Novel Technologies to Support Patient Centric Drug Product Development: FDA Perspective

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The views and opinions expressed in this presentation are only of the author, and should not be construed to represent FDA views or policies

Patient Centric Drug Product Development

Patient-centric drug development considers the patient from the start of the formulation process through the selection, design and manufacture of the finished dosage form

Outline

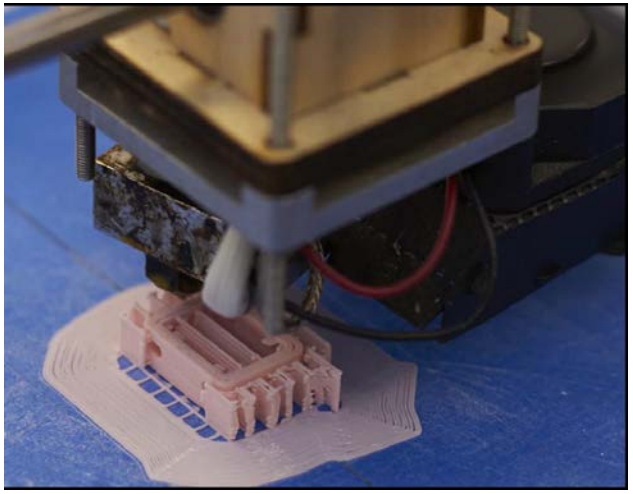
- FDAs experience with some innovative technologies to support development of patient centric dosage forms
- Regulatory considerations for implementation of CM (Continuous Manufacturing)
- Conclusion

Examples of Innovative Technologies

- On demand 3D printing
- Portable manufacturing units
- Digital pill
- Continuous manufacturing
  - Flexibility in batch sizes based on size of patient population and market demand

3D Printing

- On-demand 3D printing of finished dosage forms
- Technology Specific Considerations
  - Enabling on-site and on-demand assessment of quality of finished product
  - Labeling considerations for personalized dosing
  - Control strategy requirements
    - Raw material controls
    - Process parameter settings
    - Environmental settings
  - Setting equipment performance criteria



https://eandt.theiet.org/content/articles/2018/01/3d-printer-for-pharmaceuticals-adapted-to-create-drugs-on-demand/

Portable Manufacturing Units

- Portable continuous manufacturing units to make finished products on demand, anywhere in the world
- Technology Specific Considerations
  - Quality over sight system that would allow implementing CGMP requirements for such portable units
  - Enabling methodologies for assessment of quality of finished product
  - General CM specific control strategy considerations also apply, e.g. detection and removal of non-conforming product

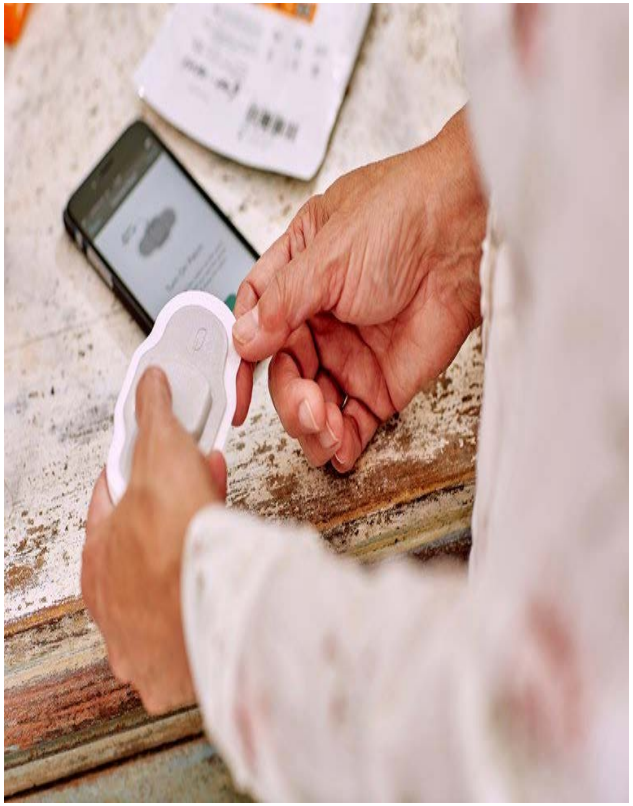
Credit: James Kegley

A team at the University of Maryland, Baltimore County, has developed this Bio-MOD system, easily packed in a suitcase for transport, to synthesize biopharmaceuticals on-site.

https://cen.acs.org/biological-chemistry/biotechnology/Making-biologics-demand/96/i45

Digital Pill

- In 2017 for the first time FDA approved a digital pill - a medication embedded with a sensor that can tell doctors whether, and when, patients take their medicine
- Technology Specific Considerations
  - Consistency of placement of the sensors within the pill
  - Setting of sensor specifications
  - Assessment of functionality of the embedded sensor



FDAs Emerging Technology Initiative

What is Emerging Technology?

