FDA Experience with Continuous Manufacture

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Disclaimer

This presentation reflects the views of the authors and should not be construed to represent FDA's views or policies

Outline

Current Perspectives on CM: Review

– Elements of Control Strategy:

FDA Emerging Technology Team

– Trends in continuous manufacturing

Regulatory Research

– Risk Management for Continuous Manufacturing

FDA

OPQ
Office of Pharmaceutical Quality

ONDP
New Drug
Products

OLDP
Lifecycle Drug
Products

OBP
Biotechnology
Products

OPF
Process and Facilities

OTR
Testing and Research

OPRO
Program and Regulatory Operations

OPPQ
Policy for Pharmaceutical
Quality

OS
Surveillance

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

Vision for 21st Century Manufacturing

OPQ Objectives

- Provide seamless integration of review, inspection, surveillance, and research across the product lifecycle
- Assure that all human drugs meet the scientifically-sound quality standards to safeguard clinical performance
- Enhance science- and risk-based regulatory approaches
- Transform product quality oversight from a qualitative to a quantitative, expertise-based assessment
- Encourage development and adoption of emerging pharmaceutical technology

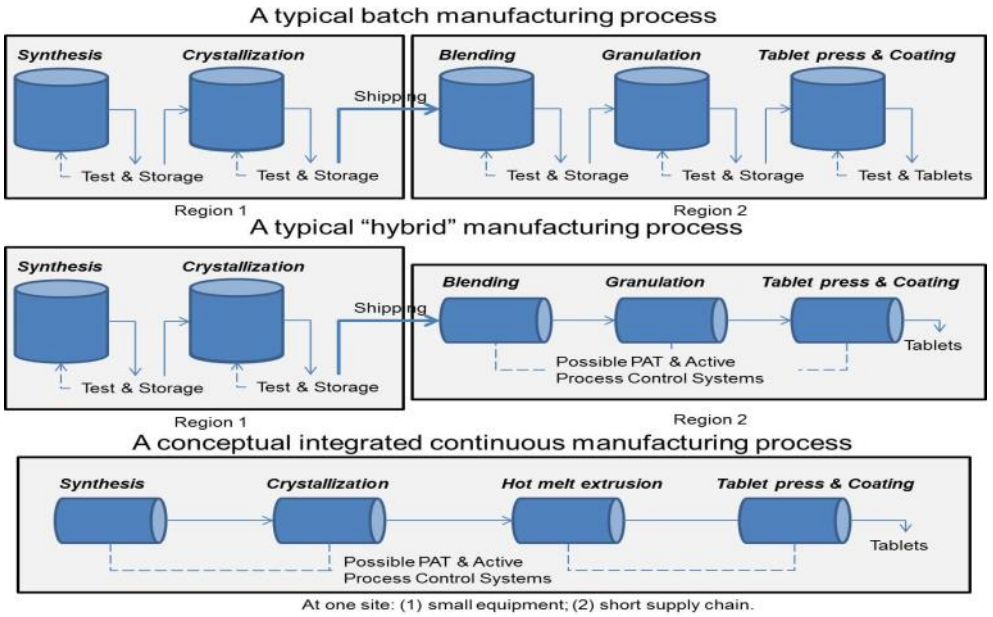
http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM442666.pdf

What is continuous manufacturing?

In a continuous manufacturing process, the material(s) and product are continuously charged into and discharged from the system, throughout the duration of the process[1].

From ChE 101: continuous flow operation.

- Concepts such as mass flow, residence time distribution, time constants, etc.



1. Lee S. *et. al.* J Pharm Innov. **2015** DOI 10.1007/s

Why go continuous?

- Reduction in processing time per unit dose (minutes vs. days).
- Reduction in equipment footprint requirements.
- Potential flexibility in duration of manufacturing campaigns based on knowledge of process.
- Rapid response to drug shortages, emergencies, patient demand

Opportunities for increased product quality assurance and product availability

- Implementation of PAT, quality by design, and process control tools. (systems approach)
- Implementation of integrated quality systems that are responsive to process and product observations in real time.
- Wealth of process knowledge for trending, decision making, and continuous improvement.
- Modernization of manufacturing processes.

