Challenges and Opportunities for Continuous Manufacturing in a QbD Framework

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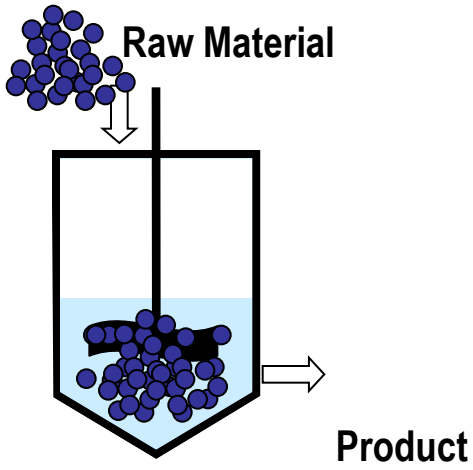
Outline

- Background on continuous manufacturing
  - Definitions of “continuous” and “batch”
  - Examples of continuous processing
  - Advantages of continuous manufacturing
- Regulatory considerations for continuous processing
- Example PAT and RTRT approaches
- Concluding remarks

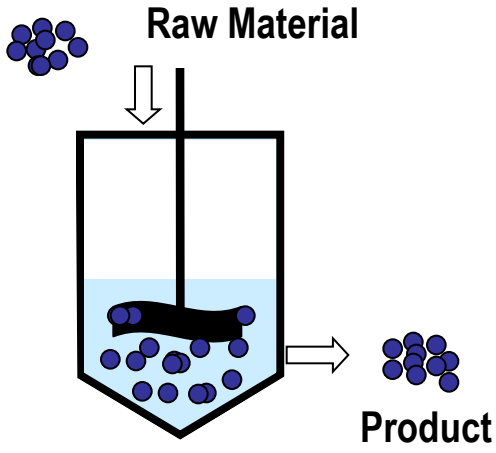
"Batch" vs. "Continuous": Engineering Definition

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



Examples: Roller bottles, lyophilization, some reactions

Continuous Manufacturing
Material is simultaneously charged and discharged from the process

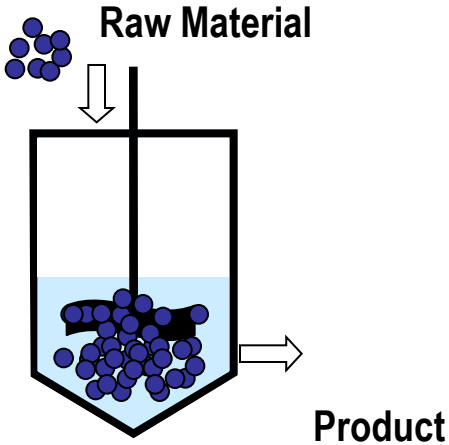


Examples: Petroleum refining, much of food processing

Other Manufacturing Variations

Semi-Batch (Fed-batch) Manufacturing

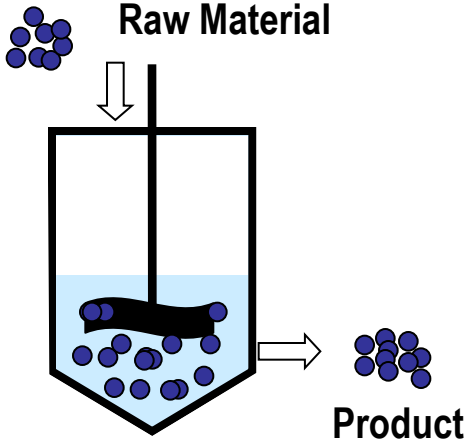
Materials are added during processing and discharged at the end of processing



