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# Fast HPLC Enables Online Process Analyzer Technology

## Abstract # 148 Paper - 10/11/2016 - 2:10 PM - Room 380 A


## Ernie Hillier Principle Systems Manager

## Waters Corp

# Agenda

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- HPLC/UPLC Technology
  - Define: Speed/Sensitivity/Resolution
  - What does this all mean?
  - What is the impact?
- Online UPLC
  - How does it work?
  - What problem does it solve?
  - What is the impact?
- Case Study #1
    - Solving for time
      - Yield/Efficiency/Productivity
- Case Study #2
  - Process/Product Monitoring
      - Is the process under control?
      - Is the product good?
- Case Study #3
  - More tools & capability
  - Close loop connection & communication

# ACQUITY UPLC®
## Speed – Timeliness of Information

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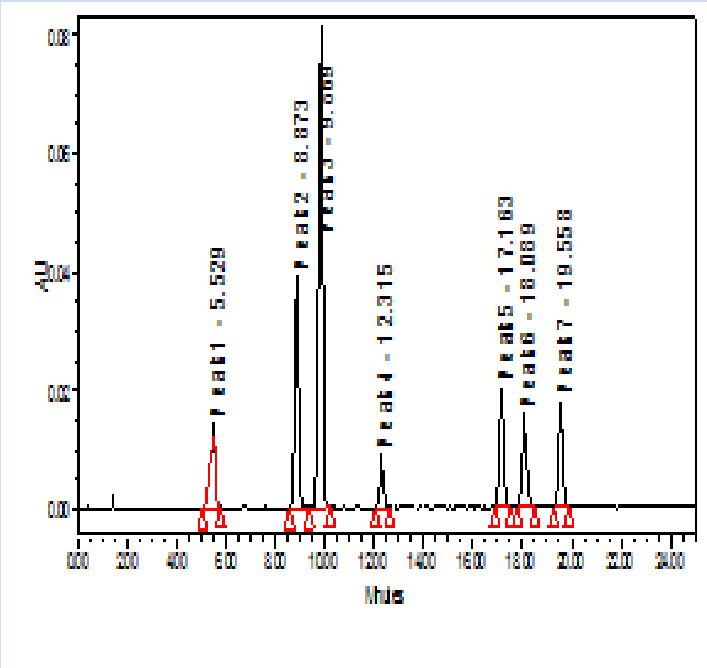
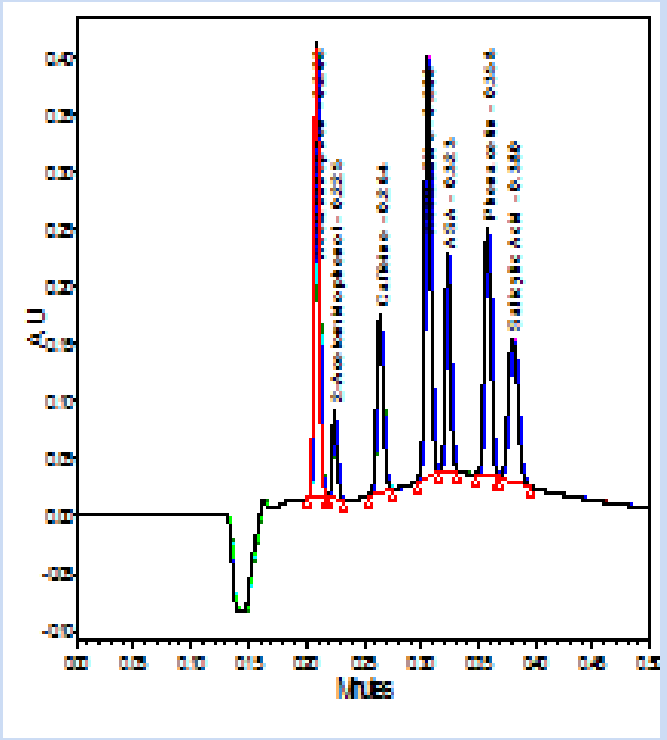
Original HPLC Separation




25 Minutes

Transfer and Optimize

New UPLC Separation




30 seconds

# ACQUITY UPLC®

## Sensitivity – allowing for lower levels of detection

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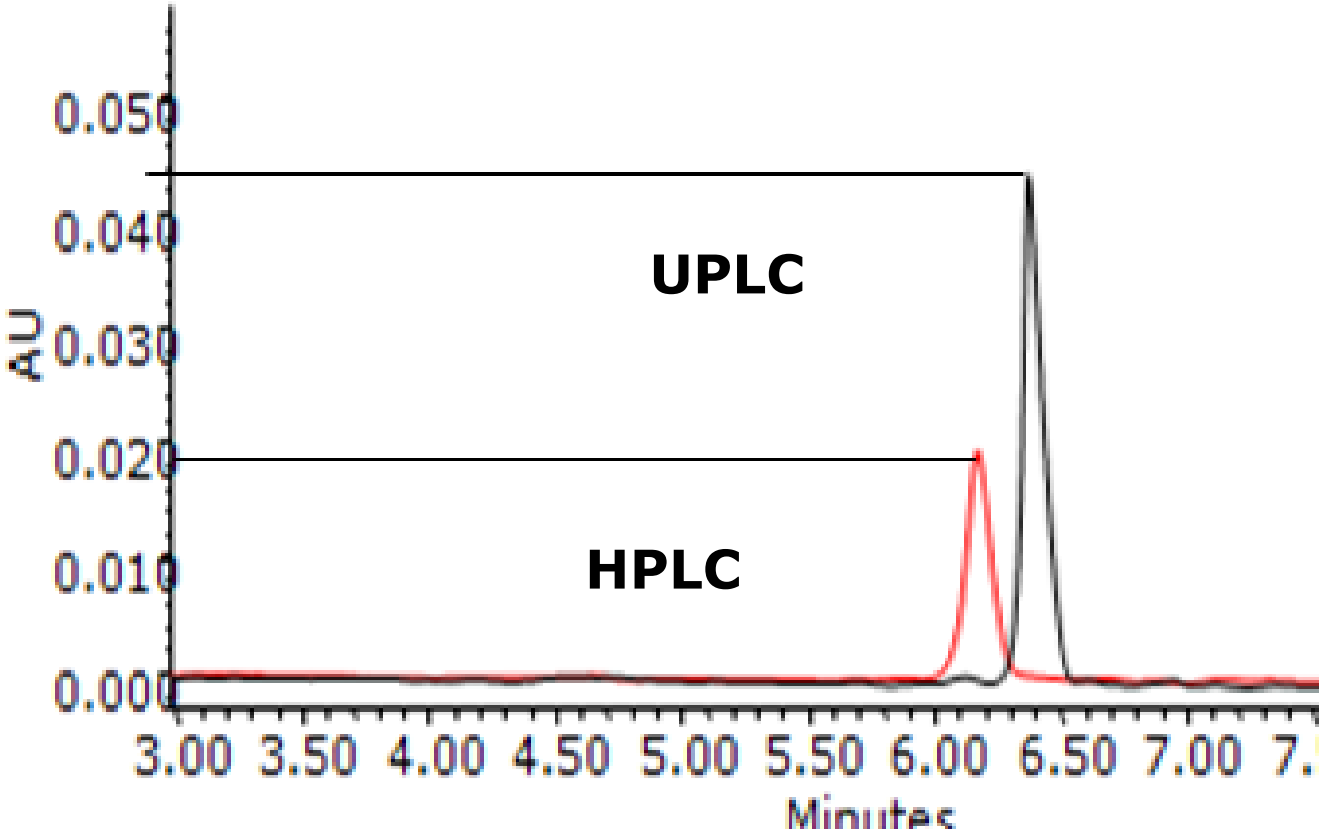