- Technology with 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

- **Innovative** or novel product, manufacturing process, or analytical technology subject to quality assessment (including review and inspection)

Objectives of this Program

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

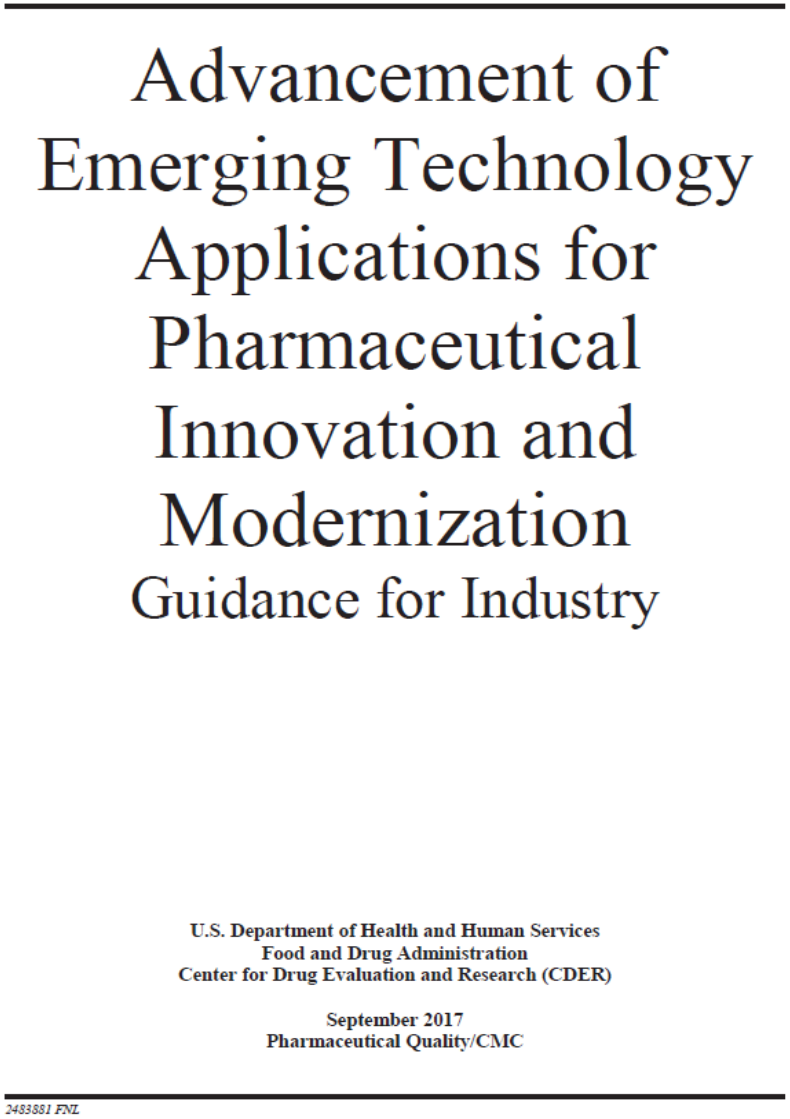
To help establish **scientific standards** and **policy**, as needed

