Evolving Regulatory Landscape for Emerging Technology: Continuous Manufacturing

Sau (Larry) Lee, Ph.D.
Associate Director for Science
Office of Pharmaceutical Quality
US FDA Center for Drug Evaluation and Research

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Outline

- FDA Emerging Technology Team (ETT)
- Regulatory Considerations for Continuous Pharmaceutical Manufacturing
- Concluding Remarks

Emerging Technology

- What is an Emerging Technology?
  - Technology with the potential to modernize the body of knowledge associated with pharmaceutical development to support more robust, predictable, and/or cost-effective processes or novel products and with which the FDA has limited review or inspection experiences, due to its relative novelty
  - Innovative or novel product, manufacturing process, or analytical technology subject to CMC review

- Examples of Emerging Technology include:
  - **Continuous manufacturing of drug substance and drug product**
  - "On-demand" manufacturing of drug products
  - Use of robots in pharmaceutical manufacturing
  - 3-D printed tablets
  - New container and closure system for injectable products

Emerging Technology Team (ETT)

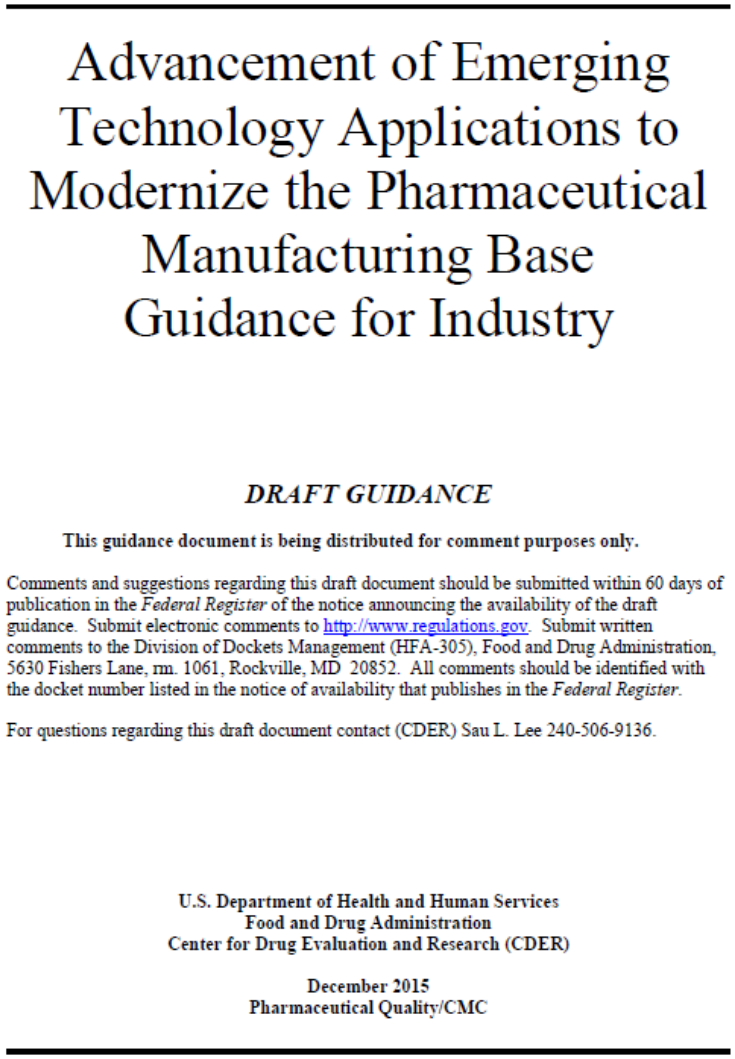
- Vision
  - Encourage and support the adoption of innovative technology to modernize pharmaceutical development and manufacturing where the Agency has limited review or inspection experience

- A small cross-functional team with representation from all relevant FDA quality review and inspection programs (OPQ/CDER & ORA)
  - Chair: Sau (Larry) Lee, Associate Director of Science, OPQ
  - PM: Cheryl Kaiser (OPQ/OPRO)
  - Members: Thomas O'Connor(OPQ/IO-SRS), Celia Cruz (OPQ/OTR), Mohan Sapru & Ray Frankewich (OPQ/ONDP), Geoffrey Wu (OPQ/OLDP), Kurt Brorson (OPQ/OBP), Grace McNally, Sharmista Chatterjee & Bryan Riley (OPQ/OPF), Rebeca Rodriguez & Susanne Richardson (ORA), Rick Friedman (OC)
  - Other subject matter experts as needed

