Continuous Manufacturing of Drug Product

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Outline

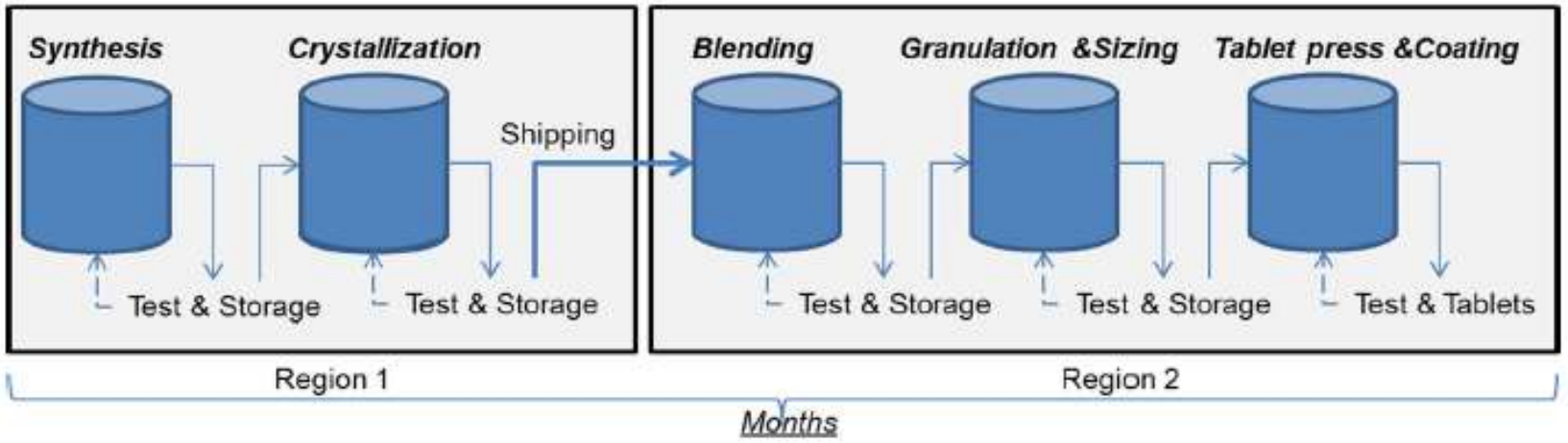
- Introduction
- Implementations of continuous pharmaceutical manufacturing
- Control strategy considerations
- Facility considerations
- Conclusions

Learning Objectives

- Describe operational and control strategy differences between batch and continuous drug product manufacturing
- Explain importance of material control for a continuous manufacturing process
- Identify factors impacting mixing dynamics in a continuous manufacturing line
- State at least one factor impacting in-process measurements
- Recognize role of pharmaceutical quality system in a continuous manufacturing environment

Pharmaceutical Manufacturing

A Typical Batch Manufacturing Process

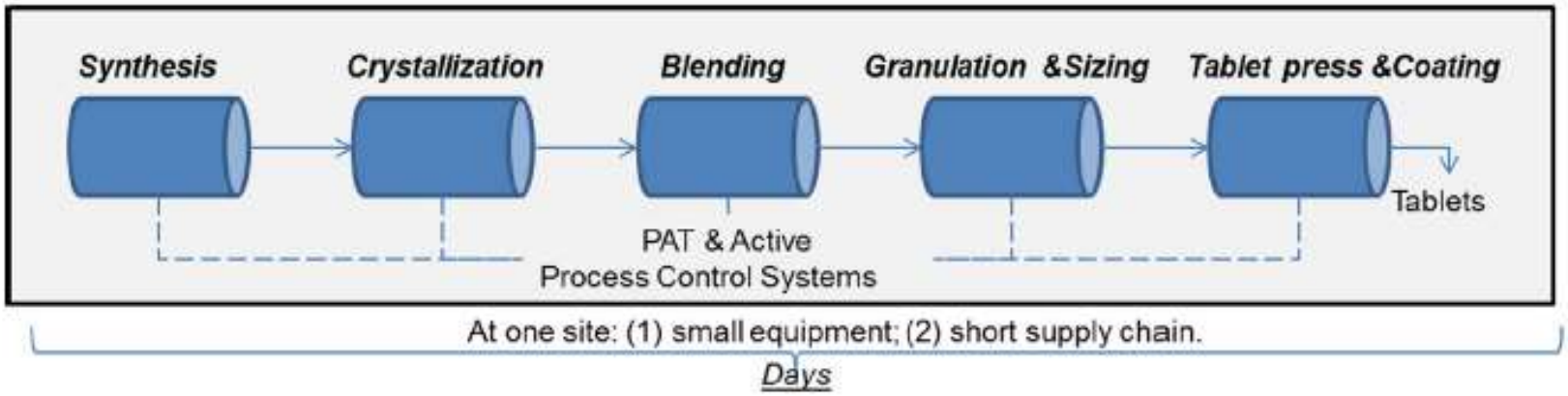


-Discrete unit operations
-In-process material are collected/tested at the end of each unit operation
-Hold time studies allow for investigation