# ACQUITY UPLC®

## Resolution …more information, & higher quality data = better & faster decision making

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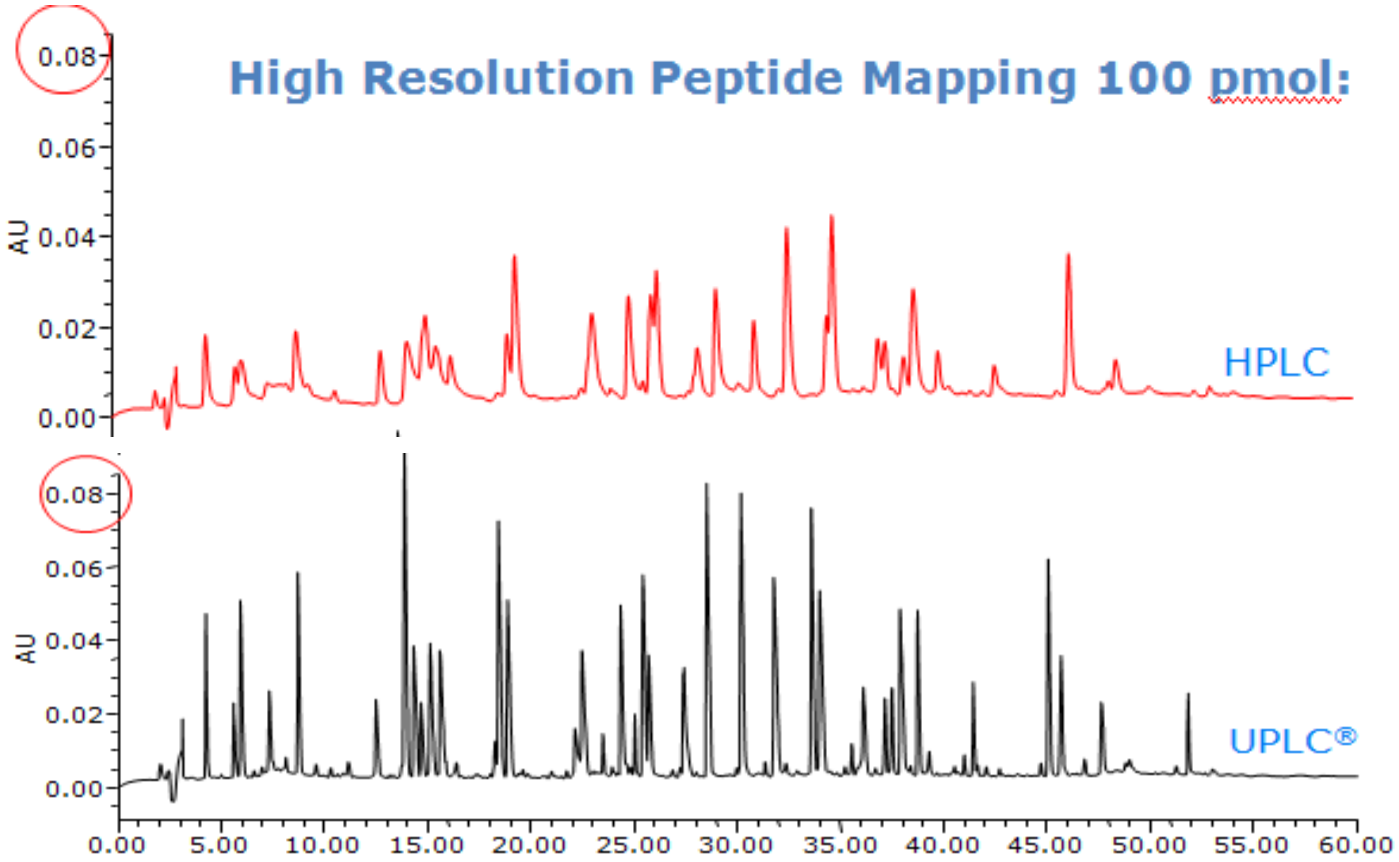


5 µm
Peaks = 70
*P* = 143

1.7 µm
Peaks = 168
*P* = 360

# MIT Study – Waiting for QC Testing

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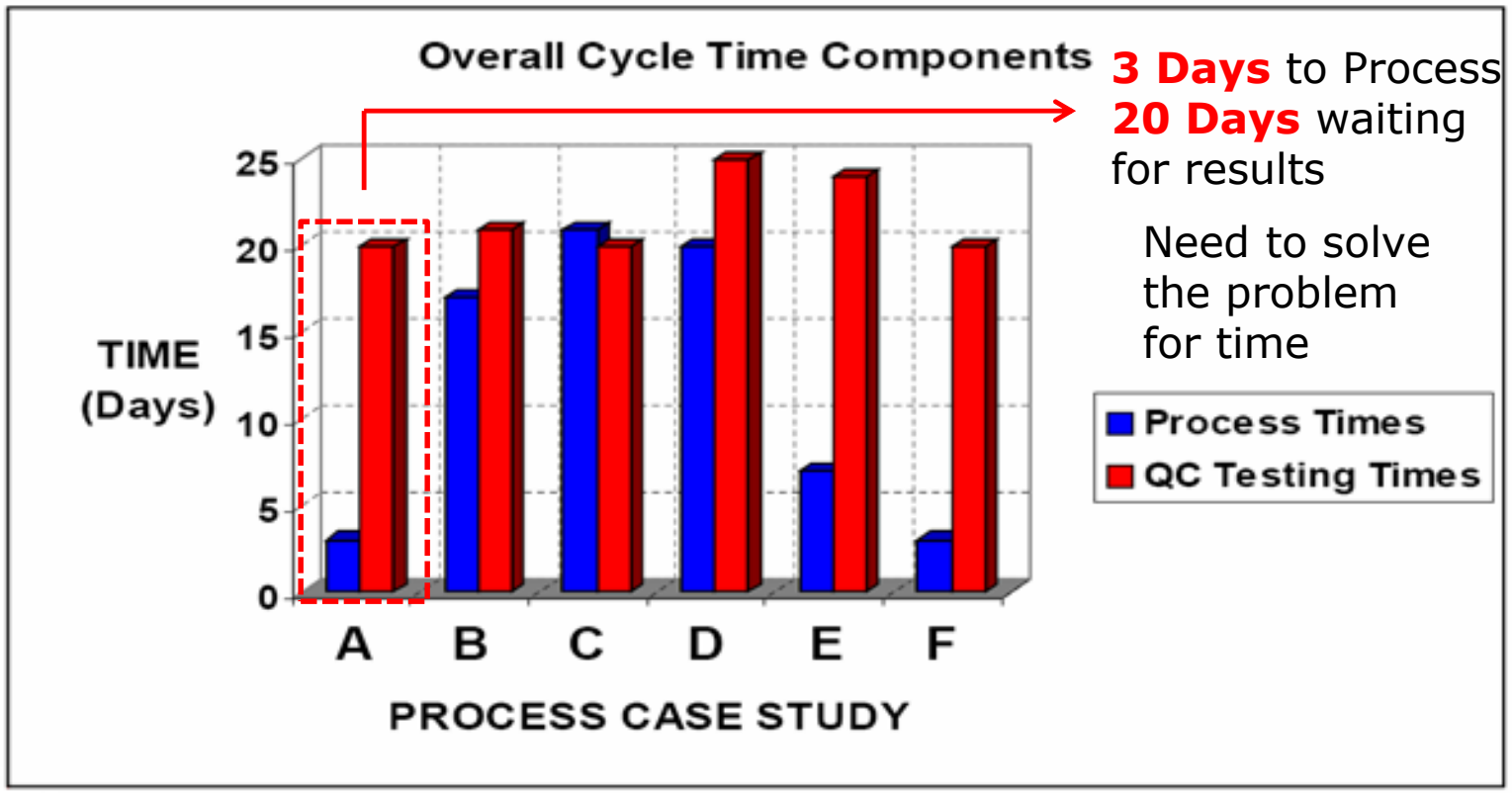
## OVERALL CYCLE TIMES:
## QC TESTING TIMES ARE SIGNIFICANT




G.K. Raju, MIT PHARMI, *Pharmaceutical Manufacturing: New Technology Opportunities*, presentation at USFDA 16NOV01

