A Forum Report on Continuous Manufacturing for Biologics

CMC Strategy Forum
Jan 28, 2019 in Washington, DC

Andrew Chang, Ph.D.
Vice President, Quality and Regulatory Compliance, Novo Nordisk Quality
Novo Nordisk A/S
Agenda

1. Overview the Forum Program
2. Key Learnings: Small Molecules vs. Biologics
3. Panel Discussion Outcome
Opportunities and Challenges

Central Questions Raised for planning the CMC Strategy Forum on Continuous Manufacturing for Biologics

- What are the business opportunities for introducing continuous manufacturing for biologics?
- What are current gaps and hurdles for implementing continuous manufacturing for biologics?
- What levels of automation in biopharmaceuticals is needed for continuous manufacturing?
- What novel analytical technologies are needed for continuous manufacturing?
- What can we leverage from our knowledge of small molecule continuous manufacturing to enable or accelerate continuous manufacturing for biologics?
The Forum Overview (1)

Morning Session (Co-Chairs: Lindsay Arnold, MedImmune and Min Zhu, Boehringer Ingelheim Biopharmaceuticals)

- Industry Perspectives
  - Small molecule experience - Thomas Garcia, Pfizer, Inc.
  - Continuous biomanufacturing: experience and emerging opportunities - Erik Fouts, BioMarin Pharmaceutical Inc.

- Analytical Technologies
  - Control of continuous bioprocess (PAT) - Mark Brower, Merck & Co., Inc.,

- Panel Discussion
  - Participants will discuss pre-identified issues and brainstorm new ideas and potential resolutions
    - Mark Brower, Merck & Co., Inc., USA
    - Manon Dubé, Health Canada, Canada
    - Erik Fouts, BioMarin Pharmaceutical Inc., USA
    - Thomas Garcia, Pfizer, Inc., USA
    - Ingrid Markovic, Genentech, a Member of the Roche Group, USA
    - Eike Zimmermann, Boehringer Ingelheim Biopharmaceuticals, USA
The Forum Overview (2)

Afternoon Session (Co-Chairs: Manon Dubé, Health Canada and Arne Staby, Novo Nordisk A/S )

- Automation Approaches and Gaps
  - BioPhorum technology roadmap on continuous downstream processing for biopharmaceuticals - Carl Carlson, Exyte
  - Integrated continuous biomanufacturing platform - Marina Hincapie, Sanofi

- Equipment and Facilities
  - Advances in next generation drug substances manufacturing of biologics - Ganesh Vedantham, Amgen Limited

- Business Case Studies
  - iSKID: A Next-Generation Continuous Manufacturing Platform for Biologics - Nuno Fontes, Boehringer Ingelheim Biopharmaceuticals

- Panel Discussion
  - Participants will discuss pre-identified issues and brainstorm new ideas and potential resolutions
    - Nuno Fontes, Boehringer Ingelheim Biopharmaceuticals, USA
    - Steffen Gross, Paul-Ehrlich-Kustitut, Germany
    - Stephen Hadley, The Bill and Melinda Gates Foundation, USA
    - Marina Hincapie, Sanofi, USA
    - Ganesh Vedantham, Amgen Limited, Puerto Rico
    - T.G. Venkateshawaran, Merck & Co., Inc., USA
Acknowledgement

Forum Co-Chairs
• Joslyn Brunelle, CDER, FDA
• Andrew Chang, Novo Nordisk Inc.
• Manon Dubé, Health Canada
• Rick Lu, AstraZeneca

Session Co-Chairs
• Lindsay Arnold, MedImmune, A member of the AstraZeneca Group
• Min Zhu, Boehringer Ingelheim Biopharmaceuticals
• Manon Dubé, Health Canada
• Arne Staby, Novo Nordisk A/S

Speakers
• Thomas Garcia, Pfizer, Inc.
• Erik Fouts, BioMarin Pharmaceutical Inc.
• Mark Brower, Merck & Co., Inc.
• Carl Carlson, Exyte
• Marina Hincapie, Sanofi
• Ganesh Vedantham, Amgen Limited
• Nuno Fontes, Boehringer Ingelheim Biopharmaceuticals
• Carmilia Ramirez, Ajinomoto Bio-Pharma Services

Scientific Organizing Committee
• Lindsay Arnold, MedImmune, A member of the AstraZeneca Group
• Alexey Khrenov, CBER, FDA
• Joseph Kutza, MedImmune, A member of the AstraZeneca Group
• Arne Staby, Novo Nordisk A/S
• T.G. Venkateshawaran, Merck & Co., Inc.
• Veena Warikoo, Roche Diagnostics GmbH
• James Weidner, Amgen Inc.
• Min Zhu, Boehringer Ingelheim Biopharmaceuticals

Panelists
• Mark Brower, Merck & Co., Inc.
• Manon Dubé, Health Canada
• Erik Fouts, BioMarin Pharmaceutical Inc.
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• Ganesh Vedantham, Amgen Limited, Puerto Rico
• T.G. Venkateshawaran, Merck & Co., Inc.
• Bobo Qiao, CBER/FDA
Why Is CM Drawing Attention?

