Continuous Pharmaceutical Manufacturing: Scientific Considerations for Developing a Robust Manufacturing Process and Control Strategy

Arwa El Hagrasy, Ph.D.
Office of Process and Facilities
OPQ/CDER/FDA

IFPAC®/QbD/PAT Summit
Carolina, Puerto Rico
June 21, 2016
Outline

• Background

• Process Development and Control Strategy Considerations
  – Original Continuous Manufacturing Applications
  – Conversion from Batch to Continuous Manufacturing

• Summary and Conclusions
Pharmaceutical Manufacturing

Batch Process

Continuous Process

S. Lee et al., Modernizing Pharmaceutical Manufacturing: from Batch to Continuous Production, J. Pharm. Innov., 2015
Integrated Framework for 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*
Part I: Scientific Considerations

PROCESS DEVELOPMENT AND CONTROL STRATEGY
Integrated Process Flow
Solid Dose Manufacturing

- 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
Control Strategy

• A planned set of controls, derived from current product and process understanding that assures product performance and product quality

• Comprehensive Control Strategy:
  – Material attributes of drug substance and drug product components
  – Facility and equipment operating conditions
  – In-process controls
  – Finished product specifications

Guidance for Industry: Q10 Pharmaceutical Quality System, April 2009
Control Strategy

Product and Process Understanding

Operational Flexibility

Residual Risk

Control by End Product Testing

Multivariate Design Space & Controlling Mechanisms

Fully Quantitative & Predictive Models

More Suited for Continuous Manufacturing
Considerations for an Integrated Continuous Manufacturing Line

- Identification and adequate characterization of relevant physico-chemical material attributes
- Risk-based determination of an acceptable range of relevant material attributes taking into consideration lot to lot variation
- Identification of critical process parameters and control points
Considerations for an Integrated Continuous Manufacturing Line

• Description of equipment interconnections
  – Ensure steady material flow/absence of dead zones
  – Understand cyclical behavior/back-mixing

• Characterization of disturbance propagation throughout the line
  – Tracking of raw material lots used in a given run
  – Filtering capacity of downstream equipment
  – Accept/reject decisions during operation
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 or predictive modeling

Courtesy: Escotet-Espinoza, Rogers, Muzzio, Ierapetritiou, Engineering Research Center - Rutgers University
RTD: Essential Component of 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
- Tracking of material/disturbances throughout the line
- Support accept/reject decisions,
  - e.g. during start-up, shut down, pauses and restarts
- Support the sampling strategy during manufacturing
Real Time Release Testing (RTRt) and Process Control

- RTRt is the ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls
  - On-line/in-line/at-line measurements
  - Surrogate models e.g. multivariate models
  - Process control models

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

- Optimum points of testing/collecting model input parameters based on risk assessment
- Sampling strategy supported by system dynamics
- Valid sampling interface throughout the process
- Adequate model development and validation
  - Model impact on the overall control strategy
- Procedures in the firm’s quality system for monitoring model performance and updating the models as necessary

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

- Flexibility of batch size is possible
- Can be defined as a function of run time, quantity of processed material, throughput rate, parallel lines, equipment size, etc.
  - *A-priori* definition of batch size

- Demonstrate manufacturability within the expected range
  - Build-up of material
  - Localized heating
  - Equipment performance
  - Change in process dynamics
  - Uniformity of quality
Part II: Scientific Considerations

CONVERSION FROM BATCH TO CONTINUOUS MANUFACTURING
Raw Material Attributes and Feeding

**Batch Process**
- Established drug substance and excipient specifications as part of initial formulation and process development
- Material added into process via manual/pneumatic feeding
  - Dispensed quantity of drug substance adjusted per assay, water content, etc.
  - Minor excipients weighed and added by co-blending, geometric dilution, etc.

**Continuous Process**
- Reassess appropriateness of existing drug substance and Compendial excipient specifications
- Material continuously added into the process via LIW feeders
  - Handling of lot to lot assay variation of the drug substance
  - Feeding accuracy of low dose API and minor functional excipients
  - Impact of spikes, refill cycle frequency and duration
Powder Blending

Batch Process

• Developed process for a given equipment based on optimized process parameters
• Timescale is in minutes to allow adequate blending of formulation components

• Standalone unit operation

• Conventional BU testing/PAT

Continuous Process

• Re-assess impact of critical process and equipment design parameters on mixing performance
• Timescale is in seconds but total operation is over several hours
  - Characterization of RTD to ensure adequate blending, material traceability, rejection, etc.

• Integrated with upstream/downstream processes
  - Evaluate capacity to handle upstream disturbances and impact of inadequate mixing on downstream processes

• Continuous process monitoring
Wet Granulation

Batch Process
- Developed process for a given equipment based on optimized process parameters
- Capable of handling hard to process powder e.g. low density, cohesive, poor flowability
- Timescale is in minutes which allows for wetting, agglomeration and wet massing to occur
- Constant quantity of powder and granulating liquid results in defined liquid/solid ratio
- Microbial evaluation for planned hold times before drying

Continuous Process
- Re-develop process based on unique equipment and process design parameters
- Similar material attributes may pose challenges in a continuous feeding/granulator system
- Timescale is in seconds and so RTD characterization is critical e.g. ensure powder wetting/binder activation
- Feed variation of input powder and granulating liquid compared to filtering capacity of granulator
- Microbial evaluation to cover planned/unplanned pauses
Drying

Batch Process
- Developed process for a given equipment based on optimized process parameters
- Drying process carries on until drying end point is achieved e.g. measured %LOD
- Dried batch is deemed of uniform quality

Continuous Process
- Re-develop process based on unique equipment and process design parameters
- RTD characterization and select process parameters for adequate drying within that timeframe
- Robustness of drying process
  - Handling of variation in moisture content of incoming granules to ensure drying consistency
  - Handling of broad span of input granule size distribution to ensure drying uniformity
- Stability of the proposed product
In-Process PAT Methods

**Batch Process**
- Developed PAT and/or reference analytical methods for monitoring one or more unit operations
- Sample acquisition time << unit operation dynamics
- Unit operation timescale is in minutes

**Continuous Process**
- 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
Summary and Conclusions

- FDA supports implementation of continuous manufacturing using a science and risk-based approach
- Continuous manufacturing can be implemented for new/generic drugs in both original applications as well as post-approval supplements
- Science and control strategy considerations for continuous manufacturing remain the same irrespective of submission type
- Re-exploring process development and control strategy in converting from batch to continuous to ensure uniformly high quality
Summary and Conclusions

• Early engagement with FDA
  – Emerging Technology Team
  – Meeting Requests
  – Pre-operational visit

*Advancement of Emerging Technology Applications to Modernize Pharmaceutical Manufacturing Base Guidance for Industry, December 2015*
Acknowledgements

• Office of Process and Facilities
  – Rapti Madurawe, Ph.D.
  – Christina Capacci-Daniel, Ph.D.
  – Sharmista Chatterjee, Ph.D.
Questions