Key elements of a CM control strategy

★ *Lessons learned*

Process understanding

- Impact and interactions of parameters within a process step and within processes
- Characterization of process dynamics ★

State of Control

- Process monitoring
- Level and integration of controls ★
- Handling of deviations and disturbances in real time ★
- Raw materials

Material traceability and diversion of non-conforming material ★

Batch definition strategy ★

Process understanding:

The understanding of process parameters and material attributes impact on product quality.

- To establish design space around process steps using design of experiment to build predictive models and/or using simulation tools (ICH Q8)
- To inform alarm and action limits and an approach to process deviations (e.g. adjustments).
- To establish criteria for incoming and in process materials.

Process understanding: dynamics

The evaluation measurement of residence time distribution for nominal conditions. *Line rate is a variable to be considered*

- Degree of back mixing and dampening of disturbances between points of material entry and diversion.
- Typical failure modes or deviations (long term vs. short term), e.g. feeding variability.
- Response to a set point change
- Impact of Startup and Shutdown on product quality.

Process Modeling and Simulation

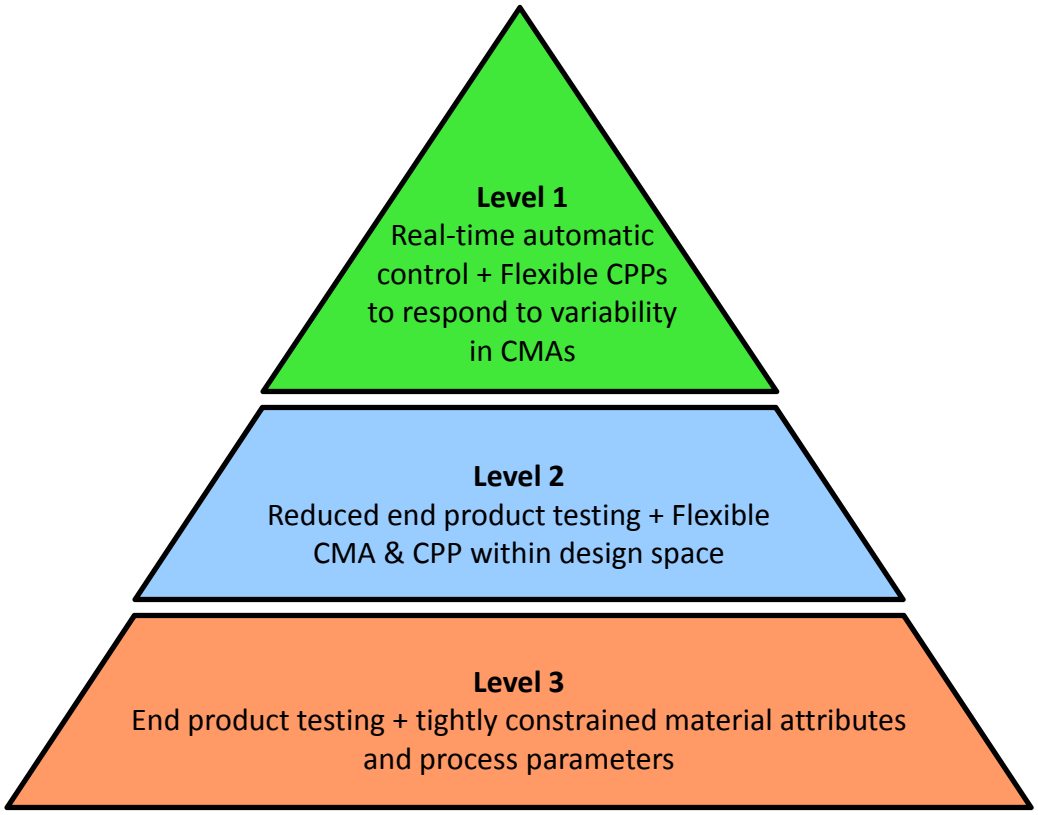
- Common tools (e.g. design of experiments) may be used to increase process understanding
- CM offers a great opportunity to develop and utilize improved process models to gain process knowledge
- Predictive process models can be used as a simulation tool to supplement experiments throughout process development, enhancing process understanding and evaluate risk
  - Models can be used to conduct evaluation of design and optimization studies
  - Dynamic modeling can be used to understand traceability and the propagation of variability
  - Opportunities for integrated process models (i.e. flowsheet or “plant” models) including process controls
- Area of research for FDA, academia and industry.