- Are there any problems with conventional batch manufacturing?

There is nothing wrong with batch manufacturing. Batch production remains as one of the manufacturing methods to be used in the future. However, CM may offer us what is difficult to achieve in batch manufacturing.

Expectations for CM

- Flexible manufacturing
  - Production in response to demand
- Detectability of poor quality products
  - Prevention of drug shortage problem
- Prevention of waste
  - Promotion of green chemistry
- Cost reduction

Yoshihiro Matsuda (PMDA) Regulatory Chair for ICH Q13, 4th PQRI/FDA Conference
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Session 1

INDUSTRY PERSPECTIVE
ANALYTICAL TECHNOLOGIES
Industry Experience with Small Molecules
Thomas García, Pfizer Inc.

- What is continuous manufacturing (CM)?
  - Input material continuously fed to process
  - Material is transformed in the process
  - Output is continuously removed from the process
  - At least two unit ops in a row

- Applications for small molecules
  - API to DP (DP applications mainly for solid oral dosage forms.)
  - Hybrid approach: batch + continuous unit ops

- Meet early and frequently with the FDA is the key for success
Industry Experience with Small Molecules (2)
Thomas García, Pfizer Inc.

- Batch definition
  - May be based on number of units or throughput, or consumption of input material
  - Incorporate a validated range

- Process Validation
  - Depart from 3X tradition batches and apply 3-stage approach using Continuous Process Validation (CPV)
    - Must demonstrate control at beginning, end and over time
  - Shutdown and startup considerations
  - Demonstrate State of Control
Industry Experience with Small Molecules (3)
Thomas García, Pfizer Inc.

- Stability – define number and size of batch required for implementation and post-approval changes (PACs)
- Product lifecycle management (*more questions than answers*)
  - Can it be part of Pharmaceutical Quality Systems instead?
  - Are PACs necessary? How often should sponsors notify the regulatory agency?
- Tech transfer
  - How to demonstrate “like for like” for non-identical equipment?
- Contingency plans when components are down
Industry Experience with Biologics
Erik Fouts, BioMarin Pharmaceutical, Inc.

• Limited CM experience in biologics
  • hybrid systems in place: continuous cell culture with batch purification

• Points to Consider for Perfusion Cultures
  • Maintains stability of proteins and host
  • Increases productivity
  • Smaller foot-print and costs
Industry Experience with Biologics (2)
Erik Fouts, BioMarin Pharmaceutical, Inc.

- Scenarios for extending CM processes
  - Continuous chromatography steps using multiple single-use columns
  - Semi-Continuous processes from perfusion step to secondary sterile containment of harvest material for input into chromatography steps
  - On-line/in-line analytical capabilities

- Challenges
  - PAT is behind technology advancements compared to production technologies
  - Molecular complexity increases complexity of design space
  - Automation produces significant increase on data outputs and require complex systems for monitoring (e.g. multivariate, predicting monitoring)
• Eliminates need for sampling, chain of custody, QC testing and reporting in electronic systems
• Integrates raw materials spectroscopy tools - Raman
• Raman for nutrients, metabolites and VCD
• Online LC – aggregates, impurities, concentration
• ELISA and sensors – potency, biomass
• Multi-attribute Methods – identity, glycans, process impurities, product impurities
• Product Attribute Controls - MVDA
• Rapid Micro methods – sterility, bioburden, air monitoring
Session 1: Panel Discussion – Q/A

- Similarities between biologic and small molecule processes
  - Use of reactors
  - Use of chromatography steps for purification
  - Use of filtration processes
  - Use of hybrid processes
- Major differences
  - Prior knowledge is richer for small molecules on CM
  - Process monitoring and analytical tools

Dr. Rapti D. Madurawe, FDA/CDER/OPQ/OPF, 2019
DIA CMC Workshop
Session 1: Panel Discussion- Q&A (2)

- How do you tailor analytical method development and validation for CM for inclusion in a new marketing application? For post-marketing approvals?
  - For biologics, the intent should be to submit application using CM platform. Not an option to submit both batch process and CM for manufacturing
  - For small molecules, it is more feasible to incorporate both processes. It prevents issues with markets that will not approve a CM process
  - Perfusion is usually an approach to get faster to the clinic. The intention is not to go back to batch processing.