FDA ETT (Continued)

- Objectives
  - To serve as a centralized location for external inquiries on novel technologies
  - To provide a forum for firms to engage in early dialog with FDA to support innovation
  - To ensure consistency, continuity, and predictability in review and inspection
  - To identify and evaluate roadblocks relating to existing guidance, policy, or practice
  - To help establish review and inspection standards and policy, as needed
  - To facilitate knowledge transfer to relevant CDER and ORA review and inspection programs
  - To engage international regulatory agencies to share learnings and approaches
  - Contact us: **CDER-ETT@fda.hhs.gov**

Draft ETT Guidance



Advancement of Emerging Technology Applications to Modernize the Pharmaceutical Manufacturing Base Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Sau L. Lee 240-506-9136.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2015
Pharmaceutical Quality/CMC

- Provides recommendations to companies interested in participating in a program involving the submission of CMC information containing emerging manufacturing technology to FDA.

- Applicable to companies that intend the technology to be included as part of an: investigational new drug application (IND) or original or supplemental new drug application (NDA), abbreviated new drug application (ANDA), or biologic license application (BLA) reviewed by the Center for Drug Evaluation and Research (CDER), and where that technology meets other criteria described in this guidance.

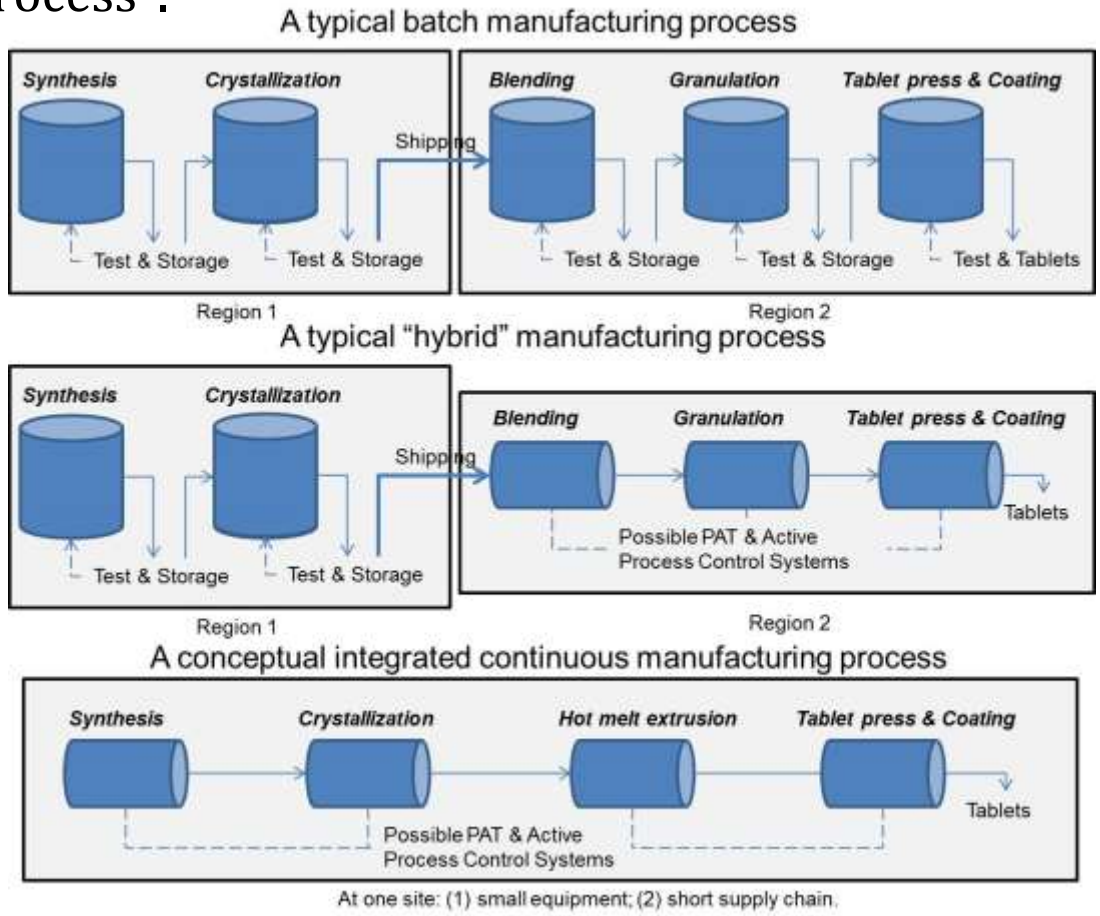
What is Continuous Manufacturing (CM)?