# How to Move Liquid Chromatography into Process Monitoring

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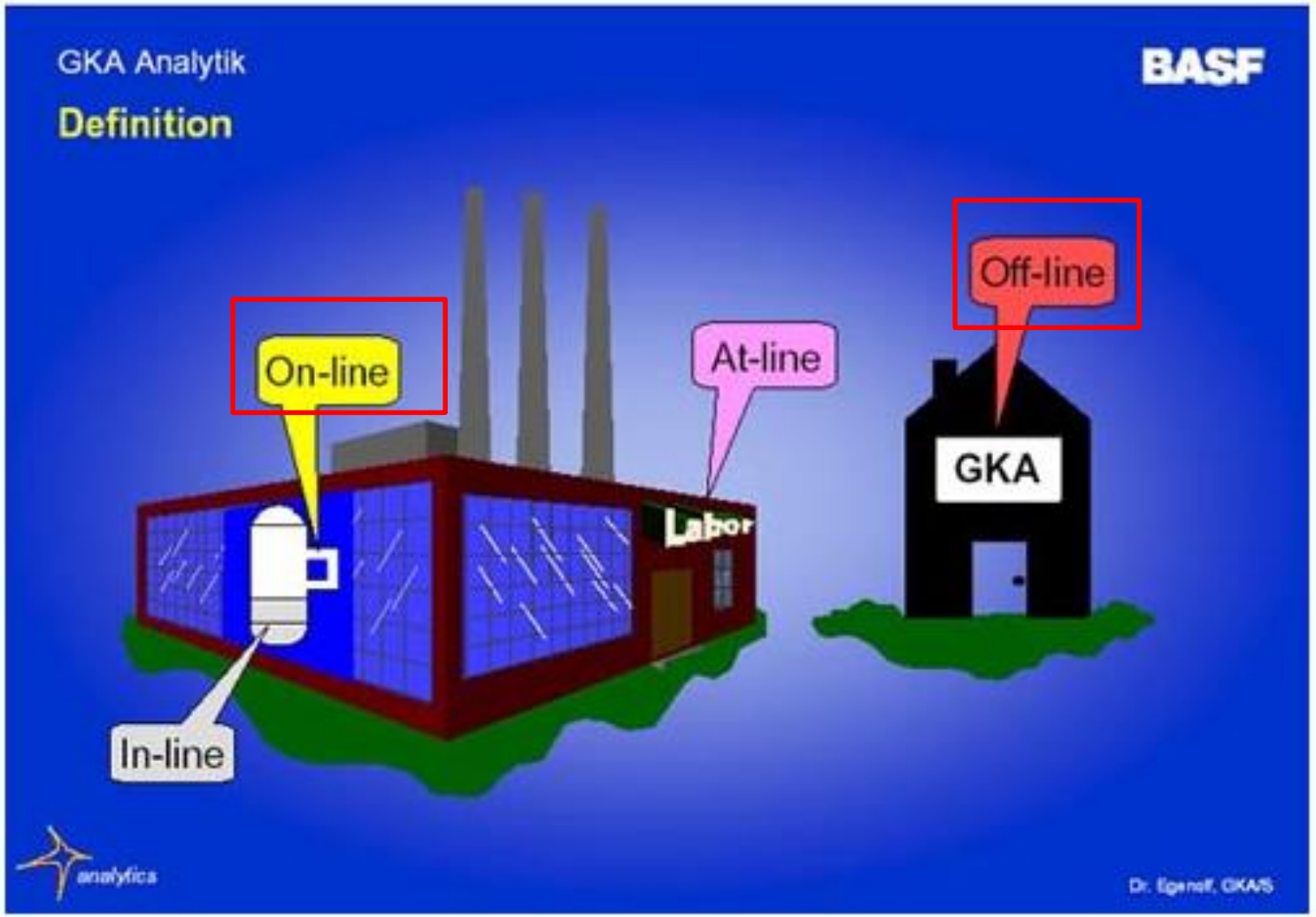


http://www.analyticjournal.de/glossar_beitraege_einzeln/pa_monitoring.html

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# How does the PATROL UPLC Online System Work?

# Process Sample Manager (PSM): Pumps and Valves

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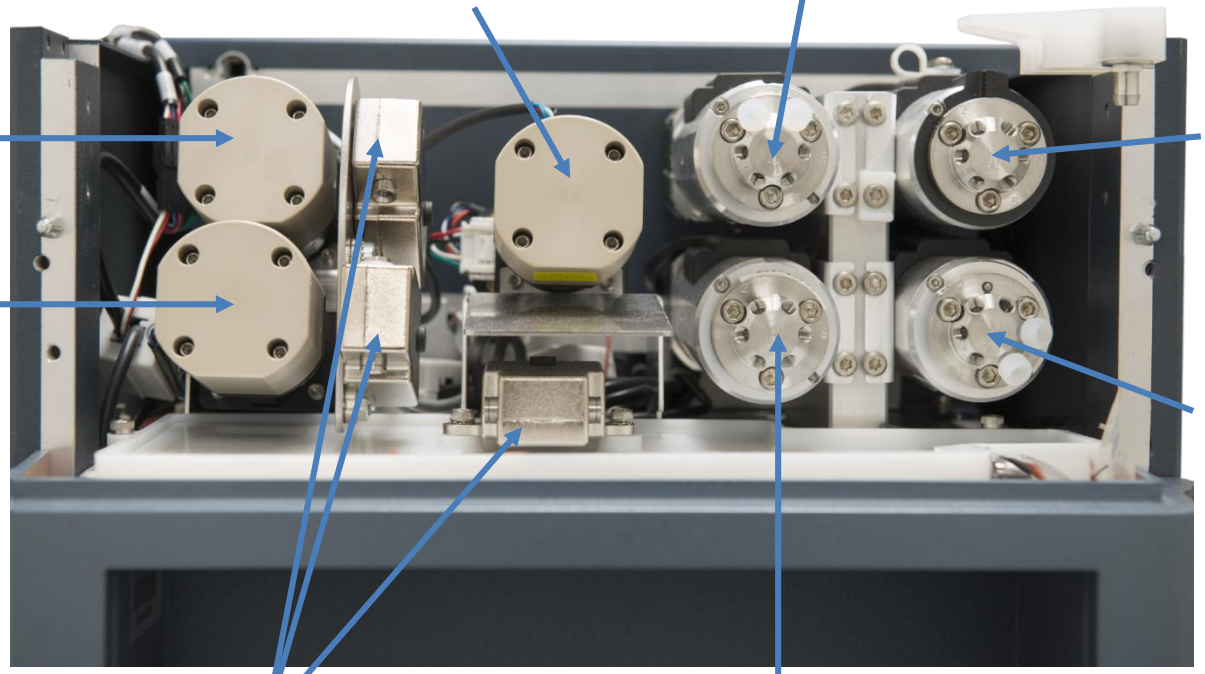


250 µL Process Pump: pulls sample from the "process" into the PSM

Sample Valve: directs the movement of the process sample to waste or to fill the needle

100 µL Sample Pump: moves the sample in and out of the injection needle

200 µL Dilution Pump: works with the Sample Pump to deliver a diluted sample to the injection valve

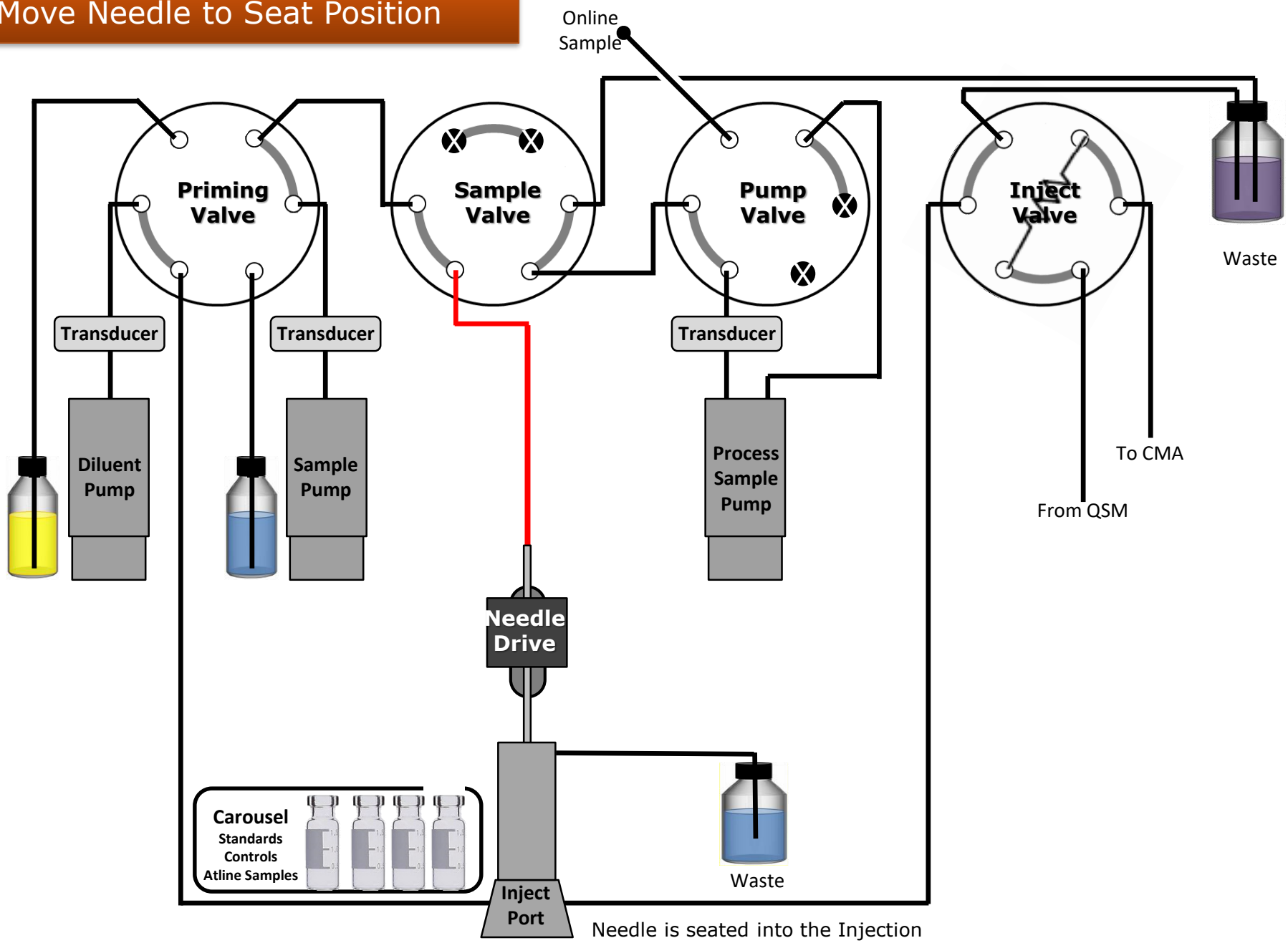
ACQUITY UPLC 15 kpsi Fixed Loop Injection Valve