Examples: Fermentation, wet granulation

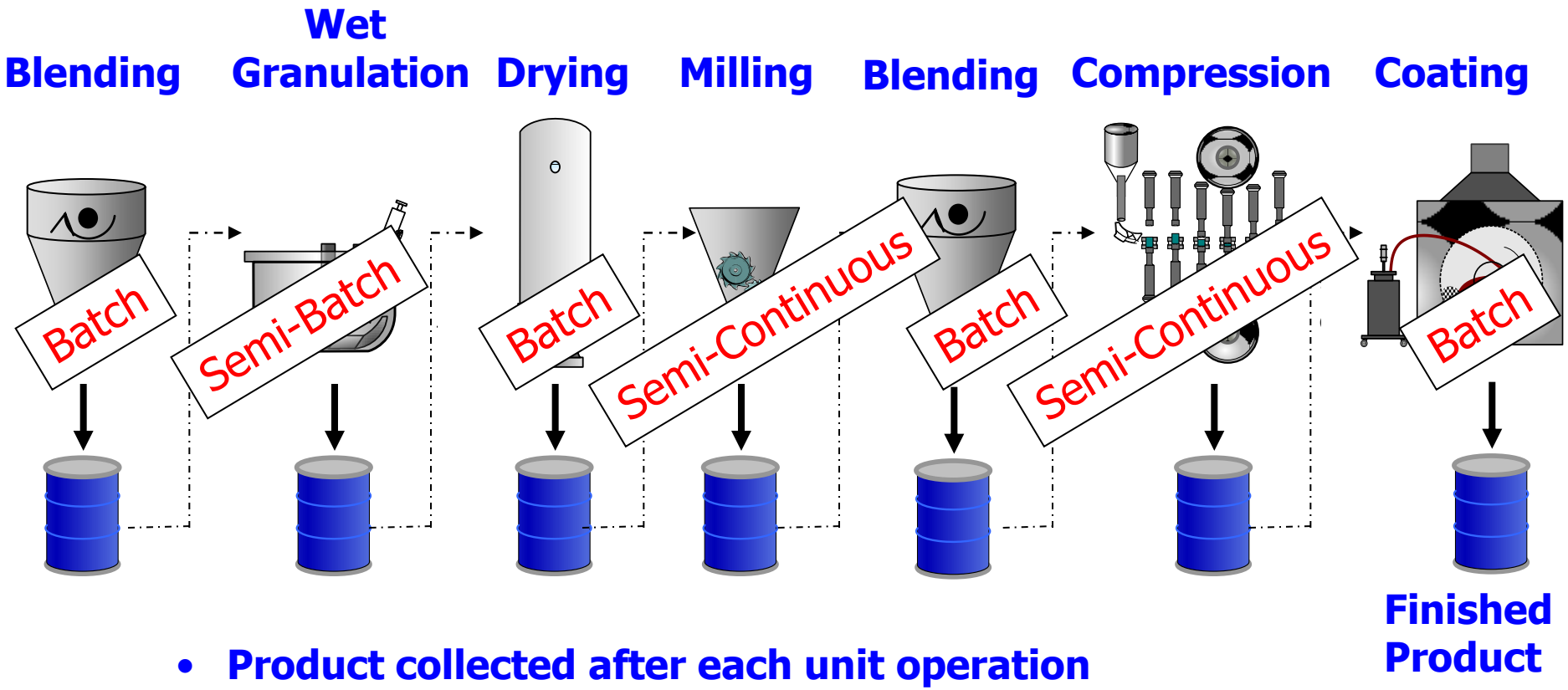
Semi-Continuous Manufacturing

Like continuous manufacturing, but for a discrete time period



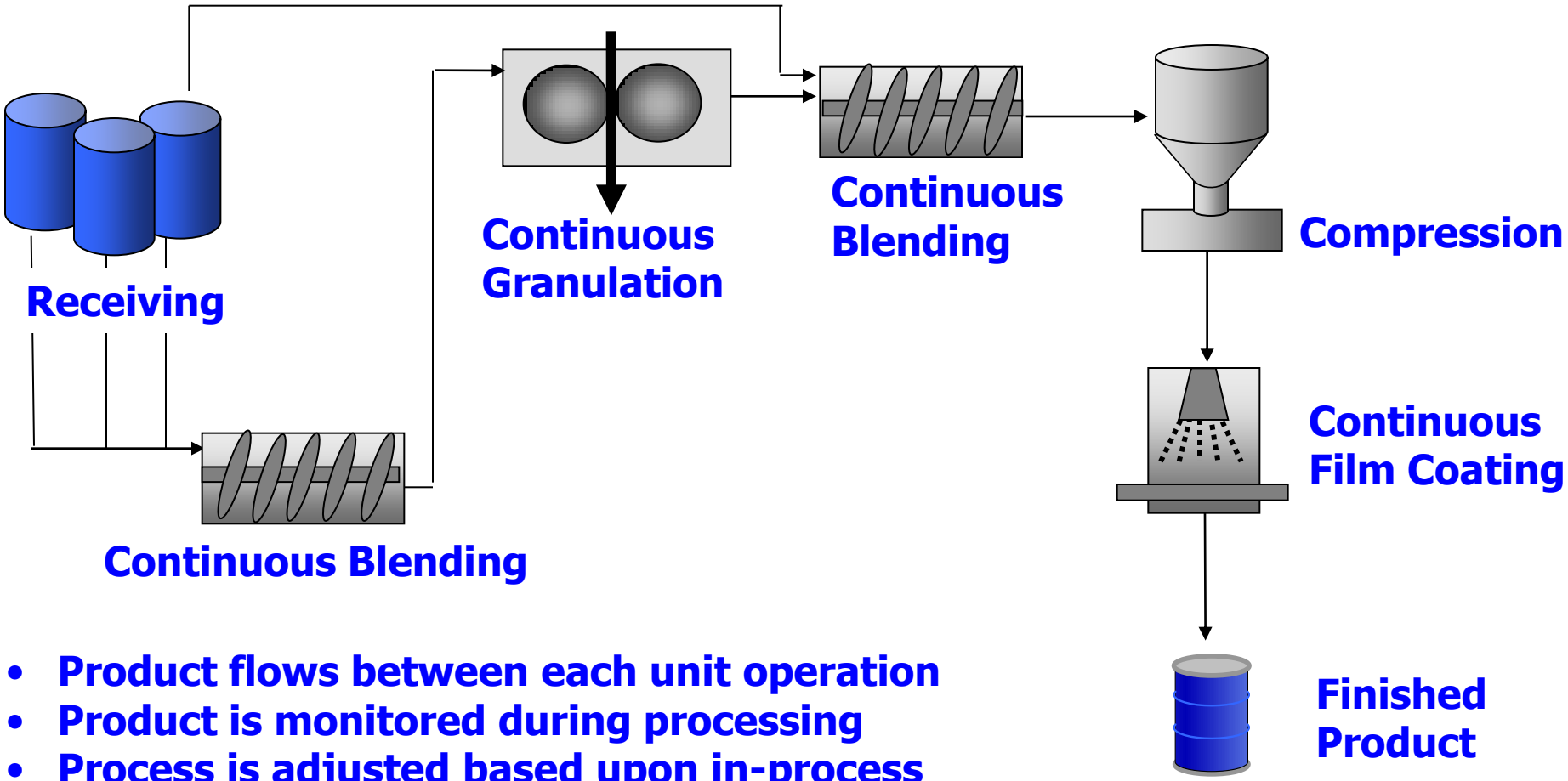
Examples: Perfusion bioreactors, tablet compression