S. Lee et al., J. Pharm. Innov., 2015

Pharmaceutical Manufacturing

A Conceptual Integrated Manufacturing Process

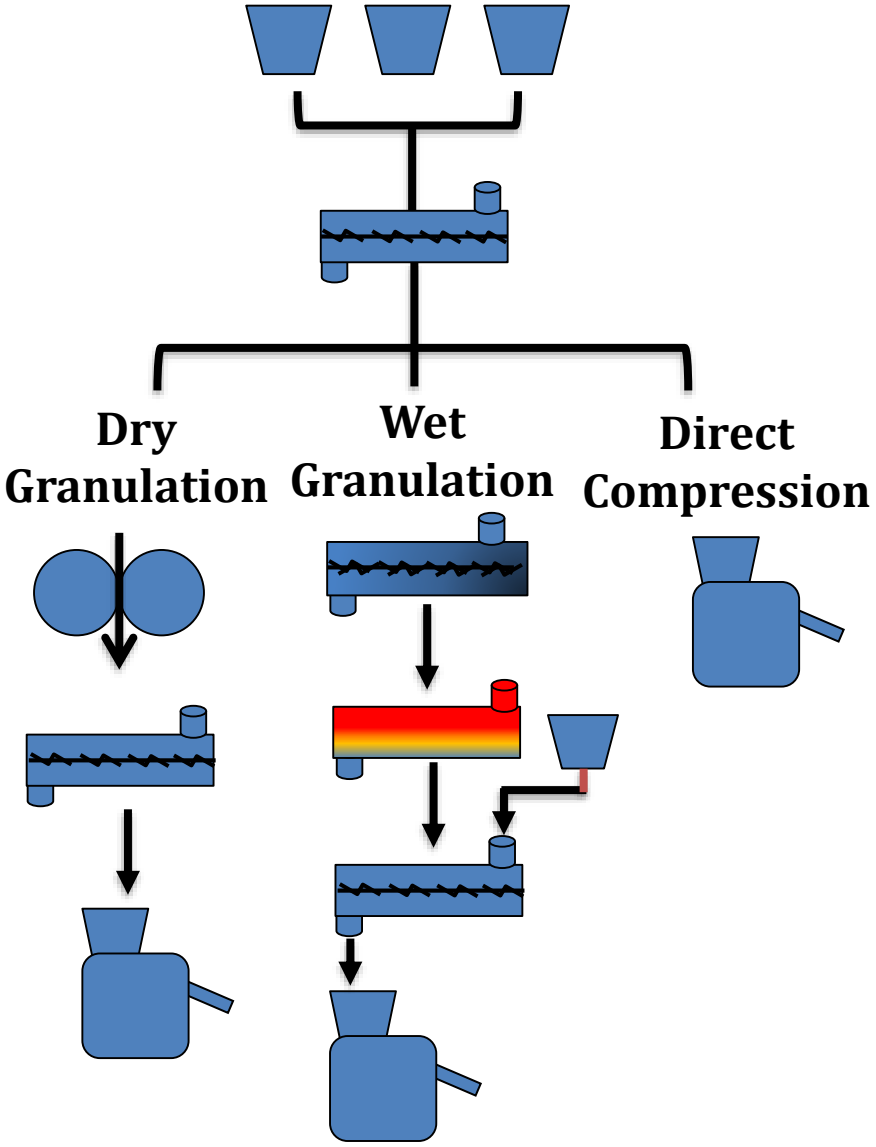


-Integrated unit operations
-Material is constantly generated and flowing between unit operations
-Process is monitored during processing
-Data-rich manufacturing environment

S. Lee et al., J. Pharm. Innov., 2015

CM Platforms for Drug Product

- Different manufacturing processes can be implemented
- Equipment of the same or different operating principles compared to batch processing
- Different control strategy considerations for an integrated continuous manufacturing process



