SBIA-DMF Drug substance workshop

March 3 & 4, 2021 (Virtual)

Quality Considerations for Continuous Manufacturing of APIs

Anjali Bain[1], Yun J. Wang[1], Ramnarayan Randad[1], David Skanchy[1], Adil Mohammad[2], Raymond Frankewich[3], and Thomas O'Connor[2]
[1]Division of Lifecycle API/Office of New Drug Products/Office of Pharmaceutical Quality, FDA/CDER
[2]Division of Product Quality Research/Office of Testing and Research/Office of Pharmaceutical Quality, FDA/CDER
[3]Division of New Drug API/Office of New Drug Products/Office of Pharmaceutical Quality, FDA/CDER

PURPOSE

FDA recognizes that continuous manufacturing (CM) has the potential to increase the efficiency, flexibility, agility, and robustness of pharmaceutical manufacturing. CM of drug substances can enable new synthetic routes and improved S/H/E performance. FDA has drafted "Quality Considerations for Continuous Manufacturing guidance for Industry" and published the draft guidance in February 2019. The guidance describes several key quality considerations and provides recommendations for how applicants should address these considerations for small molecule, solid oral drug products that are produced via a continuous manufacturing process. Scientific principles described in this guidance are also in general applicable to continuous manufacturing technologies for APIs.

OBJECTIVE(S)

This poster is based on this draft guidance and provides brief information regarding FDA's current thinking on the quality considerations for continuous manufacturing of small molecule drug substances.

OUTLINE

This presentation has five parts:

1. Characterization of the process dynamics
2. Process flow diagram with sufficient detail
3. Definition of batch size
4. Process monitoring and control including supporting information for PAT
5. Equipment and systems integration.
6. FDA Science and research initiatives

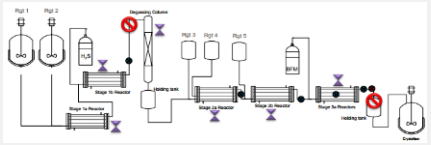
RESULT(S)

1. Characterization of the process dynamic:

Flow rate ranges and resulting residence time distributions should supported by available design of experiment (DOE) data, or modeling approaches. Relate process dynamics to characteristic times for transformations. It is important to understand the dynamic of start-up, shut down, and other transient disturbances to establish criteria for a state of control and product collection. Integrated process lines often contain surge capacity that decouple segment of the process train and significant impact on process dynamics

2. Process flow diagram with sufficient detail to illustrate continuous flow operational elements such as:

- Material flow including hold up steps and recycle loops; description of continuous and batch operations
- Rejection and/or diversion points
- Critical process parameter ranges; design space (if applicable)
- In-process controls, sampling and PAT locations
- Advanced process controls used (e.g., feedback control)
- Entry and exit of materials
- Reaction conditions and telescoped reactions



The continuous processing train of equipment that produces the API for the recently approved multistage process for Fluticasone Propionate

3. Definition of batch size

A batch can be defined based on the production period, quantity of material processed, quantity of material produced or production variation (e.g., different lots of incoming raw material), and can be flexible in size to meet variable market demands by leveraging the advantage of operating continuously over different periods of time. In processes that include both integrated continuous and batch process steps, the size of a batch may be defined by the capacity of a downstream batch operation.

The actual batch or lot size should be established prior to the initiation of each production run.

For batches that are defined based on time (e.g., a production period), a connection between material traceability and batch must be established to identify the specific quantity of the drug (21 CFR 210.3).

4. Process monitoring and control including supporting information for PAT

Critical process parameters include flow rate which impact both process dynamics and stoichiometry. In-process controls may combine process parameter limits with a specified duration

Criteria for collecting product include
- Description of the divert to waste system
- Material diversion: potential triggering events and amount of material diverted
- Criteria for rejection of the entire batch
- Approach for monitoring process robustness (e.g., measure of yield and multivariate tracking and trending)

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

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

Consider instrument aspects: Interference due to flow; time of acquisition vs. flow rate; probes – number, location, probe failure, probe maintenance, etc.

