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Current FDA Perspective for Continuous Manufacturing

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MIT-CMAC 2nd International Symposium on
Continuous Manufacturing of Pharmaceuticals
September 26-27, 2016

Trends in Continuous Manufacturing (CM)

- Vertex's ORKAMBI™ (lumacaftor/ivacaftor)
  - 1st NDA approval for using a CM technology for production of the Cystic Fibrosis drug (tablets) (July 2015)[1]
- Prezista (darunavir)
  - 1st NDA supplement approval for switching from batch manufacturing to CM process for an FDA-approved HIV drug (tablet) (April 2016)[2]
- 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 – accessed January 16, 2016

[2]http://www.pharmtech.com/fda-approves-tablet-production-janssen-continuous-manufacturing-line

Quality Risk Management and CM

The expectations for product quality are the same for CM as for traditional batch manufacturing. However, some differences are:

1. Risk assessment: hazards identified for a CM process are different than for batch
   - Understanding process dynamics in relation to process conditions and material properties is the foundation for effective risk management
2. Risk mitigation: control strategies may be different for CM than for batch
   - Examples include more frequent use of model-based control, multivariate monitoring, analysis of large of data sets, automation, and/or Real-Time Release Testing (RTRT)
3. Risk communication: communicating residual levels of risk
   - Linking adopted control strategy approaches to the risk assessment can be an effective mechanism for communicating product and process development, as well as life cycle management

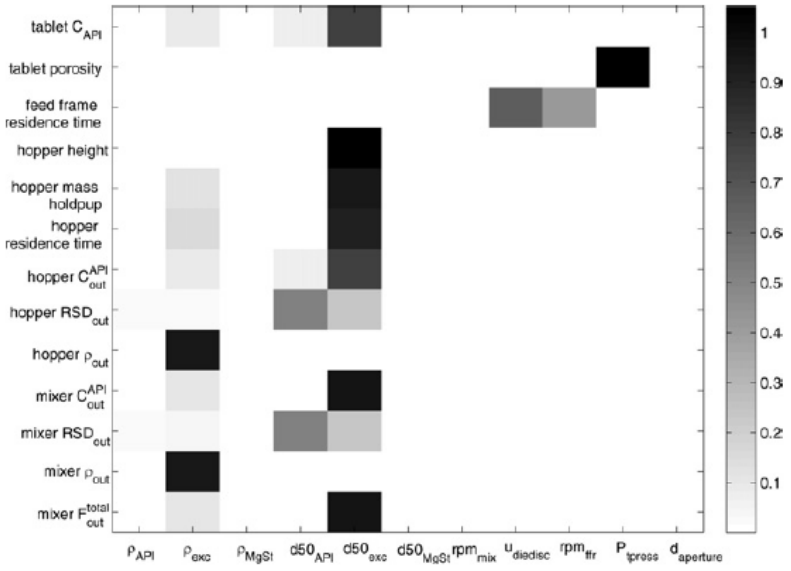
Key Elements for CM

- Process Understanding and Dynamics
  - Impact and interactions of process parameters and material attributes
  - Characterization of process dynamics
- State of Control
  - Levels of control
  - Raw material control
  - Process monitoring
  - Detecting and handling of deviations and disturbances in real time
- Real Time Release Testing
- Definition of Batch
- Control Strategy Verification

Process Understanding

Use the understanding of the impact of process parameters and material attributes on product quality to:

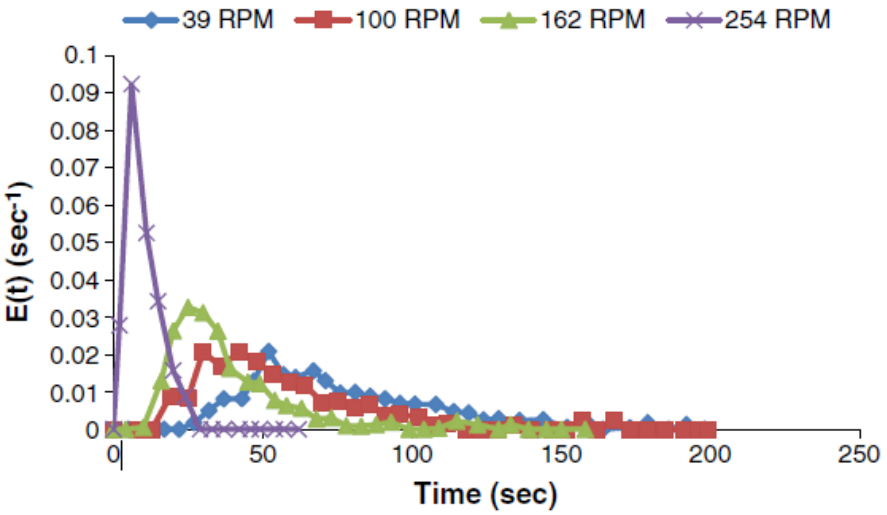
- Establish design space based on the design of the experiments
- Build predictive models and simulation tools (ICH Q8)
- Inform alarm and action limits and an approach to manage process deviations (e.g., adjustments)
- Establish criteria for incoming and in process materials