Aspects of CM Implementation

Process Design

- Engineering design
- Process dynamics
- Equipment configuration
- Critical control points

Batch and Lot Definition

- Batch size definition
- Throughput rate(s)
- Yield & rejection limits

Control Strategy

- Raw material control
- Process monitoring & control (e.g. RTD/PAT models)
- Sampling strategy
- Start-up & shut down
- Product collection & diversion

Facility Implementation

- System integration, equipment qualification & cleaning
- Process performance qualification
- Data processing & management
- Model maintenance & update
- Process verification

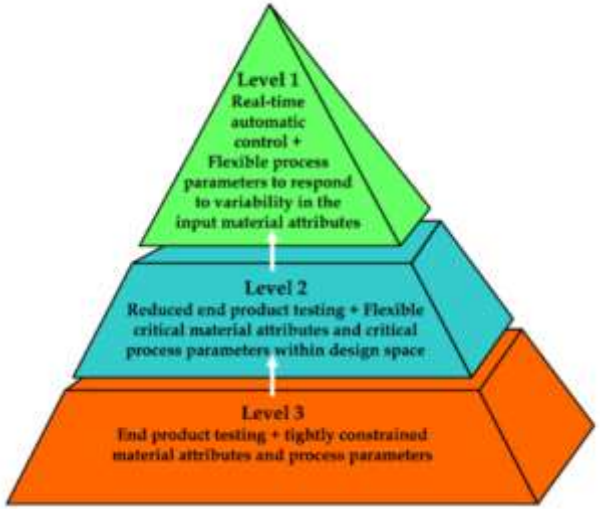
State of Control

- A planned set of controls, derived from current product and process understanding that assures product performance and product quality
- Comprehensive Control Strategy for CM:
  - Material attributes of drug substance and drug product components
  - Facility and equipment operating conditions
  - In-process controls
  - Finished product specifications
  - Methods and frequency of monitoring and control
- CM requires different control strategy than batch processes

Guidance for Industry: Q10 Pharmaceutical Quality System, April 2009

Implementation Options for Control Strategy

- **Level 1:** Active control system with real time monitoring of process variables and quality attributes
- **Level 2:** Operation within established ranges (multivariate) and confirmed with final testing or surrogate models.
- **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.