Justification of sampling strategy, including any backup methods when PAT device is unavailable.

<u>Supporting information for PAT and model development</u>
Provide supporting information and rationale for advanced process control approaches (e.g., feedback, feedforward, model predictive), including identification of the controlled and manipulated parameters

PAT methods used for product quality monitoring and control, including Real Time Release Testing (RTRT) methods:
- Description of primary and alternate methods
- Description of the statistical analysis of data
- For submission of NIR based spectroscopic PAT methods, refer to guidance for industry Development and Submission of Near Infrared Analytical Procedures
- For submission of model based methods, refer to guidance for industry Q8, Q9 & Q10 Questions and Answers | Appendix Q&As from Training Sessions
- Summary of the overall control strategy

5. Equipment and systems integration

Equipment design can be an essential element of control strategy for CM processes of drug substances. The level of details regarding equipment design and integration to be provided should be commensurate with their impact on a state of control operation in the context of the overall control strategy.

Equipment used in continuous manufacturing processes are used for long periods of time and equipment performance can decrease gradually with time due to fouling and normal wear and tear. Solids may be present in the reaction as reagents, intermediates, byproducts, or as the product. Lack of convective mixing and the small reactor cross-sectional area in continuous flow systems increase the probability that solids clog the channel

Therefore instruments used in continuous manufacturing should use following additional strategies:

- Equipment qualification-should address both individual unit operations and integrated systems. Qualification protocols to include flow rates, pressure speeds and duration of continuous run.
- Maintenance-control strategy for equipment failure modes including appropriate corrective action plan
- Cleaning -Cleaning procedures to be based on closed monitoring of materials during operation and after disassembly. Cleaning frequency and preventative maintenance should be established based on elapsed operating times, quantity of materials processed, history of process conditions or deviations and product change over

6. FDA Science and Research supports implementation of CM for drug substances

CONCLUSION(S)

FDA recognizes and supports adoption of continuous manufacturing as emerging technology to modernize pharmaceutical sector to help patients by reducing drug quality issues, lower manufacturing costs and improve availability of quality medicines.

WHERE TO GET MORE INFORMATION & LINKS.

FDA Draft Guidance, Quality Considerations for Continuous Manufacturing
https://www.fda.gov/media/121314/download

ICH Q13: Continuous Manufacturing of Drug Substances and Drug Products Final Concept Paper
https://database.ich.org/sites/default/files/Q13%20Concept%20Paper.pdf

USP PF 44(6) Stimuli to the Revision Process: USP (Pharmacopeia) Perspective for Pharmaceutical Continuous Manufacturing

Berry, M.B. Filing a Multistage Continuous Process for API. American Pharma Review, 2020, March.

Cole, K.P., et al., Kilogram-scale prexasertib monolactate monohydrate synthesis under continuous-flow CGMP conditions. Science, 2017. 356(6343): p. 1144-1150.

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Background

- FDA has identified continuous manufacturing (CM) as a novel technology for the pharmaceutical industry
- In 2019 FDA published the draft guidance “Quality Considerations for Continuous Manufacturing”
- The scope of the draft guidance is solid oral drug products.
- This presentation will describe how the FDA’s current thinking on scientific principles described in this guidance are also applicable to continuous manufacturing technologies for APIs

Outline

This presentation has six parts that cover different quality considerations:

1. Characterization of the process dynamics
2. Process flow diagram with sufficient detail
3. Definition of batch size
4. Process monitoring and control including PAT
5. Equipment and systems integration
6. FDA Science and research initiatives

Characterization of Process Dynamics

- Understand the Residence time distribution (RTD) over proposed process flow rate ranges
- Relate process dynamics to characteristic times for transformations
- Understand the dynamic of start-up, shut down, and other transient disturbances to establish criteria for a state of control and product collection
- Integrated process lines often contain surge capacity that decouples segment of the process train and has a significant impact on process dynamics

