Modernizing Pharmaceutical Manufacturing – Continuous Manufacturing as a Key Enabler

MIT-CMAC International Symposium on Continuous Manufacturing of Pharmaceuticals

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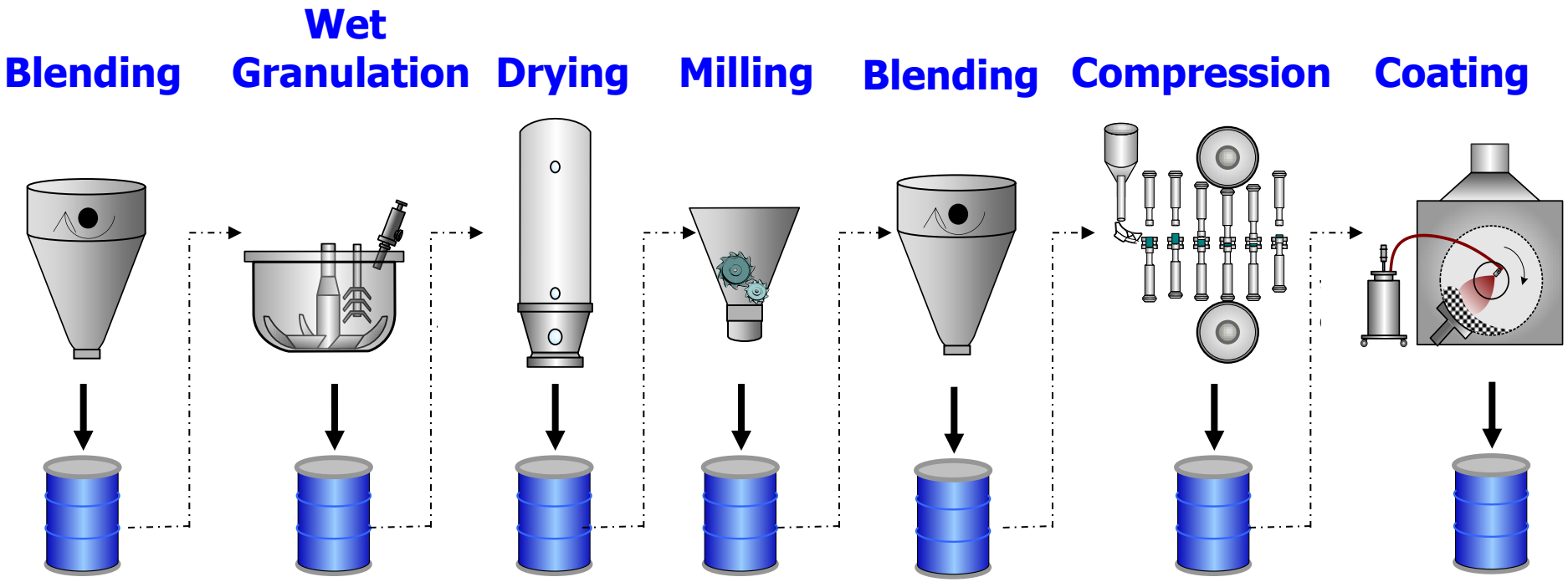
Overview