Process Valve used with the Process Pump (acts as the check valve for the Process Pump)

1000 psi Pressure Transducers for pumps

Priming Valve used with both the Sample and Dilution Pumps

# Move Needle to Seat Position




Needle is seated into the Injection Tower = "INJECT PORT Bottom"

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# Case Study #1

## Workflow & Process Time Impact

# PAT Assay Business Process

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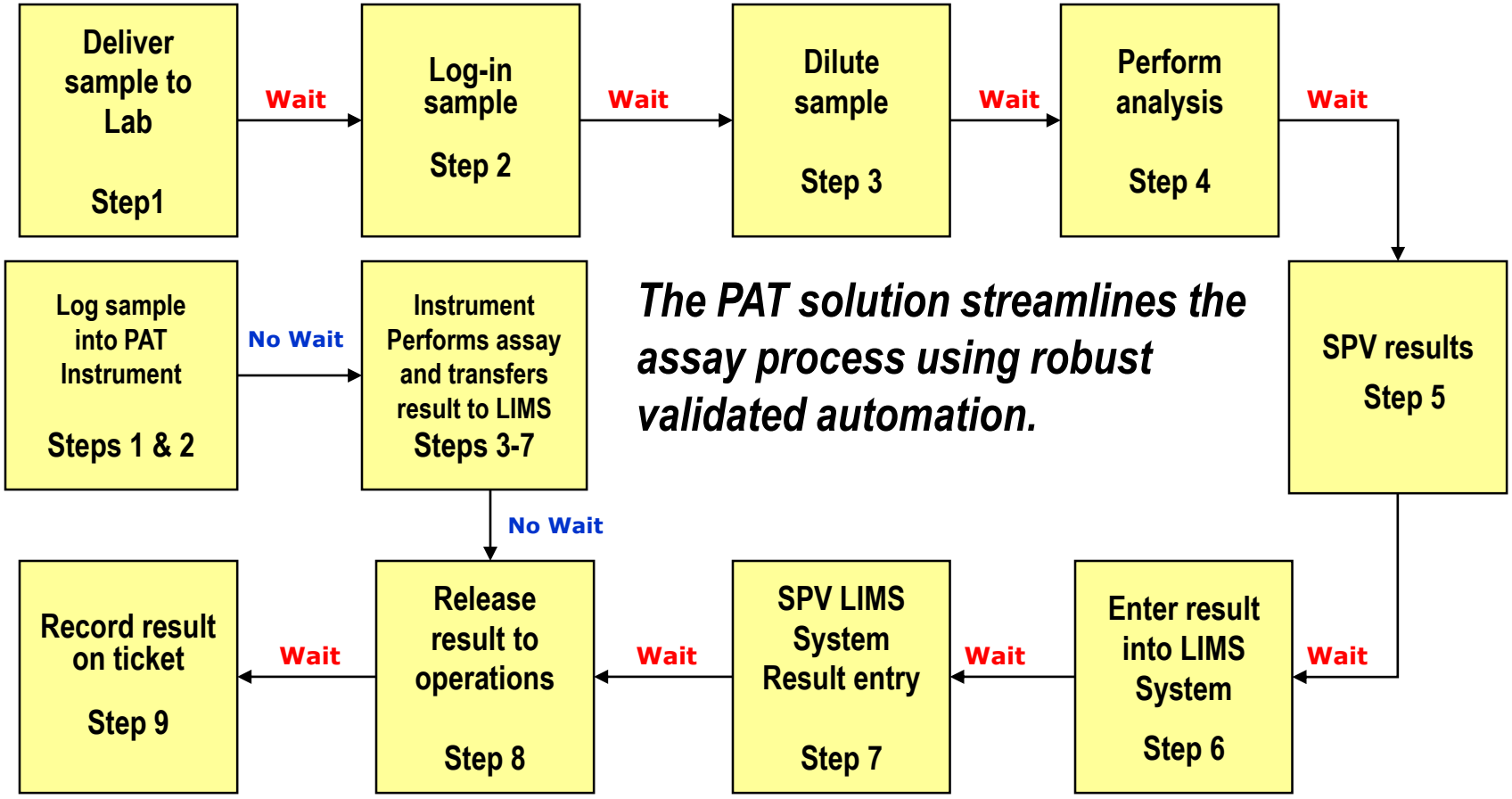
Time is the rate limiting step!




Genetic Engineering News March 10, 2010
Key Collaborator

# Downstream Process
## Biopharmaceutical Purity Analysis

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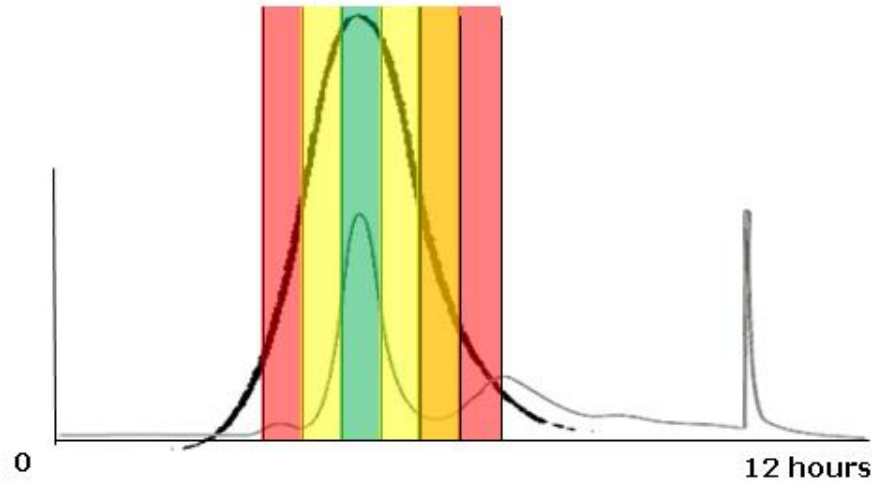
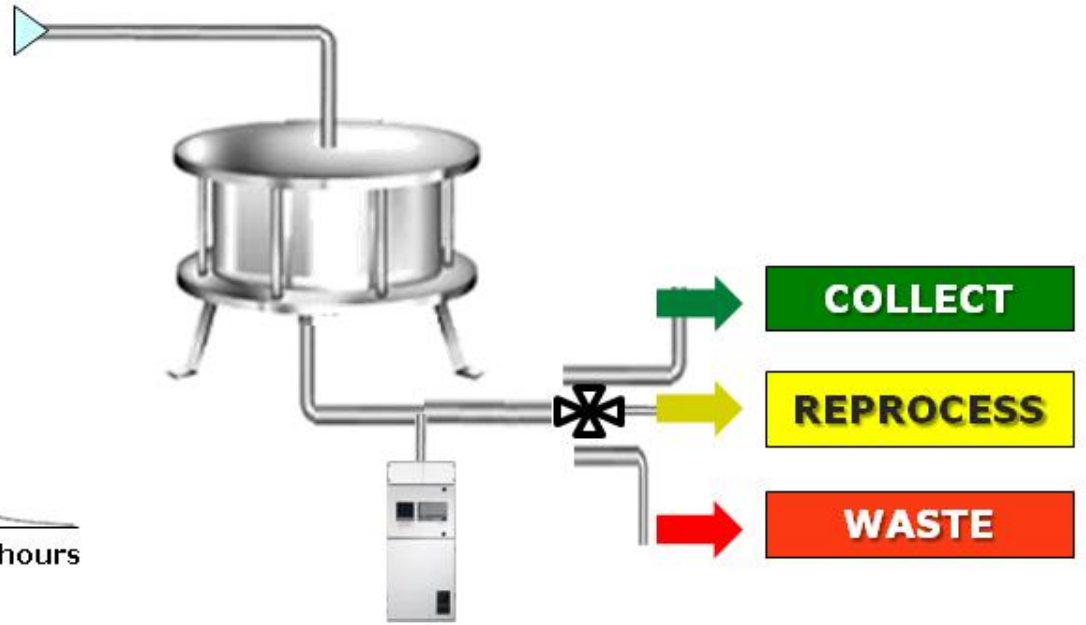
### HPLC Analysis