State of Control

State of control will depend on the control strategy implementation

- Level 1: Active control system with real time monitoring of process variables and quality attributes
- Level 2: Operation within established ranges (multivariate) and confirmed with final testing or surrogate models.
- Level 3: Low detectability for addressing natural variance in CM without significant end product testing.

Monitoring of in-process variability and detectability of disturbances.



Control Strategy Implementation Options[1]

2. Yu, L *et. al.* AAPS J. **2014** Vol. 16 771-783

Process Monitoring: detectability

Statistical Quality Control (SQC)

- Variability in quality attributes of the product are monitored over time

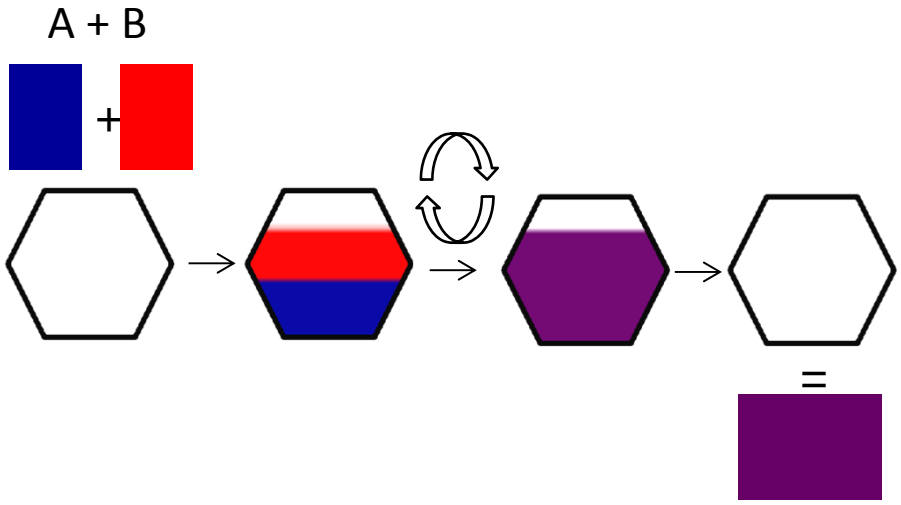
Statistical Process Control (SPC)

- The variability in critical process parameters and in-process quality measurements are monitored over time
- Monitoring the process variables expected to supply more information (e.g., detection and diagnosis)
- May generate a large number of univariate control chart that need to be monitored

Multivariate Statistical Process Control (MSPC)

- Takes advantage of correlations between process variables
- Reduces the dimensionality of the process into a set of independent variables
- May detect abnormal operations not observed by SPC