Boukouvala F et. al. *Comput. Chem. Eng*. 2012;42;30-47

Process Dynamics

- Evaluate back-mixing of the system over time to predict the propagation of disturbances and materials through the system
- Obtain an understanding of process dynamics by characterizing the **Residence Time Distribution (RTD)**
- Identify typical failure modes or deviations (long term vs. short term) (e.g., feeder variability)

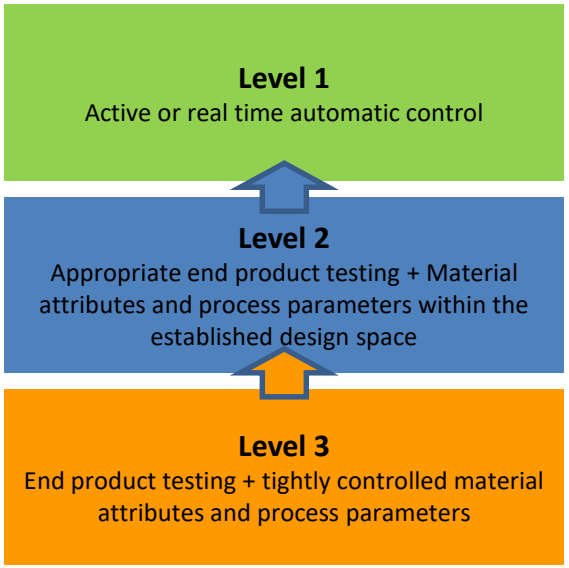


Aditya and Muzzio. *Powder Technology* 2011; 208, 26-36

- Evaluate response to set point changes (e.g., change in line rates)
- Assess the impact of Startup and Shutdown on material quality

Control Strategy – State of Control

- A control strategy should:
  - Be appropriate for each individual process and product based on the risks to product quality
  - Consistently provide assurance of process performance and quality
  - Be designed to mitigate product quality risks in response to potential variations over time for CM

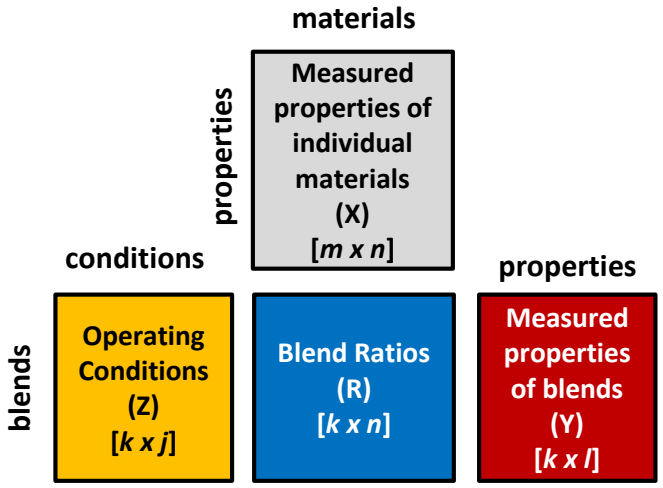


- For CM, this can include integration of process parameter limits (set points and alarms), in-process monitoring (including PAT), process controls (feedback and feed forward), material diversion, and Real Time Release Testing (RTRT)
- Many continuous manufacturing systems promote the adoption of higher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

S.L. Lee et al., J Pharm Innov. 2015; DOI 10.1007/s12247-015-9215-8

Raw Material Control Considerations

- Use of multiple raw material lots in a batch
  - Establish traceability of different lots to finished products
- Characterization of input materials
  - Evaluate raw material attributes (e.g., particle size distribution and density) affecting the formulation flow behavior, segregation potential, etc.
- Appropriate material specifications
  - Impact of drug substance or excipient lot-to-lot variations on feeding
  - If legacy product, appropriateness of the existing drug substance specifications for CM
  - Appropriateness of the compendial specification for excipients



S. G. Munoz et al. (2014) *Chemometrics and Intelligent Laboratory Systems.* 133, 49-62

Process Monitoring and Control

Specify the role of PAT and Models

- Provide process understanding during development; process monitoring during production; process control; and/or real-time release testing (RTRT) method