- 40 minute chromatography
- 160L reprocessed at minimum
- Final recovery after reprocessing

**9 Steps 80 Minutes**



# Downstream Process
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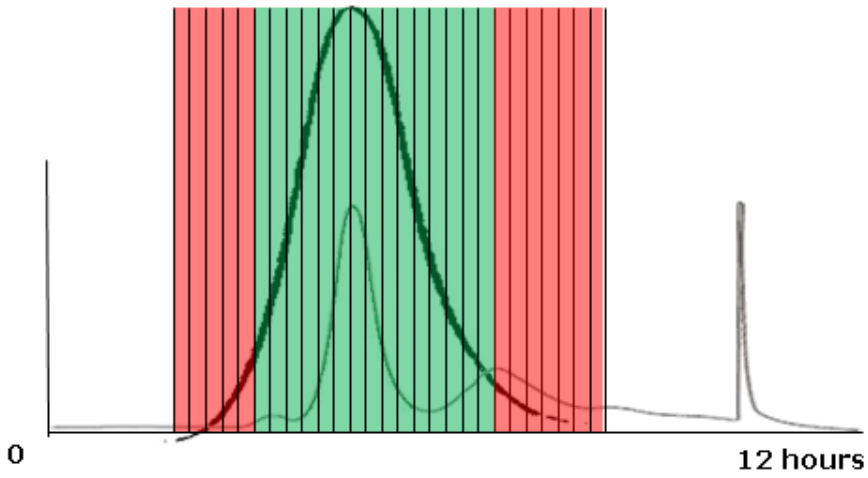
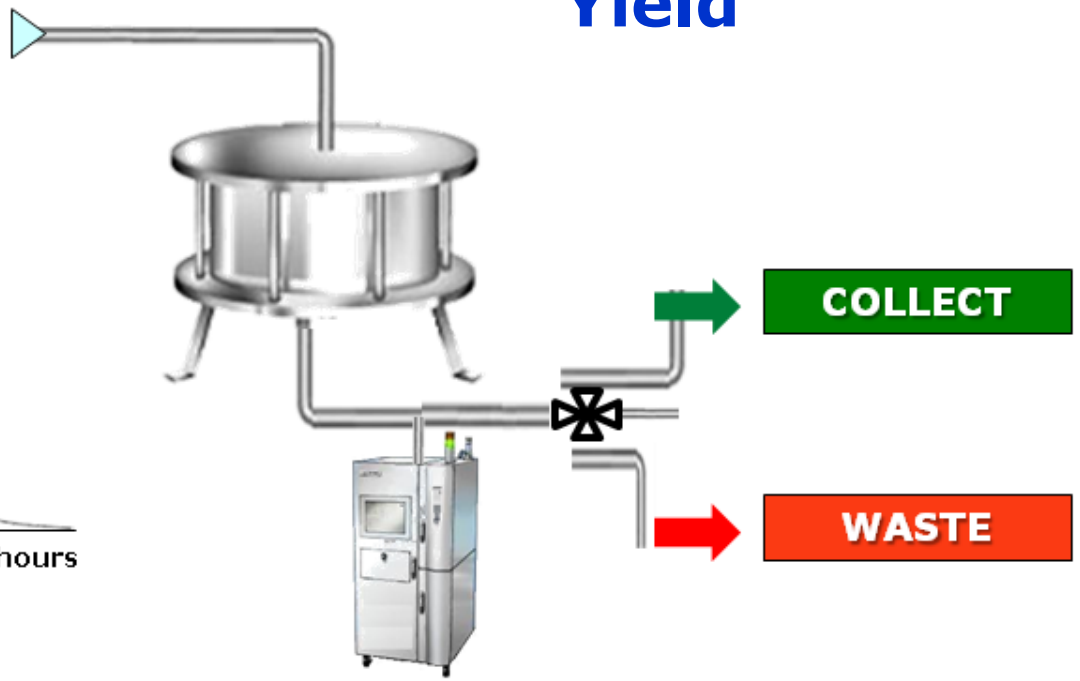



### UPLC Analysis

- ⇨ 3.5 minute chromatography
- ⇨ No reprocessing required

**4 Steps 5 Minutes**

**Yield**



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# Case Study #2 - Part 1

## Small Molecule
## Monitoring the Process and Product

# Process issue – timeliness of understanding and fix (hours not days!!!)

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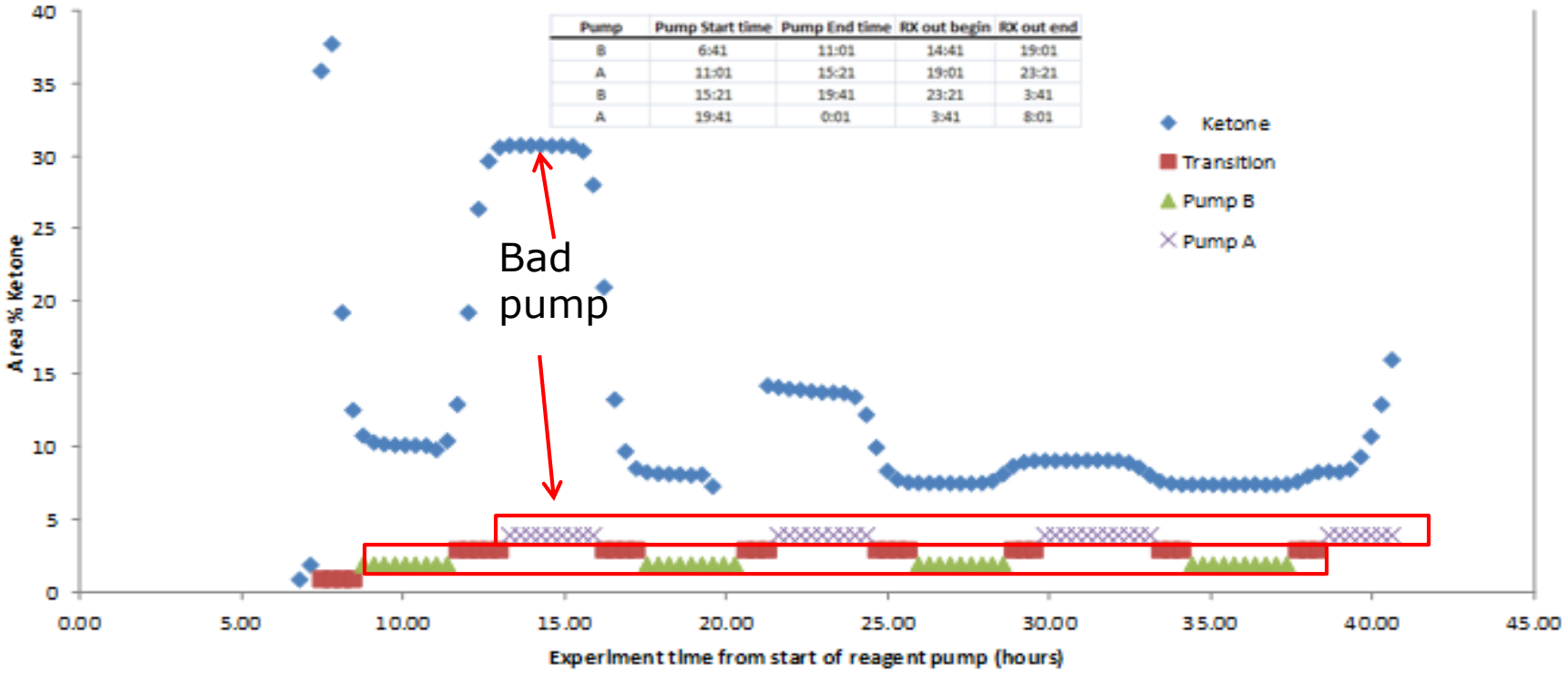
## On-line HPLC Process Control

**Investigation into higher than expected impurity formation indicated hydrolysis of starting material within the process pump. Process pump cycle times were plotted vs. on-line HPLC data correlating observed area % of impurity with pump cycle times.**

| Pump | Pump Start time | Pump End time | RX out begin | RX out end |
|---|---|---|---|---|
| B | 6:41 | 11:01 | 14:41 | 19:01 |
| A | 11:01 | 15:21 | 19:01 | 23:21 |
| B | 15:21 | 19:41 | 23:21 | 3:41 |
| A | 19:41 | 0:01 | 3:41 | 8:01 |



