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

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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 ECI Integrated Continuous Biomanufacturing II Berkeley, CA 01-05 November 2015



Merck's Motivation



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



Facility of the Future CHO mAb Processing Vision at Merck





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



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



- PAT & sampling integration
- Process monitoring and MVDA modeling
- Adaptive/feedback unit operation control
- Robust control strategies
- Connections and piping
- Component engineering
- Component change-outs (filters etc.)
- Liquid and RM management
- Medium-scale operation
- PAT & control implementation
- Batch demonstrations
- Applying facility of the future principles
- Robust manufacturing platform





PRO Lab Timeline





PRO Lab: Fully automated mAb drug substance ĦĦ Media \rightarrow Feed **BioSMB BioSMB** J Delta¥ Oper 9 Vodule 🖧 🖤 🗉 🔢 学 t 🔗 🗿 🚳 🛯 🍠 🎛 👥 🚄 🔶 🔲 🍠 🛄 2 🐸 🎭 🔯 🤗 🌉 0 8 $\langle \phi | \phi \rangle$ Distributed control for all unit ops • PA1 PAF1 TK pH VIF1 TK pH DF2 DF2F TK pH AFXF TK pH VIT AEX1 7.00 pH 7.00 pH Overview & unit-ops level views PA1FB1DP AEX1 FB1 DP Pre-Loop pH 7.00 pH 7.00 pH PAF1 TK Con DF2 FB2 DP AEXF TK Cond VI1 Loop pl Filter Bank 2 Activ Deltay Oper Main: PA1 **Nodule** Main: DF1 🥘 🥌 📗 💩 🖤 🖻 👖 学 E 🤞 🧉 🧄 🔳 🔎 🛄 🛃 🖤 📰 👯 👕 💷 🎭 🖓 🐣 1 8 2 4 🔲 🐸 🍇 🔤 🤗 👹 0 8 **a** III /T 🕵 👥 👙 🎥 🚾 🚝 🌉 PERF TK Acid Pr Depth Filtration 1 PAF1 TK pH **ProteinA** DF1 ProcBreak MCC Skid Perf Filtration ProcBreak Inlet CA 2 6.87 pH PA1 ProcBrea PERF1 TK pH Ctrl DF1 ProcBreak PAF1 TK Cond PA1 FB Out Pres 0.00 * DF1 Filter EM PERF TK Rase Pr PERF1 TK pH 0.50 psi * PA1 ProcBre 11 64 mSk FEED -DF1 FB1 Temp PAF1 TK pH 7.00 pH PAF1 TK Temp CA S 7.00 eH Feed in Progress Switchover in Progre 25.0 0 VIF1 TK pH 20.5 C PERF1 TK Cond -DF1 FB1 DP DF1 FB1 Cond PAF1 TK Cond PA1 FB Out Cond 4.09 50.00 mS/c PROA FEED PAF1 TK Weigh PROA WE1 TK Cond 0.0 pt 50.00 mS/c 50.00 mS/c PERF1 TK Tmp **105** g 1.73 mS/cr 25.0 C DF1 FB1 In Pres DF1 FB1 Mid Pres DE1 FB1 Out Pres PAF1 TK Temp -0.09 mS/c 25.0 C Pressure Flow Rate 3 ml/min 25.0 p 25.0 ps VI FEED VIF1 TK Temp 25.0 psi 50 inH20 PERF1 TK Weight DF1 FB1 In DF1 FB1 Out PA1 FB1 Out PA1 FB2 Out --Concentration Stage PAF1 TK Weight 20.8 C 21.6 C 0.00 kg CA CH .01 M PA1 FB Temp **FA** VIF1 TK Weight 0.00 Tarpon 1 Filter Skid EM 1 DF1 Filter Bank 1 EM FEED -45 g PA1 FB1 DP PA1 FB2 DP PAI FEED DF1 FB2 Temp State: Undefin VI1 Feed in Progress. Fast Speed State FEED 2.4 psi 2.8 ps DF1 Fit Feed Pmp Feeding, Mont Sequence Ide 25.0 DF1 FB2 DP DF1 FB2 Cond PA1 FB1 In Pres PA1 FB2 In Pres CA Q DF1 TK Buff Pm DE1 TK Waste W 9.6 psi 0.0 pei 50.00 mS/cm Buffer 10.1 ps DE1 EB2 In Pres DF1 FB2 Out Pres DE1 FR2 Mid Pres PA1 FB1 In DF1 WASTE PA1 FB2 Ir 25.0 ps 25.0 psi 25.0 ps DE1 ER2 In DF1 FB2 Out CA T CA D 0.00 PA1 TK Buff Pmp CA DF1 Filter Bank 2 EM PA1 Filter Bank 1 EM × PA1 Filter Bank 2 EM 📑 Undefined **FEED** FILT CHANGE REQ ¥ * Ŧ State: FEED Feeding. Monitoring Filters tate: Undefined Waiting for Operator Respo Filter Change Required Procedure ocedure it Droveckure 0.00 mi 0.00 min Operation peration PA1 Batch List View DE1 Batch List View PA1-EM-FILT i DF1-EM-FILT AIC-VI1-PH i 🏒 💇 🖓 2 9 Om AEX1-EM-FILT DF2-EM-FILT i i i 😕 P-SFF1-TK-ACID i P-SFF1-TK-BASE i P-SFF1-TK-CNDM i -SF1-BUFFLSH i / VF1

PRO Lab Layout



- 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





Upstream Operation Performance

Cell Culture Operation



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

Downstream Operations

Protein A Chromatography

Protein A Chromatography

- Predictable reproducible elution
- Low feed pressure
- Accelerated column lifetime







• Guard Filter Performance

Public

- 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*



- End Product Testing transition to Real Time Release Testing
- Real time automated control: process responds to variability & disturbances

Public

- End to end prediction models for complete process



Multi Attribute Method via Peptide Mapping

"Direct measurement of CQA's at molecular level"



PAT UPLC Process Monitoring







• SEC quality and permeate monitoring

Public

- Water soluble vitamins with QDA MS Detector
- Multi-attribute peptide mapping methods installation in 1Q 2016





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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