Continuous Blending

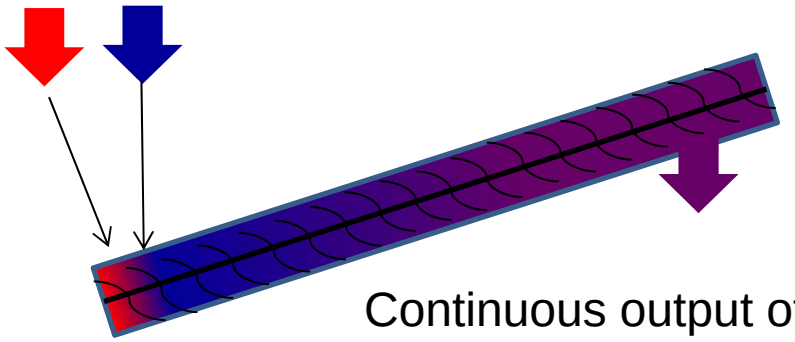


C scale

Batch

Parameters: speed, time, fill level

Continuous feeding of materials at A + B = C rate



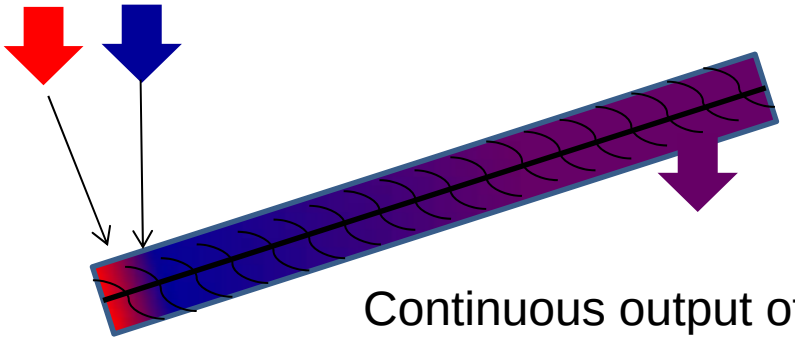
Continuous output of blend at C rate

Continuous

Parameters: feed rate and speed

Blending: Process Understanding

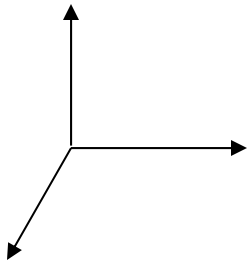
Continuous feeding of materials at A + B = C rate



Continuous output of blend at C rate

Parameter limit setting considerations:
Feed rates
Blender speed ranges
Incoming material properties
Start up time
Sampling Frequency

Parameters

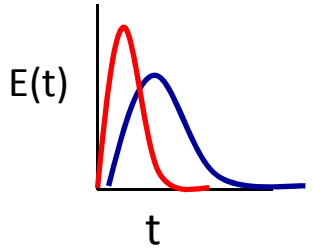


Impact of blender speed, line rate and material properties on time variations in assay

Interactions

Blender & line rate adjustments possible based on degree of fill

Dynamics



Average residence time ~ at nominal line rate?

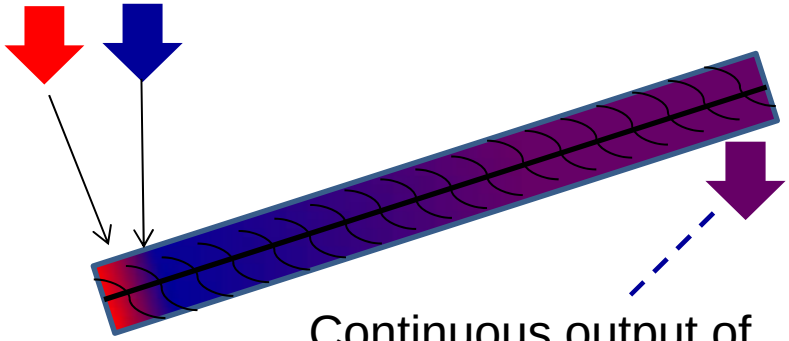
Initial time to reach state of control?

Dampening capacity for a feeder perturbation of up to X% target?