- Hybrid processes seem easier to introduce as scope of change is narrower, and allows use of existing facilities.

- What is the argument for introducing PAT for a highly characterized process with already minimized analytics?
  - It is necessary to demonstrate cycle consistency and process understanding to determine the extent of PAT.
Session 1: Panel Discussion- Q&A (3)

- **What is the opinion for comparability exercise needed to switch from batch to CM?**
  - It is important to meet often with the regulators.
  - The expectations for comparability do not change. You have to define design space and critical quality attributes.
  - It is necessary to demonstrate comparability of commercial material to clinical material.

- **Regarding future of CM, where do you see minimization of product testing and more reliance of in-process testing? Do you anticipate Q13 will address those questions?**
  - Use of modeling is critical for real-time release. Tests may be streamlined to determine which testing is necessary.
  - An argument can be made on the submission to use minimized release testing and rely on in-process testing.
  - Intent is to incorporate elements of validation in Q13 to potentially realize real-time release.
Session 1: Panel Discussion - Q&A (4)

- What are the arguments to push for CM of mAbs? Current process highest cost is Protein A resin, all else is fairly inexpensive
  - Reduction of bioreactor size
  - Reduction of chromatography resins
  - Need to consider demand and use of the mAb therapeutic
    - Current process for high demand
    - CM for low demand products
BioPhorum Technology Road Map: CM for Downstream Processes for Biopharmaceuticals
Carl Carson, Exyte

• Charter on Continuous Downstream Processing
  • In scope – definitions, business case, gap analysis, regulatory considerations
  • Out of scope – technical solutions

• Working on a white paper, focusing on
  • Technology Gaps
  • Bioburden Control
  • Multi-column chromatography, continuous flow-through column separation
  • Continuous or semi-continuous flow to VI
  • Continuous VF, UF/DF, formulation
  • Continuous buffer preparations
  • On-line monitoring and instrument probes
  • Start-up
  • Automation
  • Leveraging benefits for other processes (e.g. cell therapy)
Integrated CM Bio Platform (ICB) - Addressing Challenges in Automation and Gaps
Marina Hincapié, Sanofi

• mAb platform hybrid approach
  • Continuous process from perfusion through mAb capture steps. The rest of the process is batched
• R&D process is developed at the same scale as manufacturing, reducing tech transfer risk

Approaches used
• Chemically defined-media increases cell density and productivity
• A state of control is maintained for 30 days

Challenges with developing end-to-end process at-scale
• Synchronizing flow rate for purification with perfusion rate
• Slow establishment of PAT
• Maintaining sterility
• High cost of implementation
Integrated CM Bio Platform- Addressing Challenges in Automation and Gaps
Marina Hincapié, Sanofi

- FTIR provides excellent prediction models for attributes such as titer, charge variants, aggregation compared to off-line methods

- Issues with PAT
  - Great amount of data collected
  - Data mining and identifying critical attributes requires complex models
  - Need integration for bioburden detection
  - Need autoclavable probes
  - Automation challenges connecting acquisition between different hardware and software
Advances in Next-Gen CM Platform for Biologics
Ganesh Vedantham, Amgen Manufacturing Limited

- Next-Gen Facility benefits
  - Reduced footprint in size
  - Manufacturing at less cost and less time
  - High productivity in small reactors
  - Single-use bioreactors – 95% surface contact is single use
  - Connected purification processes; no pool vessels needed
  - Cell culture and VF is a closed process.
  - Closed processes allows most operations in ISO 9
  - In-line and at-line testing
  - Mixing vessels are single-use
  - Harvest technologies for high-density cell culture
    - Flocculation at end of production with cationic properties with minimal filtration steps for clarification (4 hr process)
Advances in Next-Gen CM Platform for Biologics
Ganesh Vedantham, Amgen Manufacturing Limited

- Downstream Process: Connected Process
  - Large pool vessels not required
  - Column equilibration occurs in parallel with previous purification step
  - Column cleaning occurs right after purification process step
  - UF/DF steps was used to control the upstream purification processes
- Process and product control using real-time analytics based in light scattering technology
- Microbial control is achieved by using the closed process and systems
  - Pool holds are not necessary, thus reducing potential for microbial proliferation
  - Single-use vessels and connectors eliminate liquid hold ups on pipes and tanks
- Reduced environmental impact
  - Less water utilization, reduced CO2 production, reduced utilities in mostly ISO 9 environment
iSKID: Next-Gen CM Platform for Biologics
Nuno Fontes, Boehringer Ingelheim Pharmaceuticals in collaboration with Pfizer