# Reaction Characterization

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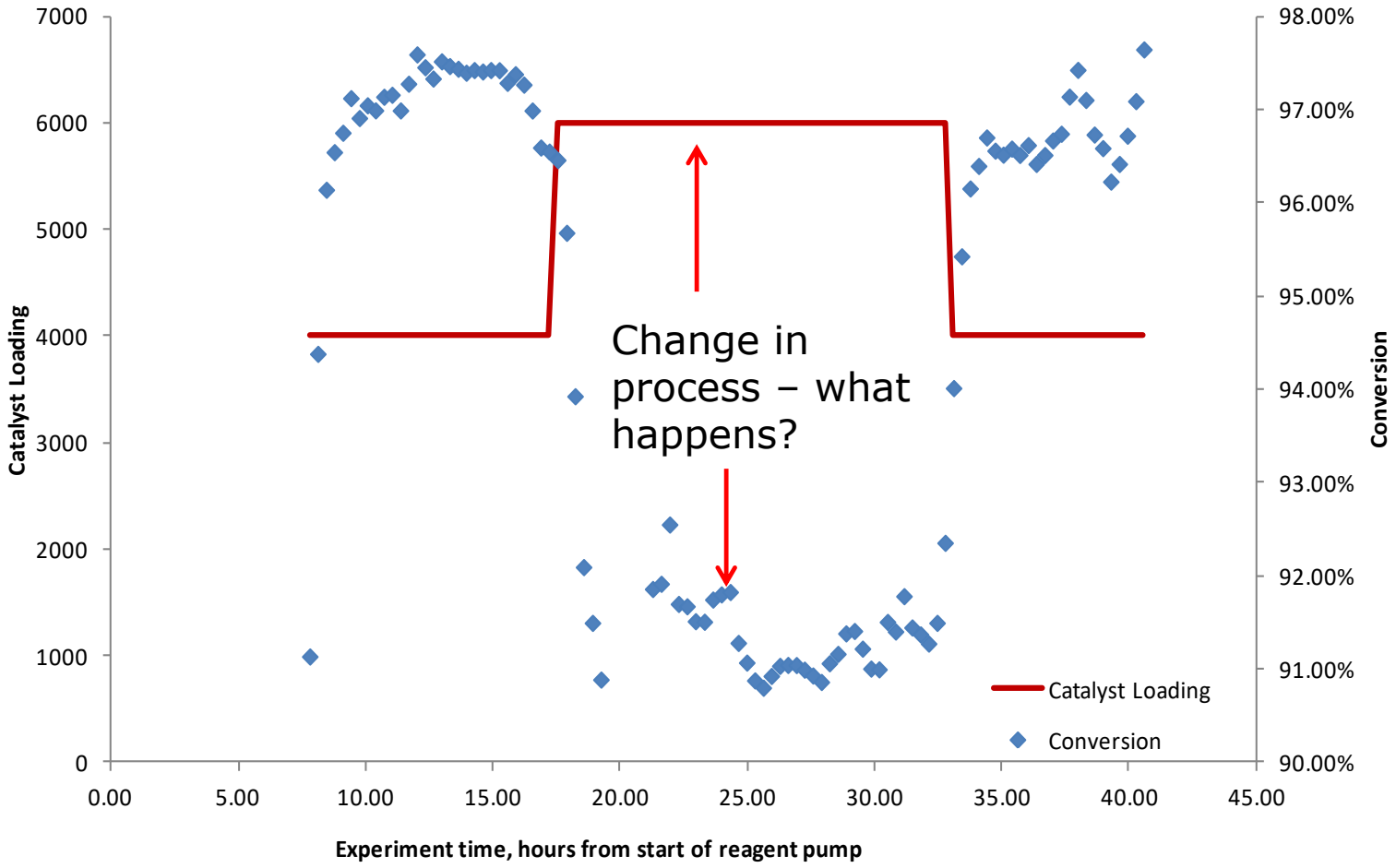
On-line HPLC enables real time changes to process parameters to characterize reactions



# PATrol for Monitoring Continuous Thermal Tube Reactors – Steady State

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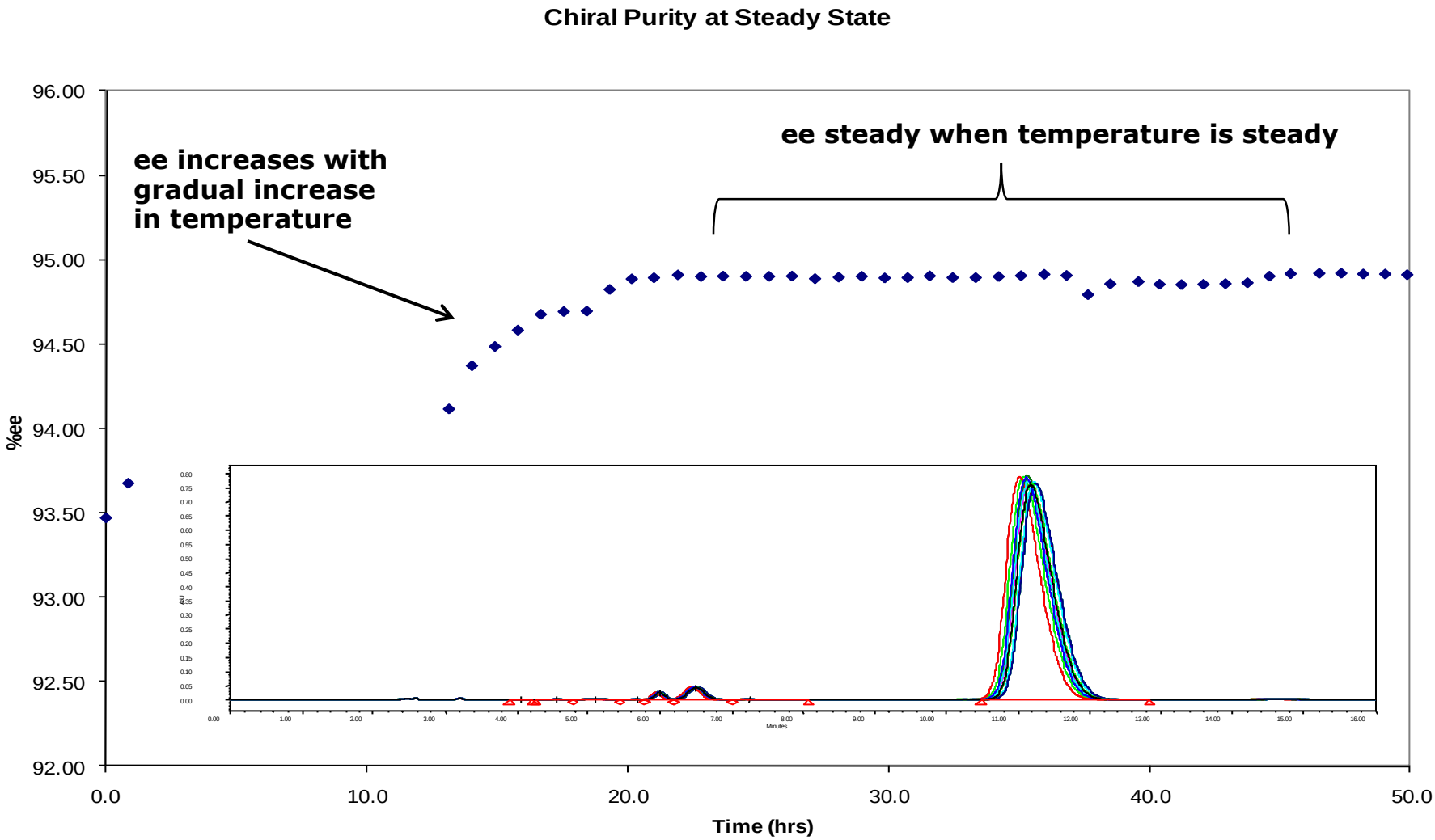

