Manufacturing of Pharmaceutical Solids: Challenges and Opportunities

Sau (Larry) Lee, Ph.D.
Associate Director for Science (Acting)

Science and Research Staff
Immediate Office, Office of Pharmaceutical Quality
Center for Drug Evaluation and Research (CDER)
Food and Drug Administration

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Early 2000s: FDA Embarks upon Pharmaceutical Quality for 21st Century Initiative

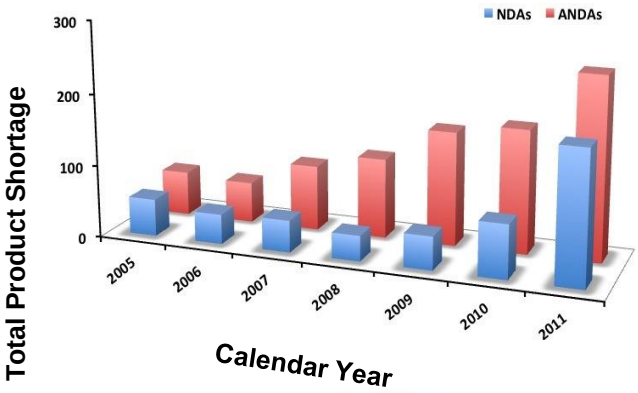
Vision

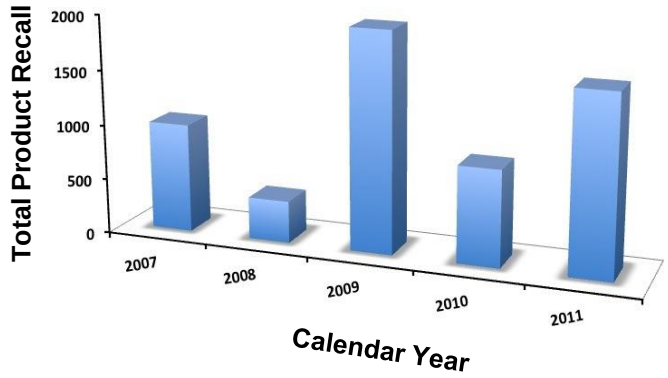
"A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight."

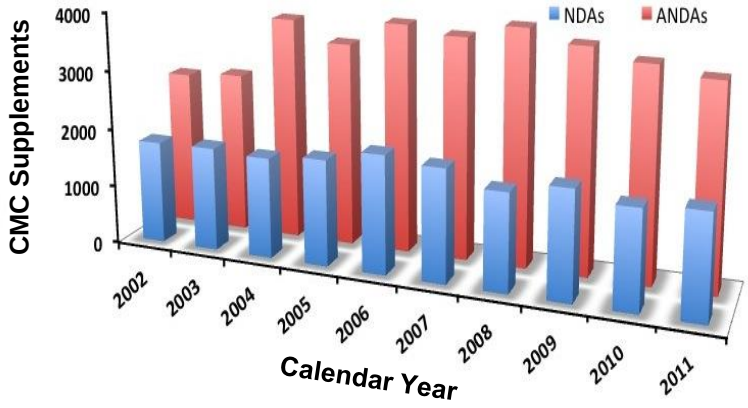
21st Century Initiative

- Success at many levels:
  - 'Enabling' of modern technology (e.g., PAT and Continuous Manufacturing)
  - Updates to GMP regulations; revised GMP guidance
  - Multiple ICH documents:
    - Pharmaceutical Development and QbD
    - Quality Risk Management
    - Quality Systems
  - Formation of Pharmaceutical Inspectorate
  - Risk-based selection of facilities for inspection

We Aren't There Yet....







Current Challenges

- Generic application (ANDA) review backlog and large number of manufacturing supplements
  - Time required for regulatory approval holds back or blocks facility improvements, e.g., site changes, major upgrades
- Need for ongoing innovation in manufacturing
  - Regulatory oversight is one factor limiting industry's adoption of modern manufacturing technology
- State of drug quality
  - Lack useful quality indicators across industry
  - Can we predict product quality problems?

