SINGLE USE AND CONTINUOUS PROCESSING COMPATIBLE - OR MUTUALLY EXCLUSIVE?

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NEW TECHNOLOGIES ARE TRANSFORMING THE WAY WE MANUFACTURE PRODUCT
OUR FOCUS IS TO ENSURE SUPPLY; BUT NEW CHALLENGES OFFER OPPORTUNITIES TO IMPROVE

Past
• Low competition, high margin environment
• Creating capability to produce sufficient biological product was greatest challenge

Present
• Increasing competition with downward cost pressures
• Drug product capabilities progressively more differentiating

Cost, speed and flexibility have become key differentiators

- Maturing capabilities in manufacturing and process development platforms
- Ready access to biomanufacturing capabilities through CMOs
- Biosimilars, new modalities
- International expansion, patient experience
- Increasing cost pressure from patients and payers

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NEXT GEN BIOMANUFACTURING ENABLES FAST AND FLEXIBLE OPERATIONS TO MEET CHANGING NEEDS

Conventional

Key Enabling Technologies
- High titer processes
- Single-use systems
- Modular design and construction
- Connected processing
- Online / At-line analytics
- Real-time remote monitoring
- Raw material variation control

Flexible

SINGLE USE – ADVANTAGES FROM ASTM-FDA WORKSHOP

- Offers flexibility (changeovers, scale-up/number up)
- Reduced risk of contamination
- Increased productivity
- Cost savings (capital, facility utilization)

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CONTINUOUS MANUFACTURE (CM)

- FDA strongly supports advancement of pharmaceutical manufacturing technologies, including CM
- CM is expected to benefit both patients and industry
- FDA recommends early and frequent discussion of advanced manufacturing and analytical approaches with the Agency prior to submission
- FDA is fully staffed, capable of and ready to review CM applications

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SINGLE-USE (AND OTHER) TECHNOLOGIES ARE DEPLOYED TO VARYING EXTENT

- Seed train
- Continuous perfusion cell culture
- Periodic Cycling Capture Chromatography
- Virus Inactivation in plug-flow reactor
- Periodic Cycling Polishing Chromatography 1
- Periodic Cycling Polishing Chromatography 2
- Periodic Switching Virus Filtration
- Single Pass TFF Concentration & Formulation
WE ARE ADDING FLEXIBILITY TO OUR MANUFACTURING OPERATIONS WITH THE INVESTMENT IN AMGEN SINGAPORE

Modular with Connected Processing

Single-use technologies

Real-time Remote Monitoring

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AMGEN’S RECONFIGURABLE MANUFACTURING SYSTEM INCORPORATES ELEMENTS OF BOTH APPROACHES

- High cell culture productivity in small bioreactors
  - Significantly reduces facility footprint

- High utilization of single-use equipment
  - 95% of product contact surface is single-use

- Connected purification processing
  - Eliminates product pools between unit operations

- Integrated manufacturing layout
  - Smaller facility impact to process and equipment changes
BENEFITS OF DESIGN MITIGATE RISK OF PRODUCT CONTAMINATION

• Closed operations
  – Aseptic connectors or aseptic tube welds
  – Gamma-irradiated components and tubing
  – No process transfer piping

• Single-use equipment
  – No process transfer piping
  – No stainless steel hold tanks or reactors in central suite
  – 95% reduction in surface area requiring cleaning
WHY CONTINUOUS MANUFACTURING (CM)

- Modern approach amenable to QbD
  - Potential for unprecedented control
- Advantages of agility and flexibility to meet patients needs
- Shorter times for development
- Cost and operational advantages
- Major step towards “Desired State”

CONTINUOUS PERFUSION CELL CULTURE

- Continuous perfusion is well established for many years
- Several established cell retention technologies allow management of cell age and viable cell count
- Limited by cell line stability
- Goal: maximum productivity with minimum perfusion rate
ASPECTS OF CONTINUOUS PERFUSION

Sources of variability

• Cell growth
  – Cell bleed
  – Product loss
  – Volume loss

• Fouling of cell retention
  – Product accumulation
  – Reduced product output
FOULING OF CELL RETENTION DEVICE

Fouling of cell retention device can lead to drop in product sieving
⇒ varying product concentration in harvest stream

Effect of product sieving (S) in a cell retention device with fouling on product concentration in the reactor (P) and in the harvest stream (P_H).
DOWNSTREAM TYPICALLY NOT ALL FLOW THROUGH

- Filters and membrane adsorbers limited by fouling (change out)
- Hold steps (viral inactivation) can be simulated in plug flow mode
- Bind and elute through continuous load/discontinuous elution and column turnaround
- Provides necessary concentration

Design requirement: Load duration > duration for $\Sigma$ of all other steps
CONTINUOUS CYCLING CAPTURE CHROMATOGRAPHY

- Capture is capital intensive in mAb production
- CCC allows utilizing smaller columns and buffer savings
- Biggest benefit for low load titers
ADVANTAGE OF CONTINUOUS CHROMATOGRAPHY

- Continuous load stream minimizes load velocity & surge volumes
- Catching load breakthrough allows higher loading per column and higher load flow rates
- Higher loading per elution cycle results in lower buffer consumption

![Graph showing load capacity utilized in batch chromatography and extra load capacity utilized in 3C-PCC. The graph illustrates the load amount breaking through to column 2 in 3C-PCC and the usual load limit for batch chromatography.]
VIRUS INACTIVATION IN ALTERNATING BATCH TANKS

