Strategies for Monitoring and Troubleshooting Biopharmaceutical Manufacturing Operations

Jack Prior
john.prior@genzyme.com
Director, Manufacturing Technical Support
Genzyme Corporation
Strategies for Monitoring and Troubleshooting Biopharmaceutical Manufacturing Operations

OUTLINE

- Assessing the Data Bottleneck for a Process
- Statistical Process Control Case Study
- Chromatography Troubleshooting Approaches
- Five Keys to Successful Process Data Systems
Assessing the Data Bottleneck for a Process

What hinders improvement/troubleshooting most?

Organizational Barriers
- Not Trusted
- Not Analyzed
- Not Acted On

Physical Barriers
- Not Measured
- Not Recorded
- Not Accessible

Process Data

Process Understanding and Improvement
Process Troubleshooting Overview

Outlier Detection
- MFG Deviation
- Specification or IPC Violation
- SPC Alert

Process and Data Investigation

Lot Disposition
Preventative Actions
Process Insight

Resolution
How to Monitor Large Quantities of Data?

-> Statistical Process Control Rules

Western Electric Rules

- 1 outside 3 $\sigma$
- 2 out of 3 outside 2 $\sigma$
- 4 out of 5 outside 1 $\sigma$
- 8 or more same side of $\mu$

<table>
<thead>
<tr>
<th>Variable</th>
<th>Run Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu +3\sigma$</td>
<td>0.135%</td>
</tr>
<tr>
<td>$\mu +2\sigma$</td>
<td>2.14%</td>
</tr>
<tr>
<td>$\mu +1\sigma$</td>
<td>13.6%</td>
</tr>
<tr>
<td>$\mu$</td>
<td>34.1%</td>
</tr>
<tr>
<td>$\mu -1\sigma$</td>
<td>34.1%</td>
</tr>
<tr>
<td>$\mu -2\sigma$</td>
<td>13.6%</td>
</tr>
<tr>
<td>$\mu -3\sigma$</td>
<td>2.14%</td>
</tr>
<tr>
<td>$\mu -3\sigma$</td>
<td>0.135%</td>
</tr>
</tbody>
</table>
Most data fall within formal alert limits.
SPC Case Study: Purification Column Recovery

- Most data fell within formal alert limits
- Low recovery triggered formal investigation
SPC Case Study: Purification Column Recovery

- Most data fell within formal alert limits
- Low recovery triggered formal investigation
- SPC Alert (8 < mean) visible 10 runs earlier
- ~10% of each batch went to drain for 20 batches

Allston Automated SPC System:
- Immediate e-mail notifications
- Hyperlinked trends & lot trees
Chromatography System Overview

- Pump
- Column
- Flowmeter
- Bubble Trap
- Vent Valve
- Vent Filter
- Level Sensors
- Bubble Trap
- Bypass Valve
- pH T Cond
- P
- UV
- pH T Cond
- P
- genzyme Therapeutics
What Can Go Wrong in Chromatography?

DATA
• Data entry
• Assay
• Sampling
• Sensor
• Assumptions

EQUIPMENT
• Control system
• Valve leaks
• Bed channeling
• Bed compression
• Other…

PROCESS & MATERIALS
• Mixing
• Material stability
• Precipitation
• Parameter sensitivity
• Procedural gaps
• Operator errors
• Raw material issues

60 cm Chromatography Column, Skid, and Piping
Chromatography Investigative Options

**Equipment Checks**
- Pressure check system
- Examine valves
- Check/Recalibrate sensors
- Test HETP/asymmetry

**Assay Checks**
- Review raw QC data
- Trend assay control
- Re-assay retain
- Resample from process

**Data Compilation**
- Paper batch records
- Chart traces
- MRP (lot tracking & usage)
- Raw material attributes

**Experiments**
- Buffer/Raw material testing
- Scale-down experiments
- Stability studies
- Resin life/cleaning studies
Is Data Consistent with Adjacent Operations and Batches?

Component Balances Across Adjacent Process Operations

Internal Consistency Checks

Historical Online Profile Comparison

Historical Runs

pH
UV
pressure
flow rate
conductivity
temperature

Adjacent Operations

Column A

Column B

Column C

product recovery
protein recovery
volume balance
Is Data Internally Consistent?

Component Balances Across Adjacent Process Operations → Internal Consistency Checks → Historical Online Profile Comparison

- **Total Flow vs. Volume**
  - $y = 0.97x$
  - $R^2 = 0.99$

- **Elution Profile Attributes**
  - UV Absorbance vs. Measured Buffer Volume (CV)

- **Total Protein vs. Area under curve**
  - $y = 0.78x$
  - $R^2 = 0.74$
Systematically Choosing Investigative Steps…

SPC Alert: Unusually Low Product Recovery

Initial Assessment Activities

Protein recovery also low?

NO

Online data available?

YES

Request resample

NO

Dig for more data

YES

Protein accounted for in load/wash?

NO

Check equipment

YES

Perform experimental investigation

NO

Request retest of eluate

Request retest of load

Following column product recovery high?

YES

Preceding column product recovery high?

NO

Dig for more data
Allston Landing Process Data Flows

**Process Operations**
- Utilities
- SIP/CIP
- Media Prep
- Buffer Prep
- Cell Culture
- Microfiltration
- Chromatography
- Lyophilization

**Manual Data**
- QC Results
- Monitoring Logs

**Control Systems**
- Rosemount RS3
- Intellution FIX
- AB PLC
- Delta V

**Data Historians**
- AIM
- Rapid Pharma
- MRP
- LIMS
- MS Access

**Manual Analysis**
- Excel
- JMP
- MATLAB

**Automated Analysis**
- MATLAB
- Web Trends/Reports
- SPC Alerts
Five Keys to Successful Data-Driven Process Improvement

#1: Create broad awareness of how the process is running
#2: Ensure manual data entry has both immediate and long-term benefits.
#3: Exploit Metcalfe’s Law:
- *the value of a network grows by the square of the number of its users*
Five Keys to Successful Data-Driven Process Improvement

- #4: Lower barriers (activation energy) to explore ideas and confirm theories
Five Keys to Successful Data-Driven Process Improvement

- #5: Create efficient cross-functional teams to drive and close-out investigation and improvement initiatives