Successfully Implementing Advanced Manufacturing

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Pharmaceutical Quality: Midnight Madness
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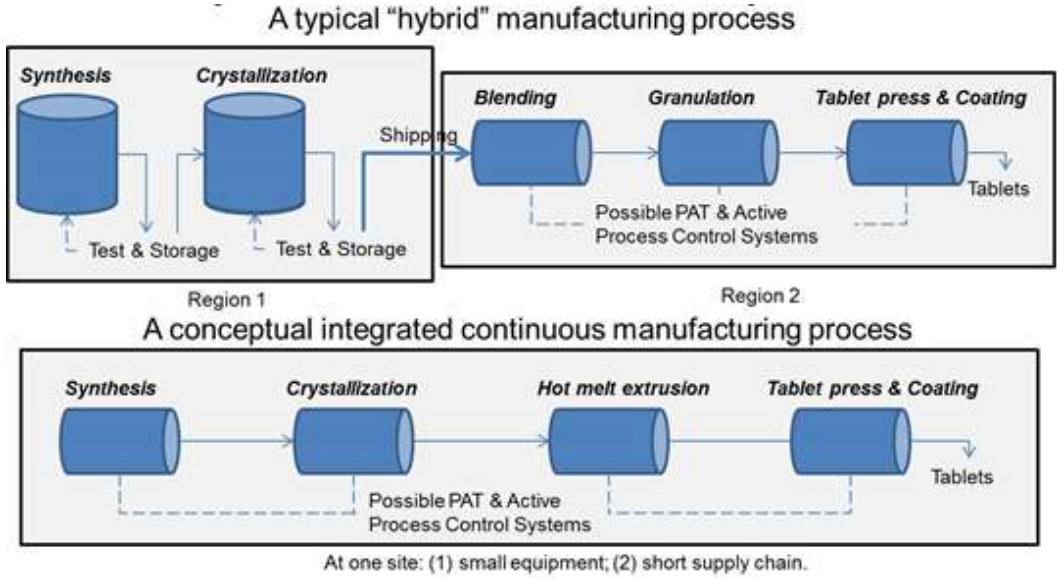
Advanced Pharmaceutical Manufacturing – Why?

- Deliver reliably quality pharmaceuticals over product lifecycle
- Enable efficient & flexible manufacture of high quality drug products without extensive regulatory oversight
- Support new clinical development to meet unmet patient needs & shorter CMC development timelines
- Strong FDA leadership support to make advanced manufacturing of pharmaceuticals a reality
- Continuous manufacturing is a key example of advanced manufacturing technology that could enable this “desired state”

Benefits Patients & Industry

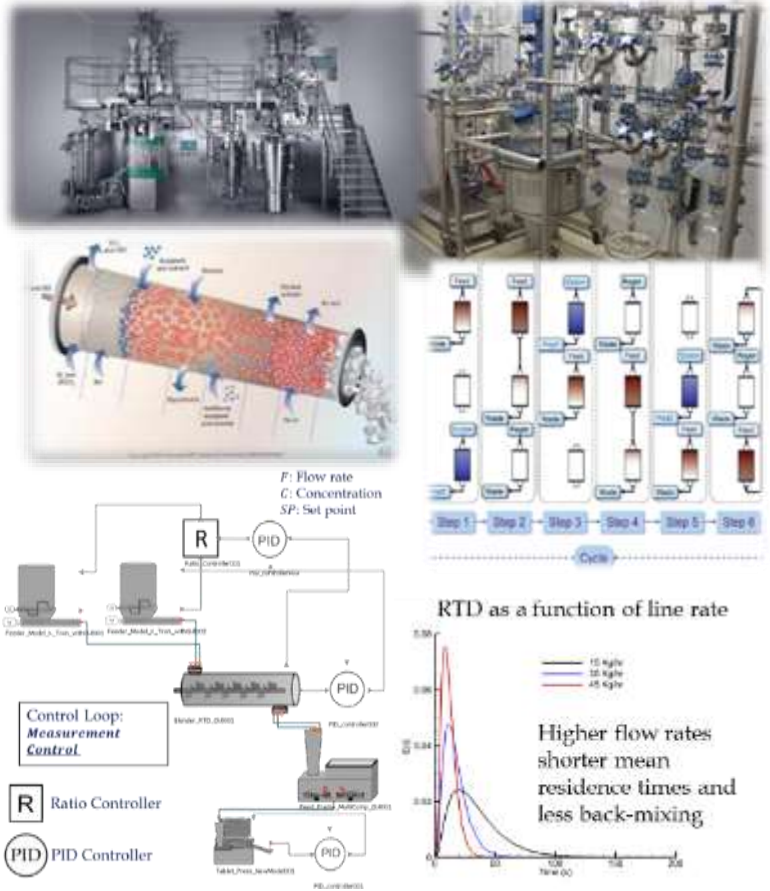
What is Continuous Manufacturing?

