CDER Perspective on Continuous Manufacturing

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FDA/CDER Small Business and Industry Assistance
Regulatory Education for Industry (REdI) Generic Drug Forum

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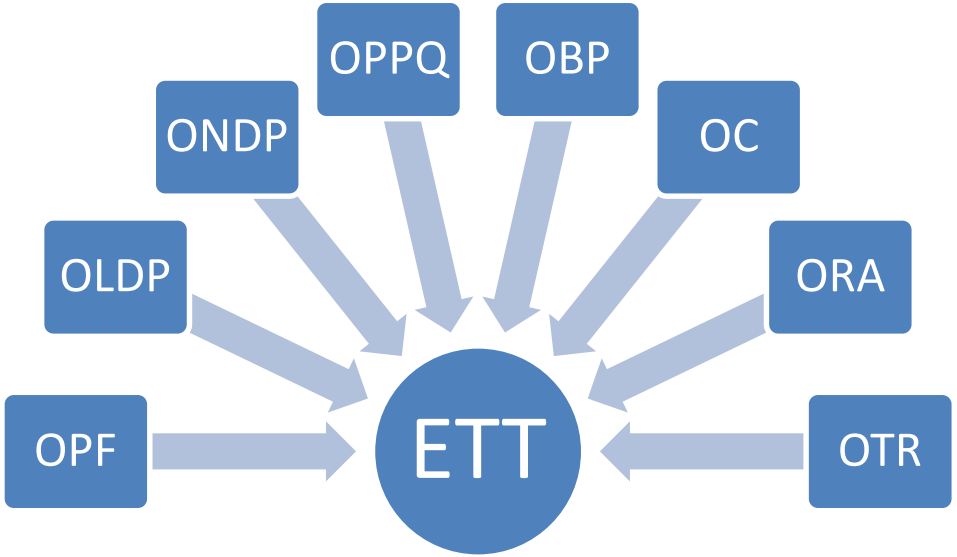
Why CM?

- FDA has identified CM as an emerging technology
- CM has the potential to increase the efficiency, flexibility, agility, and robustness of pharmaceutical manufacturing
  - Integrated processing with fewer steps
    - Reduced manual handling
    - Shorter processing times
  - Smaller equipment and facilities
    - More flexible operation
    - Lower capital costs, less work-in-progress materials
    - Reduced environmental foot print
    - Feasible to manufacture small batch sizes

  - On-line monitoring and control for increased product quality assurance in real-time
    - Amenable to Real Time Release Testing approaches
- Benefits to both patients and industry

Emerging Technology Team

Vision: Encourage and support the adoption of innovative technology to modernize pharmaceutical development and manufacturing through close collaboration with industry and other relevant stakeholders



A small cross-functional **Emerging Technology Team (ETT)** with representation from all relevant FDA quality review and inspection programs (OPQ/CDER & ORA)

Program Objectives

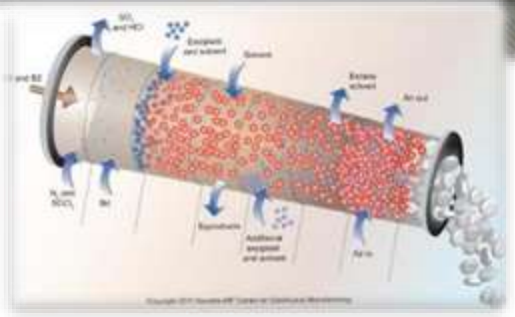
- To serve as a **centralized location** for external inquiries on novel technologies
- To provide a forum for firms to engage in **early dialog with FDA** to support innovation
- To ensure **consistency**, **continuity**, and **predictability** in review and inspection
- To identify and evaluate potential **roadblocks** relating to existing guidance, policy, or practice
- To help establish **scientific standards, guidances** and **policies**, as needed
- To facilitate **knowledge transfer** to relevant CDER and ORA review and inspection programs
- To engage **international regulatory agencies** to share learnings and approaches
- Contact us: **CDER-ETT@fda.hhs.gov**

