Continuous Biomanufacturing:
Relevant Experiences with Development, Hybrid Implementation, and Emerging Opportunities

Erik Fouts, Ph.D.
VP and Site Head, Novato Operations
• *Continuous Process* - a process where, during normal operation, raw materials are continuously fed into the system at the same time as acceptable product is continuously removed from the system.
Continuous Biomanufacturing (CM):
Relevant Experiences with Development, Hybrid Implementation, and Emerging Opportunities

Why CM for biologics?

Current state of CM

Challenges

Guidance for CM Implementation and LCM

Conclusions & Future Directions
The benefits of continuous manufacturing (CM) have been demonstrated for decades in industries as diverse as steel milling, food, electronics, and petrochemical manufacturing.

CM has the similar potential to improve agility, flexibility, robustness, product heterogeneity, and reduce cost in the manufacture of pharmaceuticals.

These benefits have driven many pharmaceutical manufactures to adopt CM processes for small molecule products.
• 4 approved small molecule applications

Adoption of CM in the biomanufacturing space has been limited, and exists primarily is in the form of a hybrid CM upstream / batch downstream process format for large molecules (i.e. antibodies and enzymes).
For more than 25 years several companies have employed CM technologies.
- Bayer, Janssen, BioMarin, Shire, Merck-Serono, Novartis, Pfizer, Boehringer-Ingelheim (BI), Genzyme-Sanofi, Amgen.....

- Most are CM hybrids (i.e. perfusion cell culture with batch purification)
- Efforts underway to advance CM, including partial and fully integrated bioprocessing.
  - Sanofi CM Skill Center within BioPharmaceutical Development
  - BI/Pfizer iSKID collaboration: Integrated continuous single use process and equipment

- Small and pilot scale CM systems are offered by several equipment manufacturers enabling the development of integrated continuous upstream and downstream processes.
  - Bioreactors, Chromatography, SPTFF, Viral Inactivation, Fluid Handling and Adjustment

- Several recurring meetings (i.e. ECI’s Integrated Continuous Biomanufacturing, CHI’s Continuous Processing in Biopharm Manufacturing)...... CMC Strategy Forums.

- Numerous scholarly and industry review and POC papers.
BIOMARIN’S CONTINUOUS BIOMANUFACTURING JOURNEY
Proven Capabilities For Manufacturing Complex Biologics

- 5 Approved Biological Products
- 2 Licensed & Approved Biological Facilities
- Conducted 7 PPQ Campaigns for Biologics
- >70 GMP Inspections by FDA, EMA, MHRA, HPRA, AGES, ANVISA, PMDA, TMMDA & Others
Developing promising new therapies for patients with rare genetic diseases

<table>
<thead>
<tr>
<th>MOLECULE/INDICATION</th>
<th>PRECLINICAL TESTING</th>
<th>PHASE 1</th>
<th>PHASE 2</th>
<th>PHASE 3</th>
<th>BLA/ NDA/MAA</th>
<th>COMMERCIALIZATION</th>
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<td>FOR MPS I</td>
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<td><strong>VSOR/TIDE</strong> (BMN 111) ANALOG OF CNP</td>
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<td><strong>BMN 307</strong> GENE THERAPY</td>
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- Hybrid CM Process
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<tr>
<th>Product</th>
<th>Approval Date in Japan</th>
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<tr>
<td>Aldurazyme (submitted by Genzyme)</td>
<td>20 October 2006</td>
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<td>Naglazyme (submitted by AnGes)</td>
<td>28 March 2008</td>
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<td>Vimizim (submitted by BioMarin KK)</td>
<td>26 December 2014</td>
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Typical Continuous Perfusion Process

- Media Pump
- Media
- Bioreactor
- Cell Recycle Pump
- Inclined Settler
- Harvest
Typical Hybrid Continuous Biomanufacturing Process

Perfusion Bioreactor → Clarification & Filtration → Concentration

Column Chromatography → pH Adjustment → Column Chromatography

Viral Inactivation → Column Chromatography → Concentration & Formulation

Fill Site
Batch Definition Pictorial

- Multiple Harvest lots are pooled into a single Initial UF lot from multiple Bioreactors
Drivers for Considering Perfusion Cultures

**PROTEIN**
- Labile
- Toxic
- Product Quality

**PRODUCTIVITY**
- Cell Density
- Cell Viability
- Culture Volume
- Flexibility

**PRICE**
- Footprint
- Capital Investment
- Raw Material Costs

Retrovirus has a half-life of 4 hours under normal cell culture conditions due to loss of envelope glycoproteins.