- CM is an integrated process that consists of a series of two or more unit operations ("the system"). In such a process, the input material(s) are continuously fed into and transformed within the process, and the processed output materials are continuously removed from the system



FDA's Evolving 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
- *Control Strategy*
  - Increasing use of active process control, PAT tools, RTRT, process models for material traceability, non-conforming material diversion, and blend uniformity
- Continuous bioprocesses
  - Continuous purification platform for monoclonal antibody (e.g., continuous chromatography and viral filtration)
- End-to-end CM processes
  - Integrated synthesis, purification, and final dosage formation



FDA's Regulatory Approach for CM

Science and risk-based approaches	• Understand key CM concepts and identify CM specific risks to product quality – CDER supports internal and external research projects • Develop a framework for control strategy considerations
Regulations and guidance	• Existing regulations and ICH guidances (e.g., Q8, Q9, Q10, Q11 and Q12) – Generally applicable to CM • Emerging Technology Guidance and MAPP – Emerging Technology Program led by a multidisciplinary Emerging Technology Team (ETT) with OPQ (lead), OC and ORA representation
Regulatory Assessment	• Early engagement with the ETT to address scientific and regulatory gaps • Pre-operational visits (POVs) • Integrated application and facility assessments including pre-approval inspection
Maturation of regulatory basis	• Evolution of regulatory basis as experience gained with CM regulatory applications • Knowledge management • Regulatory guidance (e.g., FDA and/or ICH)

CM Elements Discussed Between FDA and Industry

Examples

Control Strategy

- System dynamics, RTD and transient disturbances
- Raw material control
- Sampling strategy
- Material traceability
- Start up and shut down
- PATs, models and RTRT
- Product collection and material diversion
- Process monitoring and control

Facility and Process Validation

- Model maintenance and update
- System integration, data processing and management
- Equipment qualification, maintenance and cleaning
- Process performance qualification
- Continued process verification

Bridging Batch to Continuous Manufacturing

- Minor formulation changes
- Comparability and bioequivalence
- Stability data package

Batch and Lot definition

- Batch size – flow rate and run time
- Scale up – run time increase
- Primary stability batch size
- Mass balance or yield

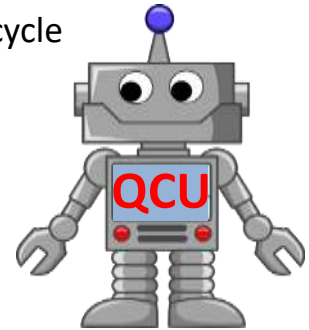
Quality Assessment Focus

- Characterization of process dynamics for critical steps and integrated system
  - Residence time distribution for a proposed mass flow rate
  - Understanding of the system response to transient disturbances
- Evaluation of the proposed attributes and specifications of raw materials
  - Impact of variations in material properties on the performance of CM and product quality
- Process monitoring and control strategy
  - Monitor and detect transient disturbances and process deviation
  - Frequency of PAT measurements
  - Active process controls
- Material collection and diversion
  - Start up and shutdown
  - Strategy to identify, isolate and divert non-conforming materials
- Real-time release testing
  - PAT tools for assay and content uniformity
  - Dissolution models