Example of Traditional Tablet Manufacturing Process



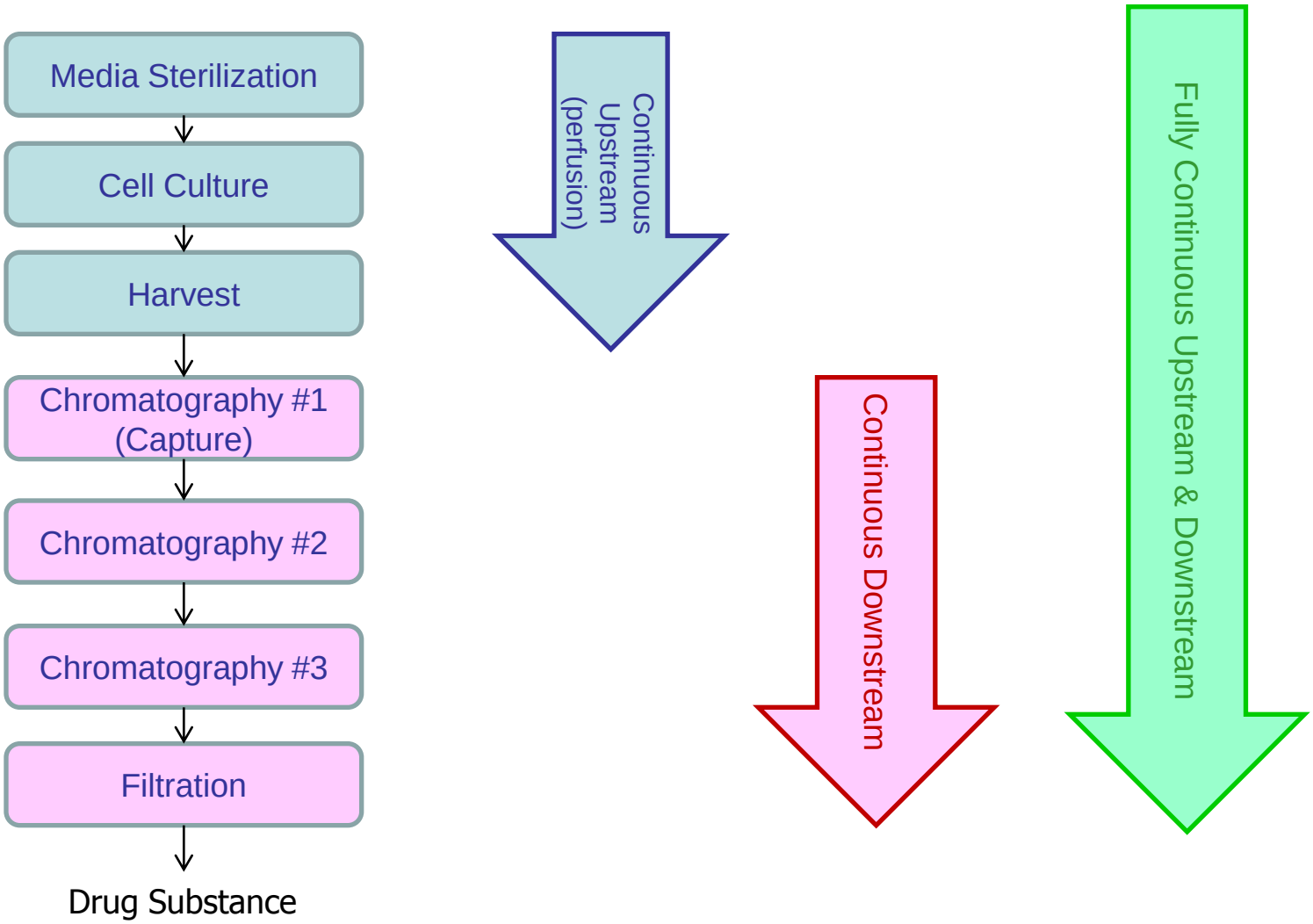
- **Product collected after each unit operation**
- **Finished product is tested at off-line laboratories, after processing is complete**
- **Actual processing time = days to weeks**

