Present and Future for Continuous Manufacturing: FDA Perspective

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3rd FDA/PQRI Conference on Advancing Product Quality
March 22-24, 2017
Outline

• Where are we now?
  – What is current regulatory landscape?
  – What types of continuous manufacturing (CM) technologies have we seen so far?
  – What progress have we made?

• Where are we heading?
  – What new CM approaches are coming?
  – What are the opportunities or challenges?

• How are we getting ready?
Current Regulatory Landscape

• Regulatory Agencies, including the FDA, European Medicines Agency (EMA), and Pharmaceuticals and Medical Devices Agency (PMDA), support the adoption of CM for pharmaceutical production based on science- and risk-based approaches.
Current Regulatory Landscape

• There are no major regulatory hurdles for CM implementation.

• Perceived risk or fear still exists because regulators may lack experience in CM, leading to many unwarranted questions and deficiencies.

• Each agency (FDA, EMA, and PMDA) established specialized teams to encourage early interaction with industry
  – FDA Emerging Technology Team
  – EMA Process Analytical Technology (PAT) Team
  – PMDA Innovative Manufacturing Technology Working Group
CM Technologies Thus Far

• Hybrid CM models for drug product
  – Mostly **continuous direct compression**
  – Continuous wet granulation
  – Immediate-release solid orals
  – New drugs under a breakthrough pathway
  – Existing FDA approved products switching from a batch to CM process

• Hybrid CM models for drug substance
  – Continuous drug synthesis plus batch crystallization
  – Existing FDA approved products

• Continuous upstream bioprocessing
  – Existing FDA approved product
CM Technologies Thus Far

• Control Strategy
  – Increasing use of active control systems
    • Feedback or ratio control for mass flow rates
  – Increasing use of PAT tools for real-time process monitoring and control
    • NIR for blend uniformity
    • Analyzers for process parameters (e.g., mass flow rates)
  – Increasing use of real time release testing (RTRT) approaches
    • Dissolution models
  – Process Models
    • Resident time distribution model for material traceability, non-conforming material diversion, and blend uniformity
  – Increasing use of automation
  – Off-line end product testing
Progress Made

• Vertex’s ORKAMBI™ (lumacaftor/ivacaftor)
  – 1st NDA approval for using a CM technology for production of the Cystic Fibrosis drug (tablets) (July 2015)\(^1\)
  – Met the PDUFA timeline

• Prezista (darunavir)
  – 1st NDA supplement approval for switching from batch manufacturing to CM process for an FDA-approved HIV drug (tablet) (April 2016)\(^2\)
  – Met the PDUFA timeline (4 mouths)

• Over 15 ETT-Industry meetings since the launch of ETT program in early 2014 providing feedback on the development of CM processes
  – Drug substance
  – Drug product
  – Small-molecule and biotechnology products
  – Control strategy utilizing models

\(^1\)http://connect.dcat.org/blogs/patricia-van-arnum/2015/09/18/manufacturing-trends-in-continuous-mode

\(^2\)http://www.pharmtech.com/fda-approves-tablet-production-janssen-continuous-manufacturing-line
Upcoming CM approaches

• Modular continuous processing systems with standardized plug-and-play equipment
  – Small footprint
  – Highly flexible (may be even movable) for manufacturing of a wide range of products
  – Supervision via an integrated process control system
  – Pfizer’s Portable Continuous, Miniature and Modular (PCMM) Manufacturing for Solid Oral Dosage forms

• Opportunities or Challenges
  – Knowledge platform development and management to support faster development of products using the same equipment modules
  – Efficient cleaning approaches to allow rapid switching from manufacturing one to another product while avoiding cross-contamination between different products

http://www.facilityoftheyear.org/winners/2016-equipment-innovation
Upcoming CM approaches

- Increasing applications of Process Models
  - Process and product understanding
  - Material traceability
  - Non-conforming material diversion
  - Advanced process control
  - In-process control or product release

- Opportunities or Challenges
  - Useful tools for risk communication and knowledge management to support faster product development
  - Regulatory expectation for information to support model development, validation, maintenance and update
    - Intended purpose of the model
    - Risk to product quality
    - Firm’s quality system
Upcoming CM approaches

• **Performance-based Approach for Control Strategy**
  – On-line and/or at-line measurements (i.e., PAT tools) at high sampling frequencies for monitoring and controlling quality attributes
  – Real-time information informing the state or “health” of the process
  – Quality assurance by conformance to the specification at relevant control points (e.g., in-process controls of quality attributes) in the process.

• **Opportunities or Challenges**
  – *Effective regulatory oversight* (e.g., established conditions?)
  – *Operational flexibility* desired by industry to manage and improve the process within its quality management system
  – Establishment of *clear linkages of control points to finished product critical quality attributes* (e.g., what information is needed in a regulatory submission to support this approach?)
  – Can *process parameters* be part of this approach (e.g., multivariate analysis)?
Upcoming CM approaches

• Pharmacy on Demand
  – Portable systems that can be configured to produce different drugs on demand
  – Rapidly deployable to produce drugs needed to address urgent health crises
  – Better fit for low-volume drugs (e.g., orphan drugs)

• Opportunities or Challenges
  – Mini-manufacturing platform requiring robustness evaluation similar to that for device and environmental considerations?
  – New approaches, criteria or considerations for validation and product release?
  – Any CGMP implications?

http://news.mit.edu/2016/portable-pharmacy-on-demand-0331
Upcoming CM approaches

• End-to-end CM processes
  – Integrated synthesis, purification, and final dosage formation
  – Regional manufacturing and distribution network

• Opportunities or Challenges
  – New considerations for control strategy as there is no isolated drug substance?
  – Adapting to the current Common Technical Document (CTD) format?

https://iscmp2016.mit.edu/
Getting Ready

• Right Mindset and Culture
  – Regulatory agencies
    • Willing to learn/understand and recognize the potential of new technologies with an open mind
    • Make science- and risk-based assessments and decisions
    • Be transparent to industry and not afraid to ask questions
    • Multi-disciplinary approach (collaborative)
  – Industry
    • Be transparent and willing to share with the agency early
    • Not afraid to receive and answer many questions from the agency
    • View regulators as part of your team

• We are getting there!
Getting Ready

- Building collaborative knowledge platform
  - Promote regulatory science and research
    - Growing OPQ in-house research (e.g., process modeling and simulation, continuous crystallization, and continuous perfusion bioreactors)
    - External research collaboration (e.g., BARDA, MIT, Rutgers, Purdue, UMass Lowell, CONTINUUS Pharmaceuticals)
  - Industry working together to develop and implement CM technology
    - Joint development of enabling technologies for CM
    - Early joint technology-focus discussions with FDA through the Emerging Technology Program
  - Academia working with industry and agencies to advance CM technologies
    - Get early input from industry and agencies on their CM research
    - Be innovative but understand what industry and agencies need
Getting Ready

• Building Standards and Guidelines Together
  – Agencies’ guidelines to ICH guideline
    • Moving towards global alignments on key regulatory aspects of CM
  – Common technical standards or best practices
    • ASTM and USP
  – Dynamic guidelines and standards
    • Revision warranted to reflect advancement in knowledge

• Continued knowledge sharing
  – Sharing what you learned in public forums
  – Enhanced information sharing among different regulatory agencies
  – Research publications
The Desired State

The Vision

“A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight.”
Acknowledgement

• Christina Capacci-Daniel
• Celia Cruz
• Sharmista Chatterjee
• Arwa El Hagrasy
• Tara Gooen
• Rapti Madurawe
• Thomas O’Connor
• Emerging Technology Team