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Scientific Considerations for Continuous Manufacturing Processes

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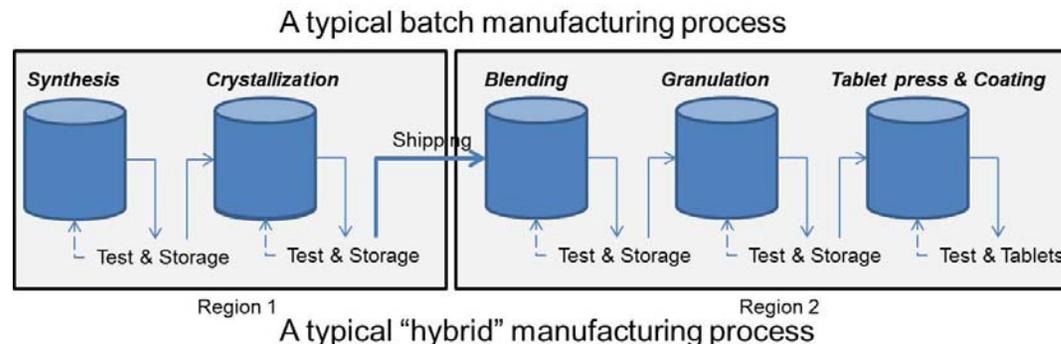
Outline

- Introduction
- Quality Risk Management
- Risk Assessment: Process Understanding
- Risk Mitigation: Control Strategy
 - Batch Definition Connection to Control Strategy
- Risk Communication
- Conclusions

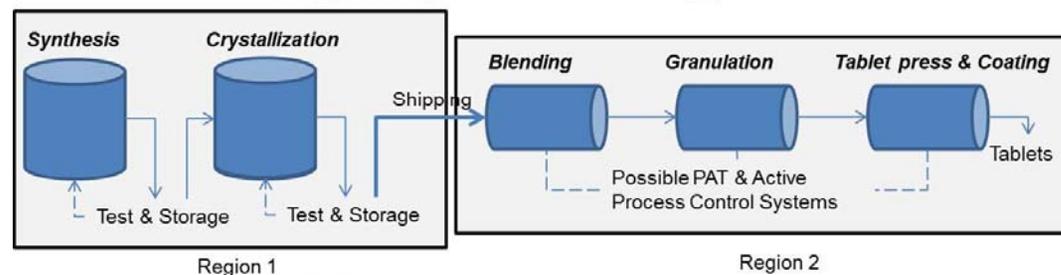
What is Continuous Manufacturing (CM)?

- CM is a process based on flow: the material(s) and product are continuously charged into and discharged from the system, throughout the duration of the process

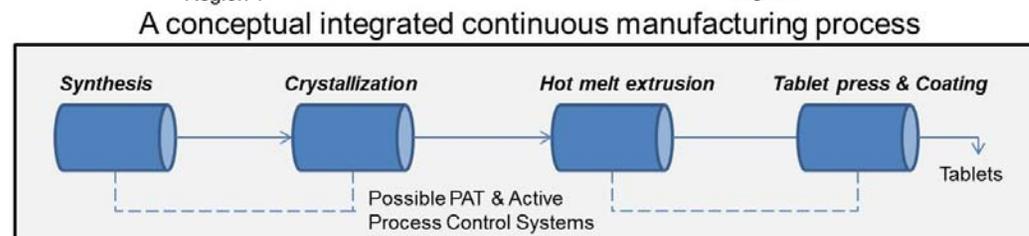
(1) Batch



(2) Hybrid



(3) End-to-End



At one site: (1) small equipment; (2) short supply chain.

Why Continuous Manufacturing?