In a continuous manufacturing process, the material(s) and product are continuously charged into and discharged from the system, throughout the duration of the process[1].

(1) Batch

(2) Hybrid

(3) End-to-End



[1] Lee S. *et. al.* J Pharm Innov. 2015 10:191-199

Why CM?

- FDA has identified CM as an emerging technology
- FDA recognizes that CM has the potential to increase the efficiency, flexibility, agility, and robustness of pharmaceutical manufacturing
  - 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
- Benefits to both patients and industry

Trends in CM

- FDA has approved Vertex's ORKAMBI™ (lumacaftor/ivacaftor) tablets for Cystic Fibrosis—that is manufactured using CM technology (July 2015)[1]
- About 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 molecules and biotechnology products
  - Facility visits

- Prezista (darunavir)
  - 1st NDA supplement approval for switching from batch manufacturing to CM process for an FDA-approved HIV drug (April 2016)

[1]http://connect.dcat.org/blogs/patricia-van-arnum/2015/09/18/manufacturing-trends-in-continuous-mode – accessed January 16, 2016

Quality Risk Management and CM

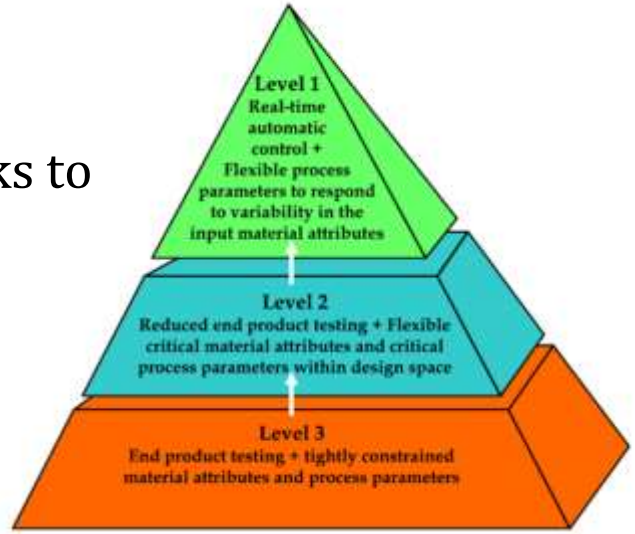
- General expectations regarding the science and risk-based understanding and control of processes and product quality are the same for CM as for traditional batch manufacturing
- Risk assessment: hazards identified may be different for a CM process
  - Process understanding forms the foundation for effective risk management
    - Impact of process parameters and material properties on powder flow and product quality
    - Impact of process dynamics on material traceability, and propagation of disturbances
- Risk mitigation: control strategy approaches implemented may be different for CM
  - Model based control, multivariate monitoring, analysis of large of data sets, and/or Real-Time Release Testing (RTRT)
- Risk communication: communicate residual levels of risk
  - Linking adopted control strategy approaches to the risk assessment can be an effective mechanism for communicating product and process development

Key Elements for Developing a Risk-Based CM Control Strategy

- Process understanding
  - Impact and interactions of process parameters and material attributes
  - Characterization of process dynamics
- State of Control
  - Raw material control
  - Process monitoring
  - Level and integration of controls
  - Handling of deviations and disturbances in real time
- Real Time Release testing
- Batch definition
- Verification of Control Strategy

Control Strategy – State of Control

- Control strategy should be appropriate for each individual process and product based on the risks to product quality
- Consistently provides assurance of process performance and quality
  - Should be designed to mitigate product quality risks in response to potential variations over time