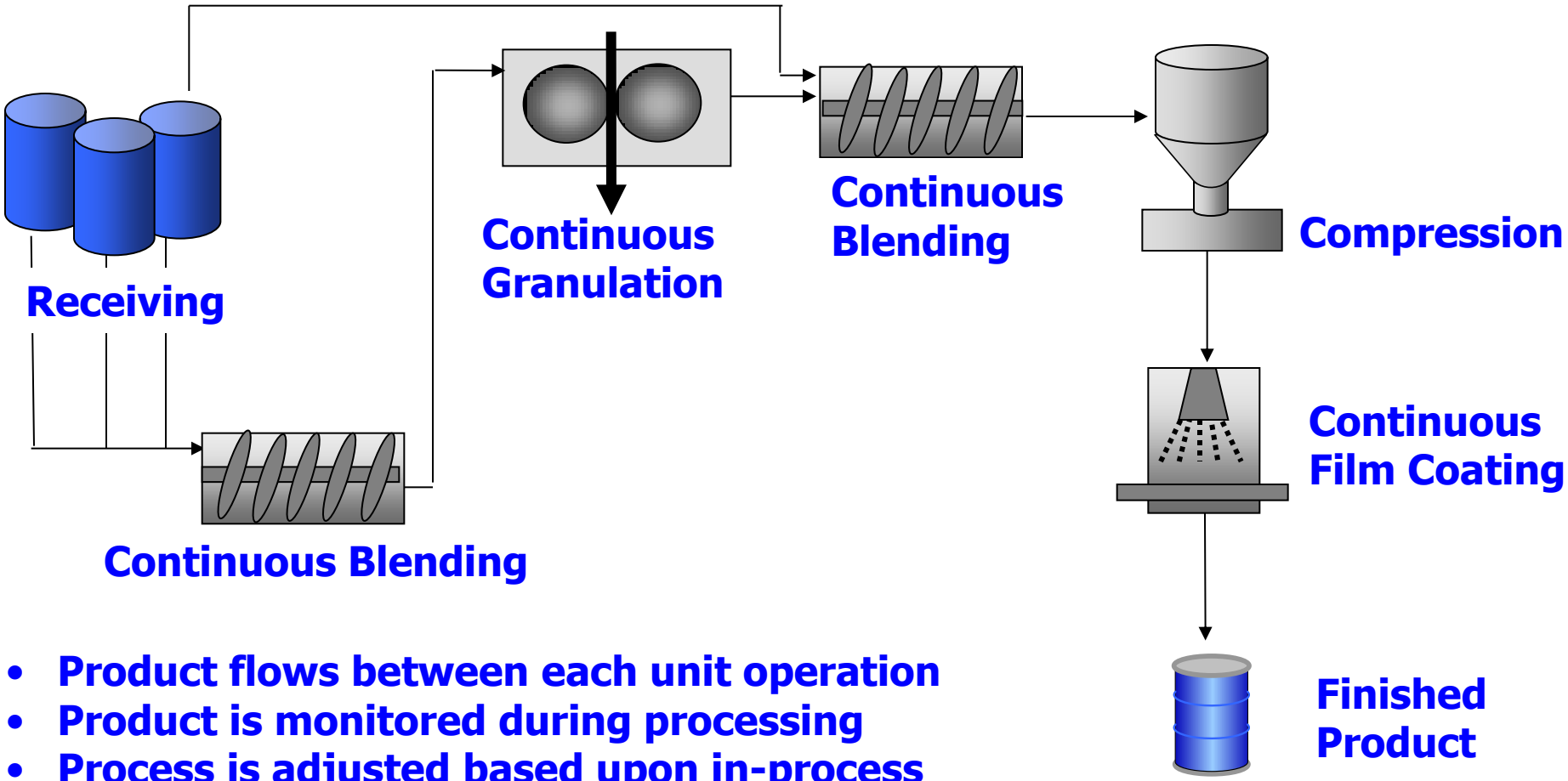
- Why Move to Continuous Manufacturing?
- FDA Initiatives and Ongoing Activities to Modernize Pharmaceutical Manufacturing
- Challenges and Opportunities; Research and Collaboration

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

WHY MOVE TO CONTINUOUS MANUFACTURING?

