Matching Flows: The Development of Continuous Manufacturing of Biotech Products

Jeffrey C. Baker, Ph.D.
Deputy Director,
Office of Biotechnology Products, CDER

By telecon to ECI’s Integrated Continuous Manufacturing Conference in Castelldefels, Spain
The Disclaimer

This presentation represents the views and perspectives of the speaker and should not be viewed or acted upon as FDA Policy or assumed to be an all inclusive list of FDA requirements. For official policy and guidance, contributors are directed to http://www.fda.gov/
The speaker may be contacted at jeffrey.baker@fda.hhs.gov
Continuous Manufacturing has become a high visibility topic

“Right now, manufacturing experts from the 1950s would easily recognize the pharmaceutical manufacturing processes of today. It is predicted that manufacturing will change in the next 25 years as current manufacturing practices are abandoned in favor of cleaner, flexible, more efficient continuous manufacturing.”

Dr. Janet Woodcock, AAPS Annual meeting October 2011
Priority Area 3: Support New Approaches to Improve Product Manufacturing and Quality

“Investigate the effects of continuous manufacturing (manufacturing using a continuous process, rather than a batch approach) on product quality.”

http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm267719.htm
Frequently Cited Advantages of Continuous Manufacturing in Pharmaceutical Development

- Rapid screening of performance space over many conditions
- Potential to conduct development studies at commercial scale
- Potential for less material usage for development
- Potential for automated experimentation
- Ability to run chemistry under new conditions
  - Highly exothermic reactions
  - Ultra high, ultra low temperatures
Projected Value Proposition of Continuous Manufacturing (CM)

Integrated processing with fewer steps
   - No manual handling, increased safety
   - Shorter processing times

Smaller equipment and facilities
   - More flexible operation
   - Lower capital costs, less work-in-progress materials
   - Reduced environmental foot print
   - Feasible to manufacture small batch sizes

On-line monitoring and control for increased product quality assurance in real-time
   - Amenable to Real Time Release Testing approaches
“Pharmaceutical Trade Press Cover Story du Jour Identifies Continuous Manufacturing as the Greatest Thing Ever”.

PharmaBlog International
“Pharmaceutical Trade Press Cover Story du Jour Identifies Continuous Manufacturing as the Greatest Thing Ever”.

PharmaBlog International

(Ok- I made that quote up but you all know what I mean...)
Yet in this environment,

**Biotechsters have contained their enthusiasm...**
The biotech community is having a different conversation about continuous manufacturing than Small Molecule Pharma.

It’s frequently a conversation without a forum or one that occurs in the hallway.

There’s a lot to be learned from listening in on the flow of those conversations.

After all, continuous manufacturing is all about flow.
So why aren’t biotechsters on fully on board?
Been there, done that, got the t-shirt
Continuous manufacturing concepts are not new to commercial biotechnology...

- Induced bioreactors
- Perfusion bioreactors
- Continuous solid-liquid separations
- In line mixing of concentrated buffers or feeds
Continuous manufacturing concepts are not new to commercial biotechnology...

- Induced bioreactors
- Perfusion bioreactors
- Continuous solid-liquid separations
- In line mixing of concentrated buffers or feeds

Processing algorithms in column chromatography and tangential flow filtration

In line and at line analytical control of solutions or off-gases with feedback loops.
Continuous manufacturing concepts are not new to commercial biotechnology...

- Induced bioreactors
- Perfusion bioreactors
- Continuous solid-liquid separations
- In line mixing of concentrated buffers or feeds

Processing algorithms in column chromatography and tangential flow filtration
In line and at line analytical control of solutions or off-gases with feedback loops.

Multivariate statistical design of experiments in process development
Multivariate response control loops in manufacturing.
Data historians direct linked to statistics packages
The state of the art in biotech is not radically different from the continuous manufacturing vision: Continuous manufacturing in biotech is evolution not revolution.

“It is the function of art to renew our perception. What we are familiar with we cease to see. The writer shakes up the familiar scene, and, as if by magic, we see a new meaning in it.” ----Anais Nin
The regulators tie our hands...
The cGMPs require “batches” and “lots”...

**Laboratory determination of final specifications for release**

21 CFR 211.165(a): *For each batch of drug product*, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product..... prior to release

**Extended investigations of unexplained discrepancies**

21 CFR 211.192: The investigation shall extend to other batches... that may have been associated with the specific failure of discrepancy.

**Documentation of Manufacturing**

21 CFR 211.188 Batch product and control records shall be prepared for each batch of drug product produced and shall include complete information relating to the production and control of each batch

**Recall situation**

21 CFR 211.150(b): Distribution procedures shall include... a system by which the distribution of each lot of drug product can be readily determined to facilitate its recall if necessary
...but the cGMPs do not require batch manufacturing!

**Batch** - a **specific quantity** of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture (21 CFR 210.3)

“**Batch**” does **not** specify the **mode of manufacture**
Semi-continuous batch operations have been used in commercial biotech processing for 25 years.