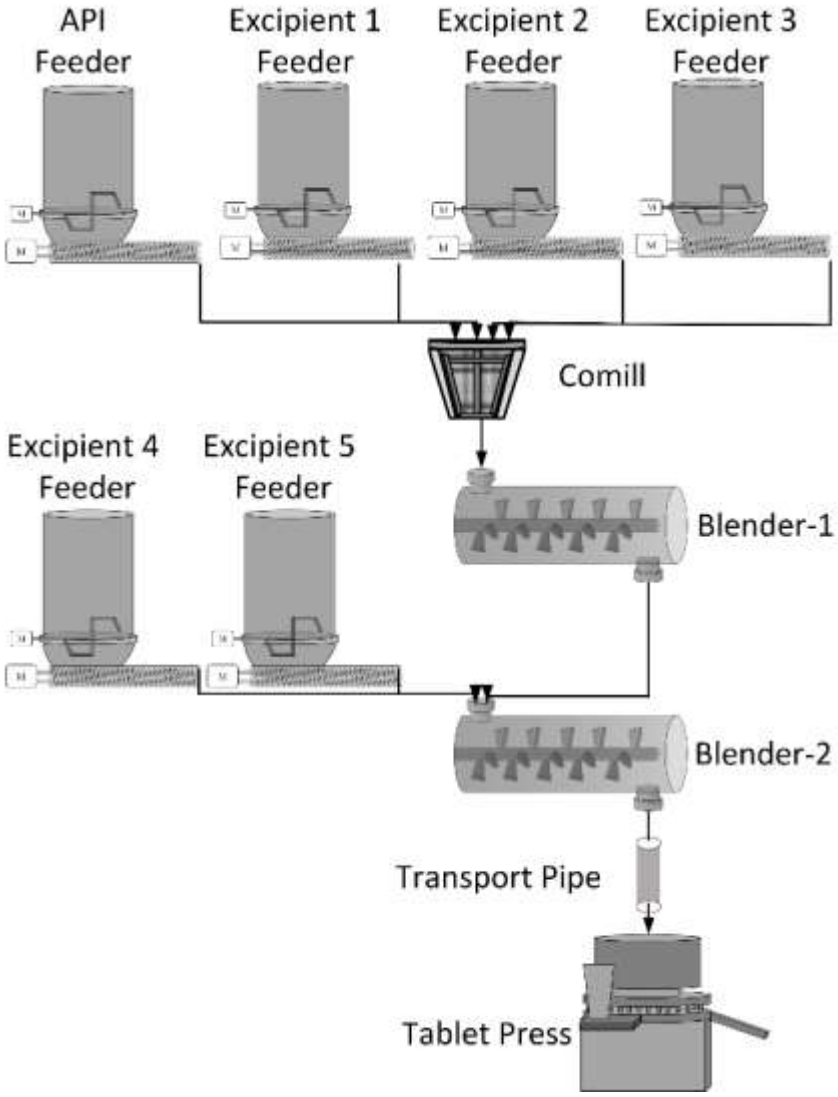
Impact of Raw Material Attributes

Material Attributes	API, Process & Product Design Considerations
• Particle Size Distribution	BCS classification
• Shape	Drug Load
• Density	Excipient Ratios
• Friction Angle	Feed flow consistency
• Flow Function	Process dynamics
• Powder Cohesivity, …etc.	Segregation potential

Product Performance

A Risk-Based Approach is Recommended in Establishing Criteria for Raw Material

Considerations of Material Attributes



Hopper Design- consider bulk density, wall friction, cohesive strength of the material to ensure mass flow.

Feeder - Initial feed factor, feeding performance, and deviations during refill can be dependent on material flow properties.

Mixer - Tracers used for characterizing Residence Time Distribution (RTD) need to have similar bulk properties with the bulk.

Tablet press - Tablet weight uniformity can be impacted by flow properties of in-process material.

Raw Material Attributes and Risk to the Process and Product

- Material attribute control is important for continuous feeding and developed PAT/process models
- Impact of lot to lot variation in material attributes
  - Accuracy and precision of material feeding
  - Mixing dynamics (RTD) and downstream processes
  - Predictability of in-process and/or RTRT PAT models