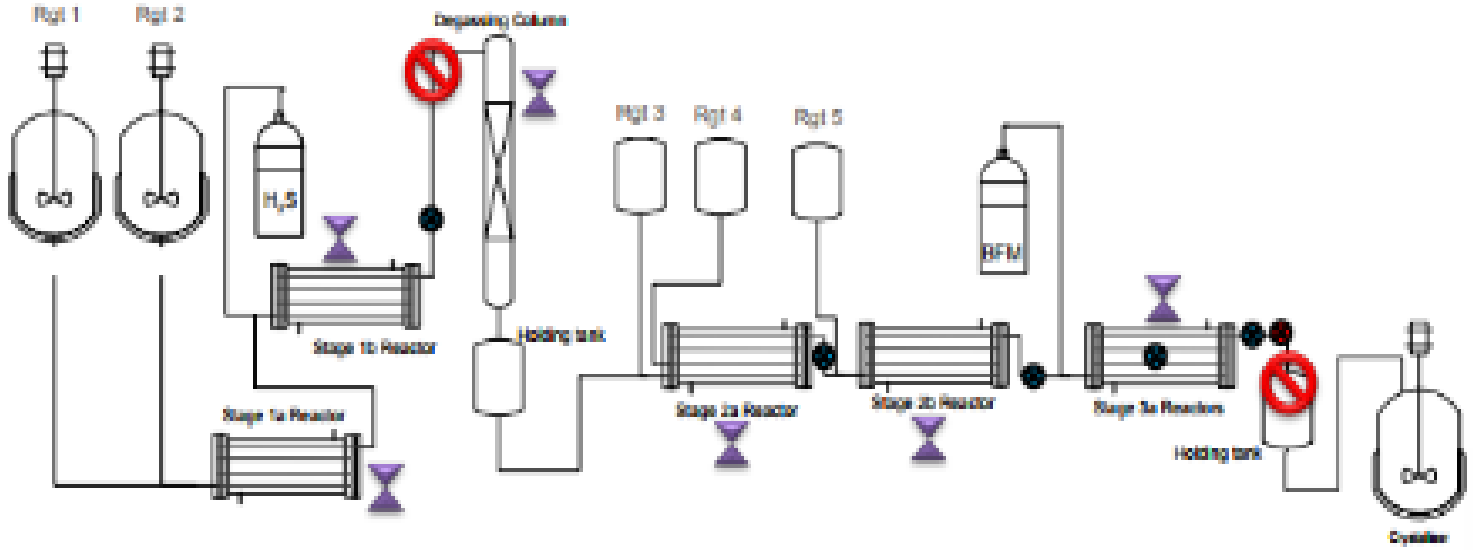
Process Flow Diagram

To support the quality review sponsors should submit a process flow diagram with sufficient detail to illustrate continuous flow operational elements such as

- Material flow including hold up steps and recycle loops
- Rejection and/or diversion points
- Critical process parameter ranges; design space (if applicable)
- In-process controls, sampling and PAT locations
- Advanced process controls used (e.g., feedback control)
- Entry and exit of materials
- Reaction conditions and telescoped reactions

Process Flow Diagram (Cont.)

The continuous processing train of equipment used for the recently approved multistage process



Berry, M.B. Filing a Multistage Continuous Process for API. American Pharma Review, 2020, March.

Batch Definition

- A batch can be defined based on the production period, quantity of material processed, quantity of material produced or production variation
- Batch sizes can be flexible
- In processes that include both integrated continuous and batch process steps, the size of a batch may be defined by the capacity of a downstream batch operation.
- The actual batch or lot size should be established prior to the initiation of each production run.
- For batches that are defined based on time (e.g., a production period), a connection between material traceability and batch must be established to identify the specific quantity of the drug (21 CFR 210.3).

Process Monitoring and Control

- Critical process parameters include flow rate which impact both process dynamics and stoichiometry.
- In-process controls may combine process parameter limits with a specified duration.