Conceptual Example of Continuous Manufacturing



- Product flows between each unit operation
- Product is monitored during processing
- Process is adjusted based upon in-process measurements
- Actual processing time = minutes to hours

Examples of Continuous Bioprocessing



Manufacturing Advantages of Continuous Manufacturing

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

Potential for reduced cost

Development Advantages of Continuous Manufacturing

- Rapid development screening over many conditions
- Potential to conduct development studies at commercial scale
- Potential for less material usage for development
- Potential for automated experimentation
- Ability to run chemistry under new conditions
  - Highly exothermic reactions
  - Ultra high, ultra low temperatures

Potential for reduced cost

Potential Advantages of Continuous Manufacturing for Bioprocessing

- Ability to handle less stable/ more labile proteins
  - Less residence time
- Potential for increase product consistency (e.g., glycoforms)
- Reduction of degradation due to decrease hold times between steps
- Potential for higher cell densities, which may lead to lower impurity levels

From DRAFT "White Paper on Continuous Bioprocessing:, C. L. Cooney, K.B. Konstantinov, International Symposium on Continuous Mnaufacturing of Pharmaceuticals

Continuous bioprocessing is not new!

- Continuous unit operations have long been available for use in bioprocessing
  - Perfusion reactors
  - Filtration systems
  - Precipitation
  - Chromatography
  - Sterilization

It is up to the applicant to determine which manufacturing technology is best for their product

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1990 Review Article

AN OVERVIEW OF CONTINUOUS PROTEIN PURIFICATION PROCESSES

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ABSTRACT

As the sphere of influence of recombinant technology moves away from the laboratory bench, towards product commercialization, development of manufacturing and large scale process technology is becoming a major challenge and determinant for commercial success. The challenge is particularly acute for protein purification process development where protein purification costs tend to dominate overall process economics. The primary objective for process scale purification is to minimize cost for a purified product which meets specifications. Continuous processes may be used to facilitate achievement of the overall objectives. This review critically examines the use of continuous processing for protein purification and recovery operations. The processes have been divided into three general areas: adsorptive and chromatographic, electrophoretic, and extractive. Consideration is given to the operational advantages and limitations of the reviewed processes.

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
- **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.
- **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
- **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

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

Main Questions for Ensuring Quality in Continuous Manufacturing

- Is your measurement representative of the whole?
  - Location of measurement
  - Frequency of measurement
  - Effective sample size (challenging in a flowing system)
- How do you trace raw materials and disturbances through the system?
  - Tracing of raw materials to finished products
  - Diversion of disturbances
- What is your criteria for “good product”?