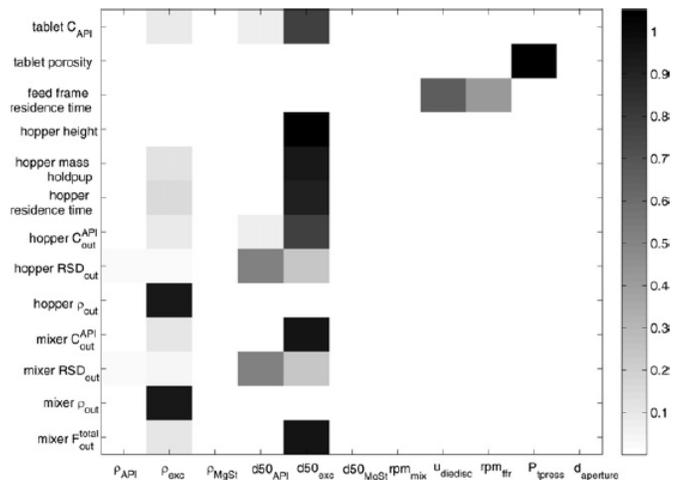
- FDA has identified CM as an emerging technology
- FDA recognizes that CM has the potential to increase the efficiency, flexibility, agility, and robustness of pharmaceutical manufacturing
 - Reduction in processing time per unit dose (minutes vs. days).
 - Reduction in equipment footprint requirements.
 - Potential flexibility in duration of manufacturing campaigns based on knowledge of process.
 - Rapid response to drug shortages, emergencies, patient demand
- Benefits to both patients, and industry

Quality Risk Management

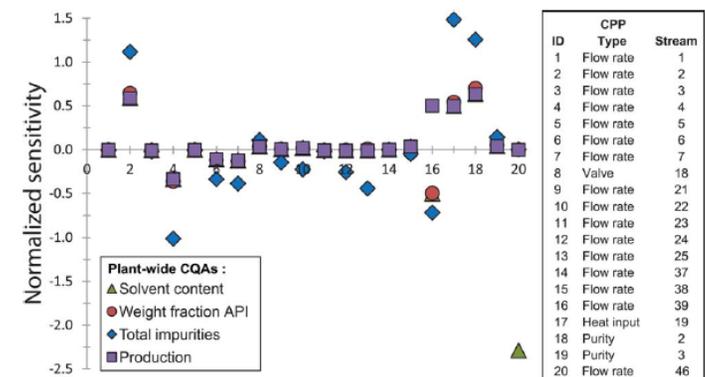
- General expectations regarding the science and risk-based understanding and control of processes and product quality are the same for CM as for traditional batch manufacturing
- Risk assessment: hazards identified may be different for a CM process
 - Process understanding forms the foundation for effective 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
 - Important to enable real-time decision making during manufacturing
 - Additional process understanding gained and communicated throughout the lifecycle of the drug product could be utilized as part of continual improvement of the process

Process Understanding: Input Parameters

- Common tools (e.g. design of experiments (DOE)) may be used to increase process understanding
 - Fast response of CM process allows for gathering a larger amount of experimental information in a short time
- CM offers a great opportunity to develop and utilize process models to efficiently investigate the input parameter space
- Sensitivity analysis can indicate the magnitude of the effect of inputs on quality attributes
 - Identify material properties that have a potential to impact quality due to continuous processing
 - Introduce appropriate material specifications
 - Identify control/manipulated variables that should be incorporated into the control strategy



