Scientific and Regulatory Considerations for Continuous Manufacturing Implementation for Drug Product

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PQRI March 2017
Outline

• Key Elements for Process Development and Control Strategy
  – Original Continuous Manufacturing Applications
  – Conversion from Batch to Continuous Manufacturing
• Considerations for Pharmaceutical Quality System
• Summary and Conclusions
Modernizing Pharmaceutical Manufacturing

- Science and risk-based approaches to process design and product development
- Assurance of consistent product quality
- Robust Pharmaceutical Quality System
- Lifecycle approach to continuous process improvement


*US FDA Guidance to Industry: Process Validation: General Principles and Practices*

*ICH Q8(R2), Q9, Q10 and Q11*
Key Elements of CM Control Strategy

• Process understanding
  – Impact and interactions of process parameters and material attributes over time
  – Characterization of process dynamics
• Development of methods for detection and control
• Batch definition as it relates to a “state of control”
• Verification of Control Strategy
How is the CM Line Designed?

Components
- Active Ingredient
- Filler
- Binder
- Water
- Disintegrant
- Lubricant

Unit Operations
- Wet Granulation
- Drying
- Milling
- Blending
- Tablet Compression

In-Process Controls
- Granule Size
- LOD
- Granule Size Distribution
- Blend Potency
- ID, Assay, Content Uniformity, Weight, Thickness Friability, Dissolution

Top Level
- Feeding
- Pre-blending & Wet Granulation

Mid Level
- Drying
- Milling
- Feeding & Blending

Bottom Level
- Tableting
- Rejection Point I
- Rejection Point II
- Rejection Point III

Pneumatic Feed

FDA
What are Relevant Raw Material Attributes for Continuous Manufacturing?

- Particle Size Distribution
- Shape
- Density
- Friction Angle
- Flow Function
- Powder Cohesivity
- ...
- ...
- ...
- It depends

A Risk-Based Approach is Recommended in Establishing Criteria for Raw Material
Dynamics of a Continuous Process

- **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
  - Understand material transport inside different unit operations and the entire system dynamics
  - Measured by tracer experiments and/or predictive modeling

*Courtesy: Escotet-Espinoza, Rogers, Muzzio, Ierapetritou, Engineering Research Center - Rutgers University*
How can RTD be Utilized in Process Development and Control Strategy?

- Evaluation of unit operation/process performance taking into consideration expected variation in material attributes and process parameters including throughput rate
- Optimization of equipment design and/or configuration
- Tracking of material/disturbances throughout the line
- Assessment of filtering capacity of downstream equipment
- Support accept/reject decisions during operation
- Support the sampling strategy during manufacturing
What are Different Methods of Detection and Control?

- Process parameter limits
- Disturbance propagation
- In-process monitoring
- Real Time Release testing
- Process decisions to maintain a state of control
  - Material segregation
  - Feedback/Feedforward
- Implementation options for control strategy

What are the Scientific Considerations for Process Sampling and RTRt?

- Optimum points of testing/collecting model input parameters based on risk assessment
- Sampling strategy supported by system dynamics
- Valid sampling interface throughout the process
- 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 as appropriate
- Instrumental aspects
  - Routine maintenance
  - Instrument failure

Guidance for Industry Q8(R2) Pharmaceutical Development, November 2009
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/throughput rate, quantity of processed material, production variation
How is Batch Definition Linked to the Control Strategy?

- *A priori* definition of batch size
- State of control during product collection
  - Defining procedures for start-up/shut down
  - Traceability of input materials to final product
  - Identification and control of sources of variability
  - Adequate in-process measurements for assurance of uniform product quality
- Disposition strategy of non-conforming product
- Material reconciliation
Additional Considerations

CONVERSION FROM BATCH TO CONTINUOUS MANUFACTURING
Raw Material Considerations

- Reassess appropriateness of existing drug substance and compendial excipient specifications

- Existing material attributes may pose challenges in a continuous feeding/granulator system
  - Feeding accuracy of low dose API
  - Handling of lot to lot assay variation of the API
  - Consistent feeding of cohesive, low density, minor functional excipients
  - Impact of spikes, refill cycle frequency and duration
Operational Considerations

- Re-assess impact of critical process and equipment design parameters on process performance
- Timescale is in seconds but total operation is over several hours
  - Characterization of RTD e.g. ensure adequate time for blending, powder wetting, binder activation, adequate drying.
- Evaluate capacity to handle upstream disturbances and impact on downstream processes, e.g. feed rate variability, variation in incoming granule moisture content, granule size distribution, etc.
- Continuous process monitoring
- Microbial evaluation to cover planned/unplanned pauses
Process Control Considerations

- Impact of minor formulation/process/sensor interface change on developed PAT and reference analytical methods
- Evaluate sample acquisition time relative to system dynamics
- Process timescale in hours/days
  - Instrument robustness
  - Potential for sensor fouling
  - Data storage capacity
- Reconciliation of discrepancies between multiple sensing locations
- Dealing with OOS results
PHARMACEUTICAL QUALITY SYSTEM (PQS) IN A CM ENVIRONMENT
Paradigm Shift for PQS

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

- Integrated unit operations
- Material is constantly generated and moving
- Data-rich manufacturing environment
- QC oversight must be built into process decision-making

S. Lee et al., J. Pharm. Innov., 2015
US FDA Guidance to Industry: Process Validation: General Principles and Practices, ICH Q10
Quality Risk Management

• Proactive approach based on process understanding
  – Identification of potential failure modes
  – Detectability: process parameters, PAT signals, sampling frequency, lag time, alarm limits
  – Clear plan of action justified and determined in advance
• Maintain process in a state of control
  - Robust control strategy
  - Detect and remove OOS material
  - Process stability consideration
• Deviation investigation and feedback into knowledge base
• Batch Review
  - Assess robustness considering % yield and % efficiency

US FDA Guidance to Industry: Process Validation: General Principles and Practices, ICH Q9
Knowledge Management

• Documentation: development reports, technology transfer activities, process validation protocols and reports, batch records

• Establish programs to collect, analyze, and maintain data related to product quality
  – Design a monitoring plan: attributes/metrics, frequency of trending/analysis, statistical approach(es)
  – Intra-batch and inter-batch comparisons
  – Long term assessment of impact of raw material attributes on system dynamics and process
  – Equipment performance indicators over time
  – PAT Model maintenance activities

• Monitor and improve process capability
Quality Control Unit and Automation

• Quality decision making must be programmed
  – Interlocks, communication checks, recipe integrity, data collection frequency
  – Monitoring, alert & alarm limits, segregation points, automatic stops
  – Start up sequence, restart, material collection criteria, and shut-down processes

• Some oversight is delegated to the automation but the QCU is ultimately responsible for the product

• Design, validation, and qualification of automation with equipment is critical

• Maintenance of Automation Control System
  – Robust change control process for code improvements
  – Monitoring of ACS performance
  – Version control, back-ups, and security
Summary and Conclusions

• Continuous manufacturing can be implemented for new/generic drugs in both original applications as well as post-approval supplements

• Science and risk-based approach for process development and control strategy for continuous manufacturing remain the same irrespective of submission type

• Re-explore process development to establish an appropriate control strategy when converting from batch to continuous

• Role of PQS in a continuous manufacturing environment is critical to its long term success
Acknowledgements

• Rapti Madurawe, Ph.D.
• Sharmista Chatterjee, Ph.D.,
• Christina-Capacci-Daniel, Ph.D.