Product Collection Considerations for Continuous Manufacturing

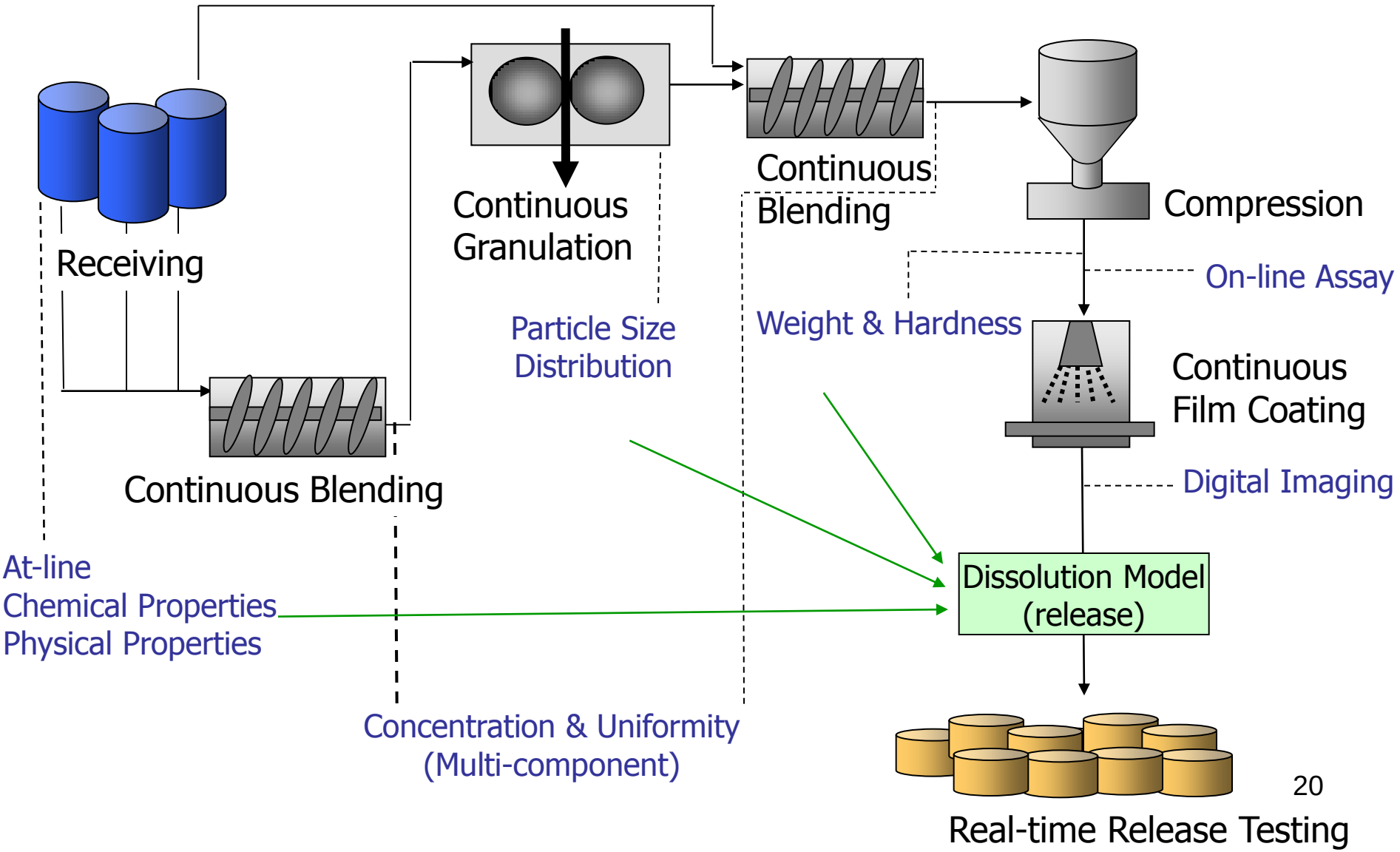
- When is product deemed acceptable to collect?
  - During process start-up
  - After a disturbance (e.g., spike in feed rate)
- When do all component concentrations and physical properties reach desired levels?
  - May necessitate measurements other than concentration of active component(s)
- How do you describe when to collect product?
  - Steady state vs. steady operation vs. controlled state
  - Time for system to level out depends upon flow properties and control system