Over-expression of certain proteins (e.g. enzymes) cause a “disease state” in the production cell line resulting in low levels of productivity.
Drivers for Considering Perfusion Cultures

Because of the supply of nutrients, perfusion cultures can achieve up to 10x higher cell densities that can be maintained for extended durations.

Productivity = Area under the curve
Drivers for Considering Perfusion Cultures

PRODUCTIVITY
- Cell Density
- Cell Viability
- Culture Volume

PROTEIN
- Labile
- Toxic
- Product Quality

PRICE
- Footprint
- Capital Investment
- Raw Material Costs

Conventional Fed-Batch Process
- Standard WCB
- 1 mL @ 2 x 10^7 cells/mL
- 125-mL to 10-L
- 50-L SS batch (n – 3)
- 250-L batch (n – 2)
- 2,500-L batch (n – 1)
- 10,000-L SS batch production

Conventional Perfusion Process
- Standard WCB
- 1 mL @ 2 x 10^7 cells/mL
- 125-mL to 10-L
- 20-L Wave Bioreactor
- 250-L Perfusion
What we have Learned Operating Perfusion Cultures

• Steady State Does Not Exist!
  o Cells aggregate over time impacting cell settler efficiency and accuracy of cell density measurement
  o Cell debris accumulates over time which can impact mixing, gas transfer efficiency, cell settler efficiency, cell bleed efficiency, in-line sensors
  o Small changes can have a large cumulative impact over time
  o Cultures require constant monitoring and adjustments

• Maintaining a Sterile Boundary is Critical
  o There are lots of points of potential failure including sample ports, wear & tear on disposable tubing in peristaltic pumps, leaks at sterile tubing welds and sterile connect devices

• While the footprint of the production culture is considerably smaller than traditional fed-batch processes, the fluid handling considerations for media and harvest is considerable
Fluid Management - High Volume

Liquid Handling
• 1.2M Liters of HCCF Generation a Year
• 140,000L of Hold Capacity
• Disposable Pathways (minimal S/S lines)
• Aseptic Connections
• Mechanical Sterile Disconnections
Upstream Downstream Integration

**Perfusion - Batch**

Harvest Storage

Chromatography 1

Chromatography 2

Chromatography 3

**Semi-Continuous**

Harvest Storage

Chromatography 1’

Chromatography 2’

Chromatography 3’
Continuous Chromatography (SMB)

- Single-Use disposable columns
- High throughput
- Maximize use of binding capacity
- Decrease buffer utilization
- Scale up to manufacturing scale
- Real-time tracking
# Platform Comparisons

## Perfusion - Batch

<table>
<thead>
<tr>
<th>Media Prep</th>
<th>Harvest bags</th>
<th>Clarification</th>
<th>Chromatography 1</th>
<th>Batch Purification</th>
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## Semi-Continuous

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<tr>
<th>Media Prep</th>
<th>Harvest bags</th>
<th>Clarification</th>
<th>Surge tank</th>
<th>Inline concentrator</th>
<th>Chrom 1’</th>
<th>Batch Purification</th>
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Facility Scenarios

**Scenario A**
- Bioreactor: 1X
- Surge Tank
- InLine Concentrator
- Chrom 1
- Active Campaign Length: 100%

**Scenario B**
- Bioreactor: 1X
- Surge Tank
- InLine Concentrator
- Chrom 1
- Active Campaign Length: 20% Reduction

**Scenario C**
- Bioreactor: 2.8X
- Surge Tank
- InLine Concentrator
- Chrom 1
- Active Campaign Length: 30% Reduction
Integrated Continuous Biomanufacturing Process

Perfusion Bioreactors + ATF Cell Retention

In-Line Concentration

Chromatography (PCC – SMB)

In-Line pH Adjustment

Chromatography

Viral Inactivation
In line UVC or low pH

Chromatography

Concentration & Formulation SPTFF

Fill Site
Technical Challenges for Complex Biologics

• Maintaining closed system and/or control of bioburden.