Vision for FDA's "Pharmaceutical Quality for the 21st Century" Initiative:

An agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight

Agility

- Continuous manufacturing will permit increased production volume without the current problems related to scale-up
- With targeted therapies and particularly, breakthrough drugs, rapid clinical development is feasible
- Manufacturing, particularly scale-up, may become a significant bottleneck in the path to market
- Continuous-- may have a big payoff

Agility

- Opportunity to develop a much wider range of novel dosage forms
- Ability to produce wider range of doses without extensive alterations of the process
- Ability to produce convenience fixed combination dosage forms easily-has been limited by narrow range

Flexibility

- Industry currently has very limited ability to rapidly increase production in the face of shortages or need for surge in production
- Bringing up new facility or line may take up to several years
- World is facing new shortage issues; also potential pandemics and other emergencies
- We lack response capacity

Geography

- Current APIs/FDPs are “world travellers”
- Driven by economics; but results in long supply chains with multiple vulnerabilities
- Continuous manufacturing could allow regional or in-country manufacture much closer to use
- Also can allow for redundant scalable capacity in case of emergencies

Quality

- Opportunity for uniformly high quality with much less waste
- Highly meaningful statistical process control
- Demonstrably under-control processes can lead to decreased regulatory oversight
- Less dependence on end-product testing

Cost

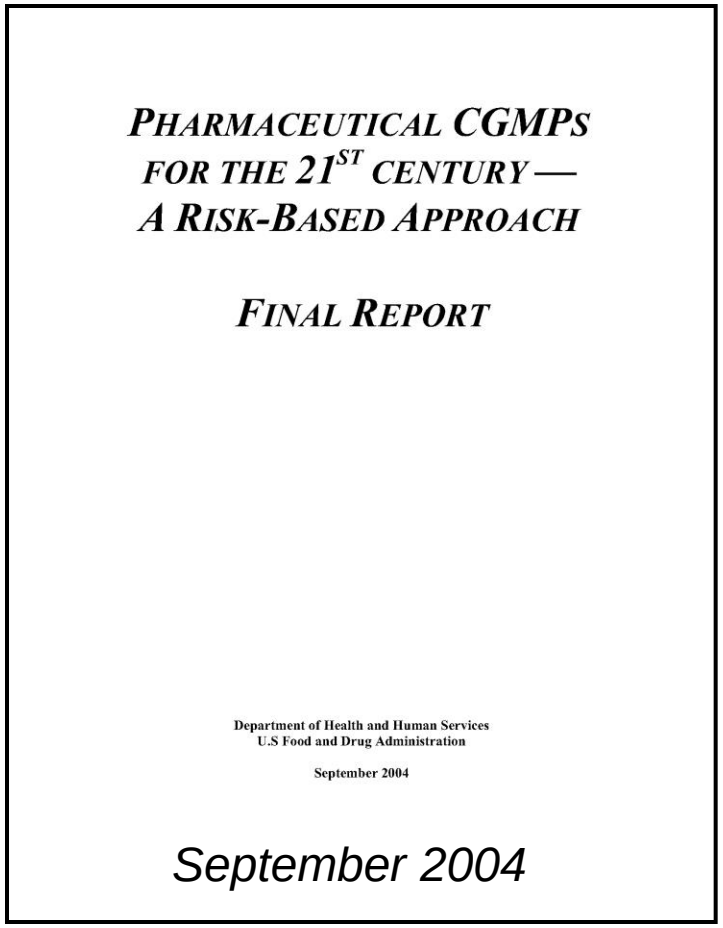
- Initial investment required
- Current inventory of large facilities an obvious counterweight
- Subsequent costs lower
- Possible candidates:
  - New molecule requiring new site
  - Approved drug with very large market requiring expansion of facilities

Societal Benefits

- Environmental impacts generally lowered significantly
- Source of high tech jobs in various regions
- Eventual lower cost of production can lead to more investment in new products
- Fewer shortages benefit healthcare system
- Uniformity of quality can reduce regulatory oversight; free resources to concentrate on higher risk areas

FDA'S PARTICIPATION: BACKGROUND AND ONGOING INITIATIVES

FDA 21st Century Initiative (2004)