Real Time Release Testing and Continuous Manufacturing

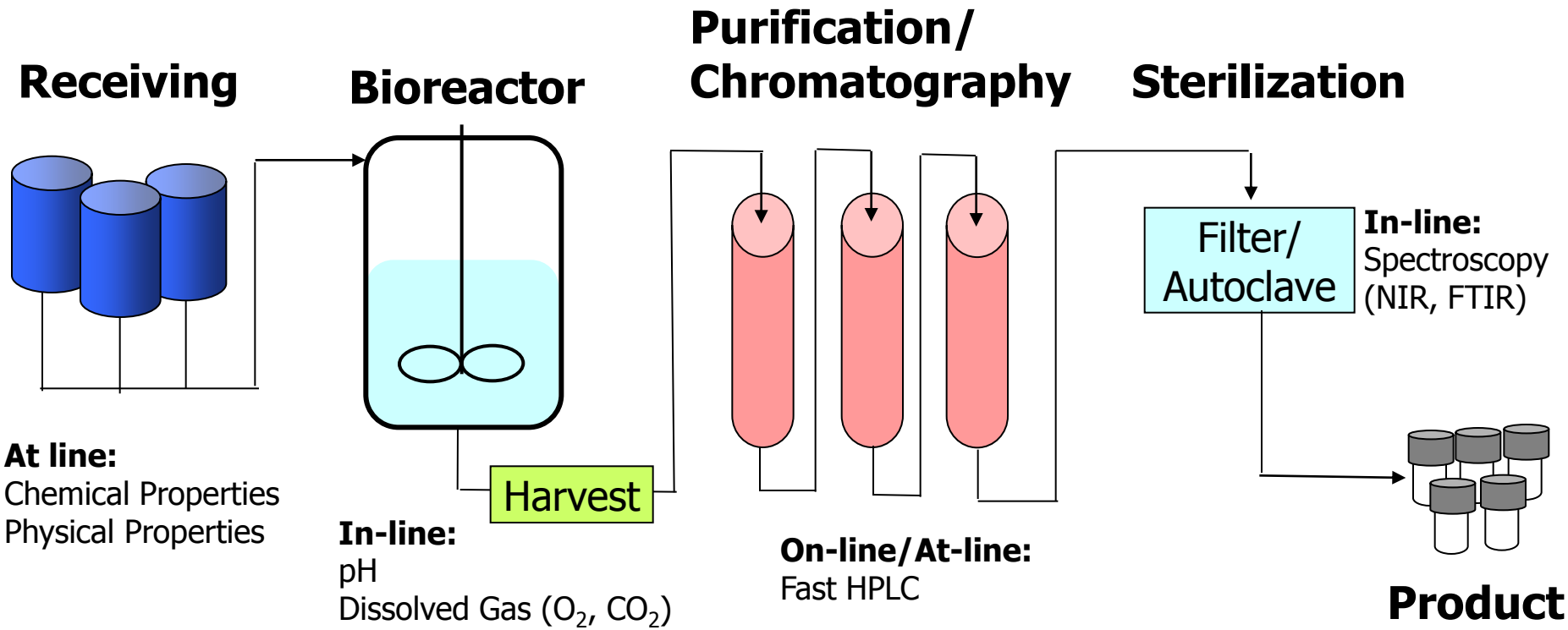
- The ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls *ICH Q8(R2)*

- Continuous manufacturing naturally lends itself to RTRT approaches
- For many continuous manufacturing systems, it would be challenging to assure quality without appropriate on-line monitoring

Conceptual Example of RTRT for Continuous Manufacturing



Enhanced Process Understanding: On-Line Measurements/PAT



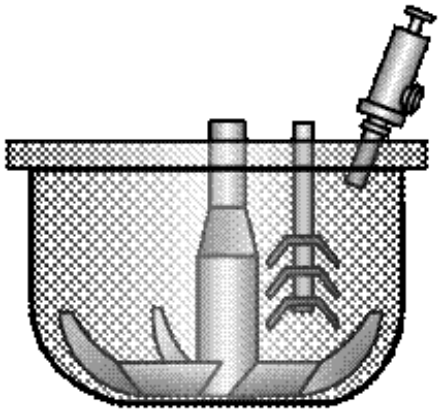
Advanced Mathematical Models for feedback & feed forward control

- Mechanistic Approach (based on kinetics, mass transfer)
- Empirical Approach (multivariate models)