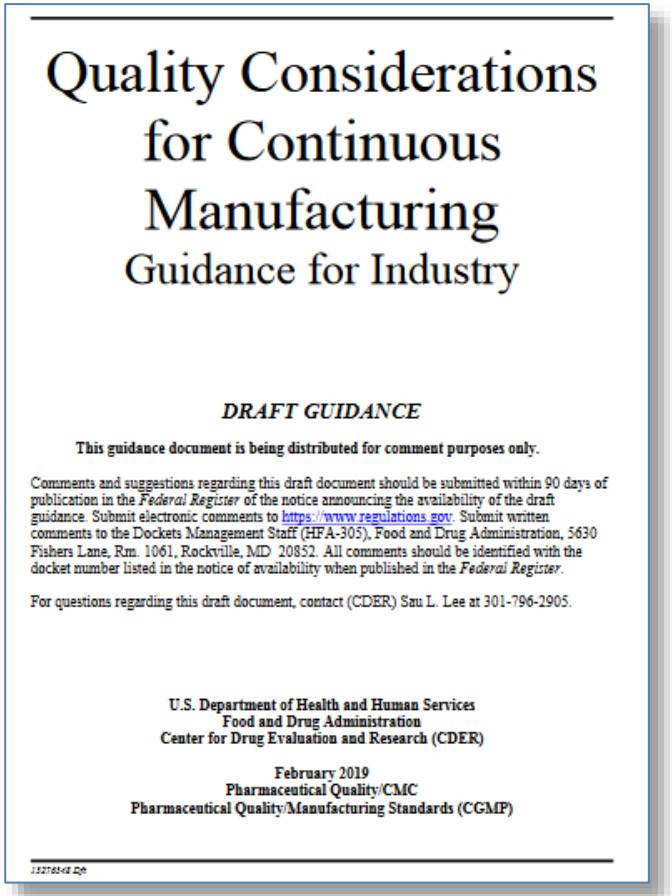
Facility Considerations

- Adjustments to existing facility pharmaceutical quality system (PQS)
  - Updates to Quality and production procedures
  - Additional controls for incoming raw materials
  - Quality oversight of automated controls, process data, RTR, and electronic batch records
- 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
- 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
- Quality evaluation when material is diverted and quarantined
  - Deviations, level of investigation, root cause analysis, corrective and preventive action, understanding diversion event (common vs. unexpected) for continuous improvement, etc.

And…..



Continuous Manufacturing Draft Guidance



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)

February 2019
Pharmaceutical Quality/CMC
Pharmaceutical Quality/Manufacturing Standards (CGMP)

- Current thinking on quality considerations for continuous manufacturing of *small molecule, solid oral drug products regulated by CDER*
- Recommendations for how applicants should address considerations in NDAs and ANDAs, including supplements
- Recommendations broadly applicable to both batch and continuous manufacturing are generally not covered in this guidance

ICH Q13

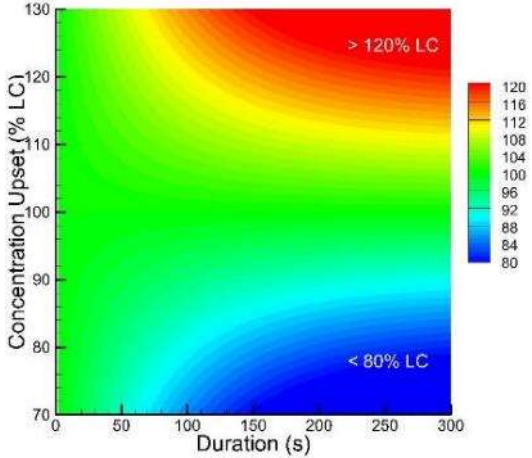
Continuous Manufacturing of Drug Substances and Drug Products

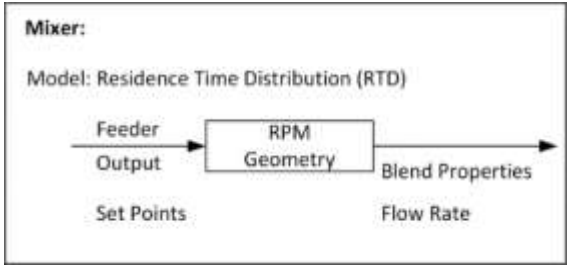
- Capture key technical and regulatory considerations that promote harmonisation, including certain CGMP elements specific to CM,
- Allow drug manufacturers to employ flexible approaches to develop, implement, or integrate CM for the manufacture of small molecules and therapeutic proteins for new and existing products, and
- Provide guidance to industry and regulatory agencies regarding regulatory expectations on the development, implementation, and assessment of CM technologies used in the manufacture of drug substances and drug products.