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

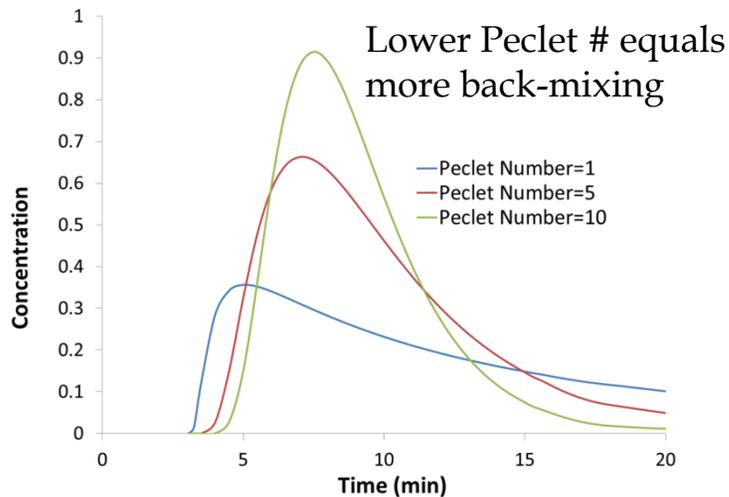


Lakerveld R *et. al.* *AICHe J.* 2013;59;3671-3685

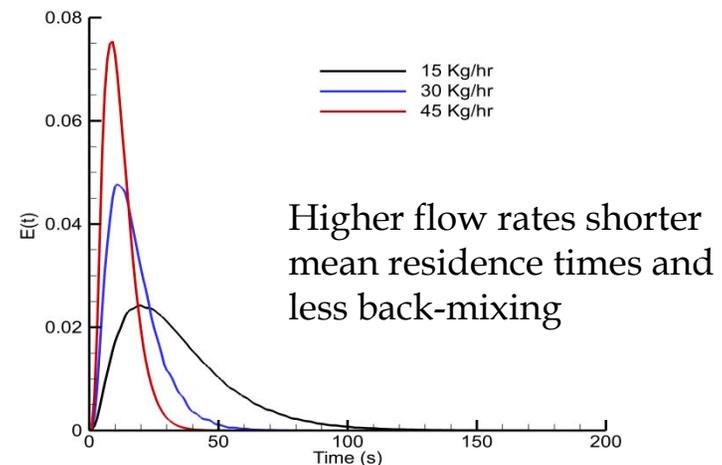
Process Understanding: Dynamics

- Understanding the interactions of unit operations in the process train help understand the behavior of the entire system (over time)
- An understanding of process dynamics can be obtained by characterization of the Residence Time Distribution (RTD)
 - In addition to characterize RTD and nominal operating conditions it is important to understand how the RTD depends material properties, process parameters, & equipment configuration
 - *Line rate is a important variable to be considered*