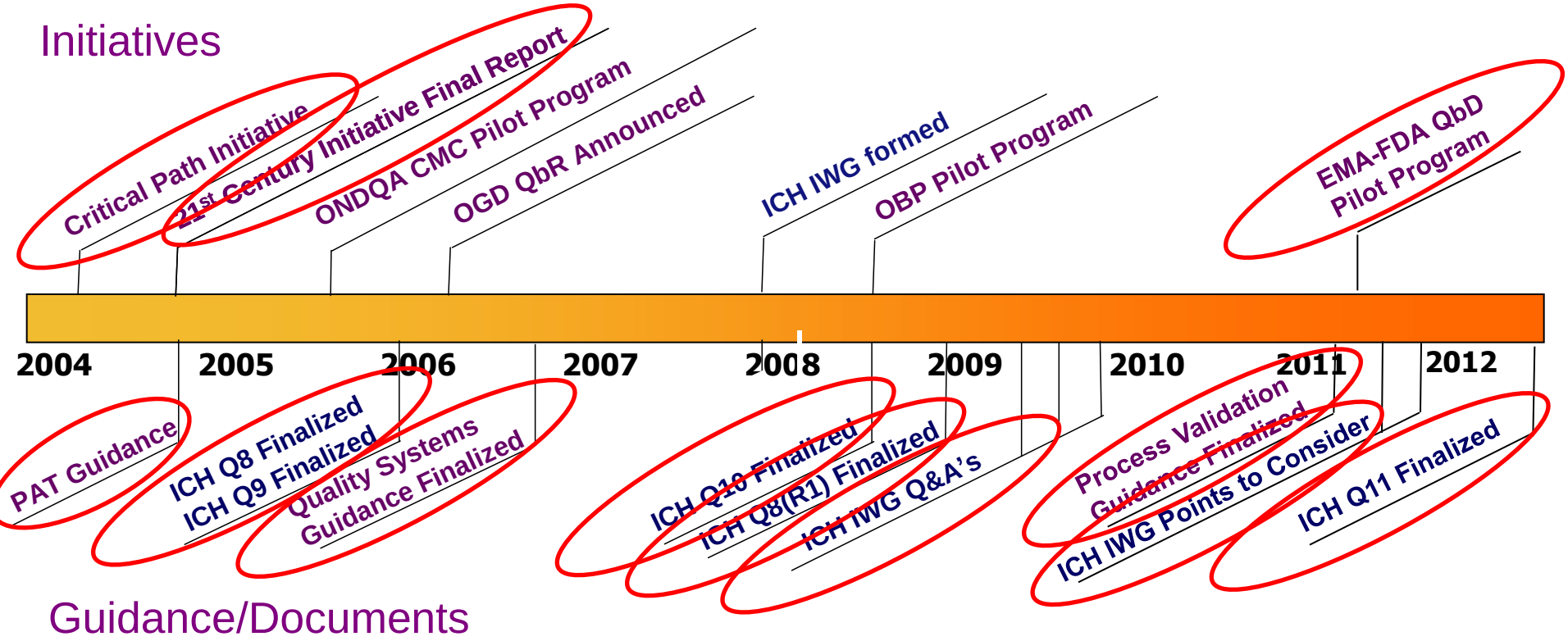
Objectives (partial list):

- Encourage the early adoption of new technological advances by the pharmaceutical industry
- Encourage implementation of risk-based approaches
- Facilitate industry application of modern quality management techniques, including implementation of quality systems approaches

Goals (partial list):

- Outreach and collaboration with industry
- Introduce new manufacturing science into regulatory paradigm
- Harmonize concepts internationally

Quality Related Guidance and Initiatives



Relevant to Continuous Manufacturing

Modernizing Pharmaceutical Manufacturing – FDA Focus Areas

- Pharmaceutical Quality Systems (PQS)
- Quality by Design (QbD)
- Process Analytical Technology (PAT)
- Real Time Release Testing (RTRT)

FDA View of Continuous Processing for Pharmaceuticals

- FDA supports continuous processing for pharmaceutical manufacturing
  - Offers potential quality advantages in both development and manufacturing
- Continuous pharmaceutical manufacturing is consistent with FDA Quality Initiatives
  - More modern manufacturing approach
  - Potential to improve assurance of quality and consistency of drugs
  - Enables quality to be directly built into process design

Regulatory Hurdles for Continuous Manufacturing?

