FDA Perspective on Continuous Manufacturing

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Pharmaceutical Manufacturing: The Path Ahead..

" *Right now, manufacturing experts from the 1950s would easily recognize the pharmaceutical manufacturing processes of today. It is predicted that manufacturing will change in the next 25 years as current manufacturing practices are abandoned in favor of cleaner, flexible, more efficient* ***continuous manufacturing*****."**

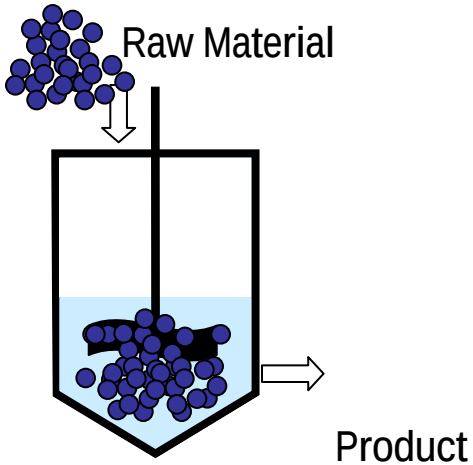
Dr. Janet Woodcock, AAPS Annual meeting, October 2011

Outline

- Difference between “Batch” and “Continuous”
  - Engineering perspective
  - Regulatory perspective
- Scientific considerations for continuous processing
- Ongoing collaborative research
- Concluding remarks

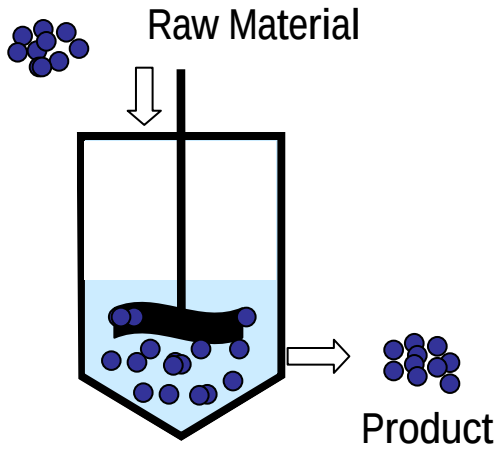
"Batch" vs. "Continuous": Engineering Definition

Batch Manufacturing
All materials are charged before the start of processing and discharged at the end of processing



Examples: Bin blending, lyophilization, some reactions

Continuous Manufacturing
Material is simultaneously charged and discharged from the process

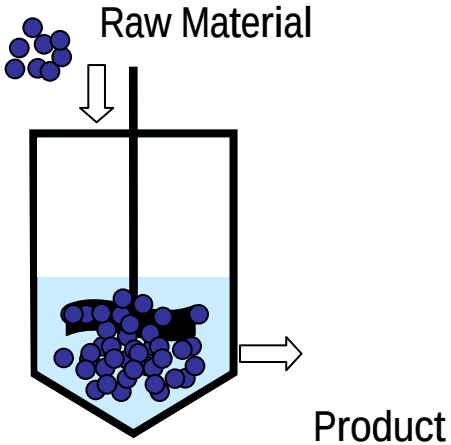


Examples: Petroleum refining, much of food processing

Other Manufacturing Variations

Semi-Batch (Fed-batch) Manufacturing

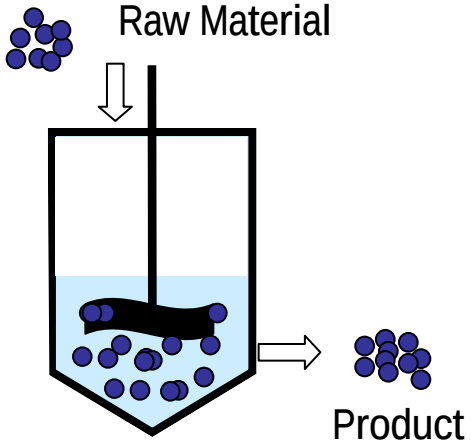
Materials are added during processing and discharged at the end of processing