Conservative option with existing technology

• Simplest and robust design by parallel batch operations in alternating tanks
  – One tank collects output of capture step while second tank performs inactivation
  – Tank sizes defined by inactivation duration and volumetric input stream
Virus clearance claim is dependent on residence time control
Long exposure time targets lead to large equipment
May need periodic verification of absence of early breakthrough. Challenging detection of trace breakthrough
CONTINUOUS POLISHING CHROMATOGRAPHY

Bind and Elute operations

- Unfavorable operational design due to high load concentrations
- Complex equipment

Flow-through operations

- Simple operational 2 column design with long load phase and quick turnaround phase
- Design focus on minimizing wash losses and product retention

If viral clearance is claimed for operation, recycling of side fractions is impossible
VIRUS FILTRATION

- Inherently discontinuous
- Consecutive filtration operations to allow continuous feed
- Simple setup analogous to flow-through chromatography
- Low flow rates favorable for filter sizing
- Closed processing poses challenge
CONTINUOUS CONCENTRATION & FORMULATION

- Simple concentration operation
- Complex formulation operation
- Buffer volume management favors multi-stage countercurrent design

Multi-stage concentration

Feed | Permeate | Permeate | Permeate | Concentrated Product

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INTEGRATION OF OPERATIONS

- Operations may need feed adjustments
  - Complex equipment & automation
- No hydrodynamic coupling of operations
  - Surge tanks between operations
- Representative sampling
  - Sanitary sampling tools with varying need for sanitary design and sampling frequency
- Data collection and analysis
- Fault recovery

100% time utilization of multiple parallel operation affects labor model
FAULT RECOVERY

- Redundant equipment
  - Low equipment utilization
- Product stream collection
  - Equipment overdesign => Low equipment utilization
  - Intermediate pool stability
  - Procedural overhead => wide design space needed
- Product stream to waste
  - Loss of productivity
DEVELOPMENT & IMPLEMENTATION TIMELINES

• Expect added time during initial process development
  – Development time needs to be off critical path
  – Allows for complexity of automation and control

• Possible efficiencies for process characterization
  – Steady state condition shifts can be shorter than fed-batch reactor duration

• Potential for significant facility impact due to extended process performance qualification duration
**HOW GOOD IS THE FIT WITH SINGLE-USE EQUIPMENT?**

- Continuous operation lowers intermediate volumes, tank sizes, pump sizes
  - reduced equipment sizes enable single use equipment for commercial production scale
- Continuous production stresses robustness of single-use equipment
  - need to determine and qualify duration of a campaign
- SUS add setup labor and risk vs fixed setup capital cost
  - compensated by flexibility for multiple products
CHALLENGES OF USING SINGLE USE

- Leaks
  - Introduced during manufacture, shipping and handling
  - Need for integrity testing methods
- Compatibility with biologics
  - Extractables, leachables, particulates
- Suppliers and interchangeability of components
  - Connectors from different suppliers
  - Supply chain and change notification, supplier CoA’s, supplier criticality
- Packaging
  - System integrity at the supplier and in the manufacturing environment – maintenance of sterility
- Lack of guidance on the use
- Disposal

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https://myastm.astm.org/KEY_DOCUMENTS/PDF_FILES/e550000wrksh16.pdf
AREAS FOR FUTURE DEVELOPMENT FOR CONTINUOUS

- Continuous drug substance manufacture
  - Biotech (large molecules) products
  - With continuous crystallization for small molecules
- Continuous manufacture of integrated drug substance and drug product
- Real time process control (monitoring and adjustment)
  - Use of feedback and feed forward control, use of predictive models for process control
- Multivariate approaches
- Sampling and statistical criteria (large N)
- Use of electronic systems and electronic batch records
- Cleaning – for sterile products, multi-use CM facilities, etc.
- More equipment designed for CM
- Robust PAT tools

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CONCLUSIONS – IT DEPENDS

- Some molecules will be more amenable than others
- Some processes will be easier to integrate than others
- Control of fully continuous process needs sophisticated process definition
- Facility implementation is less flexible than batch process
- Biggest benefit for constant fixed demand production
- Focus implementation on most value added unit operations
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TYPICAL CYCLING SEQUENCE
SYSTEM DESIGN FOR VARIABILITY

Continuous perfusion reactor has expectation of variability in productivity, cell growth, & cell retention …
Model variability of RSD=10% for productivity & cell growth, cell retention variability

- Productivity => affects load concentration
- Cell growth => affects volume and product losses by cell bleed
- Cell retention variability: sieving affects product concentration

A system designed to handle higher than nominal volume and mass, will run continuously at a fraction of capability
DESIGN TO ACCOMMODATE PROCESS VARIABILITY

- Design contingencies:
  - 40-50% for mass variability
  - 10% for volume variability
  - 20% for resin lifetime changes

Minimize variability in cell culture productivity, cell growth, & cell retention to maximize productivity

Target may best be set to NOT be able to process best case upstream output
EQUIPMENT ASPECTS: PROCESS TURNDOWN

Favorable for early process steps
• Continuous operation lowers intermediate volumes, tank sizes, pump sizes => lower capital investment

Unfavorable for final process steps
• Low process volumes make infrequent processing of larger volumes efficient
EQUIPMENT AND PLANT UTILIZATION

Overdesign affects utilization differently

• Batch: equipment executes batch in less time than allocated => equipment is idle between batches
  – Time utilization < 100%
  – Capacity utilization = 100%

• Continuous: equipment is never idle but only rarely operates at design capacity
  – Time utilization = 100%
  – Capacity utilization < 100%

Continuous operation needs wider operational design space