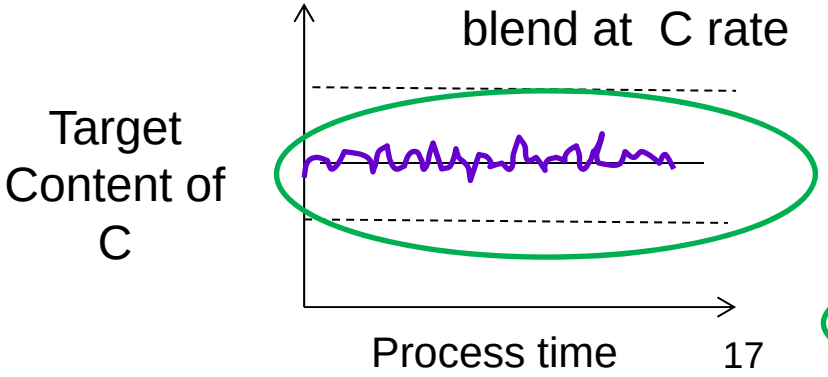
Blending: Monitoring

Parameters: feed rates and blender speed

Continuous feeding of materials at A + B = C rate



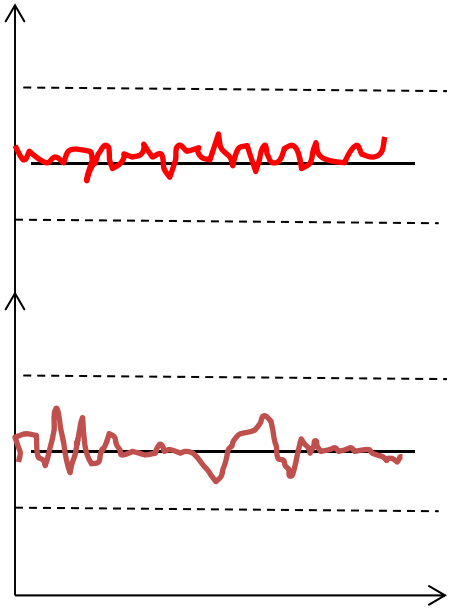
Continuous output of blend at C rate



n = based on sampling frequency (per min)

Feed Rate A

Feed Rate B



- Impact of variations of A and B on C depends on residence time distribution and blender mixing capability
- Process Models

Process deviations

Detectability and Handling

- Pre determination of which events trigger quality investigations and material diversion
- Adequacy of sampling frequency
- Real time response by active controls or working instructions based on process knowledge.
- Interaction of PAT data analysis and quality decision-making

Diverting non-conforming material and material traceability

- The evaluation of overall residence time distribution provides
  - understanding of propagation of a disturbance between detection and diversion
  - justification of the amount of material at risk due to an unexpected event or disturbance.
- Diversion of non-conformation material scheme based on severity of deviation

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.”

Batch Definition Considerations

Potential definitions based on a range of:

- Production time period; Amount of material processed; Production variation (e.g. different lots of feedstock); Amount of product produced; and others
- Batch ranges can be proposed to maintain operating flexibility; target production should be established prior to initiation of manufacturing

Batch definition considerations

- Defining procedures for start-up/shut down, and establishing a priori acceptance criteria for determining when product collection starts
- Ensuring material traceability to verify a *complete history* of the manufacture, especially in cases, for example, OOS/OOT investigations, consumer complaints, product recalls or any other situations that may have public health impact
- Material reconciliation including handling of non-conforming material
- Metrics for determining the failure of an entire continuous run vs. a batch

Trends in Continuous Manufacturing (CM)

Approvals

- Vertex's ORKAMBI™ (lumacaftor/ivacaftor)
  - 1st NDA approval for using a CM technology for production of the Cystic Fibrosis drug (tablets) (July 2015)[1]
- Prezista (darunavir)
  - 1st NDA supplement approval for switching from batch manufacturing to CM process for an FDA-approved HIV drug (tablet) (April 2016)[2]
- Represented different: manufacturing platforms, stage in lifecycle, BCS class, use of PAT tools, batch size definition, and application of RTRt

[1]http://connect.dcat.org/blogs/patricia-van-arnum/2015/09/18/manufacturing-trends-in-continuous-mode – accessed January 16, 2016
[2]http://www.pharmtech.com/fda-approves-tablet-production-janssen-continuous-manufacturing-line

Emerging Technology Team

What is an Emerging Technology for Pharmaceutical Quality?

Technology that has the potential to modernize the body of knowledge associated with pharmaceutical development to support more robust, predictable, and/or cost-effective processes or novel products and with which the FDA has limited review or inspection experiences, due to its relative novelty

- Continuous manufacturing has been identified as an emerging technology

Why is it important?

It is a national priority to modernize the manufacturing sector to ensure drug product quality and availability. Advanced Manufacturing: A Snapshot of Priority Technology Areas Across the Federal Government, Executive Office of the President, National Science and Technology Council. [1]

[1] https://www.whitehouse.gov/sites/whitehouse.gov/files/images/Blog/NSTC%20SAM%20technology%20areas%20snapshot.pdf

Draft ETT Guidance

Advancement of Emerging Technology Applications to Modernize the Pharmaceutical Manufacturing Base 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 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (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 that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Sau L. Lee 240-506-9136.