- No specific FDA regulations or guidance exist about continuous manufacturing, other than the definition of “lot”
- Nothing in FDA regulations or guidance prohibits continuous manufacturing
- Continuous manufacturing consistent with FDA’s Quality by Design (QbD) efforts
- The greatest regulatory hurdle is the concern by manufacturers that regulators will balk at implementing these processes

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

Regulatory Definition of "Batch"

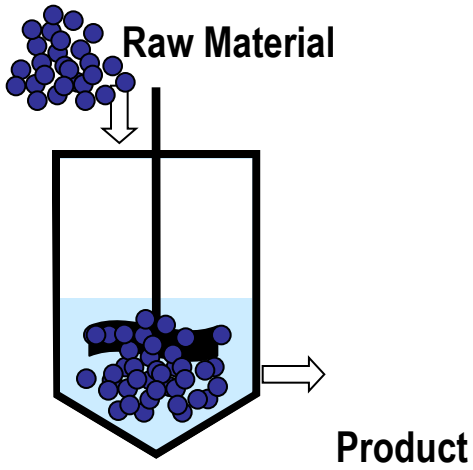
21 CFR 210.3

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***

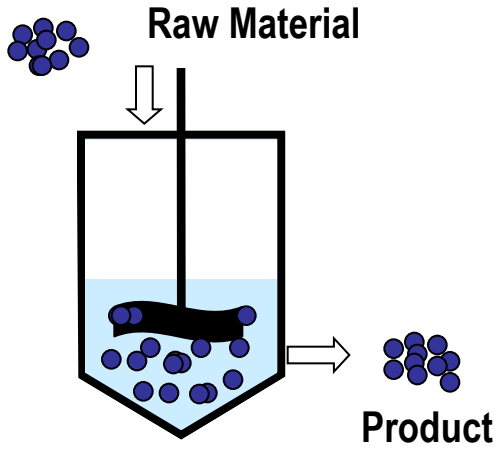
"Batch" vs. "Continuous": Engineering Definition

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

Defining a Batch/Lot
Why does it matter?

- **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

Training on Continuous Manufacturing

- 2010 Internal FDA Symposium on Continuous Manufacturing
- Multiple visits to academic institutions by review and compliance staff to see continuous manufacturing set-up
- Hands-on training of PAT at universities and internally
- Multiple industry site visits of development and manufacturing facilities with continuous manufacturing
- Partnering with NIPTE for a 40 hour web-based training session (available summer of 2014)

What has the FDA Seen?

- CDER has had interactions with multiple companies both through formal meetings and informal interactions
  - At this time, too few NDAs/sNDAs to give statistics
- 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 (Hybrid approach)
  - Fully integrated continuous drug product operation
- Applied to both existing products and new drugs

CDER Emerging Technology Team

- CDER has formed an Emerging Technology Team (ETT)
  - 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 identify and resolve roadblocks to new technologies relating to existing guidance, policy, or practice relative to review and/or inspection
  - Initial focus is innovative or novel products, manufacturing processes, or testing technology processes to be submitted in a BLA, NDA or ANDA

Proposed Office of Pharmaceutical Quality

- Would combine components of current CDER Office of Pharmaceutical Sciences and CDER Office of Compliance
- Intended to provide a unified quality assessment across multiple disciplines and activities, such as review, inspection and research
- Focus areas for new office:
  - Integration of review and inspection
  - Risk based approaches quality assessment
  - Efficiency and risk-based work prioritization
  - Modern regulatory science approaches (e.g., clinically relevant specifications, statistical sampling)