OPQ's Future Objectives

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

Moving Toward Objective and Quantitative Risk Assessments

- Failure Modes, Effects and Criticality Analysis (FMECA) was chosen because it provides more objective and quantitative risk assessments
- Algorithm scores based upon sound scientific principles and modified for initial risk profiling using cross-validation studies with semi-quantitative Preliminary Hazard Analysis (PHA)

	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	FMECA RPN	PHA
CQA1	o2	s1	d1	o2s1d1	low
CQA2	o1	s2	d1	o1s2d1	low
CQA3	o1	s1	d2	o1s1d2	low
CQA4	o1	s1	d2	o1s1d2	low
CQA5	o1	s1	d1	o1s1d1	low
CQA6	o2	s1	d1	o2s1d1	low

	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	FMECA RPN	PHA
CQA1	o6	s4	d1	o6s4d1	high
CQA2	o1	s2	d1	o1s2d1	low
CQA3	o3	s5	d2	o3s5d2	high
CQA4	o2	s3	d2	o2s3d2	medium
CQA5	o2	s2	d3	o2s2d3	medium
CQA6	o5	s6	d1	o5s6d1	high

Algorithm will be continuously improved and updated based upon additional information gathered

Opportunities for Regulatory Research Supporting Risk-based Approaches

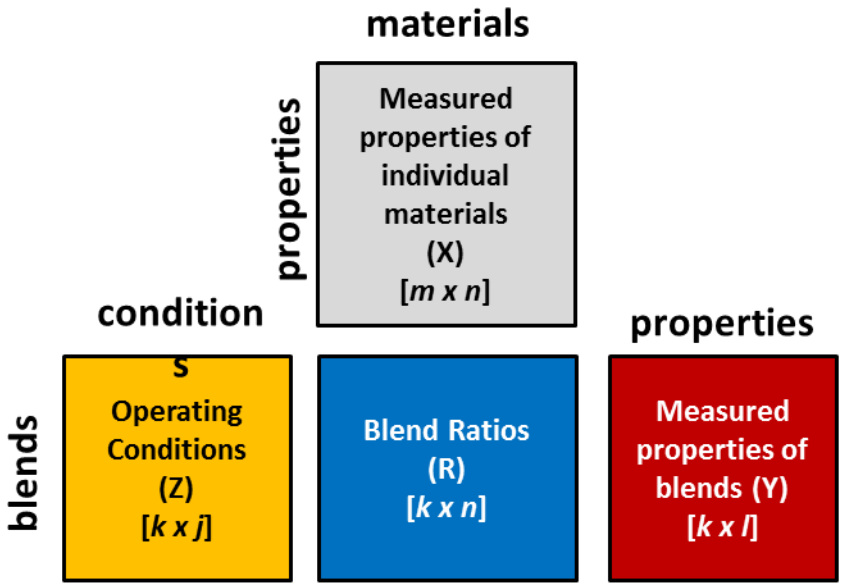
- Solid oral dosage forms constitute the majority of NDAs and ANDAs
- Manufacturing technologies (formulation and process designs) are not “new” from a fundamental science perspective for most of solid oral dosage forms
- Predictive tools are still lacking for systematic evaluation of solid oral manufacturing technologies

Opportunities for Regulatory Research Supporting Risk-based Approaches

- Developing and building a knowledge base including tools to aid a systematic and predictive quantitative assessment of high risk factors related to product and process design
- Developing appropriate quality control strategies or tools to address the high risk factors
- Developing emerging technologies to enhance product quality

Pharmaceutical Manufacturing Informatics and Process Modeling

- Material properties and equipment configurations
  - Increased knowledge regarding raw material properties and behavior with respect to flow
  - Understanding the impact of raw material properties and variability as well as equipment configuration on final product quality
  - Data source for predictive model building and validation



S. G. Munoz *et al. (2014) Chemometrics and Intelligent Laboratory Systems.* 133, 49-62

Pharmaceutical Manufacturing Informatics and Process Modeling

- Process simulation and modeling
  - Empirical or semi-empirical models (multivariate models)
  - Mechanistic models
  - Semi-quantitative or quantitative risk assessments for manufacturing scale up (e.g., a sensitivity analysis indicating the magnitude of the effect of process parameters or material attributes on quality attributes)
- Pharmaceutical manufacturing informatics
  - Integrated knowledge database on high risk factors for different combination of material properties, formulation and process designs
  - Predictive nature leading to the enhanced regulatory quality assessment