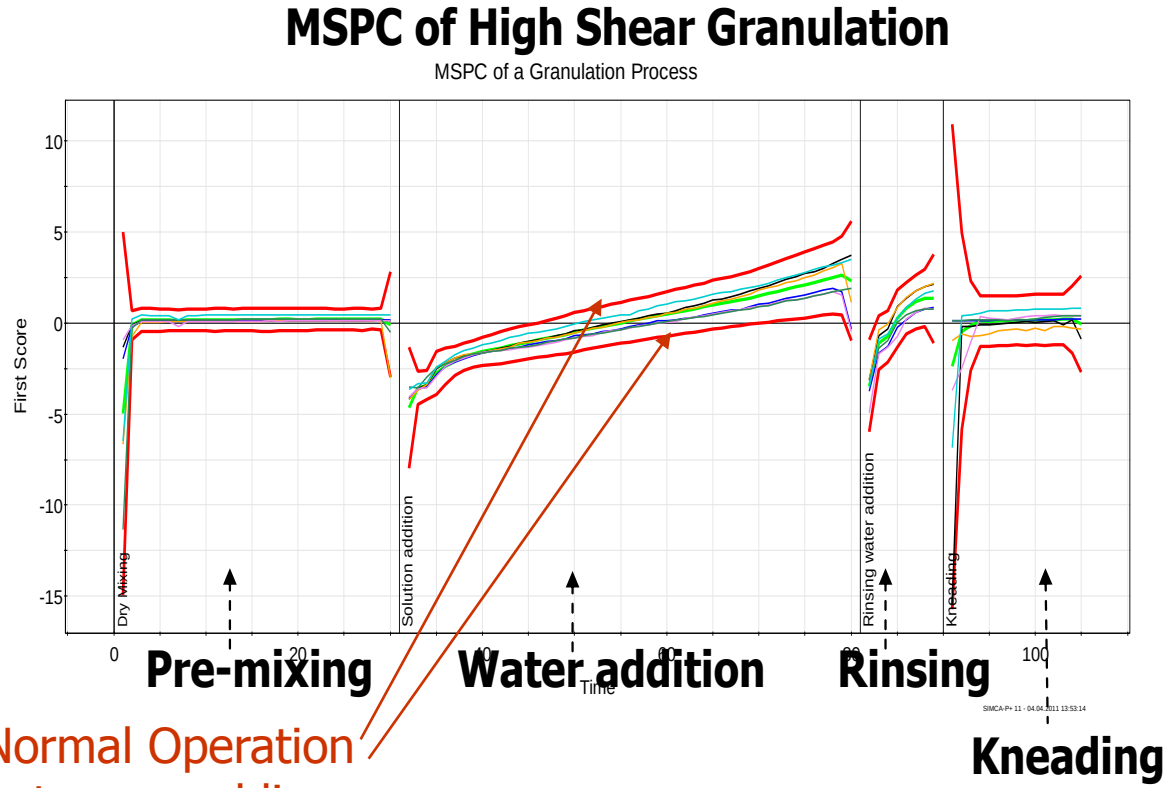
Multivariate Statistical Process Control (MSPC)

- Multivariate statistical process control (MSPC) simultaneous observes and analyzes multiple parameters in a simplified fashion
  - Process variables often track together
  - Reducing the dimensionality of the process into principle components (combined variables) can simplify fault diagnosis
  - Can identify some quality issues that univariate analysis might not detect
- Potential use:
  - Routine monitoring for monitoring consistency and identifying atypical operation
  - Part of RTRT approaches
    - Potential for use as part of RTRT control strategy
    - Potential to support reduced testing approach
  - Applicable to both new and “legacy” products