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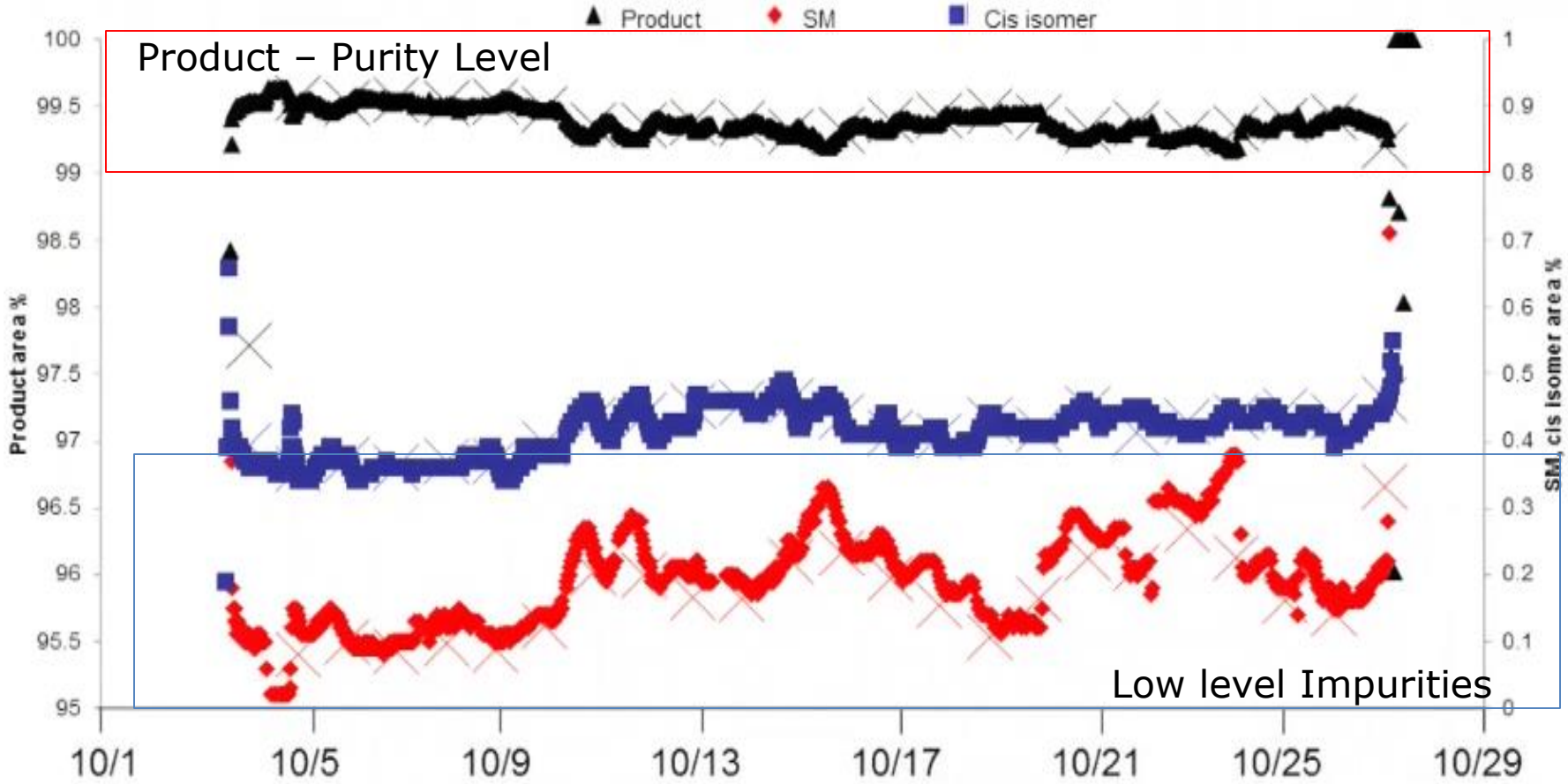
# Case Study #2 – Part 2

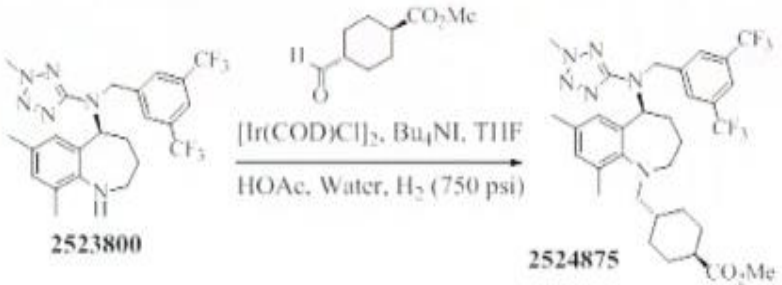
## Small Molecule
## Offline Vs Online Results
## Reliability & Robustness
## Impact

# 24-Day Continuous Hydrogenation

X's = offline lab results



# A Flow-Enabled Ir-Catalyzed Reductive Amination




- *24 days of continuous operation* in a 380L plug flow tube reactor design in manufacturing.
  - Online HPLC used to monitor the reaction
- *2 MT of 2524875 produced*
  - Crude profile shows 0.3-0.5% cis
  - >95% yield; >99.6% purity with 0.2% cis
- *Superior safety profile* vs. batch STAB reaction
  - Runs as a *low risk operation*
  - Avoids storage and handling of STAB
  - All Hydrogen is kept outside of the building .


Material Comparison in Reg. Stab. Campaign
983 kg STAB vs
1.1 kg Ir catalyst and 1.2 kg TBAI