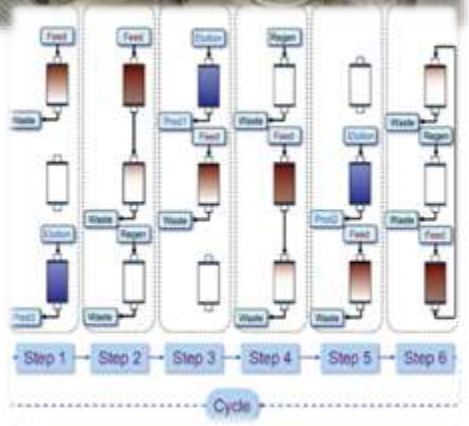
CDER Progress

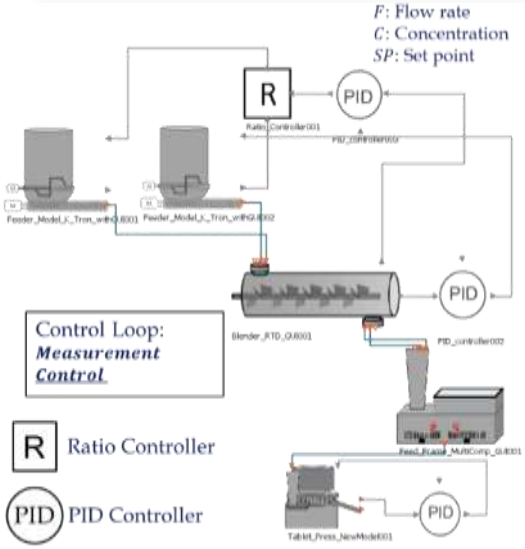
- Over 30 requests accepted to the Emerging Technology Program since the launch of the program in late 2014
  - Over 60 ETT-industry interactions (including both t-con and face-to-face meetings) and ~50% of these interactions related to CM
  - https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm523228.htm
- FDA approvals of applications utilizing continuous manufacturing (CM)
  - Vertex ORKAMBI (lumacaftor/ivacaftor)
  - Janssen Prezista (darunavir)
  - Eli Lilly Verzenio (abemaciclib)
  - Vertex Symdeko (tezacaftor/ivacaftor and ivacaftor)
  - Pfizer Daurismo (glasdegib)

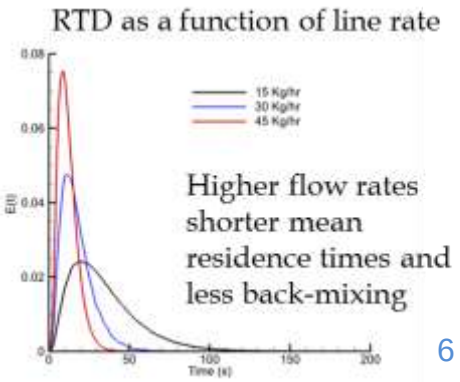
CDER Current Experience

- **CM processes for drug product**
  - Direct compression, dry and wet granulation; CM models for solid orals; modular CM processing system
- CM processes for drug substance
  - Continuous drug synthesis (flow reaction) plus batch or continuous crystallization
- End-to-end CM processes
  - Integrated synthesis, purification, and final dosage formation
- Pharmacy on Demand
  - Miniaturized, flexible manufacturing platforms using CM technologies
- Continuous bioprocesses
  - Continuous purification platform for monoclonal antibody (e.g., continuous chromatography and viral filtration)
- Control Strategy
  - Increasing use of active process control, PAT tools, RTRT, process models for material traceability, non-conforming material diversion, and blend uniformity