Examples: Wet granulation, fermentation

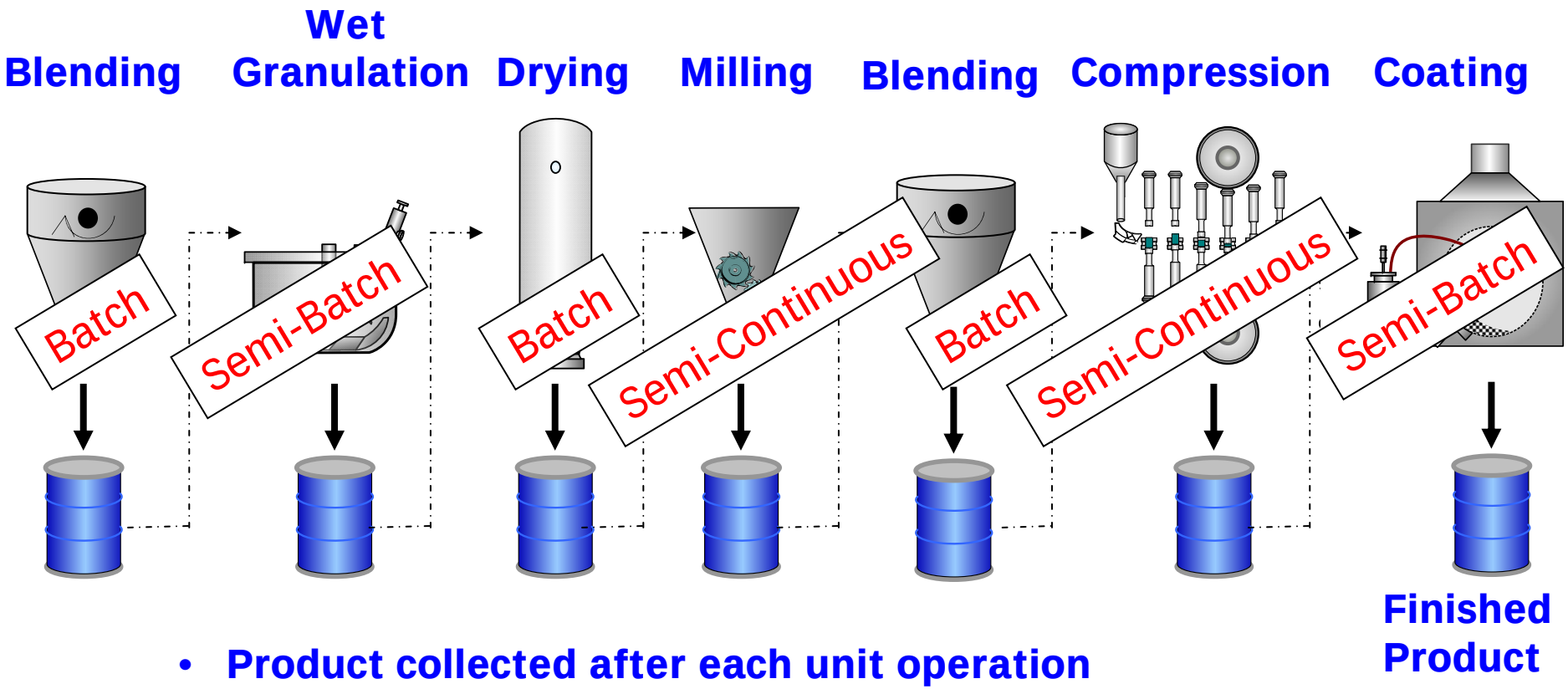
Semi-Continuous Manufacturing

Like continuous manufacturing, but for a discrete time period



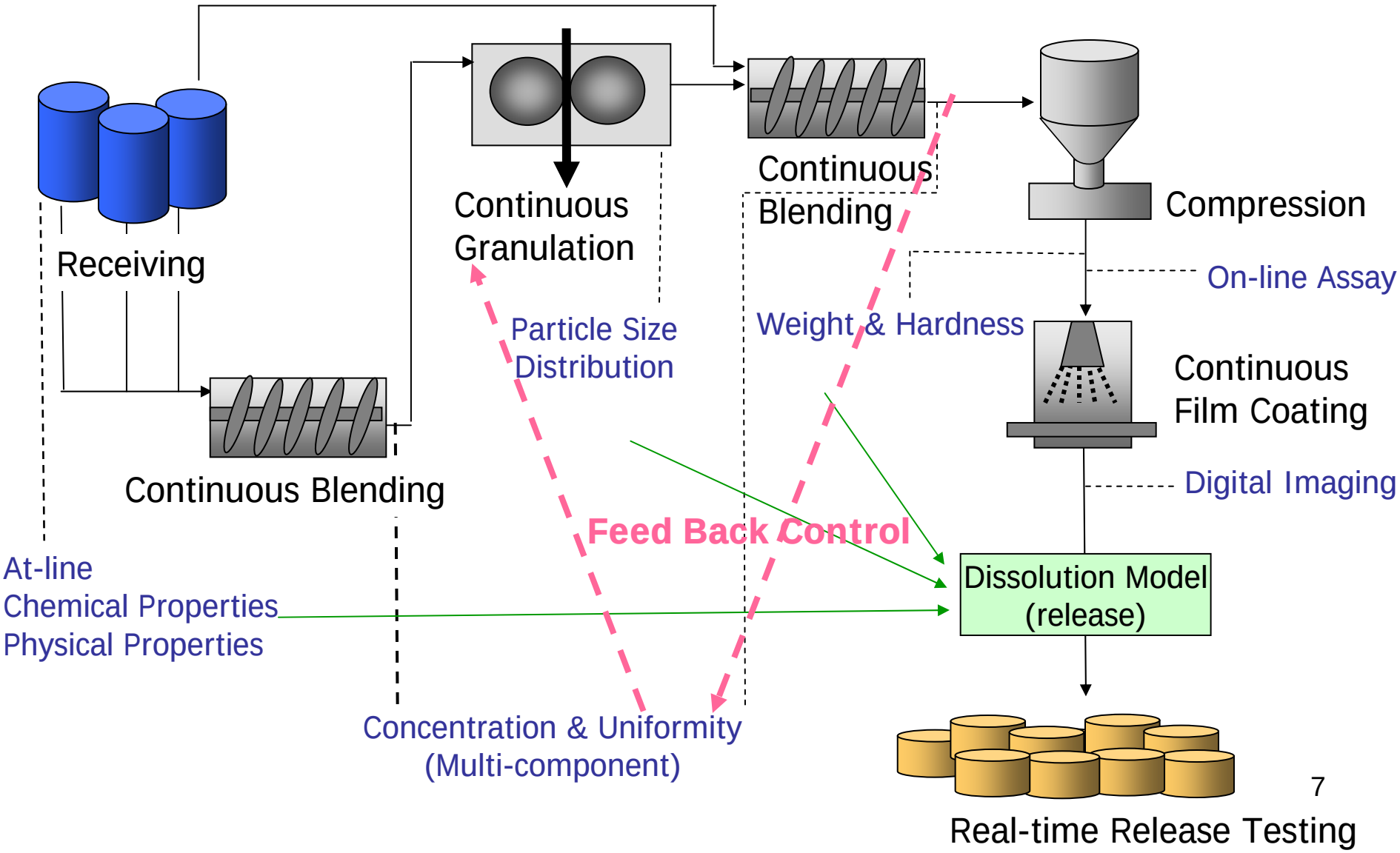
Examples: Roller compaction, tablet compression

Example of Traditional Tablet Manufacturing Process



- **Product collected after each unit operation**
- **Finished product is tested at off-line laboratories, after processing is complete**
- **Actual processing time = days to weeks**

Example of Continuous Manufacturing with On-line Monitoring



Advantages of Continuous Manufacturing (CM)

- Integrated processing with fewer steps
  - No manual handling, increased safety
  - Shorter processing times
  - Increased efficiency
- Smaller equipment and facilities
  - More flexible operation
  - Reduced inventory
  - Lower capital costs, less work-in-progress materials
  - Smaller ecological footprint
- On-line monitoring and control for increased product quality assurance in real-time
  - Amenable to Real Time Release Testing approaches
  - Consistent quality

Potential for reduced cost

Regulations & Continuous Manufacturing

- No specific regulations or guidance for continuous manufacturing, other than the definition of “lot”
- Nothing in regulations or guidance prohibiting continuous manufacturing
- Continuous manufacturing consistent with FDA’s Quality by Design (QbD) efforts
  - More modern manufacturing approach
  - Potential to improve assurance of quality and consistency of drugs
  - Enables quality to be directly built into process design

Regulatory Definition of "Batch"

21 CFR 210.3

Batch - 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

Batch refers to the quantity of material and does not specify the ***mode of manufacture***

Regulatory Definition of "Lot"

21 CFR 210.3

Lot - **a batch**, or a specific identified portion of a batch, having 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

Defining a Batch/Lot
Why does it matter under cGMP?

