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Workshop 3: Business Cases for Integrated and Continuous Biomanufacturing

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Summary of ICB IV Workshop 3: Business Cases for Integrated and Continuous Biomanufacturing

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Integrated and Continuous Bioprocessing IV
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Workshop 3 Abstract

Utilization of traditional batch processes is so entrenched in the biopharmaceutical production landscape that transitioning to a new approach, no matter how efficient or productive, is challenging. Integrated, continuous manufacturing (CM) promises higher per-bioreactor vessel productivity, smaller downstream footprints, and more consistent product quality than batch processing. However, realization of these benefits depends greatly on the scenario at hand and the proposed manufacturing strategy. A compelling business case must be presented in order to consider making the transition to CM from the traditional manufacturing approach. The degree of process integration, the target scale and facility vision toward automation, as well as the strategy toward implementation with respect to portfolio maturity are key actors to consider. This workshop will explore some of these key strategic factors and how they influence the business case for CM.

Agenda

- Workshop Welcome
- Introductions of Co-chairs
- Pre-workshop Survey
  - Review of survey questions 1-3
- Reading of workshop prompts 1-5
- 20 minutes of break-out discussions
  - 2 tables for each of prompts 1-4, no takers for prompt 5
- 50 minutes of group discussion (10 minutes per prompt)
- Wrap up and thanks

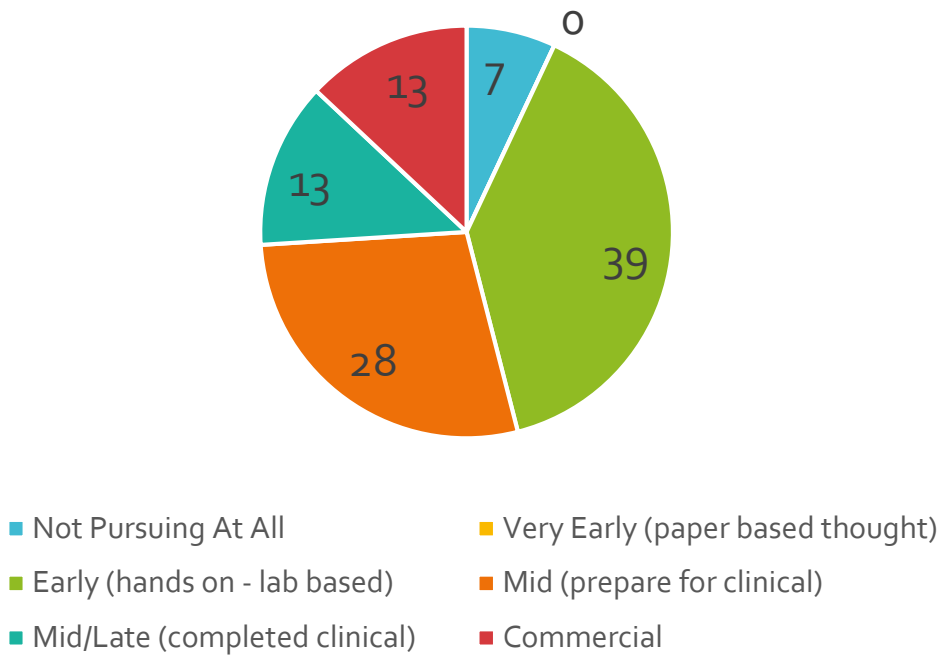
Pre-workshop Survey Questions

1. Is your company considering continuous manufacturing for early stage or late stage programs?
   a. early
   b. late
   c. both
2. How far along is your company in adopting Continuous Manufacturing?
   a. not pursuing at all
   b. very early- ie paper-based thought experiment
   c. early- hands-on lab-based process development
   d. mid- preparing for clinical
   e. mid/late- clinical mfg has occurred
   f. commercial
3. Do you foresee GMP manufacturing using a continuous manufacturing vendor-supplied platform or a custom, in-house developed platform?
   a. Vendor(s)
   b. In-house
4. What do you feel is the single biggest benefit of continuous?
5. What do you feel is the single biggest hurdle for implementation of continuous?