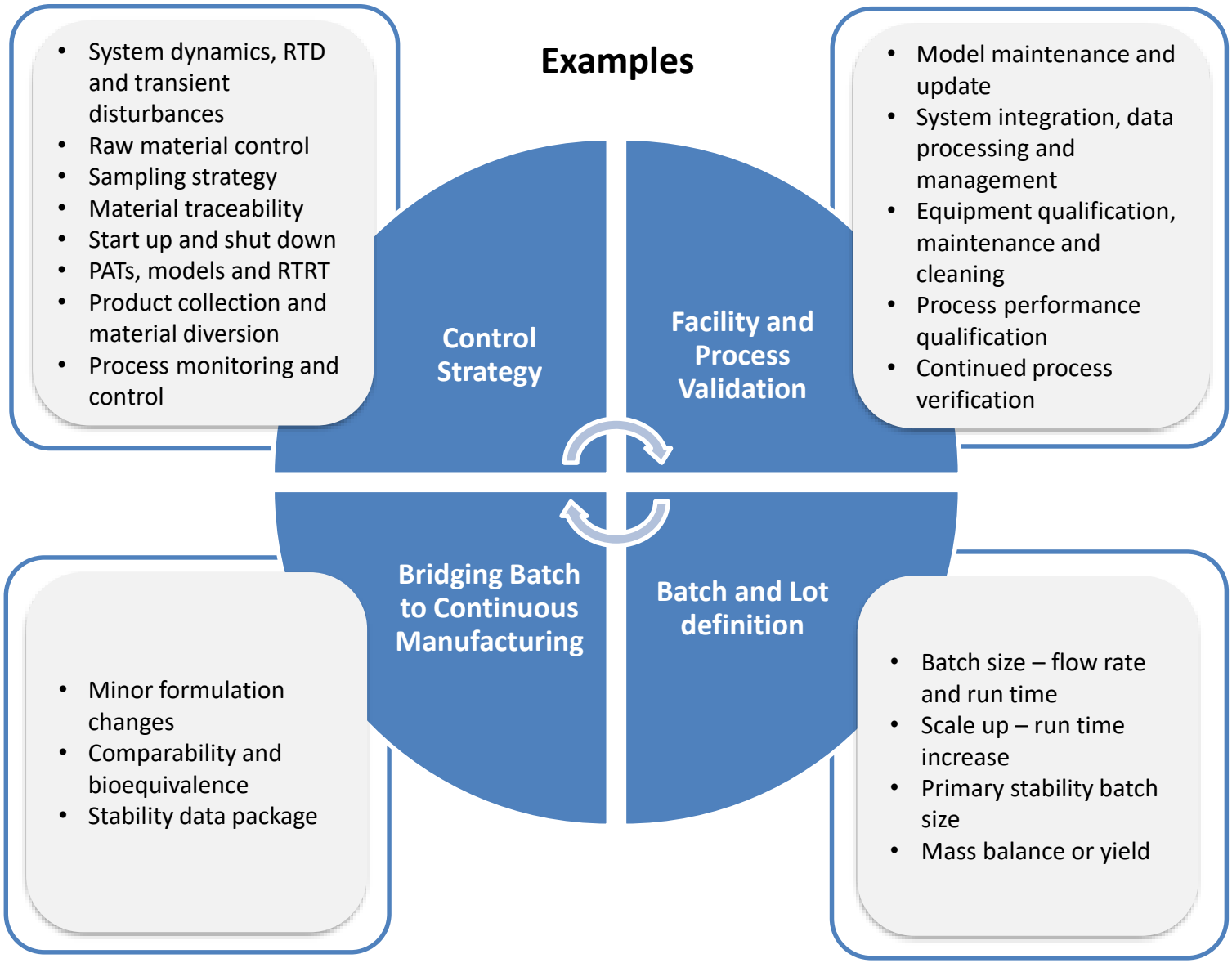






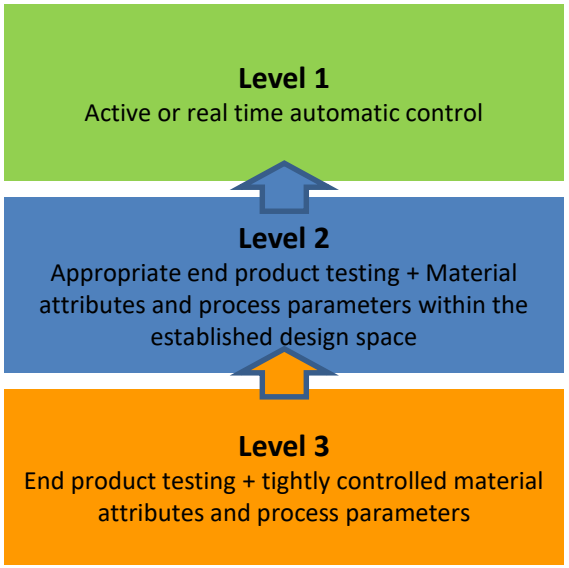


CM Elements Discussed Between CDER and Industry



Control Strategy – State of Control

- 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

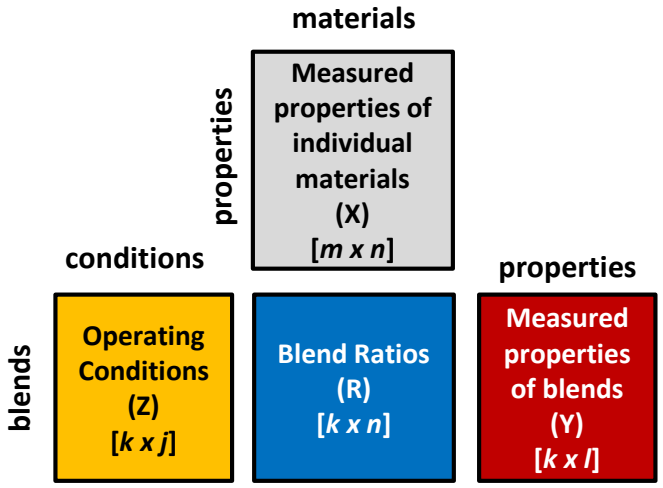


- For CM, this can include integration of process parameter limits (set points and alarms), in-process monitoring (including PAT), process controls (feedback and feed forward), material diversion, and Real Time Release Testing (RTRT)
- Many continuous manufacturing systems promote the adoption of higher level controls, although a hybrid approach combining the different levels of control is viable for some continuous manufacturing process designs

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

Raw Material Control Considerations

- Use of multiple raw material lots in a batch
  - Establish traceability of different lots to finished products
- Characterization of input materials
  - Evaluate raw material attributes (e.g., particle size distribution and density) affecting the formulation flow behavior, segregation potential, etc.
