Protein Refinery Operations Lab (PRO Lab): A sandbox for continuous protein production & advanced process control

Mark Brower
Merck & Co., Inc, mark.brower@merck.com

David Pollard
Merck & Co., Inc

Finn Hung
Merck & Co., Inc

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Protein Refinery Operations Lab (PRO Lab): A sandbox for continuous protein production & advanced process control

Mark Brower
BioProcess Development
Merck Research Labs
Merck & Co. Inc
Kenilworth, NJ

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Berkeley, CA
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Merck’s Motivation

- Merck lags other major biopharma companies on installed SS bioreactor capacity*
- Can this “disadvantage” be leveraged into a competitive advantage?

* Source: BioPlan 10th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production
Facility of the Future

CHO mAb Processing Vision at Merck

Automated Continuous Processing

Component Engng
‘lego’ building blocks

Molded parts

Adaptive Process Control

PAT tools
Predictive MDVA models

Real Time Release Testing

Equipment Performance
Real time Monitoring

Examples:
Real time sensing of Pump seal failure,
PAT sensor performance
• Proactive preventative maintenance to
limit failures
• Eqpt redundancy strategy
• Process flow strategy for deviations

SU operations

Automated Inventory
management

Single use Workflows
Buffer supply
Fluid flow management

Be well
A Sandbox for the Facility of Future
Protein Refinery Operations (PRO Lab)

Continuous Process

- PAT & sampling integration
- Process monitoring and MVDA modeling
- Adaptive/feedback unit operation control
- Robust control strategies

Operationlize

- Connections and piping
- Component engineering
- Component change-outs (filters etc.)
- Liquid and RM management

Sandbox Facility

- Medium-scale operation
- PAT & control implementation
- Batch demonstrations
- Applying facility of the future principles

Facility of the Future

- Robust manufacturing platform
PRO Lab Timeline

1H 2014
- Define Base Control Strategies & Order Components

2H 2014
- Order & Install Components

1H 2015
- MVDA Modeling & Perturbation Analysis

2H 2015
- B#1 40 Days Debugging

1H 2016
- B#2 50-70 Days (On-Going)
PRO Lab:

*Fully automated mAb drug substance*

- Distributed control for all unit ops
- Overview & unit-ops level views
• Upstream area for perfusion bioreactor
• Downstream unit operations in connected “U” shape
• Routine operations at 10L bioreactor
• Analytical hub
• Buffer/media holds outside of process area
• Hardware agnostic
Operating Principles
A Lights-Out Approach

• Each unit operation represented
• Surge vessels used to collect and feed next unit operation
• Stream adjustments & sampling in surge vessels
• Redundant filters
• Speed compensated methods with breakpoints
• SU/closed processing methodology
Upstream
Perfusion Operations

- Routine operation at 10L scale
- 50L scale-up demonstrations
- SU AutoTFF cell retention device
- Weldable filter replacements
Baseline Perfusion Performance

- Stable cell density
- Viability maintained >99%
- Productivities > 1g/(L·Day)
- Membrane fouling and antibody sieving
- Significant cell lysis

Capacitance Measurement

- Capacitance for “in-vivo” biomass monitoring
- Correlation of online and offline biomass measurement
- Used to automate cell bleed and maintain constant biomass

*Kistler, Napoli, Chen, Xu*
Downstream Operations

Protein A Chromatography

Protein A Chromatography
- Predictable reproducible elution
- Low feed pressure
- Accelerated column lifetime

Systems Closure
- Guard Filter Performance
  - 1 Guard filter per day → 1 guard filter per batch
  - Volume based filter switching
Automated Sample Collection & Analysis

**In-tank clarification**
- Ceramic membrane sampling device
- Automated sample management
- Integration with 3rd party analytics
- Sieving of product with surface fouling

**External clarification**
- Sanitized sample port
- Cell removal device
- Automated sample management & integration with 3rd party analytics
- Hybrid solution targeted January 2016
Continuous Processing:
**PAT, Automated Control & Real Time Release**

- **QbD Design Space**
- **KPA’s & CQA’s**
- **Process monitoring**
- **BioProcess Control**
- **Adaptive control**
- **Critical inputs (raw materials)**
- **RM Screening Experience learning**
- **MVDA**

- **End Product Testing transition to Real Time Release Testing**
- **Real time automated control**: process responds to variability & disturbances
  - End to end prediction models for complete process
  - RM control → Process input → Product quality & yield
Multi Attribute Method via Peptide Mapping

“Direct measurement of CQA’s at molecular level”

<table>
<thead>
<tr>
<th>Quality Attribute</th>
<th>Current Method</th>
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<tbody>
<tr>
<td>Identity</td>
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<tr>
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<td>rCE-SDS</td>
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<tr>
<td>Process Impurities</td>
<td>HCP/ProA ELISA</td>
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</tbody>
</table>

MAM—Peptide Mapping

Characterization

Monitoring

30 min Tryptic digest—Ren, D. et. al. Anal Biochem. 2009 Sep 1;392(1):12-21
MAM—Rogers, R. S. et. al. mAbs 2015 Sep 3;7(5):881-90
PAT UPLC Process Monitoring

- SEC quality and permeate monitoring
- Water soluble vitamins with QDA MS Detector
- Multi-attribute peptide mapping methods installation in 1Q 2016
Upon reaching steady state, purity and quality attributes remain consistent.

- More complex perturbation analysis expected with MAM method
- Predicting outcomes from indicator process intermediates
Conclusions

- A fully automated continuous bioprocessing suite has been established at Merck with distributed control via DeltaV.
- The facility has been designed using “lights out” and closed processing approaches.
- Two perfusion batches have been demonstrated in the lab to date achieving steady state cell densities for >50 days.
- PRO Lab will serve as a sandbox for new sampling, PAT and MVDA strategies with ultimate feedback and adaptive control.
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