Partnering with International Regulators

- Continuous manufacturing has been an ongoing topic in the EMA-FDA Parallel Assessment Pilot for QbD
  - One continuous manufacturing application is in pilot, with the potential for additional applications
  - Multiple face-to-face discussions between EMA & FDA, some with participation of PMDA (Japan)
  - Joint site visit of a continuous manufacturing site
  - Potential for future Q&A document
  - Pilot has been extended to March 2016

CHALLENGES AND OPPORTUNITIES

Challenges in Implementation

- Appropriate measurement and control
  - Will likely be different than batch systems
- Tracking of materials through system
  - For traceability purposes
- Defining operation
  - For example, when to collect “good” product

Challenges in Implementation

- Control strategies for continuous processing will likely need be different than traditional batch processing
  - Batch definition
  - Monitoring and in-process controls
  - Sampling methodology
  - Release testing

Development Opportunities with Continuous Manufacturing

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

Manufacturing Opportunities with Continuous Manufacturing

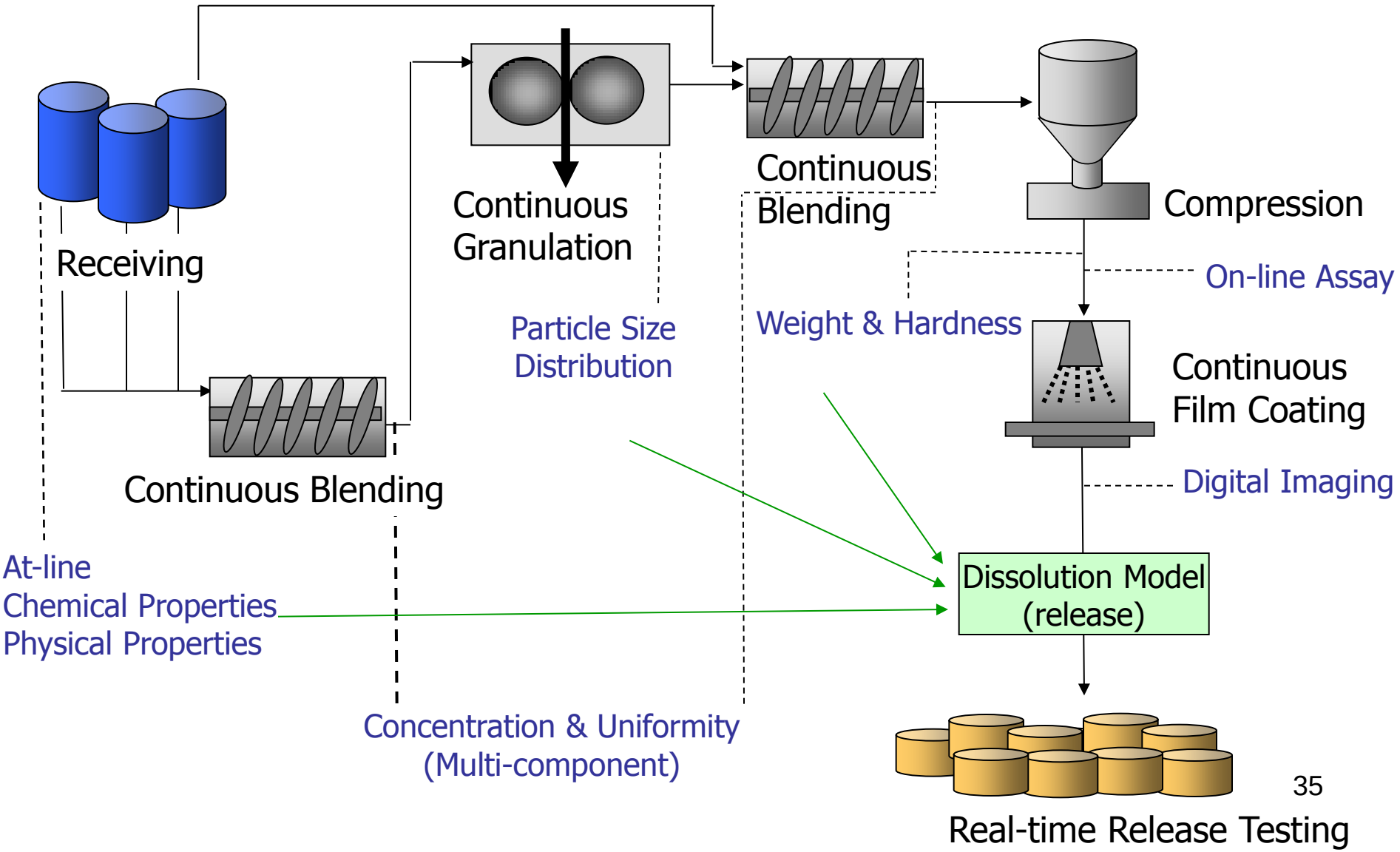
- Integrated processing with fewer steps
  - No manual handling, increased safety
  - Shorter processing times
- Smaller equipment and facilities
  - More flexible operation
  - Lower capital costs, less work-in-progress materials
  - Potential for regional manufacturing
- On-line monitoring and control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