RTD as a function of back-mixing



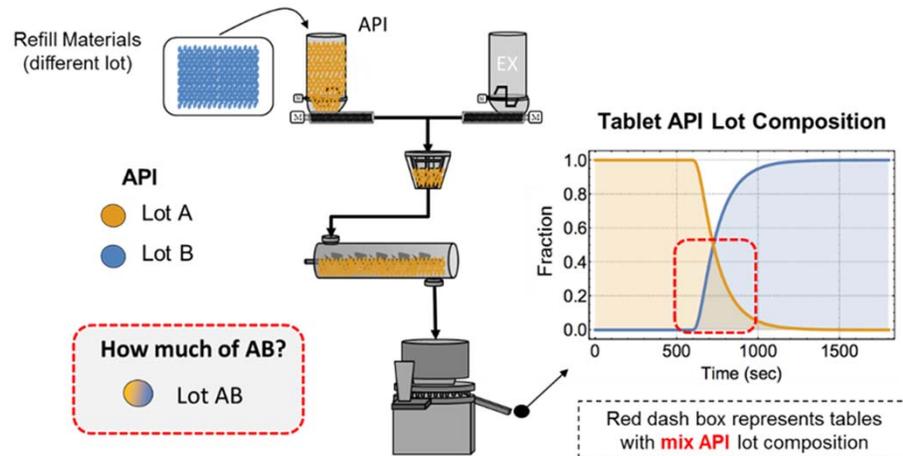
RTD as a function of line rate



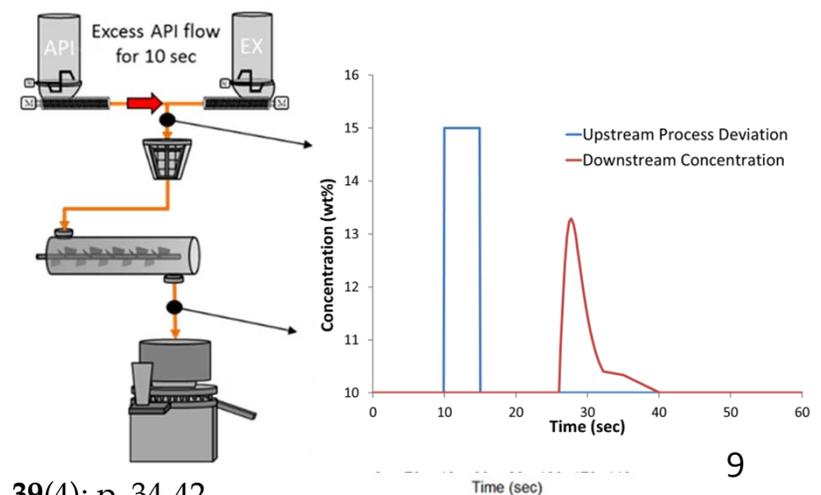
Process Dynamics: Traceability

- RTD curve can be utilized to predict the propagation of material or disturbances through the system or, in a retrospective analysis, to determine when the ingredients in a given product unit were fed to the manufacturing system
 - Traceability of different lots of raw materials to finished products
 - Characterizing back-mixing important for understanding the propagation and dampening of disturbances
 - Analysis should account for uncertainty in the measured/predicted RTD

Material Traceability

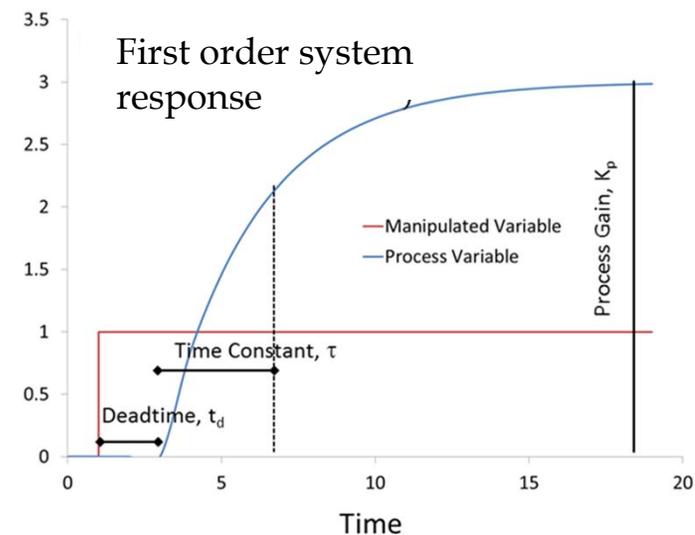
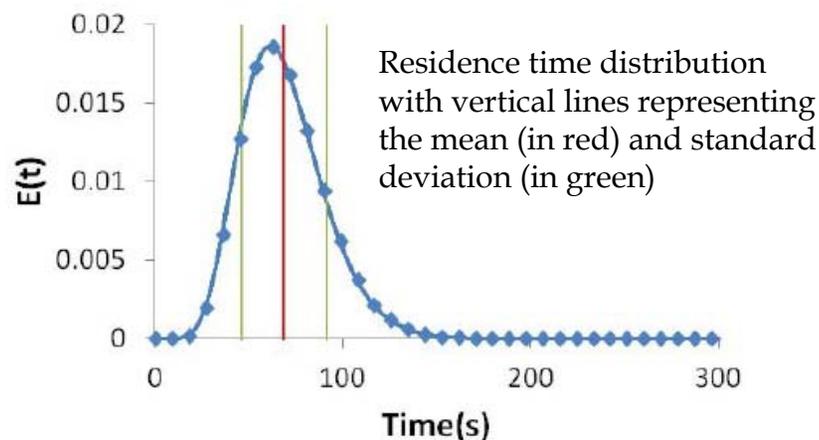