- Appropriate material specifications
  - Impact of drug substance or excipient lot-to-lot variations on feeding
  - If legacy product, appropriateness of the existing drug substance specifications for CM
  - Appropriateness of the compendial specification for excipients



S. G. Munoz et al. (2014) *Chemometrics and Intelligent Laboratory Systems.* 133, 49-62

Process Monitoring and Control

Specify the role of PAT and Models

- Provide process understanding during development; process monitoring during production; process control; and/or real-time release testing (RTRT) method

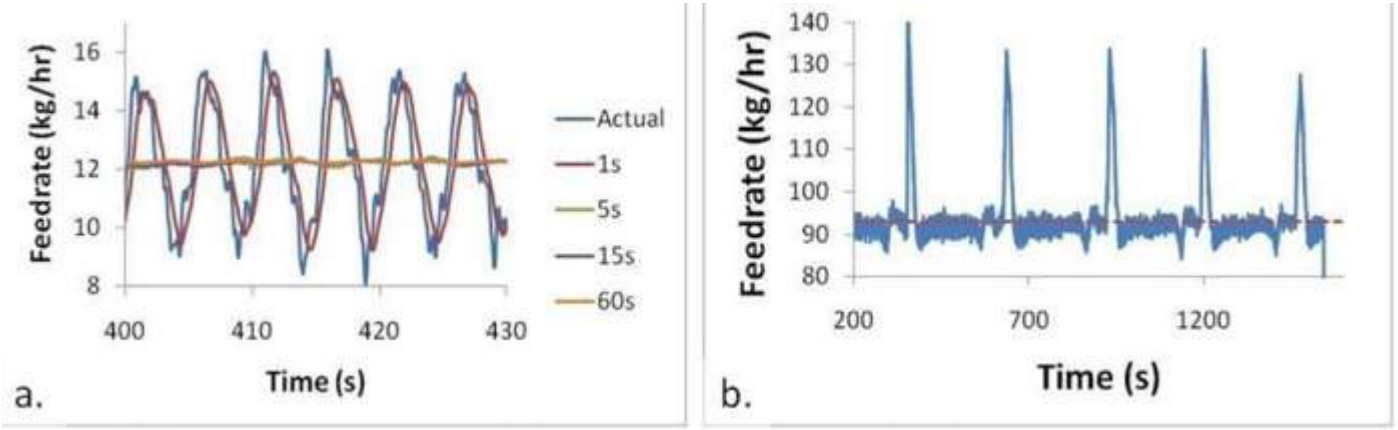
Consider instrument aspects

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

Feeding: a critical operation for CM

- Demonstrate that acceptable quality material is manufactured near the upper and lower limits to support feeding limits
- Evaluate impact of operational variations (e.g., switching from gravimetric to volumetric flow during feeder refill)
- Assess impact of feeding variations of excipients on product performance (e.g., dissolution)