- **Laboratory determination of final specifications for release**
  - 21 CFR 211.165(a): For each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product….. prior to release
- **Documentation of Manufacturing**
  - 21 CFR 211.188 Batch product and control records shall be prepared for each batch of drug product produced and shall include complete information relating to the production and control of each batch
- **Extended investigations of unexplained discrepancies**
  - 21 CFR 211.192: The investigation shall extend to other batches… that may have been associated with the specific failure of discrepancy.
- **Recall situation**
  - 21 CFR 211.150(b): Distribution procedures shall include… a system by which the distribution of each lot of drug product can be readily determined to facilitate its recall if necessary

Considerations for Defining a Batch/Lot

- Ways to define a batch/lot at the product collection step?
  - Production time period
  - Production variation (e.g., different lots of feedstock)
  - Dependent on equipment cycling capability
  - Other definition

Steady-State in Continuous Manufacturing

- Steady state is when material properties in the system remains constant with time
  - Not the same as equilibrium!
  - Time to reach steady state depends upon flow properties
- When is product acceptable or not acceptable to collect?
  - During process start-up and shut-down
  - After a disturbance (e.g., spike in feed rate)
  - Handling of rejects?
- When do all component concentrations and physical properties reach steady state?
  - May necessitate measurements other than concentration of active component(s)

Considerations for Control Strategy for Continuous Manufacturing (CM)

Methods to assure that product has “uniform character and quality within specified limits”?

- Characterization of in-coming materials
- In-process measurements
  - Selection of sampling frequency
  - In-process parameters and material attributes
  - Setting of appropriate acceptance criteria
- Dependent on cycling capacity of equipment
- Consider interactions amongst unit operations

Specific Sampling Considerations for Continuous Processing

- Dependent on system dynamics
  - Sample frequency capable of detecting process upsets
  - Residence Time distributions
  - Start-up frequency vs. steady state
  - Measurement device and controller delays
  - “Blind” times (e.g., refilling hoppers)
- Blend uniformity challenging to measure
  - Stratification
  - Interference due to flow
  - Time of acquisition of single spectra vs. flow rate
  - Number of probes and their distribution

System Integration

For continuous manufacturing, increased need to :

- Understand interaction between unit operations
  - Ensure stable operation
  - Helps support feedback/feed forward controls
  - Impact of residence time distributions
  - Impact of recycle loops
- Characterize propagation of changes and disturbances through system
  - Understand interface between different lots of raw material
  - Be able to isolate bad material from disturbances
- Have an integrated data acquisition system over all unit operations
  - Manage data from all on-line/in-line measurement systems

ONDQA/FDA Sponsored Research on Microreactors

- Joint research with CPAC (Center for Process Analytical Chemistry), University of Washington, Seattle and Corning
  - Funded by the FDA
  - Initiated in November, 2008
  - Also utilize CPAC's New Sampling/Sensor Initiative (NESSI)
- Goal of this project is to enhance our understanding of continuous manufacturing and microreactors:
  - Developing a drug substance synthesis using microreactors following the QbD paradigm
  - Effective implementation of sampling and online analytics
  - Leveraging data from analytical tools to design an integrated control strategy

Current Challenges

- Need for integration of analytical tools to the control system to support implementation of feed-back or feed-forward control
  - Sophisticated data management tools
- Defining representative sampling to consistently assure product quality over time
    - Location of sampling probes
    - Sample size and sampling frequency
- Need for enhanced process understanding
  - Availability of mechanistic models for all processing steps
  - Implementation of multivariate analysis for determination of product quality

Concluding Thoughts

- The science exists to enable continuous manufacturing of pharmaceuticals
  - Specific scientific considerations related to sampling frequency for continuous manufacturing
- There are no regulatory hurdles for implementing continuous manufacturing
  - However, there is a lack of experience
- FDA supports the implementation of continuous manufacturing using a science and risk-based approach
  - Recommend early and frequent discussion with Agency before implementation

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Thank you!

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