Disturbance Propagation



Process Dynamics: Transient Operations

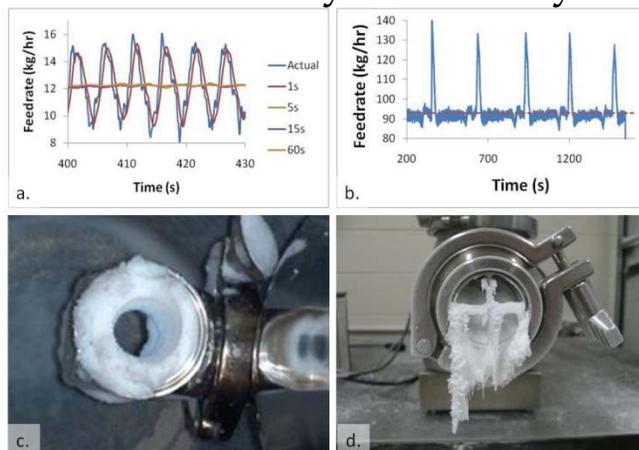
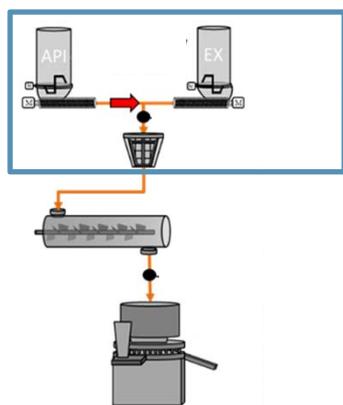
- Detectability of transient disturbances impacted by relationship between process dynamics and sampling frequency
 - Width of the RTD can provide information on adequate sampling frequency
 - Extent and duration of the transient disturbance also impacts detectability
- Characterization of the system response to step changes important for designing control strategy for transient operations
- Consider impact of process start-up and shut-down on product quality



Process Understanding: Potential Failure Mode Analysis

- Understand factors that affect variability of continuous process over total operation time
- One example is the assessment of feeder variability
 - Include analysis of downstream units ability to filter feeder variability
 - Analysis of fluctuations caused by feeder refills
 - Impact of excipient concentration variability on product performance

Potential sources of content uniformity variability from feeders



- Feeder Fluctuations
- Deviations caused by refill
- Downspout accumulation
- Feeder Bearding

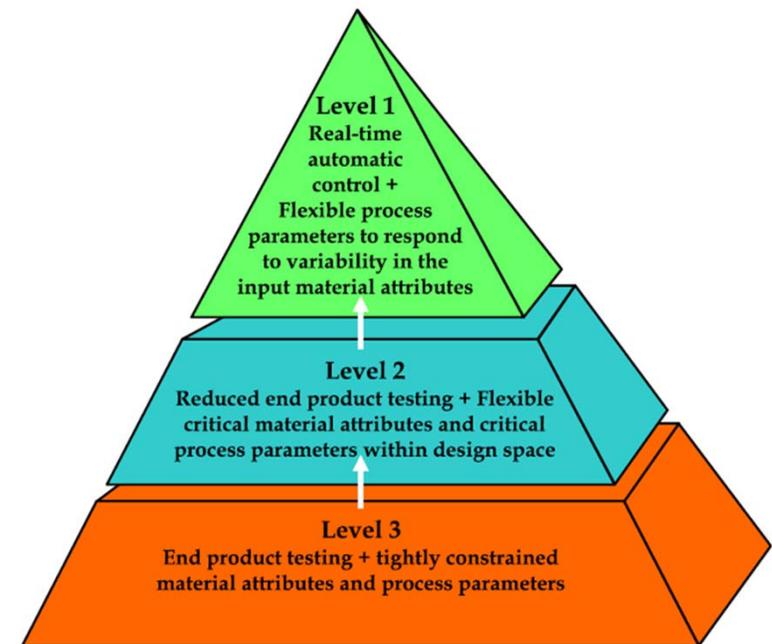
Control Strategy: State of Control

- Control strategy (CS) for a continuous process should be designed to mitigate product quality risks in response to potential variations over time
 - CS should be based on process understanding and be appropriate for each individual process
- Establishing a condition in which a set of controls consistently provides assurance of continued process performance and quality (ICH Q10)
- For CM, this can be integration of process parameter limits (set points and alarms), in-process monitoring (including PAT), process controls (feedback and feed forward), material diversion scheme (real time isolation or rejection), trending, and continuous improvement

Levels of Control

Criteria for establishing a state of control will depend on the control strategy implementation

- Level 1: Active control system with real time monitoring of process variables and quality attributes
 - Reliant on active process controls system
- Level 2: Operation within established ranges (multivariate) and confirmed with final testing or surrogate models
 - Reliant on process monitoring and diversion of non-conforming material
- Level 3: Unlikely to be operationally feasible for addressing natural variance in CM without significant end product testing



