Enabling Continuous Manufacturing

An FDA Perspective

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Innovation and Continuous Improvement

Globalization: Respond to changing business and political environments
Competition: Develop new products faster than competitor
Customer demands: New therapies, more effective and cheaper medicines
Maintain supply: Drug shortages, product defects and recalls

To improve is to change; to perfect is to change often.
Winston Churchill
Continuous Manufacturing (CM) Enablers

**Operational Cost**
- Smaller equipment and facility footprint
- Increased safety
- Less solvent use and waste

**Quality**
- High degree of process understanding
- Rapid development/QbD in commercial equipment
- Increased assurance of product quality in real time

**Patient**
- Bring new products to market quicker
- Agility and flexibility of manufacturing
- Rapid response to emergencies and drug shortages
Change from Batch to Continuous Manufacture

Only those who will risk going too far can possibly find out how far one can go.

T. S. Eliot
# Impediments to Adopting CM

<table>
<thead>
<tr>
<th>Category</th>
<th>Impediments</th>
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<tbody>
<tr>
<td><strong>Business economics</strong></td>
<td>• Existing infrastructure vs. new capital investment</td>
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<td><strong>Culture</strong></td>
<td>• Lack of experience, fear of unknown, averse to risks associated with change to CM, perceptions</td>
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<td><strong>Workforce</strong></td>
<td>• Different areas of expertise, advanced skills, training</td>
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<td><strong>Technical</strong></td>
<td>• New technology, science and control strategy concepts</td>
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<td><strong>Regulatory</strong></td>
<td>• Lack of familiarity, perceptions</td>
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Regulator Questions

Questions facilitate shared learning of new concepts, help reach consensus and lead to first cycle approval

Do not let fear of questions impede the adoption of CM
FDA’s Enabling of CM
Supporting CM

- Early buy-in from FDA leadership
- Recognition that CM needed significant nurturing to become reality
- Unprecedented external outreach
  - Numerous FDA presentations at conferences since 2009
  - 2010 FDA (internal) and many public CM workshops
  - Discussions with EMA from ~ 2013
  - Collaboration with federal agencies
- FDA development of regulatory framework
- Ongoing dialogue with Industry
Science and Risk-based Approach

Key science and engineering concepts
- CM definition
- Mass Throughput Rate
- Residence Time Distribution
- System Dynamics

Risks to process and product quality
- Sources of variability
- Variability over time

Operational differences from batch
- Integrated unit operations
- Disturbance propagation
- Segregating non-conforming material

Preliminary control strategy concepts
- State of control
- Material traceability

Experience & maturity
- Clarity
- Commercial implementation
- Bridging
Existing Regulatory Framework

- Examination of existing regulations and guidance for compatibility
  - In general, compatible with CM
  - ICH Q 8, 9, 10, 11 and PV guidance, in particular, form the framework for CM implementation
  - Founded on process analytical technology, quality by design and real-time release principles
  - Specifics of SUPAC may not apply to CM, but risk based principles of SUPAC do apply
Establish Communication Pathways

• Formation of Emerging Technology Team (ETT)
  – Avenue to obtain early feedback, even before IND stage
• Meetings requests can be submitted to
  – CDER-ETT@fda.hhs.gov
• Pre-Operational Visit or Review can be requested
  – POV for 1st CM implementation at the site facilitates approval
• Early discussion with FDA greatly facilitates first-cycle approval

References:
  ◦ December 2015 draft guidance, “Advancement of Emerging Technology Applications to Modernize the Pharmaceutical Manufacturing Base”
  ◦ March 2015 draft guidance (revision of the 2009 guidance), “Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products”
Expanding FDA Knowledge Base

- CM training modules – developed with NIPTE/academia
- Hands-on CM training at Rutgers University
- Staff participation in CM workshops and conferences
- CM facility visits and pre-operational visits
- Mentoring
- Community of Interest in Advanced Manufacturing
- Research/learning
  - FDA Office of Testing and Research activities
  - FDA-funded academic research
Challenges and Opportunities
Expanding Current CM Experience

• How can we expand CM to other dosage forms, modified release profiles, biotech, drug substance, and integrated drug substance-drug product?
  – Current CM experience only with small molecule solid oral immediate release drug product manufacture

• Explore new unit ops for CM
  – Currently little experience with continuous crystallization, lyophilization, biotech, etc.

• Address new scientific/regulatory issues. E.g.,
  – Sterility maintenance
  – Drug substance batch release in an integrated process

• Applications needed to explore regulatory gaps
Advanced Process Monitoring and Process Control Strategies

• More use of PAT tools in commercial manufacture
• Using process control strategies for monitoring and adjusting processes in real time.
  – Encourage use of process controls such as feedback and feed forward control to adjust process parameters
• Using multivariate approaches for process and product quality monitoring
  – Process and product quality monitoring,
  – Tracking and trending data for process performance/capability
• Using predictive models
  – Use of models to support RTRT (e.g., dissolution models)
• Workforce skill level
  – Multi-discipline (e.g., process, pharmaceutics, chemometrics, control, stats)
  – New hires, training
Statistics for CM

• Standards for sampling in CM
• Standards for statistically based acceptance criteria
  – Large N data handling
• Workforce knowledge base in statistics
• Methodology/statistics for residence time distribution models, material traceability, and material segregation/rejection
Automation, Electronic Systems & CGMPs

• Lack of familiarity and knowledge in automation
  – What is an appropriate level of validation and maintenance?

• Use of electronic systems and electronic batch records
  – How to maintain large data files

• Operational and CGMP issues. E.g.,
  – Strengthening the existing Pharmaceutical Quality System to handle CM
  – Maintenance of models supporting control strategy (e.g., residence time distribution models)
  – Handling material traceability and rejection
  – Increasing run time after initial approval
  – Managing a life-cycle approach to CM process validation

• Requires more experience with CM implementation.
Other Opportunities

• **Excipient/raw material characterization and quality control**
  – Continuous feeding could be a significant source of variability if not adequately controlled

• **Cleaning**
  – Currently only single product CM operation; cleaning requirements in multi-use CM facilities not yet tested
  – Currently CM used for non-sterile drugs; no experience yet with maintaining sterility under CM operation

• **Equipment**
  – More equipment designed for CM. E.g.,
    – Equipment that are readily cleanable
    – Equipment that operate continuously instead of as mini-batch equipment
    – Equipment trains with consideration to system dynamics
  – Equipment for different types of processes (e.g. lyophilization)

• **Robust and easy to use PAT tools**
Concluding Remarks

- Continuous pharmaceutical manufacturing is expected to benefit both patients and industry
- Commercial implementation of continuous pharmaceutical manufacturing is demonstrated
- There are no barriers to implementing continuous manufacturing
- The full potential of continuous manufacturing remains to be explored and offers great opportunity for further development
- The FDA strongly supports advancement of pharmaceutical manufacturing technologies, including continuous manufacturing
Continuous Manufacturing