Overview of Pharmaceutical Manufacturing Control

University of Maryland Conference
"Control Strategies for Pharmaceutical Manufacturing: Real Time Release Testing (RTRT) and Design Space Determination"
May 23, 2013

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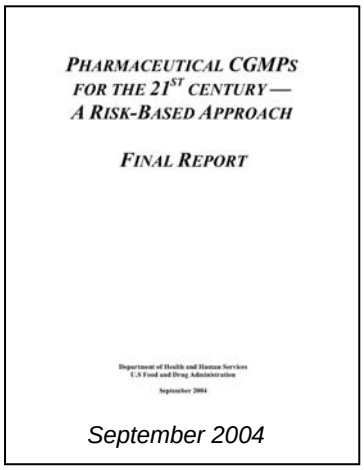
Outline

- History of FDA initiatives in manufacturing and quality
- Progress of Quality by Design (QbD) in advancing pharmaceutical manufacturing
- Current state and projected future state for pharmaceutical manufacturing control
- Conclusions

FDA 21st Century Initiative (2004)



Objectives:

♦ Encourage the early adoption of new technological advances by the pharmaceutical industry

♦ Facilitate industry application of modern quality management techniques, including implementation of quality systems approaches

♦ Encourage implementation of risk-based approaches

♦ Ensure that regulatory review, compliance, and inspection policies are based on state-of-the-art pharmaceutical science

♦ Enhance the consistency and coordination of FDA's drug quality regulatory programs

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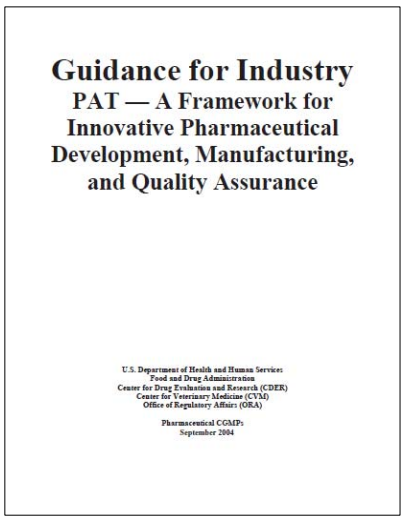
FDA's PAT Guidance (2004)



- Process Analytical Technology (PAT)
  - a system for designing, analyzing, and controlling manufacturing
  - through timely measurements of critical quality and performance attributes of raw and in-process materials and processes
  - with the goal of ensuring final product quality
- PAT Fundamental Tenet
  - ***Quality cannot be tested*** into the product; it should be built-in or ***should be by design***
- PAT Goals
  - Enhance understanding and control of processes
- Guidance included concepts new to pharmaceutical manufacturing
  - Design Space
  - Real Time Release
  - Multivariate Tools
  - Process Signatures

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Traditional Drug Product Manufacturing Approaches

- Batch processing
- Slow off-line laboratory testing
- Low equipment efficiency
- High cycle times
- “3 batch validation” paradigm
- Avoidance of process monitoring, no testing beyond minimum requirements
- Avoidance of process changes
- Reactive changes / CAPA

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Modern Manufacturing Approaches Commonly Used in Other Industries

- Lean manufacturing
- Continuous manufacturing
- Proactive changes / continual improvement
- Six sigma quality management
- Green chemistry
- Advanced analytical methods
- Real-time process monitoring and control
- Multivariate statistical process control

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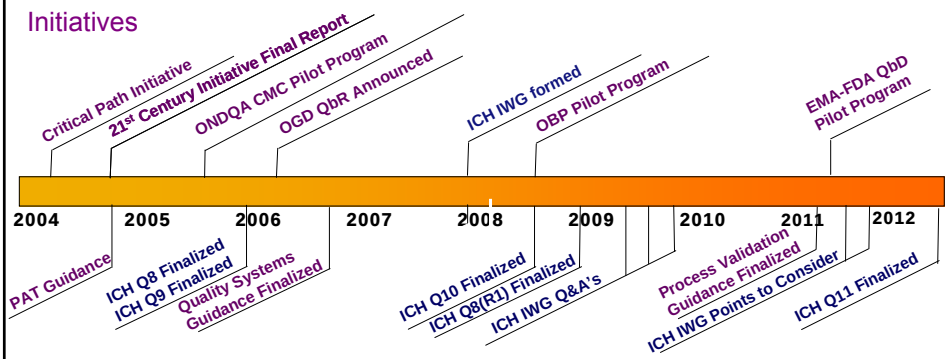
Quality Related Guidance and Initiatives