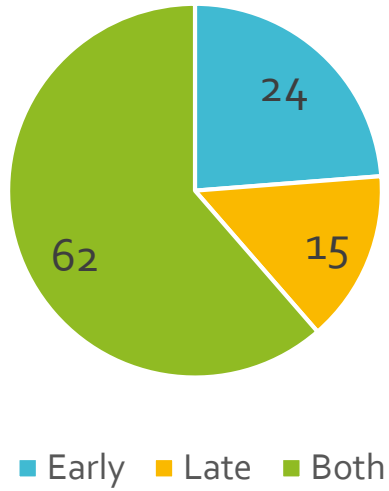
Survey Answers: By the Numbers

62 Participants in Attendance

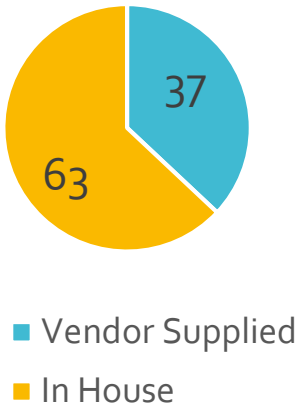
Current State



Late stage vs Early stage



Platform



Benefits


Resin
Production
Reduced
Facilities
Clinical
Control
Lower
Capture
Right
Facility
Development
Scale-Up
Affinity
Leading
Equipment
Enabling
Molecules
Savings
Single
Scale
Capex
Breakthrough
Transfer
Size
Legacy
Costs
Use
Market
Time
Speed
Cases
Cost
Product
Risk
Availability
Tech
Support
Faster
Increased
Designation
PAT
Flexible
Delay
Flexibility
Labile
Increase
Agility
Quality
Commercial
Real
Operational
Investment

Risks


Regulatory Endorsement
Energy
Quality
Resources
Internal
Deviations
Develop
Time
System
Conservatism
Robust
Productive
Established
Automation
Case
Associated
PAT
ICB
Aversion
Different
Validation
Use
Suitable
Capital
Facilities
Existing
Acceptance
Control
Legacy
Digital
Process
Cost
Space
Lack
Change
Activation
Integration
Hesitations
Comfort
Complexity
Chain
Contamination
Continuous
Management
Finding
Platforms
Fear
Connected
Business
Product
Operation
Science
Technical

Prompts

1. What do you think are the key business drivers currently influencing the biopharmaceutical industry: footprint reduction, speed to market, speed of production, speed of expansion, improved product quality, reduced capex or opex, other? In what way does continuous manufacturing meet the challenges associated with these business drivers?
2. What is the ideal level of integration for unit operations? Where are the biggest benefits to integration (eg linking perfusion bioreactor to capture columns)? What might be some of the main business case arguments which inform these decisions?
3. What are the major risks for a business to add capability of integrated continuous processing: replace/retrofitting of existing facilities, investment in greenfield, regulatory concerns, technology development, supply chain security, etc.
4. What stage of a program is best suited for implementation of continuous processing (early, late, post approval) and why? Does the degree of integration change based on the time of implementation in the product lifecycle?
5. Batch definition and associated analytical testing strategy has a major impact on the overall cost, speed to market, and supply chain strategy. How should the definition and strategy be defined to balance the benefits and risks associated with continuous manufacturing?

Prompt 1- What are the key business drivers for ICB?