- Criteria for collecting product include
  - Description of the divert to waste system
  - Material diversion: potential triggering events and amount of material diverted
  - Criteria for rejection of the entire batch
  - Approach for monitoring process robustness (e.g., measure of yield and multivariate tracking and trending)

Process Monitoring and Control: PAT

- Specify the role of PAT and Models (e.g. Process understanding, in-process control, RTRT)
- When using non-specific (e.g. conductivity) PAT measurement systems, clarify how the non-specific tests relates to monitoring the state of control for the process
- Consider instrument aspects: Interference due to flow; time of acquisition vs. flow rate; probes – number, location, probe failure, probe maintenance, etc.
- Provide justification of sampling strategy, including any backup methods when PAT device is unavailable

Supporting Information for PAT and Model Development

Supporting information and rationale for advanced process control approaches (e.g., feedback, feedforward, model predictive), including identification of the controlled and manipulated parameters

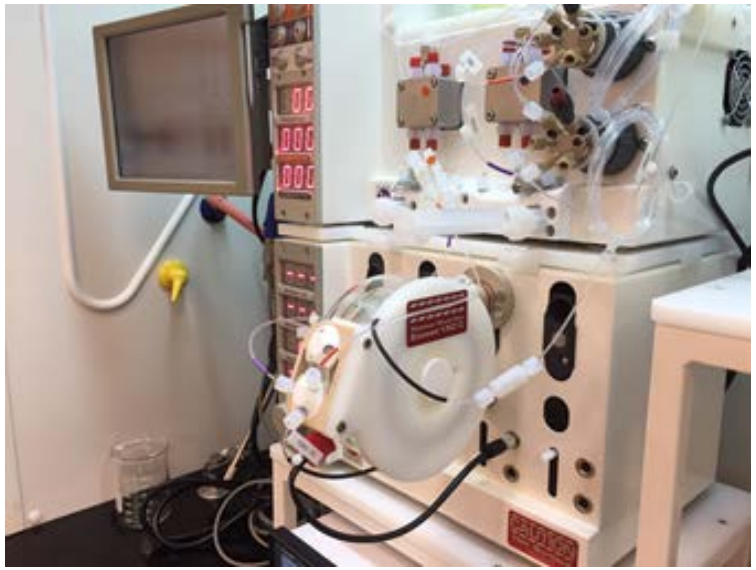
PAT methods used for release, including Real Time Release Testing (RTRT) methods:

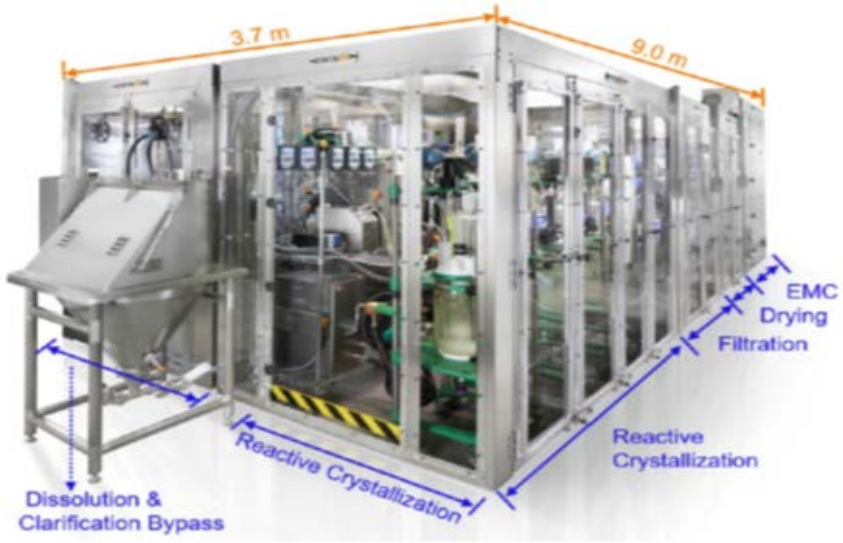
- Description of primary and alternate methods
- Description of the statistical analysis of data
- For submission of NIR based spectroscopic PAT methods, refer to guidance for industry Development and Submission of Near Infrared Analytical Procedures
- For submission of model based methods, refer to guidance for industry Q8, Q9 & Q10 Questions and Answers | Appendix Q&As from Training Sessions
- Summary of the overall control strategy