This approach allows steps in a 24/7 plant to run asynchronously, managing operations centers of varying throughputs and capacities with sophisticated monitoring and modeling.

Outputs are managed within regulatory envelopes.

“Lots” and “Batches” are defined and determined by the Control Strategy and the QMS.
Control Strategy

“A planned set of controls, derived from current product and process understanding, that assures process performance and product quality” (ICH Q10)
Control Strategy includes...

Parameters and attributes related to drug substance and drug product materials and components
Facility and equipment operating conditions
In-process controls
Finished product specifications
Methods and frequency of monitoring and control
Defining Steady-State Operations is central to the control strategy of Continuous Manufacturing trains

Steady state is when properties of the system are “constant” (highly predictive) with time.

When is product acceptable for collection following start up or after a disturbance in the process flow?

When is product acceptable for collection in tailings or ramp down?

Steady state is not the same as steady operation!
In-Process Sampling Considerations

Sample a data stream as you would a process stream

Probe/sample location(s) should generate representative samples

Sample frequency should be suitable for the system dynamics

Sample acquisition time should be relevant to process control
Potential sources of sampling bias

Sample size and scheme (stable and dynamic patterns)

Sample interface not constant over the process (e.g. fouling or oxidation)

Software and data management packages (especially if they were developed for batch processes)

Impact of autocorrelation in statistical process control

Lack of recognition of sample acquisition and analysis as part of process FMEA
Regulations & Continuous Manufacturing

No specific regulations or guidance for continuous manufacturing, other than the definition of “lot”

Nothing in regulations or guidance prohibiting continuous manufacturing

Continuous manufacturing is fully consistent with FDA’s Quality by Design (QbD) in which envelopes of performance are defined as part of the control strategy.
Validation is a mess

Stage 1 – Process Design:
The commercial process is defined during this stage based on knowledge gained through development and scale-up activities.

Stage 2 – Process Qualification:
During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.

Stage 3 – Continued Process Verification:
Ongoing assurance is gained during routine production that the process remains in a state of control.
Validation is an exercise in technical advocacy

It is necessary to demonstrate control of product and processing

A process in control is a process that reproducibly meets expectations.

“Define Demonstrate Document Maintain”
Q11 Development and Manufacture of Drug Substances (November 2012)

For biotechnological processes, ... the data provided in support of process validation is included as part of the marketing application (3.2.S.2.5).

BLA review and the CGMP program

The original product development, process design and initial process qualification studies are evaluated as part of the BLA application review.

During a surveillance inspection investigators determine if the current manufacturing process is performing as planned and predicted.

- *Is the control strategy properly targeted and working as intended?*
- *Is the state of control established and maintained?*
- *Is the identity, strength, quality, purity and potency of product on the market assured?*
- *How does current production compare with submitted data and predictions?*

Risk based assessment of process changes associated with continuous learning and improvement should be fully captured and accommodated by the Production Quality System.
Expectations for assurance of reliable and predictive processing in a commercial setting are the same for batch and continuous processing.

Assurances in both cases should be technically sound, risk based, and relevant to product quality.
“They don’t get it...”
Communicating continuous flow concepts across organizational interfaces is a challenge

For example:
Controlling a multivariate, probabilized, risk based design space in a Quality System that is binary: “pass” or “fail”

Costing out a contract operation or a business plan or calculating plant capacity with non-linear, multivariate relationships rather than “lots per year” or “batch inventory”.

Charging the cost of switch over, ramp up to steady state to… which product? Which company?
The vocabulary of continuous manufacturing is frequently not a common, shared vocabulary...
“The ability to tell a story well is a competitive advantage.”

--Jeffrey C. Baker
Career FMEA
## Scorecard Drives Behaviors and Decisions

<table>
<thead>
<tr>
<th></th>
<th>Me</th>
<th>Us</th>
<th>Them</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immediate</strong></td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
</tr>
<tr>
<td><strong>Long Term</strong></td>
<td><img src="image4.png" alt="Image" /></td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
</tr>
</tbody>
</table>

*Risk*, *Benefit*, *Cost*, *Excellence*, *Value*, *Noise*
Continuous manufacturing requires a significant investment in development and maintenance and adds failure modes and complexity.

Who owns the risk?

Who realizes the benefits?

When?
Management of residual uncertainty associated with new manufacturing flows

Management of residual uncertainty associated with complex molecules

Management of residual uncertainty associated with the value proposition
Biotech and the Value Proposition

High value, low volume products
High value, high potency products
Ratio of fixed costs and variable costs (cost of capital)
Capacity management
  Cost of switch over
  Cost of ramp up ramp down
  Cost of inventory
Mobility of process
Compare and contrast with the value proposition associated with disposables
But on the other hand...

...know your biotechsters
“We can do anything. Prices vary.”
“We can do anything. Prices vary.”

After all, that is the Biotech Story...
We need to tell a story worth changing the world.