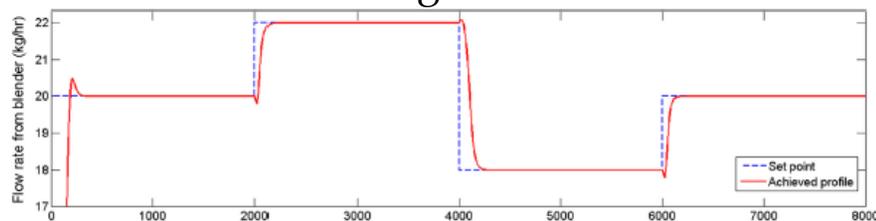
Yu LX, *et. al.* The AAPS Journal. 2014;16;771-783.

The 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

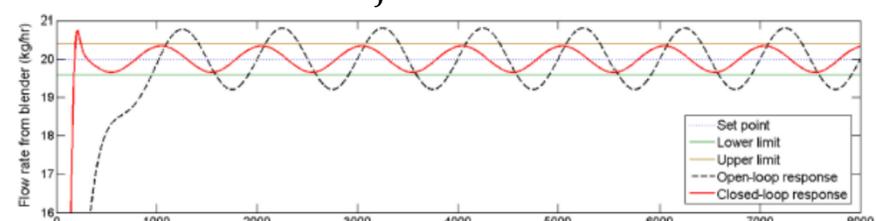
Active Control Approaches

- **Ratio Control:** used to maintain the flow rate of one stream at a specified proportion relative to another flow rate
 - Need to consider the impact of any lag time between the master feeder controller and the other slave feeders on the composition of the finished product
- **Feedback:** output information (controlled variable) is used to automatically trigger upstream action (manipulated variable)
 - Typically incorporated into the control of individual unit operation (e.g. loss-in-weight feed rate control, compression force control)
- **Feedforward:** output information is used to automatically trigger downstream action
 - Need predictive dynamic relationships among process parameters and quality attributes
- **Criteria to evaluate control system performance include set-point tracking and disturbance rejection**

Set-Point Tracking



Disturbance Rejection

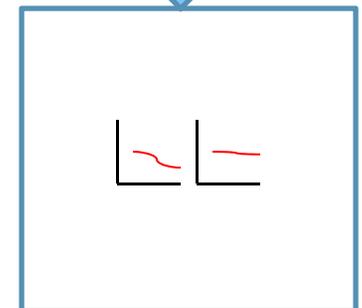
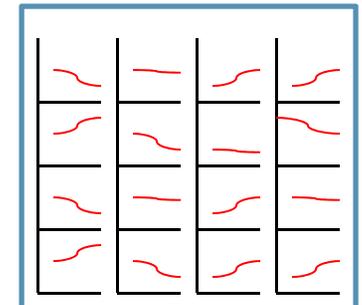
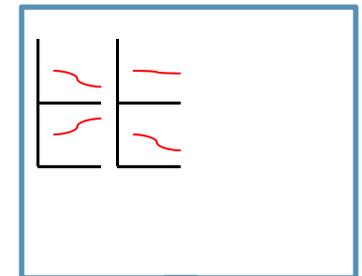


R. Singh *et. al.*, *Eur. J. Pharm. Biopharm.*, vol. 85, pp. 1164-1182, 2013

Approaches for Process Monitoring

- **Statistical Quality Control (SQC)**
 - Variability in quality attributes of the product are monitored over time
- **Statistical Process Control (SPC)**
 - The variability in critical process parameters and in-process quality measurements are monitored over time
 - Monitoring the process variables expected to supply more information (e.g., detection and diagnosis)
 - May generate a large number of univariate control chart that need to be monitored
- **Multivariate Statistical Process Control (MSPC)**
 - Takes advantage of correlations between process variables
 - Reduces the dimensionality of the process into a set of independent variables
 - May detect abnormal operations not observed by SPC

Operator Overview Display



Diversion of Non-Conforming Material

- The ability to isolate and reject material that is out of specification if the process is no longer in a state of control can be one of the key aspects of a continuous manufacturing control strategy
 - Planned process start-ups and shutdowns
 - Temporary process disturbances or upsets
- The evaluation of overall residence time distribution and the understanding of propagation of a disturbance between extraction points in the system are important to justify the amount of material at risk due to an unexpected event or disturbance
- Ideally, measurement (PAT) and material extraction points should be near where the event can occur, but downstream extraction is possible with understanding of process dynamics