Real Time Release Testing (RTRT)

- Real Time Release Testing (RTRT) is *"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
  - Can assure product quality based on process design and operation
  - RTRT approach may help reduce or eliminate end product testing
  - Potential to utilize measured parameters to provide surrogate test values, or reduced sampling

Conceptual Example of RTRT for Continuous Manufacturing



RESEARCH AND COLLABORATION OPPORTUNITIES

Research Opportunities for Continuous Pharmaceutical Processing

- Development of models for understanding and control of continuous manufacturing
- Advancement of Process Analytical Technologies for continuous manufacturing
- Standardization of systems and approaches for designing continuous manufacturing processes
- Published examples of continuous manufacturing with scientifically sound controls and testing
- Economic analysis of benefits of continuous manufacturing

Academic Opportunities for Continuous Pharmaceutical Processing

- Train the next generation of pharmaceutical researchers
  - Include flow reactors in laboratory and classroom training of chemists and chemical engineers
  - Include continuous manufacturing of solid oral dosage forms in training of industrial pharmacists and pharmaceutical engineers
- Provide outreach to current pharmaceutical researchers
  - Availability of laboratory and pilot equipment
  - Education through universities and professional symposium

Opportunities for Advancing Continuous Manufacturing

- Put the tools into the hands of the development scientists
  - Availability of laboratory and pilot equipment
  - Education through universities and professional symposium
- Publish examples of continuous manufacturing
  - Both drug substance and drug product
- Perform and publish economic analysis of benefits of continuous manufacturing
- Develop integrated control systems to support implementation of feed-back or feed-forward control
  - Move from end product testing to active control paradigm
  - Develop models for system-wide to enable optimization

Potential for more Regulator-Industry-Academic Collaboration

Potential Future Research Area: Personalized Medicine

- Personalized medicine is a potential growth area for continuous manufacturing research
  - Tailor specific drug dose and/or combination to an individual patient
- Potential continuous manufacturing technologies:
  - Drop on demand
  - Thin film strips

Policy Development

- There is clearly a need for US and international regulatory policy development and technical standards in this area
- However, need real life examples—some must be the pioneers
- Another area for government-academic-industry-collaboration

Summary

- The science current exists to support continuous manufacturing of pharmaceuticals
- Continuous manufacturing offers potential economic and quality advantages both in development and manufacturing for sponsors
- It also offers potential societal benefits
- There are no regulatory hurdles for implementing continuous manufacturing, but there is lack of experience
- FDA supports the implementation of continuous manufacturing using a science and risk-based approach
  - We stand ready to partner with industry and academia to help make these advances a reality