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**

ETT Guidance


Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization

Guidance for Industry

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

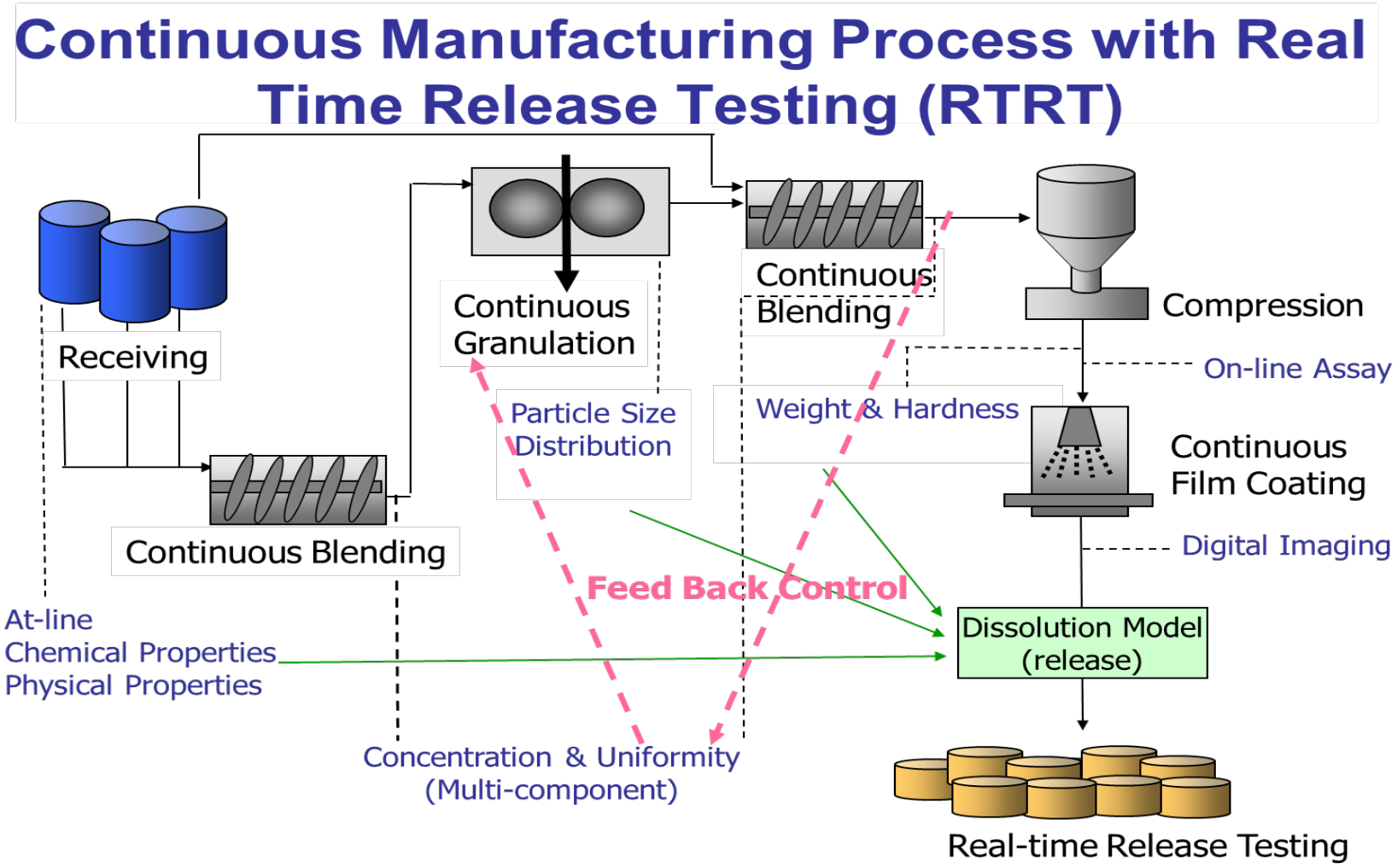
September 2017
Pharmaceutical Quality/CMC

2483881 FNL

- Provides recommendations to companies interested in participating in a program involving the submission of 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.