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

December 2015
Pharmaceutical Quality/CMC

- Provides recommendations to pharmaceutical industry interested in participating in a program involving the submission of chemistry, manufacturing, and controls (CMC) information containing emerging manufacturing technology to FDA.
- Applicable to companies that intend the technology to be included as part of an investigational new drug application (IND) or original or supplemental new drug application (NDA), abbreviated new drug application (ANDA), or biologic license application (BLA) reviewed by the Center for Drug Evaluation and Research (CDER), and where that technology meets other criteria described in this guidance.

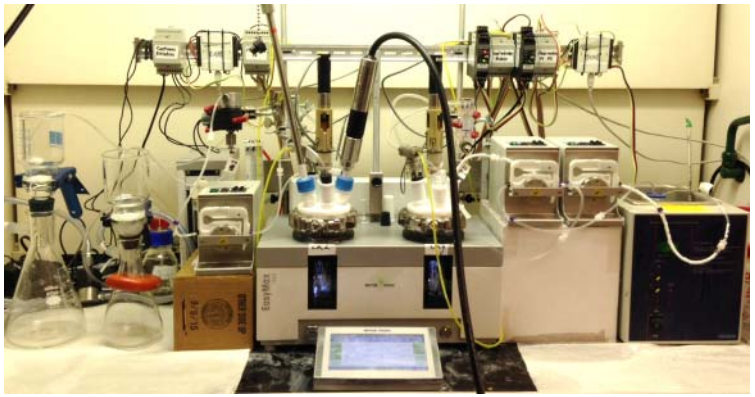
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM478821.pdf

Emerging Technology Team

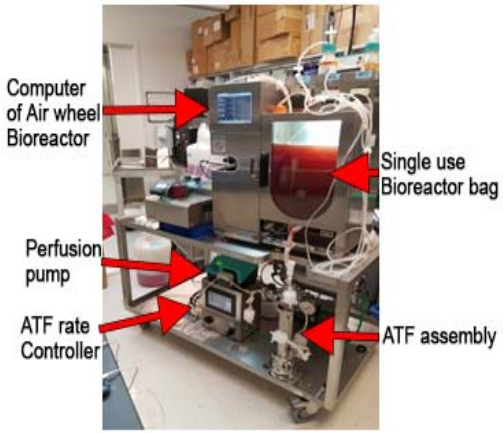
What is evolving in FDA experience with CM?	ETT engagement
Over 15 industry meetings since the launch of program in early 2014 • Drug substance synthesis • Drug product: solid oral dosage, several platforms • Biotechnology products • Control strategy utilizing process models • Continued Verification • End to End (DS to DP) • Batch size definition	• Identification and education of SMEs for continuous manufacturing via focused training (e.g. NIPTE, site tours, visit to academia). • Written comment on early control strategy proposals, • Comprehensive feedback including all review disciplines and inspections; F2F • Identification and resolution of policy or regulatory issues (e.g. potential precedents), • Pre operational visits, • Participation and co-leadership in review team and during inspections.

CM Technology in OPQ Labs

Platforms
Continuous Crystallization
Bioprocessing
Orally Dissolving Films
Hot Melt Extrusion
Twin Screw Wet Granulation
Via external grants and collaborations Liposomes (UConn) Feeding, Blending, Direct compression (Rutgers/Purdue) Orally Dissolving Films (NJIT)



Continuous crystallization skid



Continuous perfusion bioreactor

OPQ Research in CM follow Principles for innovation

- Linked to regulatory need for understanding risk
  - Automated process data acquisition, PAT development and implementation, use of models
  - Process dynamics evaluation to and impact of process to changes.
  - Challenging formulations and applications
- Interdisciplinary Teams: product and process expertise including pharmaceutics, engineering, and chemistry.
- Highly collaborative and flexible

Conclusion

- Continuous manufacturing is an opportunity for the modernization of pharmaceutical manufacturing and operations.
- Process understanding and robustness of the control strategy are the key to CM successfully delivering quality products while enabling flexible operations.
- FDA/OPQ continues to learn and engage on CM via
  - Reviews
  - Inspections
  - Research
  - Grants
  - Training
  - Participation on emerging technology efforts across the Agency.

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Thank you!

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