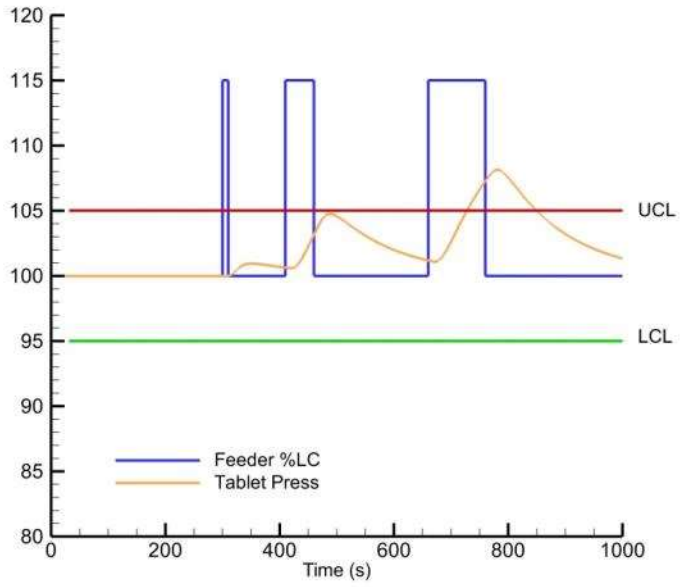
Feeder Monitoring



Engisch W. and Muzzio F.. J Pharm Innov. 2015; DOI 10.1007/s12247-015-9238-1

Diversion of Non-Conforming Material

- The ability to isolate and reject non-conforming material can be one of the key aspects of a CM control strategy
  - Planned process start-ups and shutdowns
  - Temporary process disturbances or upsets
- The evaluation and understanding of propagation of a disturbance in the system are important to justify the amount of material at risk
- Models of process dynamics are being assessed as part of the control strategy to detect and track non-conforming material due to upstream disturbances