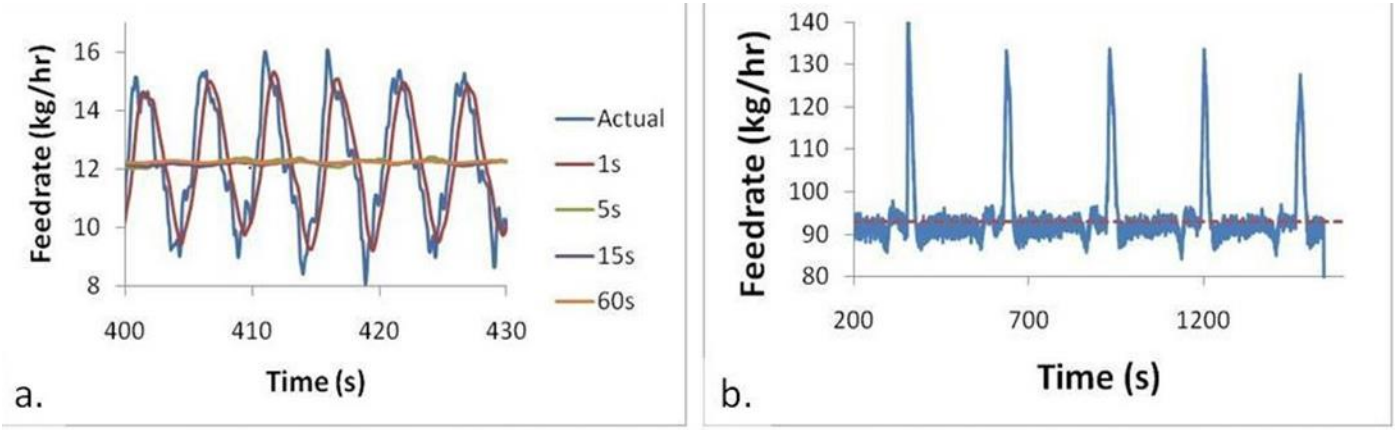
Consider instrument aspects

- Interference due to flow; time of acquisition vs. flow rate; probes – number, location, probe failure, probe maintenance, etc.

Feeding: a critical operation for CM

- Demonstrate that acceptable quality material is manufactured near the upper and lower limits to support feeding limits
- Evaluate impact of operational variations (e.g., switching from gravimetric to volumetric flow during feeder refill)
- Assess impact of feeding variations of excipients on product performance (e.g., dissolution)

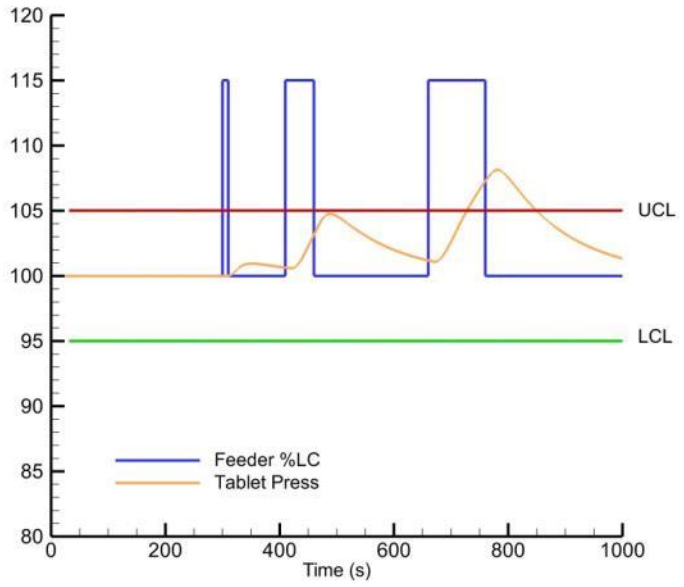
Feeder Monitoring



Engisch W. and Muzzio F.. J Pharm Innov. 2015; DOI 10.1007/s12247-015-9238-1

Diversion of Non-Conforming Material

- The ability to isolate and reject non-conforming material can be one of the key aspects of a CM control strategy
  - Planned process start-ups and shutdowns
  - Temporary process disturbances or upsets
- The evaluation and understanding of propagation of a disturbance in the system are important to justify the amount of material at risk
- Models of process dynamics are being assessed as part of the control strategy to detect and track non-conforming material due to upstream disturbances