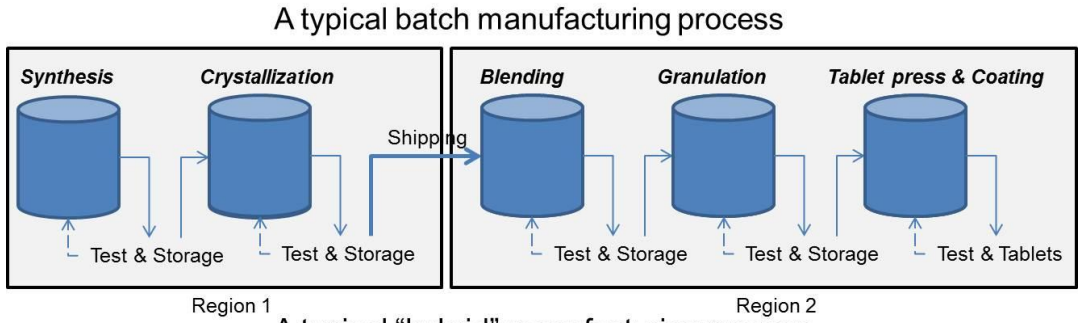
Control Strategies: Analytical Testing

- Measurements of critical quality attributes
  - Polymorphic level in a drug product
  - Particle size of API and excipient(s) in a complex formulation
  - Biorelevant dissolution
- Blend uniformity
  - Sampling
  - Lack of understanding on relationships/correlations among blend uniformity by the thief sampling, blend uniformity by the PAT tool, and content uniformity and the effect of blend properties on these relationships.
- Statistical sampling
  - Quality statements (confidence level, coverage and target range) based on product risk

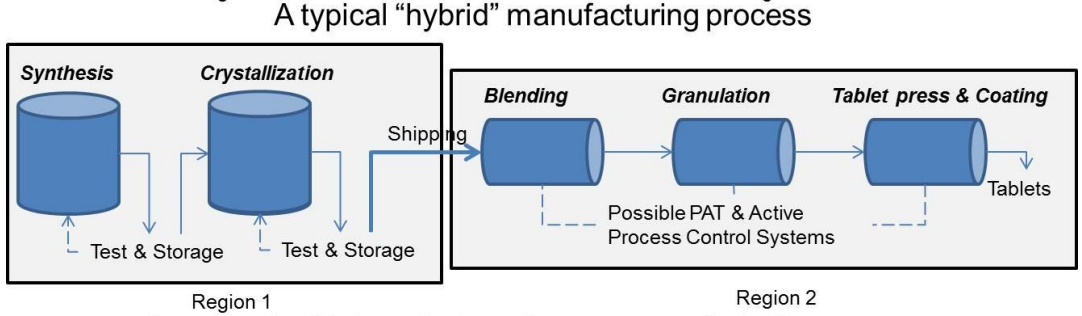
Emerging Technologies

- FDA has identified CM as an emerging technology

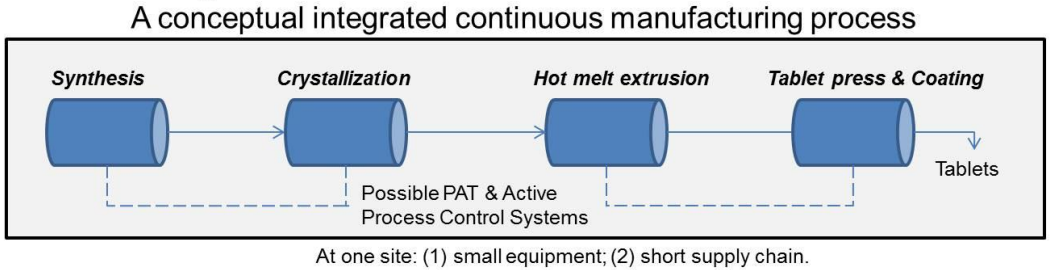
(1) Batch



(2) Hybrid



(3) End-to-End



S.L. Lee, T.F. O'Connor, X. Yang, C.N. Cruz, S. Chatterjee, R.D. Madurawe, C.M.V. Moore, L.X. Yu, and J. Woodcock. Modernizing Pharmaceutical Manufacturing: from Batch to Continuous Production. J. Pharm. Innov. 2015.

Three Presentations

- Detection and Quantification of Trace Crystallinity in Amorphous Formulations Using Second Harmonic Generation Microscopy
  - Lynne Taylor, Ph.D., Paul Schmitt, Purdue University
- Pharmaceutical Co-Crystals and Their Anomalous Formation Properties
  - Lian Yu, Ph.D., University of Wisconsin-Madison
- Development of a Real-Time Release Continuous Crystallization System With Anti-Crust Control
  - Zoltan Nagy, Ph.D., Purdue University