Scientific Considerations for Continuous API Manufacturing

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Outline

• Continuous Synthetic API Manufacturing
• Trends in Continuous API Manufacturing
• Scientific Considerations for Continuous API Manufacturing
  – Process Understanding
  – Control Strategy
• Concluding Thoughts
Continuous Synthetic API Manufacturing

• Characterized by diversity in unit operations and process sequence configurations

• Continuous unit operations
  – Continuous flow reactors
  – Continuous purification (e.g. continuous crystallization)

• Manufacturing process configuration
  – Isolated continuous and batch unit operations
  – Integrated continuous unit operations and isolated batch unit operations
  – Integrated continuous manufacturing process
Advantages of Continuous Manufacturing

- **New synthetic pathways**
  - Increased safety
- **More flexible operation**
  - Adjust production to meet demand, emergencies,
    - Simplified scale-up
- **Smaller equipment and facilities**
  - Lower capital, operational and environmental costs
- **Integrated processing with fewer steps**
  - Total processing times shorter; faster product release
- **Higher degree of quality assurance**
  - Opportunities for process control
Trends in Continuous API Manufacturing

Approved examples of continuous unit operation for API manufacturing

Trend towards increased process integration and more advanced control strategy approaches

~5 Emerging Technology Team (ETT) - Industry meetings since the launch of ET program providing feedback on the development of CM API processes

• New APIs
• Conversion of existing batch processes
• Facility visits
Regulatory Science Initiatives Supporting CM for API

1. Advancing Continuous Flow Reactor Technology through Real-Time Control
   – Completed two year sponsored project with MarqMetrix, and University of Washington

2. Process dynamics and disturbance study of continuous crystallization
   – In-progress FDA led laboratory project

3. Advancement of Integrated Continuous Manufacturing
   – In-progress three year sponsored project with Continuus
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
Scientific Considerations for Continuous API Manufacturing

• Process understanding
  – Impact and interactions of process parameters and material attributes on impurity profile
  – Characterization of process dynamics

• Control Strategy
  – Equipment Design
  – Process monitoring
  – Level and integration of controls
Drug Substance CQAs

Critical drug substance attributes can be aligned with one of two groups:

- **Purity and Impurities**
  - Formation, fate, and purging of impurities impacted by changes to synthetic route, reagents and solvent, principles of operation for continuous unit operations

- **Physical characteristics of the drug substance**
  - Physical properties determined by operations at the end of the manufacturing process (e.g. final crystallization, milling, micronizing)
Process Understanding

• Risk assessments can lead to identification of critical material attributes and process parameters
  – Raw material properties
  – Operating conditions
  – Equipment design parameters

• Use the understanding of the impact of process parameters and material attributes on product quality:
  – Establish design space
  – 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
Process Understanding: Impurity Formation

- Combination of input controls, reactor design and control of process parameters shapes product quality

\[ A + B \rightarrow C \]

\[ \frac{d[C]}{dt} A = k[A]^a[B]^b \]

- Rate constant depends upon reactor design & geometry, temperature, pressure
- Reactant concentration depend upon reagent purity, flow rate, feed make
- Reaction time is a product of reactor design and flow rates
- May implement different control strategies depending upon if an impurity is not purged, very well purged, or partially purged by the downstream purification operations
Sensitivity Analysis and Risk Assessment

• Complex telescoped process with many different reactions taking place in each reactor
• Side products from one stage often react in later stages
• In silico kinetic model evaluation can facilitate the visualization of significant factors and interactions
• Gaining experience with model and multivariate experimental approaches to advancing process understanding
Process Dynamics

- The dynamics of how materials or disturbances flow through the process is a critical aspect of process understanding
  - Identify typical failure modes or deviations (long term vs. short term) (e.g., feeder variability)
  - Evaluate response to set point changes (e.g., change in line rates)
  - Assess the impact of Startup and Shutdown on material quality

- Obtain an understanding of process dynamics by characterizing the Residence Time Distribution (RTD)
Control Strategy

• 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), equipment design, in-process monitoring (including PAT), process controls (feedback and feed forward), material diversion, and Real Time Release Testing (RTRT)

• For a hybrid process, the control strategy should be designed at the system level encompassing both the continuous and batch segments of the manufacturing process

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

Opportunity for equipment design to be a component of control strategy

• Appropriate residence time for production rate
  – Enough time for reaction to reach completion or mass transfer to take place

• Appropriate mass transfer
  – Mixing sensitivity of reaction
  – Distribution of mixing for concentration control
  – Distribution of mixing for traceability

• Appropriate heat transfer
  – Heat balance requirement for safety
  – Heat balance requirement for selectivity
Process Monitoring

• Process monitoring approach is one key element of the control strategy for a continuous manufacturing process
  – Generates real-time information on process parameters and attributes of input materials, in-process materials and final product for the duration of the manufacture

• Enables high detectability of transient disturbances and other key elements of control strategy such as active process control, material diversion and real time release testing (RTRT)

• Process monitoring approach should consider:
  – Variables being monitored
  – Sampling plan and relationship to process dynamics
  – Data analysis
Process Analytical Technology (PAT)

• Specify the role of PAT and Models
  – Provide process understanding during development; process monitoring during production; process robustness; 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.

• Specific (e.g. HPLC) and non-specific (e.g. conductivity) measurement systems available
  – Important to assess for non-specific tests how it relates to monitoring the state of control for the process
Importance of Flow Control

- Accurate flow measurement can lead to identification of inaccurate or fluctuating flow rates
  - There can be interactions between multiple pumps in the system
- Pulsation can create issues with maintaining reaction stoichiometry and flow control
- Fluctuations in flow due to periodicity of pumping action may be less important as long as sufficient mixing occurs before measurement or reactions
- Excess reactor volume can be deleterious to control over reactor conditions

Marquardt et. al.
Diversion of Non-Conforming Material and Surge Capacity

- The ability to isolate and reject non-conforming material can be one of the key aspects of a CM control strategy.
- Surge capacity that decouple segment of the process train can offer distinct points where the quality of the material can be assessed and segregated in the event of a process upset:
  - Simplifying operational logistics; allowing brief stoppages of individual unit operations for troubleshooting or scheduled cleanouts.
  - Simplifying startup and shutdown transitions as the entire continuous train does not need to be started at the same time.
  - Reducing the complexity of automation and control.
  - Creates buffers that can increase processing times.
- Creates possibility that segments of the integrated process will be operating at different flow rates:
  - Need to evaluate process dynamic over the range of proposed flow rates.
CM as a Potential Driving Force for Advanced Process Control Adoption

- Many continuous manufacturing systems promote the adoption of higher level controls
  - Inherently data rich processes
  - Availability of plant wide information systems
  - Advancements in process modeling and simulation

Marquardt et. al.
Concluding Thoughts

• No regulatory hurdles for implementing CM
  – Both the Agency and industry are gaining experience
• Continuous synthetic API manufacturing is characterized by diversity in unit operations and process sequence configurations
  – Trend towards increased process integration
• Material and 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
  – For a hybrid process, the control strategy should encompass both the continuous and batch segments of the manufacturing process
• FDA supports the implementation of CM technologies using science and risk-based approaches
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