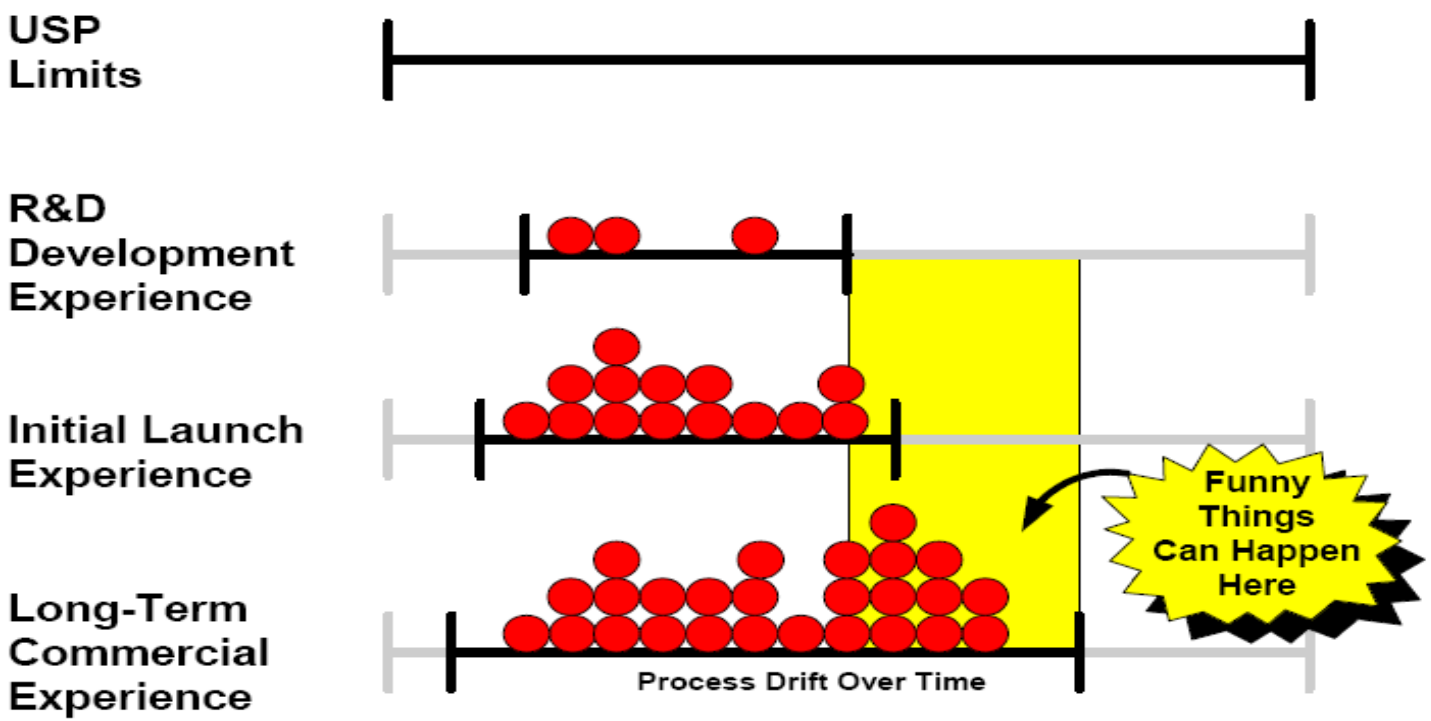
Drug Product CQAs

Assay

Content Uniformity

Dissolution

Lot to Lot Variation Over Product Lifecycle



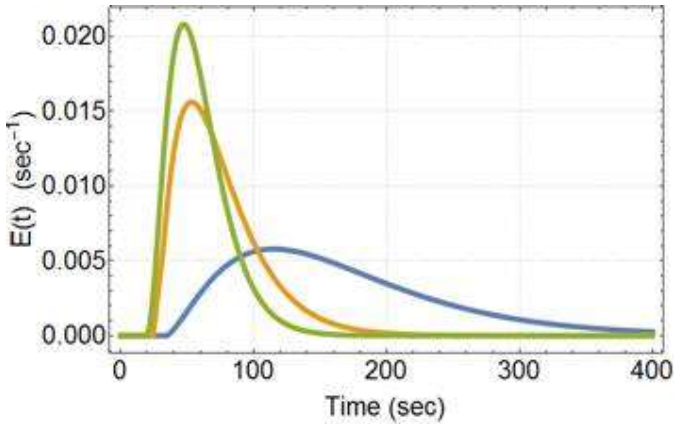
Considerations for Raw Material Control

- Compendial specifications may not always provide adequate material control
- Understand impact of material attributes during development
- Develop procedures within the firm's pharmaceutical quality system (PQS) to monitor incoming material lots
- Perform model maintenance and update as necessary

System Dynamics and Process Development

Residence Time Distribution (RTD): Probability distribution of time that solid or fluid materials stay inside one or more unit operations in a continuous flow system

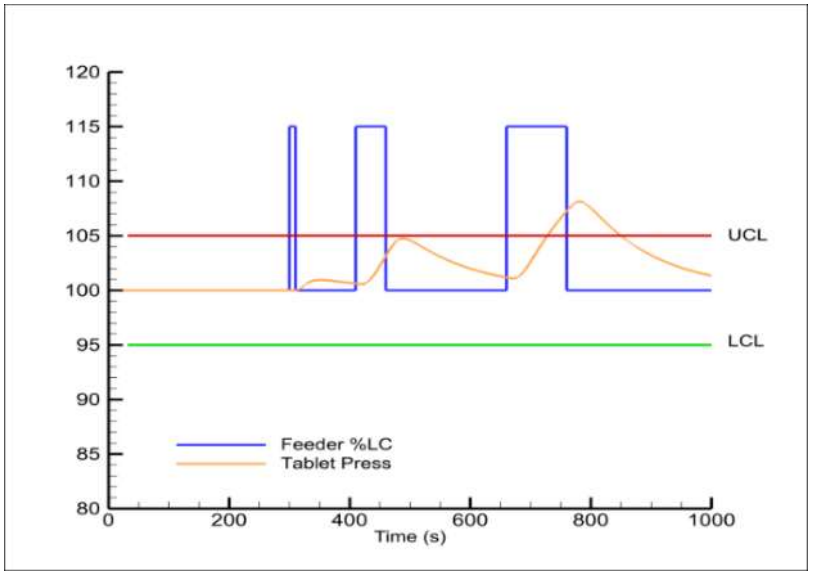
- RTD is a characterization tool of system dynamics and depends on:
  - Material properties
  - Process parameters
  - Equipment configuration



Courtesy: Escotet-Espinoza, Rogers, Muzzio, Ierapetrirou, Engineering Research Center - Rutgers University

RTD Utilization in CM

- Evaluate equipment design and/or configuration
- Evaluate response to set point changes
- Assess filtering capacity of downstream equipment
- Track of material/disturbances throughout the line
- Support the sampling strategy during manufacturing
- Support accept/reject decisions, e.g. during start-up, shut down, pauses and restarts



How is the Batch Size Defined in CM?