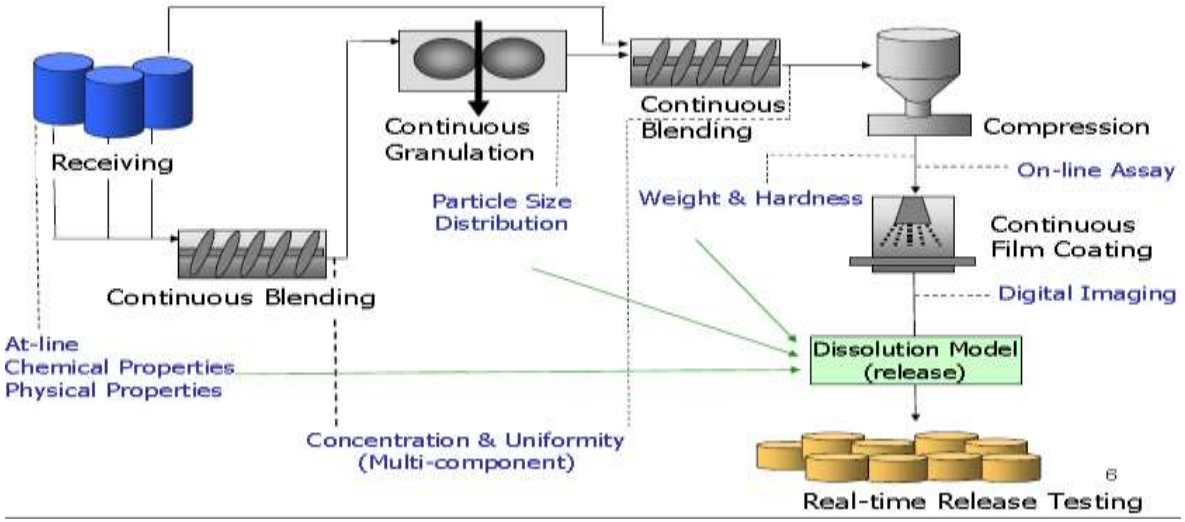


Scientific Considerations for Model Based Material Diversion

- Develop models using scientifically-sound principles and conditions that reflect routine commercial production
- Validate performance for high-impact models
  - Capability of the model to trace the identified non-conforming material segment through the system to the rejection point
  - ICH Q8, Q9, & Q10 Questions and Answers -- Appendix: Q&As from Training Sessions (Q8, Q9, & Q10 Points to Consider)
- Understand model assumption and risks to validity of model predictions
  - Model parameter uncertainty
  - Expected variations in process parameters and material attributes (e.g., line rate)
  - Product quality risks resulting from potential transient disturbances
  - Process failure modes that may not be identified by or included in the model
- Include model maintenance approaches within the quality system as part of a lifecycle approach
  - Routine monitoring to verify performance
  - Model updates

RTRT Considerations

- Establish a valid combination of assessed material attributes and associated process controls in relation to the final product quality
- Evaluate ability of the sampling scheme(s) to detect non-conforming materials or products
  - Assess quality of a batch (i.e., % confidence, % coverage, and target range)
  - Monitor or assess system dynamics (i.e., disturbances) during the continuous operation
  - Determine whether the process is in a state of control during start-up, shut-down, and after restarts
- If the on-line PAT methods are submitted as routine methods (without alternatives), describe what actions will be taken when analyzer is not available



Batch Definition

- 21 CFR 210.3 defines a batch as “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**”.

- Additionally, a lot is defined as “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**.”

Definitions for both “batch” and “lot” are applicable to continuous processes

Batch Definition Considerations

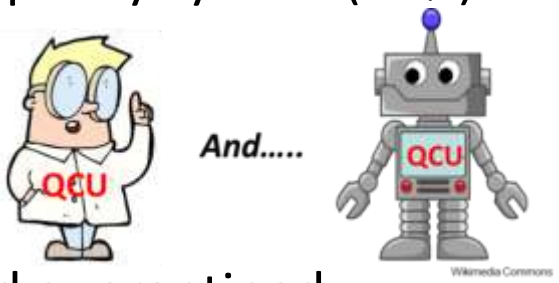
- Regulatory expectation that:
  - Product has “uniform character and quality within specified limits” and is therefore closely linked to *the control strategy* that is designed to ensure the process under a *state of control*
- Potential batch definitions based on:
  - Production time period; amount of material processed; production variation (e.g. different lots of feedstock); amount of product produced; and others
  - Established prior to initiation of manufacturing, not after the fact
- Other considerations
  - Ensure *material traceability* to verify a complete history of the manufacture, processing, packing, holding, and distribution of a batch/lot of the product and other materials (excipients);
    - Especially in cases of OOS/OOT investigations, consumer complaints, product recalls, or any other situations that may have public health impact
  - Define procedures for start-up/shutdown, and establishing a priori acceptance criteria for determining when product collection starts
  - Material reconciliation including handling of non-conforming materials

Process Validation

- Consult process validation guidance and verify performance of the process using the intended control strategy
  - Demonstrate robustness of the process including the ability to remain in a state of control and make quality decisions in real-time
- Process Qualification
  - To examine a run time or manufacturing period that should be representative of the intended commercial run time for the initial product launch
- Continuous process verification
  - Use in-line, on-line, or at-line monitoring or controls to verify process performance on an on-going basis
  - Evaluate trending for further process understanding and improvement
  - Provide the advantage of enhanced assurance of intra-batch uniformity, fundamental to the objectives of process validation
- Expect retrospective data/trending analysis as part of the process validation guidance and lifecycle management
- Comparability protocol to increase the batch size post approval

Facility Considerations

- Adjustments to existing facility pharmaceutical quality system (PQS)
  - Updates to Quality and production procedures
  - Quality oversight of automated controls, process data, RTRT, and electronic batch records



- Quality evaluation when material is diverted and quarantined
  - Level of investigation, root cause analysis, corrective and preventive action, understanding diversion event (common vs. unexpected) 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 the 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

Quality Considerations for Continuous Manufacturing

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability when published in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Sau L. Lee at 301-796-2905.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Pharmaceutical Quality/CMC
Pharmaceutical Quality/Manufacturing Standards (CGMP)

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The Desired State

The Vision

"A maximally **efficient**, **agile**, **flexible** pharmaceutical manufacturing sector that **reliably produces high quality drugs** without extensive regulatory oversight."

Thank You!