• Business Drivers
  • Productivity – up to 30-60 kg from the same cell line used for fed batch; 5-10X more material than fed batch
  • Reliability – enables single-use; no CIP/SIP required; more automation/less human errors
  • Flexibility – enables faster response for clinical demand; delays investment for pivotal trails; less re-supply campaigns
    • CONS – less manufacturing experience by PPQ/BLA
Session 2: Panel Discussion - Q&A

Is the industry ready for CM? RoW and RoEU?
- Not quite. We are still working with coming up with solutions to develop solid processes.
- Not ready yet for full CM, but close for hybrid processes.
- Technology is evolving rapidly and we hope the technical regulatory challenges are solved quickly.
- We have basic elements of CM in place for 2 decades, so we should not think we are not ready yet.
- PAT and sensors are not quite there yet.

How was comparability assessed for Amgen’s CM process vs commercial process? Were elements of Q5E used?
- Elements of Q5 were assessed and a single CQA from commercial parsed out from consideration (glycation = non-CQA for CM process). Glycosylation was controlled given the flexibility of producing media. pK studies were included in comparability package. CM facility and process were licensed successfully.
- Active consultation with several agencies was employed for the approach.
Session 2: Panel Discussion - Q&A (2)

- Now that Amgen’s CM processed is approved, what will be the comparability approach for transferring the processes to other facilities?
  - No clinical comparability will be assessed for this one process/product. Only analytical comparability will be assessed. This approach will be discussed with multiple regulatory agencies.

- Based on Amgen’s experience in Singapore, would you consider moving the sterile boundaries for the process?
  - It is best to continue with the segregation and no future plans to eliminate the boundary.
Amgen CM process:

- **For DSP, do you use closed equipment or is it placed in an isolator? Have you received challenges from inspections/lessons learned?**
  - No isolators are used in this facility.
  - Initially, there were leaks that needed rectification. Dealing with vendors was key to resolve this issue.
  - For RoEU the approach is to inspect on site with various support team members (assessors) to truly understand the process before evaluating.

- **Does eliminating hold times result in less flexibility for manufacturing process?**
  - Amgen has chosen not to hold, because chromatography steps are efficient.
Session 2: Panel Discussion - Q&A (4)

For regulators:

**What kind of information are you looking for in a submission?**
- Establish a clear difference between regular and integrated process
- Demonstrate Chrom capacity and control of quality attributes
- Demonstrate with validation input, outputs and capacity
- Show how to investigate process failures (e.g., filter integrity failures)
- Real-time data to demonstrate modelling is accurate
- Existing guidance must be followed

**Do you foresee a convergence of models for CM?**
- All 4 approaches presented today had a different flavor to them, because IP will rarely be shared by companies
- We need to come to a harmonized nomenclature for CM. Harmonize the term “integrated”, for example.
How do you segregate the non-conforming material when the analytical results are far behind the CM process step?

- It will depend on the definition of a “batch”. Pool of material, pooling rate, etc. The data have to be representative of the entire batch.
- It is a reality for non-CM processes to discard material if contamination cannot be traced back to a particular step or time. The same should apply to CM.
- This decision must be taken in conjunction with the regulatory agency.

How many failures in the CM process can be tolerated before scrapping the material?

- It’s not about the number, it is about investigation, root cause determination and addressing/controlling the issue.
Are we focusing on the right attributes picked up by P.A.T.? Should we be focusing on controllable quality attributes?
- PAT is not appropriate at early development of process. It makes more sense to use PAT after there is a good working understanding of the process.

Seems like PAT methods are developed by PD, not by AD. Is this a true observation?
- At Sanofi, BI and Amgen, PAT method development belongs in the analytical space. Parallel assessments between off-line methods and PAT are performed by AD.
- It should be a combined effort. PD provides process information, AD develops the method.

How close are we to establish parametric release approach?
- Not close...

Has CBER established a mechanism to enhance pre-dialogue with the sponsors for emerging new technologies?
- CBER encourages sponsors to approach for advice. No mechanism exists similar to CDER’s.
How to obtain sufficient representative material to set specifications and demonstrate process control, if the CM process lends itself to manufacturing less batches/less manufacturing experience?
- May take a similar approach as small molecules, generating worst-case material?
- All would be needed is data from every batch used in the clinic demonstrating safety
- Need to have data at the commercial scale
- Evaluated in a case-by-case basis for those processes with little experience. May incorporate post marketing agreements to revise specifications.