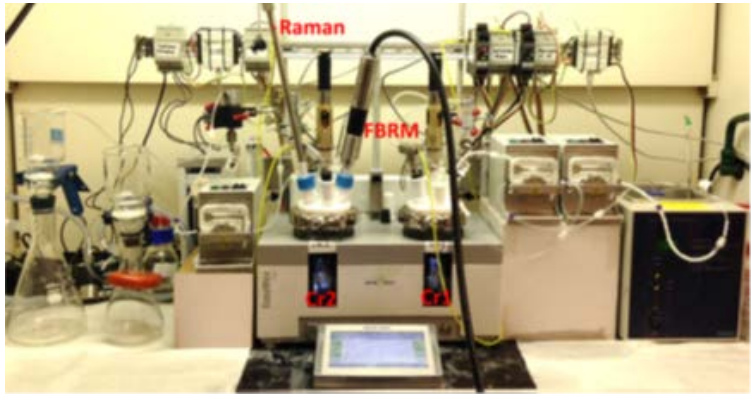
Equipment and Systems Integration

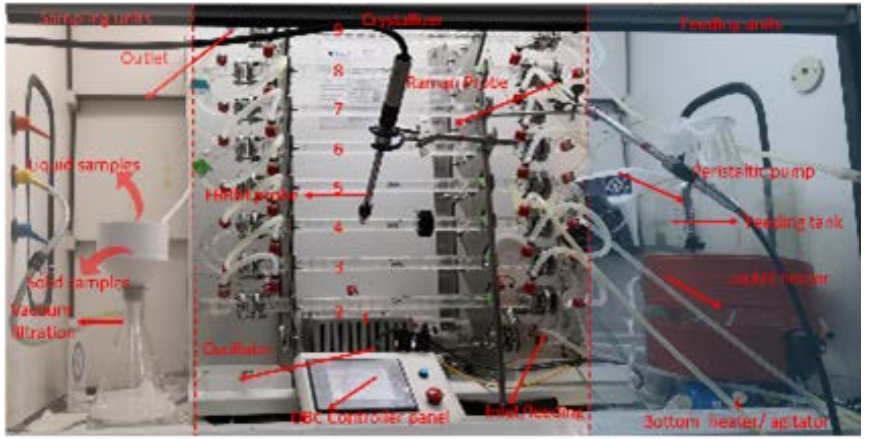
- Equipment used in CM processes are used for long periods of time and equipment performance can decrease gradually with time due to fouling and normal wear and tear
- In continuous flow systems increase the probability that solids clog the channel.
- Therefore instruments used in CM should use following additional strategies:
  - Equipment qualification - should address both individual unit operations and integrated systems. Qualification protocols should include flow rates, pressure speeds and duration of continuous run.
  - Maintenance - control strategy for equipment failure modes should include appropriate corrective action plan.
  - Cleaning - cleaning procedures and frequency should be based on closed monitoring of materials during operation and after disassembly.

FDA Science and Research Supports for Implementation of CM for Drug Substances









Conclusion(s)

- FDA recognizes and supports adoption of continuous manufacturing as emerging technology to modernize pharmaceutical sector to help patients by reducing drug quality issues, lower manufacturing costs and improve availability of quality medicines.
- Quality considerations described in FDA's draft guidance on continuous manufacturing can support the implementation and regulatory submission of continuous manufacturing technologies for APIs

Resources

FDA Draft Guidance, Quality Considerations for Continuous Manufacturing
https://www.fda.gov/media/121314/download

ICH Q13: Continuous Manufacturing of Drug Substances and Drug Products Final Concept Paper
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Thank You!

- Send questions regarding this poster to: DMFWorkshop2021@FDA.HHS.GOV by 2/15/2021 for inclusion in the poster Q&A session on March 3rd
- Follow-on webinar for both posters/presentations on April 9, 2021. Questions can be sent to the above email by 3/19/2021 for the webinar.