- ❑ Reduction in Cost of Goods/Risk
  - not over-producing at FB large scale
  - for low-demand modalities
  - Reducing CapEx/OpEx (especially by reducing size of facility)
  - Reducing $/m² or $/yr vs $/g
- ❑ Agility
  - CMO perspective
  - Single use
  - Access (less complex Supply Chain, more distributed manufacturing)
- ❑ Modality-specific drivers
  - bsAB- stability
  - LV- stability
  - mAb- high dose requirements, large patient populations. Higher titer is advantage here
- ❑ Cost pressure for healthcare
- ❑ Improved and/or more consistent product quality, enabled by PAT
- ❑ Alleviate capacity constraints of network
- ❑ Streamline control strategy (scale-out vs scale-up no change in process)
- ❑ At-scale development
- ❑ De-bottlenecking DSP
- ❑ Demonstrated benefits in other industries (auto, semiconductor, etc)

❖ Many points refer to extensive implementation of continuous, continuous/connected Upstream, and/or downstream may be more easily quantified

Prompt 2- Ideal level of Integration? Biggest Benefits?

- The problem being solved by integration often defines level of integration, each company will dictate the extent of integration for themselves. May be based on stage at which continuous is first used
- Vial to vial (ideal)– lots of back-and-forth discussion on this point, generally agreed that it really depends on the molecule and indication
  - Including analytics
  - Challenge – if have different Drug Product presentation could be different
  - API Shelf time is now not applicable so inventory only controlled on DP Stability
- Process until stable intermediate for mAbs
- Reduces affinity capture resin costs
- Most beneficial for a new facility or a new process
- Most beneficial steps to connect:
  - Perfusion- capture (especially from an intensified perfusion bioreactor)
    - No harvest, no centrifuge or filters
  - Buffer prep from concentrate
  - (stable hold points) neutralized VI
  - Automated sampling
  - Analytics on the floor
  - Polishing-rest

Prompt 3- What are the major risks of adding ICB capability?

- Capex
  - Retrofitting: costs and downtime
  - Capex concerns at outlay to convert
- Equipment
  - Familiarity of new equipment and processes
  - Immaturity of technology
  - Lack of standardization of equipment
- Need to develop relationships with new vendors
  - Nonstandardized supply chain components
  - Management of inventory
  - Highly reliant on single sources components
- Supplying both batch and ICB with enough production to fill all facilities.
  - Having to decide which type of facility to develop toward – two parallel tracks?
  - Dilution of resources to develop processes
- Regulatory Risks
  - Control Strategy
  - Process Validation
  - Comparability (late stage)
  - Bioburden control
- Highly automated
  - How to handle deviations
  - How to handle pauses when running in constant flow
- Optimization for changing portfolio
  - Quantification of benefits
  - Product / pipeline requirements
  - Importance of Cost reduction
- Automation
  - Requires platform from the beginning to be automated
  - Automation expertise required
  - Lack of standardization exists
  - Choice of CMOs becomes more limited

Prompt 4- What process stage is best for ICB? Is integration extent based on process stage?

- Implementation during product lifecycle is based on portfolio distribution and capacity availability
- Why Early Phase
  - Decrease comparability risk and will allow program to develop over time
  - FB to perfusion transition during late stage could be challenge
  - Many technologies well established, can be adopted early
  - Regulatory expectation still unknown
  - Attrition in the clinic can delay tech introduction
- Why Late Phase
  - Takes speed to clinic off critical path
  - Ability to achieve a lower additional capex cost
- General Challenges:
  - Steady State Perfusion can be difficult to achieve, increase risk of failures/ interruptions, could cause bigger timeline delays
  - Infrastructure for ICB takes time to develop
  - Shorter dynamic perfusion might be faster for timeline to clinic, but may be hard to transition to steady state perfusion during late stage development
  - Novel modalities may be more difficult to express/ purify

#5 Batch definition

- Batch definition was not problematic
- Batch could be defined in multiple different ways, but based on company need
  - Sample load could be decreased if deemed to be the best way to define a batch
- Flexibility of batch is available
- More details to be provided in ICHQ13

Entire Workshop Summary

- No "one size fits all" solution, business case highly dependent on individual company needs
- Benefits depend on portfolio (stage and modality focus) and current capacity/capabilities
- Cost of goods (including CapEx, $/g, g/m^2) reduction by ICB was brought up repeatedly, by multiple companies as a key driver
- Business cases have been successful – progression over two years on implementation (including GMP implementation session)