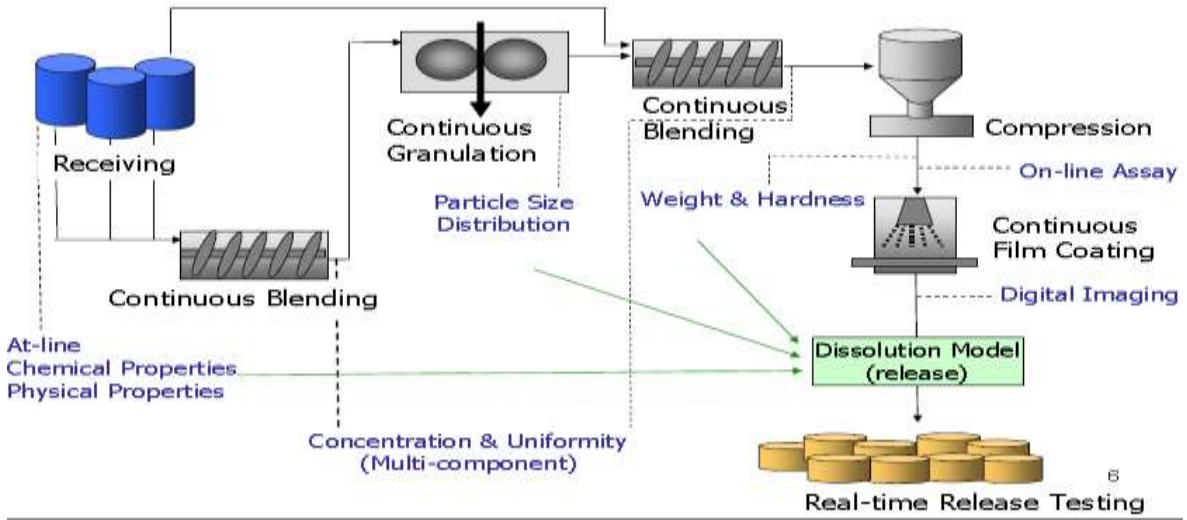


Yu, LX, *et. al.* The AAPS Journal. 2014;16;771-783.

- For CM, this can include integration of process parameter limits (set points and alarms), in-process monitoring (including PAT), process controls (feedback and feed forward), material diversion, process trending, and Real Time Release Testing
- Many continuous manufacturing systems promote the adoption of higher level controls, although a hybrid approach combing the different levels of control is viable for some continuous manufacturing process designs

RTRT Considerations

- Establish a valid combination of assessed material attributes and associated process controls
- Evaluate ability of the sampling scheme(s) to detect non-conforming materials or products
  - Scientific justification for statistical method(s) and criteria (% confidence, % coverage, and target range)
  - Relationship between the proposed sampling scheme and system dynamics
  - Sampling plan during start-up, shut-down, and after process restarts to determine that the process is in a state of control
- If the on-line PAT methods are submitted as routine methods (without alternatives), describe what actions will be taken when analyzer is not available



Batch Definition

- 21 CFR 210.3 defines a batch as "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**".

- Additionally, a lot is defined as "a batch, or a specific identified portion of a batch, that has uniform character and quality within specified limits; or, in the case of a drug product produced by continuous process, it is a specific identified amount produced in a **unit of time or quantity** in a manner that assures its having **uniform character** and **quality within specified limits**."

Definitions for both "batch" and "lot" are applicable to continuous processes

Batch Definition Considerations

- Regulatory expectation that:
  - Product has "uniform character and quality within specified limits" and is therefore closely linked to the design of the control strategy for the process
- Potential definitions based on a range of:
  - Production time period; Amount of material processed; Production variation (e.g. different lots of feedstock); Amount of product produced; and Others
  - Batch ranges can be proposed to maintain operating flexibility, but target production should be established prior to initiation of manufacturing, not after the fact
- Batch definition considerations
  - Defining procedures for start-up/shutdown, and establishing *a priori* acceptance criteria for determining when product collection starts
  - Ensuring material traceability to verify a complete history of the manufacture, processing, packing, holding, and distribution of a batch/lot of the product and other materials (excipients); especially in cases of OOS/OOT investigations, consumer complaints, product recalls, or any other situations that may have public health impact
  - Material reconciliation including handling of non-conforming material
  - Metrics for determining the failure of an entire continuous run vs. a batch

Concluding Remarks

- No regulatory hurdles for implementing CM
  - Both Agency and Industry are still gaining experience
- FDA recommends early and frequent discussion with the Agency during CM development
  - ETT can be utilized for non-product specific discussions, in the case where the drug candidate has not been finalized
- Process understanding is key to identifying product quality risks and developing a robust control strategy
- A robust control strategy for a continuous manufacturing process can include a combination of:
  - Real time monitoring of process parameters, alarm system with quality based control limits, real time monitoring of incoming and intermediate material attributes, traceability of final product attribute vs. history of the system, reliable separation of acceptable and non-acceptable materials, active process controls
- FDA supports the implementation of CM technologies using science and risk-based approaches

Thank You!

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