Continuous Manufacturing

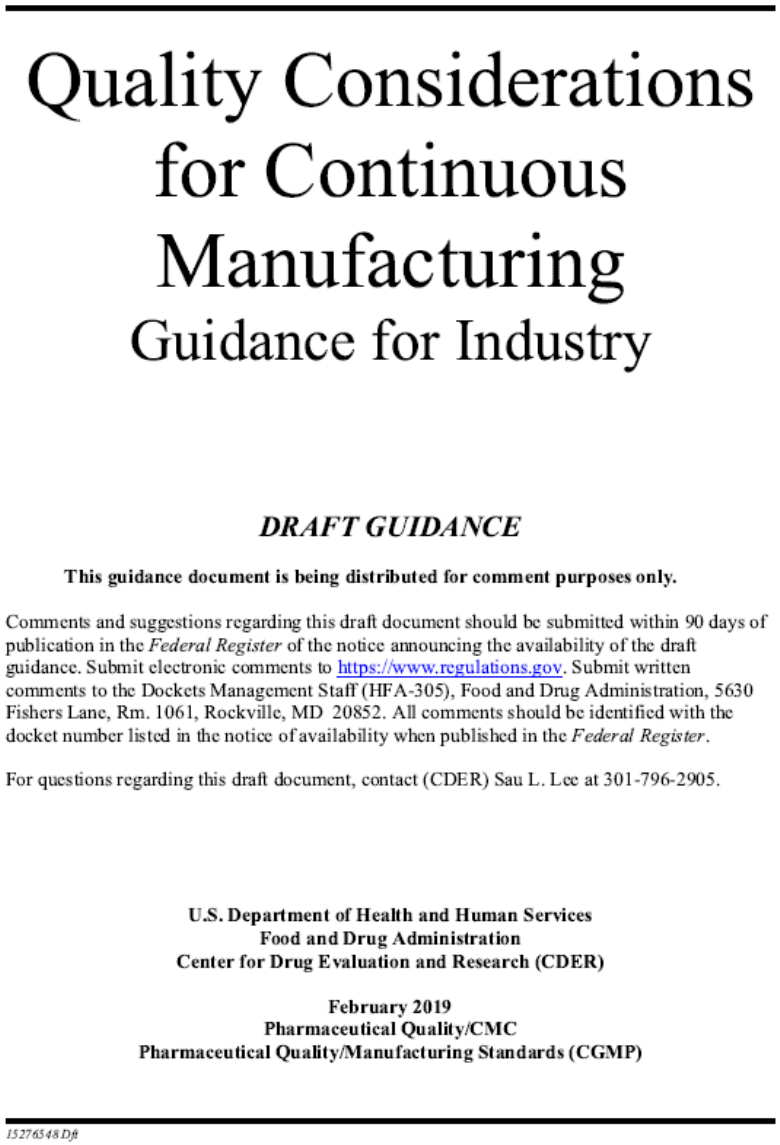


Considerations for Implementation of CM

FDA

- Quality Control Unit
- Process Validation
- Life Cycle Considerations

CM 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)

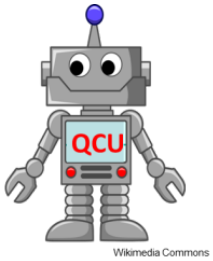
15276548.Dft

- Provides recommendations on quality considerations for continuous manufacturing of small molecule solid oral drug products
- Focuses on scientific and regulatory considerations that are unique to CM such as: batch definition, process dynamics, process monitoring and control, material diversion, real time release testing, scale up, process validation consideration
- Considerations for bridging from existing batch manufacturing to CM
- Documentation of CM specific information in an application

Quality Control Unit

- Quality Control Unit needs to adapt quality processes for CM requirements
  - Alarms, alerts, and real-time operator response
  - Investigations, deviations, and change control
- Establish metrics for overall batch quality
  - Handling of diverted material
  - Criteria for entire batch rejection
- CM systems are typically highly automated
  - Quality decision making must be programed into the automation
  - Design, validation, and qualification of automation with equipment is very important
  - Installation / Operational / Performance Qualification should consider both unit component functionality as well as the entirety of the integrated system

And.....



Process Validation

- Understanding equipment performance over expected duration of operation
- Identification of potential failure modes
- To demonstrate that the process can achieve and maintain a state of control over duration of the run
  - Length of run representative of size of commercial batch
- Assess process robustness during PPQ (Process Performance Qualification)
  - Establish metrics for yield
  - Limits for time in control, frequency of rejection
- Identify sources of variability and set approaches for mitigation
  - E.g. any additional specifications for in-coming materials beyond USP
- Design of PPQ study should be representative of intended commercial run time
  - Include interventions that could occur during routine operation

Lifecycle Considerations

- Define plans for Continuous Process Verification
- Continuous manufacturing typically generates a huge volume of data
  - Identify key indicators
  - Collect and analyze product and process monitoring data related to product quality for trending and analysis
- Statistical approach highly recommended; multivariate models can be helpful

Model Implementation Considerations

- Applicable for models that are used to support control strategy
- Document plans for model maintenance in site's quality system
  - Includes plans to verify model performance when the assumptions made to develop the model are not applicable
- Monitoring and trending model performance: a component of Continuous Process Verification

Concluding Remarks

- Emerging technologies offer the promise of novel therapies for developing patient centric dosage forms and modernizing pharmaceutical manufacture
- The Emerging Technology Program enables early FDA-Industry interactions, even before IND submission or at pre ANDA stage
- Early and frequent discussion with the Agency during technology development facilitates first cycle approval
- Integrated team based approach (technical and quality) is recommended for establishing quality decision metrics for CM systems
- Implementation of CM warrants some specific PQS considerations

Acknowledgement

- Lawrence Yu
- Sau (Larry) Lee
- Members of Emerging Technology Team (ETT)

Thank you!

Questions, comments, concerns:
CDER-OPQ-Inquiries@fda.hhs.gov