Control Strategy: Utilization of Process Models

- Adoption of higher level control approaches may lead to the implementation of process models as part of the control strategy
- Process models may be based on first principles, empirical data, or a hybrid approach
- Examples include:
 - Dynamic models for feedforward control or multiple input multiple output (MIMO) model predictive
 - Empirical MSPC models for process monitoring
 - RTD modeling for material traceability and diversion of non-conforming product

Considerations for Process Models

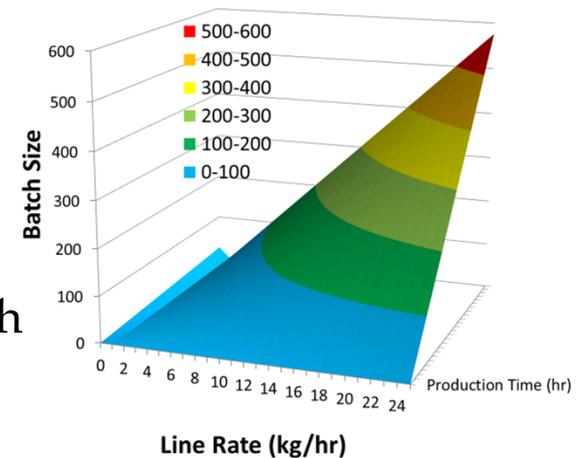
- Level of detail for model documentation based on its impact (high, medium, low) on assuring product quality
 - ICH Quality Implementation Working Group Points to Consider (R2)
- Consider providing for high-impact models:
 - Underlying model assumptions
 - A graphical summary of model inputs and outputs
 - Relevant model equations
 - Potentially the specific ranges for model parameters
- Verify performance for high-impact models
 - E.g. In case of RTD model - the capability of the model to trace the identified OOS product segment through the system to the rejection point
- Understand risks to validity of model predictions
 - Model parameter uncertainty
 - Expected variation in process parameters and material attributes
 - Assessment of product quality risks resulting from potential transient disturbances and/or 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

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.**”

Considerations for Batch/Lot Definition in CM

- Potential definitions based on a range of:
 - Production time period
 - Amount of material processed
 - Production variation (e.g. different lots of feedstock)
 - Other definitions also possible given that a continuous process may be combined with batch upstream (e.g. pre-blend of raw materials) or downstream (e.g. coating) operations
- 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
 - Definition of batch stated before start of manufacture



Risk Communication

- The output/results of the quality risk management (QRM) process should be appropriately communicated and documented (ICH Q9)
- Communications might include those among interested parties (e.g., regulators and industry; or within a company)
- Communication of the QRM process can include how risks identified based on an appropriate process understanding are mitigated by the control strategy
 - Examples of additional communication elements can include:
 - Boundaries and scope of the implemented control strategy
 - Residual level of risk to quality after the implementation of the control strategy
 - Procedures in case a disturbance occurs that is not mitigated by the control strategy - important for real-time operations
- Additional opportunities to request early communication with FDA
 - Emerging Technology Team: contact at: CDER-ETT@fda.hhs.gov

Risk Communication: Process Models

- Quality risk management requires product and process knowledge to identify, analyze, evaluate, control, and communicate the risks
- Process models can be good framework for capturing the related scientific knowledge
 - Formally stating assumptions and reasonable sources of uncertainty, which is part of the model building process, enhances confidence in this output and/or helps identify its limitations
 - Utilization of process models in risk-based quality management can become one source of common risk assessment approaches, and can be used to facilitate the communication of risk and risk mitigation approaches between industry and regulatory bodies

Concluding Thoughts

- Process understanding key to identifying product quality risks and developing a robust control strategy
 - Unique areas for focus include process dynamics and material flow
- 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
- The output/results of the quality risk management (QRM) process should be appropriately communicated and documented
 - Additional process understanding gained and communicated throughout the lifecycle of the drug product could be utilized as part of continual improvement of the process

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