• On-line or at-line analytical capability that allows for real time assessment of critical quality attributes spanning the operation and supporting real-time release.

  • Analytical capabilities are significant aspect of CM for biologics.
  • Maturity of PAT lagging behind production technologies.
  • Real time analyses of CQAs is important for all product modalities.

• Adequately address critical areas such as viral safety.
Complexity

Size

hGH
~ 3000 atoms (Mw 22,000)

Aspirin
21 atoms (Mw 180)

IgG Antibody
~ 25,000 atoms (Mw 1,200,000)

Pegylated Proteins
~ 150,000 atoms (Mw ~4,000,000)

3 Coat Proteins + DNA Gene
~ 600,000 atoms (Mw ~4,000,000)

AAV
100 trillion atoms

IgG Antibody
~ 150,000 atoms (Mw 1,200,000)

Pegylated Proteins
~ 150,000 atoms (Mw ~4,000,000)

AAV
100 trillion atoms
• Greater requirements for automation and control when integrating several unit operations.
• **Huge** quantities of data.
• Requires methodology to efficiently translate data into meaningful information.
Traditional Multivariate Monitoring

- Greatly simplifies process monitoring for Operators by combining multiple parameters into a single dimensionless parameter
Multivariate Monitoring With Predictive Modeling

- Identify deviations *before* they happen
- Predict trajectory of important process variables
- Estimate final batch conditions (yield and quality)
MV Monitoring & Control With Predictive Modeling

- Ability to optimize and control process in real time
- Enables feedback control to kpp’s and cpp’s
- Enables control of CQA’s by remaining within design space
NEW QUALITY GUIDELINE – ICH Q13

CONTINUOUS MANUFACTURING OF DRUG SUBSTANCES AND DRUG PRODUCTS

Endorsed by ICH Assembly November, 2018
ICH Q13- Objectives

The new guideline document on CM will:

• capture key technical and regulatory considerations that promote harmonisation, including certain CGMP elements specific to CM,
• allow drug manufacturers to employ flexible approaches to develop, implement, or integrate CM for the manufacture – drug substances and drug products – of small molecules and therapeutic proteins for new and existing products, and
• provide guidance to industry and regulatory agencies regarding regulatory expectations on the development, implementation, and assessment of CM technologies used in the manufacture of drug substances and drug products.

Excerpts From Approved Concept Paper

• **CM-related definitions and regulatory concepts**: Due to differences from batch manufacture, many CM related definitions or terminologies require further clarification or explanation in the regulatory context, for example, definition of continuous manufacturing, startup/shutdown, state of control, process validation, and continuous process verification.

• **Key scientific approaches for CM**: Fundamental scientific approaches for CM may differ from those encountered in batch processes, for example, concepts of system dynamics, monitoring frequency, detection and removal of non-conforming material, material traceability, process models, and advanced process controls. A common understanding of the scientific approaches will facilitate consistent science- and risk-based implementation and regulatory assessment of CM across different regions.

• Based on the current knowledge, the definitions, regulatory concepts, and key scientific approaches covered in this guideline are intended to inform small molecules and therapeutic proteins. The general scientific approaches therein may also apply to other biotechnological/biological entities.
Excerpts From Approved Concept Paper

• **CM-related regulatory expectations**: Harmonised regulatory expectations for dossier approval and aspects of lifecycle management that are pertinent to CM can facilitate the adoption of CM and result in consistent regulatory assessment and oversight. **Given the current maturity of the technology, manufacturing of – drug substances and drug products – small molecules and therapeutic proteins for new and existing products will be addressed.** The regulatory expectations with respect to marketing applications and post-approval changes, site implementation, and pharmaceutical quality systems will be addressed.
The Future of Continuous Biomanufacturing

• Great interest in the biotechnology sector for realizing the benefits of CM
  • Increased agility, flexibility, robustness
  • Reduced product heterogeneity and cost

• Equipment has advanced to greater enable development and implementation

• Challenges do exist – maintaining steady state, sterile boundary, analytical capability, automation, advanced process controls...

• Regulatory landscape is evolving to support CM for biologics (ICH Q13).

Continuous Manufacturing is the Future of Biologics
THANK YOU