recognize in a single slide.

I particularly acknowledge the significant contributions of Charles E. Stevenson (retired) to many of the PAT applications described in this presentation and the dedicated support of our PAT installations by Jerry Shrake and Mearl Gibson.



Copyright © 2003 Eli Lilly and Company