21 CFR 210.3

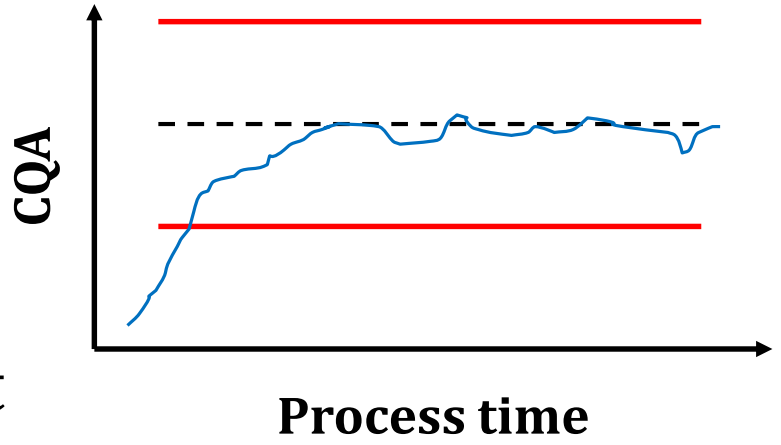
Batch: *A specific quantity of a drug or other material* ***that is intended to have uniform character and quality****, within specified limits and is produced* ***according to a single manufacturing order during the same cycle of manufacture****".*

Lot: *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****."*

- Batch size definition is flexible
- Can be defined as a function of run time, quantity of processed material, production variation
- Batch definition ensures proper documentation, conformance to batch release specifications, investigations of unexplained discrepancies, and in recall situations

State of Control and Product Collection

- During start-up, and shutdown not all unit operations within a continuous production line will be in a state of control at the same time



- Description of start-up and shutdown procedures
- Clear criteria for product disposition
  - Starting and ending product collection
  - Material diversion

Real Time Release Testing (RTRt)

The ability to evaluate and ensure quality of in-process and/or final product based on **process data**, typically include a valid combination of **measured material attributes and process controls** (ICH Q8 (R2))

Benefits:

- Data rich environment
  - Enhanced process understanding
  - Increased assurance of quality
- Increased manufacturing flexibility and efficiency

Design Considerations for In-Process Sampling

- Optimum points of testing/collecting model input parameters based on risk assessment
- Sampling strategy supported by system dynamics, e.g. sample acquisition time and sample frequency
- Valid sampling interface throughout the process, e.g. no fouling or instrument drift as a result of temperature or humidity variation
- Representative sample volume/mass

Guidance for Industry Q8(R2) Pharmaceutical Development, November 2009

Design Considerations for the PAT Method

- Appropriate model development, validation & update
  - Model impact on the overall control strategy
  - Procedures in the firm's quality system for monitoring model performance and updating the models
- Appropriate statistical criteria for large sample sizes
- Instrumental aspects
  - Routine maintenance
  - Instrument failure

Guidance for Industry Q8(R2) Pharmaceutical Development, November 2009

Facility Considerations

- Adjustments to existing facility pharmaceutical quality system (PQS)
  - Updates to Quality and production procedures
  - Quality oversight of automated controls, process data, RTR, and electronic records
- Quality evaluation when material is diverted and quarantined
  - Deviations, level of investigation, root cause analysis, corrective and preventive action, understanding diversion event for continuous improvement, etc.
- Process Validation, readiness for commercial manufacturing, and knowledge management
  - Demonstration of robustness, process monitoring, and broader control strategy
  - Assessment of change controls for total impact
- Integrated equipment train
  - Knowledge gained from equipment qualification to support proposed batch size or run time
  - Cleaning validation, maintenance, and performance monitoring to support commercial lifecycle and multiproduct manufacturing
- Additional controls for incoming raw materials

Summary and Conclusions

- FDA supports implementation of continuous manufacturing using a science and risk-based approach
- Science and control strategy considerations for continuous manufacturing remain the same irrespective of submission type (new, drugs, generic drugs original applications, post-approval supplements)
- Process design, material and process understanding are key to a robust control strategy
- Role of PQS in a continuous manufacturing environment is critical to its long term success

Challenge Question

- Compendial specifications of excipients provide adequate control of material attributes for continuous manufacturing (T/F)
- RTD as a characterization tool of mixing dynamics depends on:
  a. Material properties
  b. Process parameters
  c. Equipment configuration
  d. All of the above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