ICH Q13 Expert Working Group

Current Trends

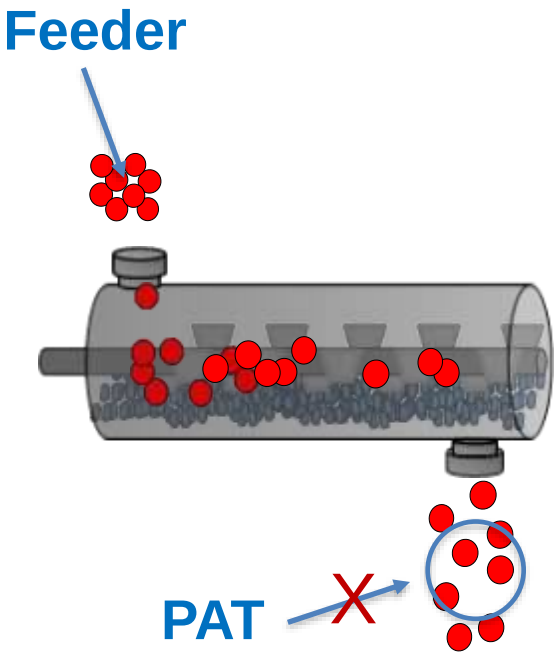
- Increasing role of models in the CM control strategy
  - Models have already been used for process monitoring or RTRT in both batch and continuous processes
    - Chemometric models for NIR measurements
    - Dissolution models
  - CM also uses models (e.g., RTD models) for:
    - Process development (e.g., supporting feeder limits)
    - Material traceability and propagation of disturbances
    - Material diversion
  - Models can potentially be used as in process control if they:
    - Consider all relevant factors and their variations
    - Reflect commercial operating conditions
    - Show adequate predictive power for the intended purpose through proper validation
- Regulatory reporting requirements for model updates or changes
  - High, medium and low impact models





Current Trends

- Increasing requests for using a parametric approach for in process control and product release
  - Feeder mass flowrate as a surrogate for API concentration in the blend
  - Removal of the PAT tool(s) for commercial production
  - Historical data on acceptable product quality (e.g., blend or content uniformity) not sufficient to support this approach
- Establish validated model to quantitatively link material properties, upstream and downstream process conditions to the final product quality attribute(s)
- Encourage early discussion with ETT



Future Topics for Collaborations

- CM and performance-based approach
  - Promote the use of PATs for high frequency measurements of critical quality attributes
  - Promote active controls and process improvement
  - Can this performance based approach be applied to the entire integrated continuous manufacturing line?
- CM and parametric-based approach
  - Require comprehensive understanding of quantitative, multivariate relationships among material attributes, process conditions, and critical quality attributes
  - Big data set to develop and validate multivariate models
  - Complexity increases dramatically with increasing number of parameters
  - Monitor the "health" of a process to make quality decision
- Combination of both performance- and parametric approaches

Performance-based approach ←

→ Parametric-based approach

Future Topics for Collaborations

- Model development, validation, maintenance and update
  - Regulatory standards for model validation currently lacking
  - Mostly considered as a “high impact” (e.g., PAT chemometric and dissolution models)
  - What does industry want?
    - Consistency among regulatory agencies for reporting requirements for model maintenance and update
    - Most updates or changes managed under the company’s PQS (e.g., post approval change management plan)
- Continuous bioprocessing
  - Emerging hot topic that should be one of the main focus in the near future
  - Lag behind small-molecule CM in many aspects
  - Need some breakthrough in PAT areas

Future Topics for Collaborations

- Data management and storage
  - Large size of process and quality data due to high-frequency measurements
  - All raw data be strictly managed according to CFR 211.180?
  - Technological advance needed for data storage
  - Data transformation or reconstruction
  - Areas related to data transformation needed to be addressed
    - Loss of information and hinder investigation in the event of a product recall or adverse event
    - Loss of information for trending analysis and continuous improvement
    - Data integrity
  - Cloud computing and AI

CDER Progress in Advanced Manufacturing

Approval of a first regulatory application utilizing 3D printing technologies

- Aprecia (Spritam, 2015)

Approvals of applications utilizing continuous manufacturing (CM)

- Vertex ORKAMBI (lumacaftor/ivacaftor, 2015)
- Janssen Prezista (darunavir, 2016)
- Eli Lilly Verzenio (abemaciclib, 2017)
- Vertex Symdeko (tezacaftor/ivacaftor and ivacaftor, 2018)
- Pfizer Daurismo (glasdegib, 2018)
- Vertex Trikafta (elexacaftor/tezacaftor/ivacaftor and ivacaftor, 2019)
- API CM (2019)

Requests accepted to the Emerging Technology program since launching in late 2014

- Received over 100 ETT proposals and accepted over 50 of these proposals into the program

The Desired State

The Vision

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

Acknowledgements

Emerging Technology Team

OPQ Leadership

Industry Partners