Applications Supporting Large Molecule Drug Development

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Presentation topics

• Monoclonal Antibodies and Bioreactors
• Bioreactor Laboratory Automation
• Feed Strategy and Observations
• Media Component Consumption
• Product Quality Measurement
• Downstream Processing
• Next Steps
• Summary
Monoclonal Antibodies (mAb)

• Monoclonal antibodies (mAb) treat several disease states.

• Examples of autoimmune diseases treated:
  – Rheumatoid arthritis (joint inflammation)
  – Crohn’s disease (inflammation of the bowels)

• Examples of oncology diseases treated:
  – B-cell lymphoma and melanoma
  – Ovarian, breast, gastric, and colorectal cancers
Bioreactors

Culture Conditions Impact mAb Production & Quality
- Temperature
- pH
- % Dissolved Oxygen
- Feed
  - Glucose
  - Amino Acids
  - Vitamins
  - Other Metabolites
Bioreactor Laboratory Configuration

Feed Pump

Raman Probe
Automation Network Integration

Bioreactor PCS

PAT Raman Analyzer PC

Model & PAT/PCS Integration PC
Feed Strategy

- Traditional feed strategy is a bolus feed once per day.
- Tested a continuous feed strategy based upon sustained glucose concentration (g/L) as measured by Raman spectra.

**PAT System**

**Chemometric Model**

[Glucose]

**Logical Control**

[Glucose] < Setpoint

Send Pump Setpoints based on Raman predicted Glucose Level
Glucose On-Demand
Observation: Sustained Increase in Glucose Level
Observation: Sustained Viable Cell Density
Observation: Improved mAb Production

Raman PAT Control Batch
Observation: Improved Lactate Profile
Observation: Reduced Ammonia (Cell Waste)
Analytical Samples

- Additional information for culture conditions and mAb quality
- 8 Reactors x 17 Culture Days x 1 Sample/Day = 136 Samples
- 136 Samples x 3 DoE’s = 408 Samples
  - Sample prep options:

  Option 1

  Option 2
Media Component Consumption

- Key media components include Glucose, Amino Acids, Vitamins, and other metabolites.
- Are we depleting media components over culture days?
- Analyze consumption of amino acids and production of NH3.
- Glutamine, Arginine, Tryptophan, Tyrosine, Serine, etc
Product Quality by Glycoform Analysis

- Glycoforms
  - Important to mAb structure
  - Metabolic pathways in patients.

- Are we forming mAb with desired target glycosylation profile?

- G0, G0F, G1F, G2F, Man5, Man6, etc.
Downstream Processing: Purification

- Cells are cultured in bioreactors expressing the antibody.
- Cell culture is harvested and the harvest is clarified.
- Antibody purification occurs in typically three steps:
  - Capture chromatography
  - Intermediate purification chromatography
  - **Polishing chromatography**

What are the Buffer system components associated with the high % Recovery?
Polishing Chromatography Buffer Screens

- Polishing chromatography is used to increase Mab purity from >90% to >98%.
- Conducted as center-point studies to optimize:
  - pH (Buffer reagents)
  - Conductivity (Salt)
  - Protein load
- Measurements of purification end points:
  - % Recovery
  - % Purity
  - Clearance of Aggregates/Impurities
Next Steps

• Continue Raman Calibrations for Chemometric modeling:
  – Lactate: alternative energy source to Glucose.
  – Ammonia: waste product and culture stressor.
  – Metabolites: amino acids, vitamins, and biochemical intermediates.
  – Viable Cell Density.
  – Titer
  – Product quality attributes?
    • Tertiary structure
    • Glycoforms

• Compound Development DoE’s using Continuous Feed Strategy

• Formalize Data Management
Next Steps

- Model and Execute Control Strategies

- Predicted Control
  - Control model for the multiple variable trajectories for optimum batch productivity with desired quality attributes.
Summary

• Gain Process Understanding and Develop Control Strategies for Monoclonal Antibody Production in Bioreactors

• Build Calibration Sets for Establishing Control Models
  - Design and Execute DoE’s
  - Collect PCS, PAT, At-line, and Off-line Measurements
  - Design Control Models

• Execute Models with Integrated Model/PAT/PCS application
  - Monitor Bioreactor PCS and In-line PAT measurements
  - Automated adjustment of Bioreactor PCS Settings to control batch trajectory for desired product amount and quality.
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Questions?