Multivariate Statistical Process Control Example



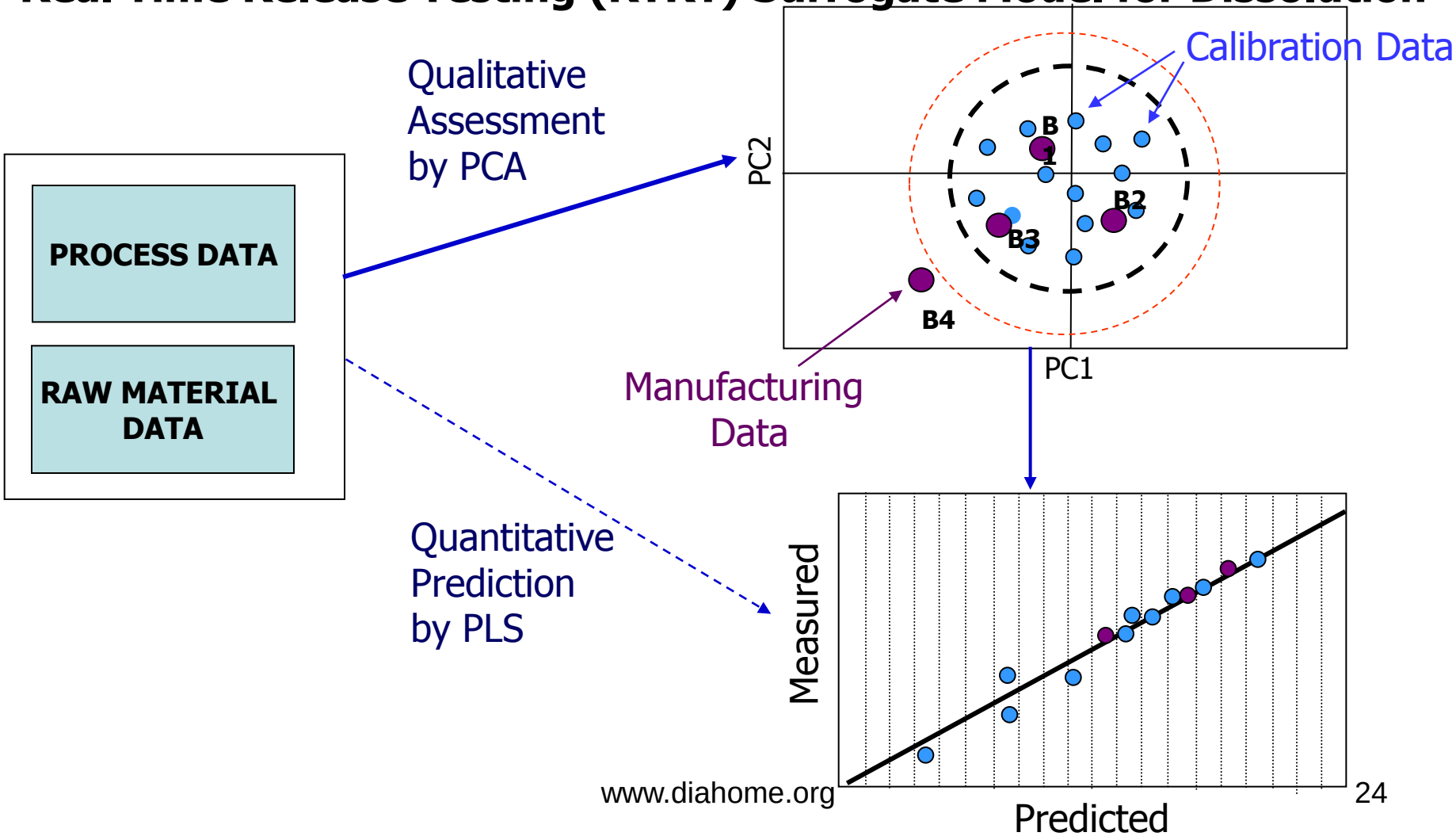
High Shear
Wet Granulator



- MSPC flags atypical or previously unseen operation
- Outliers do not mean a failed batch but trigger investigation
- Growing examples of "saved" batches due to MSPC

Multivariate Model for Predicting Dissolution

Real Time Release Testing (RTRT) Surrogate Model for Dissolution



Example In-process Methods for Continuous Manufacturing

- Spectroscopic methods (NIR, Mid-IR, Raman, Fluorescence) for concentration/assay
  - NIR is currently most common used spectroscopy
  - Raman is gaining popularity
  - Mid-IR (FTIR) is amenable to aqueous systems
  - Can be applied to active and inactive components
  - Typically need a chemometric method for data interpretation
- Laser light scattering for particle size distribution
- NIR for moisture content
- Imaging systems for appearance
- MSPC Methods for monitoring system

What has the FDA Seen?

(small molecules)

- ONDQA has had interactions with multiple companies both through formal meetings and informal interactions
- Approaches seen through meeting discussions, submissions, and site visits include:
  - Flow chemistry for drug substance reactions
  - Continuous crystallization
  - Single unit operation run in continuous mode for drug product
  - Fully integrated continuous drug product operation
- Applied to both existing products and new drugs
- Over a dozen companies are active in the area
  - At this time, too few NDAs/sNDAs to give statistics

CDER Emerging Technology Team

- Membership from all CDER review, research and inspection functions
- Will provide a primary point of contact for external inquiries
- Will partner with review offices in a cross-functional manner
- Will identify regulatory strategy and and resolve roadblocks to bew technologies relating to existing guidance, policy or practices related to review or inspection
- Initial focus in innovation on novel products, manufacturing processes, or testing technologies or processes to be submitted in a BLA, NDA or ANDA

Concluding Thoughts

- Continuous manufacturing offers potential economic and quality advantages
- There are no regulatory hurdles for implementing continuous manufacturing
  - However, there is a lack of experience
- It is up to the manufacturer to decide which technology to use
- FDA supports the implementation of continuous manufacturing using a science and risk-based approach
  - Recommend early and frequent discussion with Agency during development

Thank you!

Questions, comments, concerns:

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