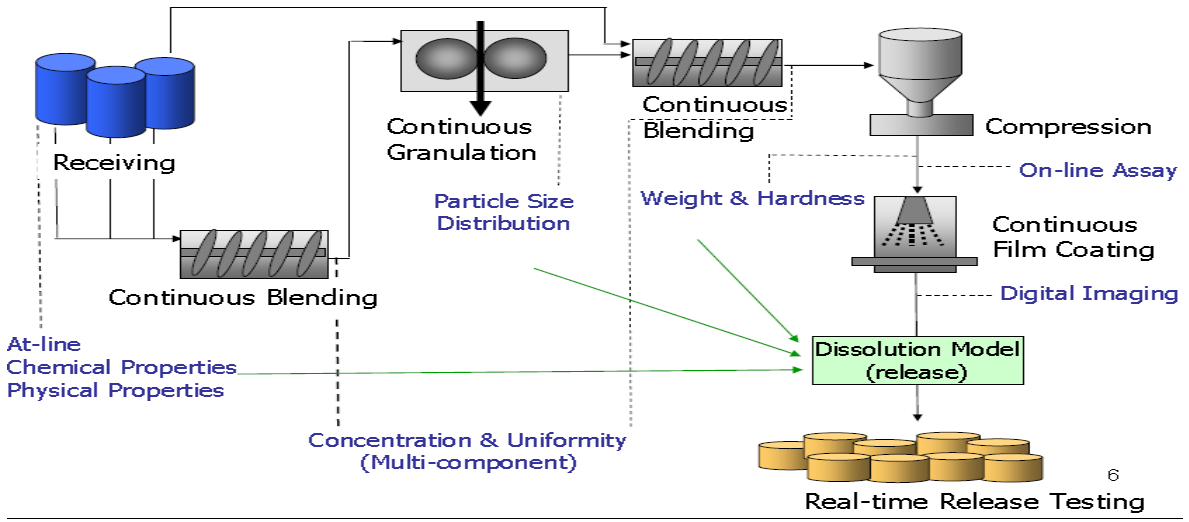


Scientific Considerations for Model Based Material Diversion

- Develop models using scientifically-sound principles and conditions that reflect routine commercial production
- Validate performance for high-impact models
  - Capability of the model to trace the identified non-conforming material segment through the system to the rejection point
  - ICH Q8, Q9, & Q10 Questions and Answers -- Appendix: Q&As from Training Sessions (Q8, Q9, & Q10 Points to Consider)
- Understand model assumption and risks to validity of model predictions
  - Model parameter uncertainty
  - Expected variations in process parameters and material attributes (e.g., line rate)
  - Product quality risks resulting from potential transient disturbances
  - Process failure modes that may not be identified by or included in the model
- Include model maintenance approaches within the quality system as part of a lifecycle approach
  - Routine monitoring to verify performance
  - Model updates

RTRT Considerations

- Establish a valid combination of assessed material attributes and associated process controls in relation to the final product quality
- Evaluate ability of the sampling scheme(s) to detect non-conforming materials or products
  - Assess quality of a batch (i.e., % confidence, % coverage, and target range)
  - Monitor or assess system dynamics (i.e., disturbances) during the continuous operation
  - Determine whether the process is in a state of control during start-up, shut-down, and after restarts
- 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 control strategy* that is designed to ensure the process under a *state of control*
- Potential batch definitions based on:
  - Production time period; amount of material processed; production variation (e.g. different lots of feedstock); amount of product produced; and others
  - Established prior to initiation of manufacturing, not after the fact
- Other considerations
  - Ensure *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
  - Define procedures for start-up/shutdown, and establishing a priori acceptance criteria for determining when product collection starts
  - Material reconciliation including handling of non-conforming materials

Process Verification (Evolving thinking)

- Consult process validation guidance and verify performance of the process using the intended control strategy
  - Demonstrate robustness of the process including the ability to remain in a state of control and make quality decisions in real-time
- Continuous process verification
  - Use in-line, on-line, or at-line monitoring or controls to verify process performance on an on-going basis
  - Evaluate trending for further process understanding and improvement
  - Provide the advantage of enhanced assurance of intra-batch uniformity, fundamental to the objectives of process validation
- Recommend *verifying the intended commercial batch size*
  - Run the process for the proposed duration of a commercial run, in order to identify and rectify potential problems that may only be visible at longer run times
  - Consider to utilize a comparability protocol to increase the batch size post approval
- Expect retrospective data/trending analysis as part of the process validation guidance and lifecycle management

Concluding Remarks

- No regulatory hurdles for implementing CM
  - Both the Agency and industry are gaining experience
- Recommend early and frequent discussion with the Agency during CM development
  - Emerging Technology Program should be utilized for early FDA-Industry interactions even before the drug molecule is identified
- Process understanding is key to identifying product quality risks and developing a robust control strategy
- A robust control strategy for a CM process can include a combination of different scientific approaches
- FDA supports the implementation of CM technologies using science and risk-based approaches

Acknowledgement

- Christina Capacci-Daniel
- Celia Cruz
- Sharmista Chatterjee
- Thomas O’Connor
- Rapti Madurawe
- Emerging Technology Team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