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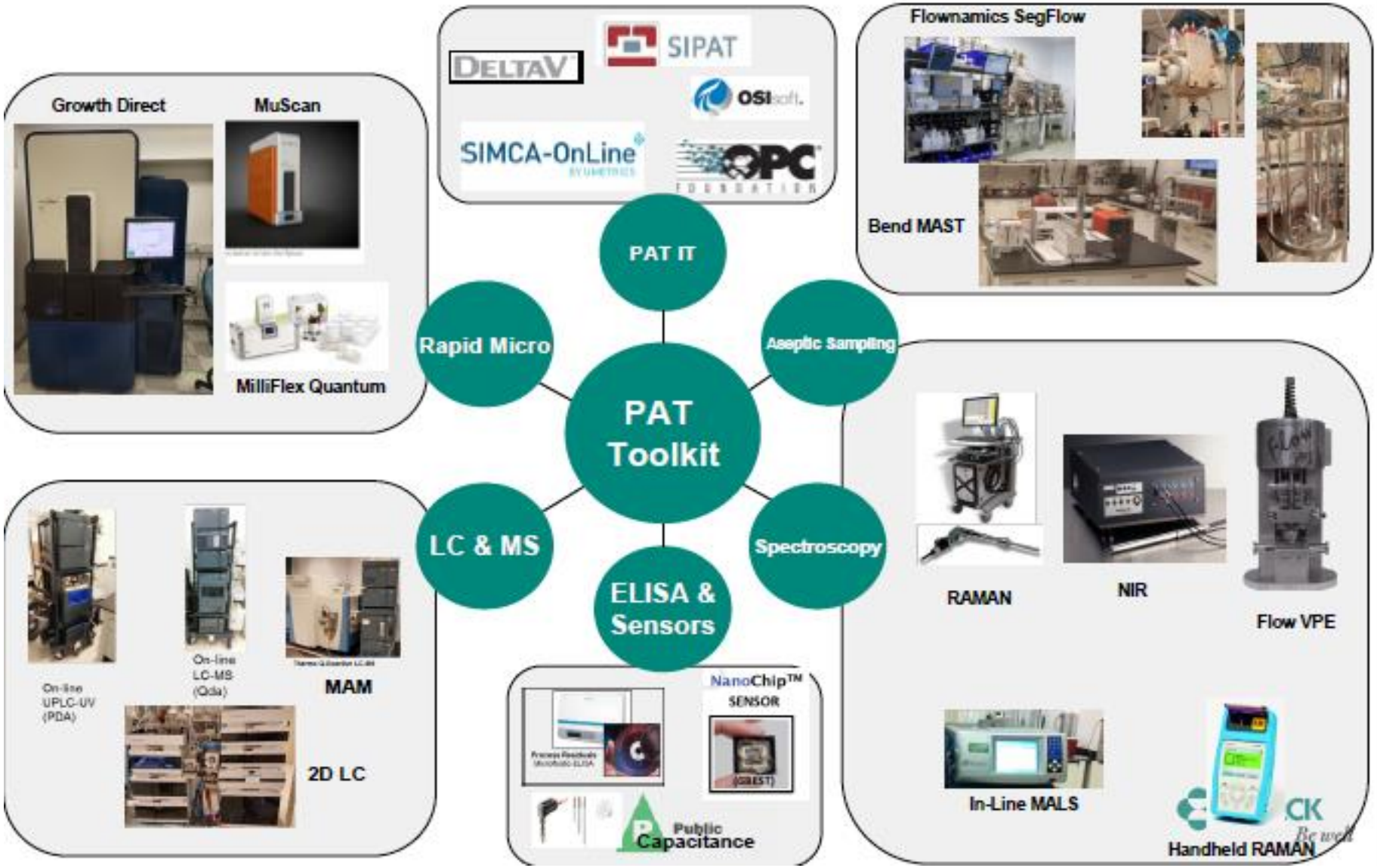
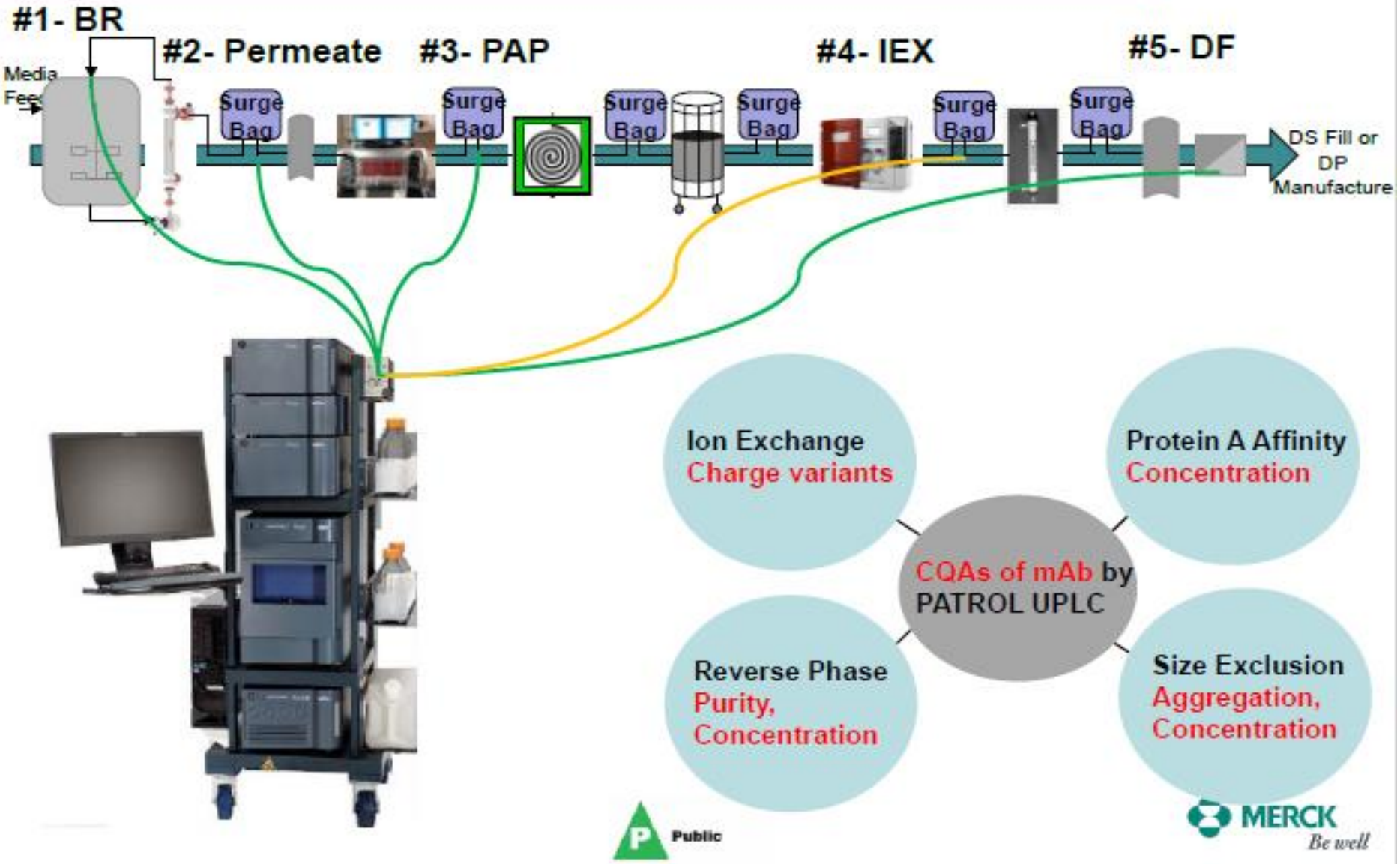
# Case Study #3

## Tools for Large Molecule
## Closed loop communications & control

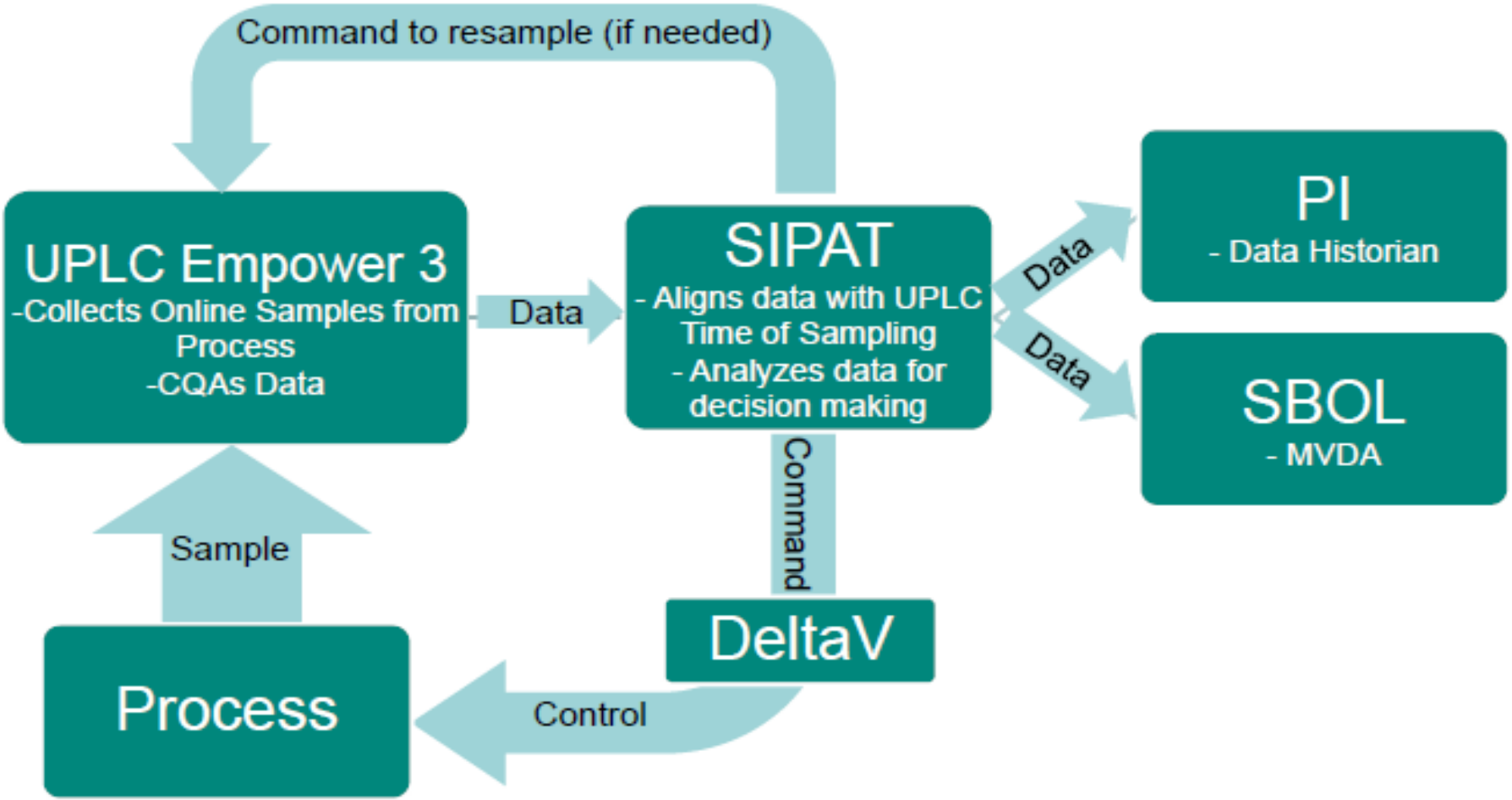
# Expanding Large Molecule PAT Toolkit



# Online LC case studies with PATROL



# UPLC Empower 3 Data Freedom




Contacts: Maria Khouzam
or Doug Richardson

Public

# Summary

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- Advances in separations technology allows for the expansion of tools in the Process space
- The increase in the amount of higher quality data available provides greater process understanding and knowledge about the process.
- The impact provides the business the following ways:
  - Higher yields
  - Faster ROI's
    - Raw materials costs
    - Personnel reduction
    - Space reduction
    - Utilization increases
- Expanded capabilities
- Closed Loop Communications & Control