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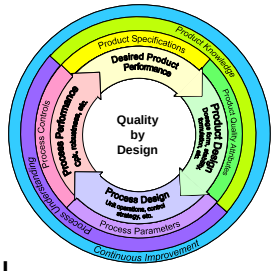
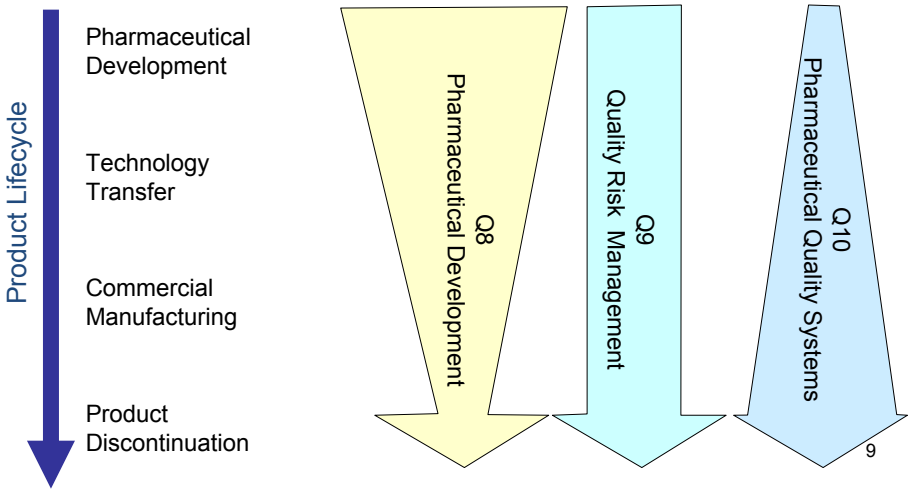
What is Quality by Design (QbD)?

- Systematic approach to pharmaceutical development and manufacturing
- Begins with predefined objectives
- Emphasizes product and process understanding and process control
- Based on sound science and quality risk management



From ICH Q8(R2)

ICH Q8, Q9 and Q10 Working Together over the Product Lifecycle



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This article presents the results of a survey conducted by the ISPE United Kingdom/Ireland PAT COP.

The Business Benefits of Quality by Design (QbD)

by Theodora Kourti and Bruce Davis

Pharmaceutical Engineering, July/Aug 2012, 32(4), 1-10

Introduction

The business case for Quality by Design (QbD) was a hot discussion topic during a meeting of the Process Analytical Technology Community of Practice of United Kingdom/Ireland (PAT COP UK/IR). The discussion concluded with a plan to conduct a survey that would aim to gather actual experiences, examples and candid industry opinions on the business benefits of QbD. The questions one questionnaire. Written answers also were produced for the telephone interviews and these were approved by the interviewees. Interviewees were from development, manufacturing and regulatory while the companies range from large and small, both small molecule and biotech.

In total, we received 15 completed questionnaires from 12 companies. The responses were received between November 2010 and September 2011. The companies agreed to have their

- Survey of 12 companies on their experiences with QbD and their opinions of QbD

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Business Benefits of QbD

- Improved Product and Process Knowledge and Understanding
- Improved Development Capability, Speed and Formulation Design
- Improvement in Product Quality and Product Robustness/ Reproducibility
- Improved Control Strategy
- Cost Reduction Benefits
- Yield Increase
- Fast and Reliably to Market
- Increased Process Capability; Reduced Atypicals
- Reduced Impact of Raw Material Variability
- Improved Product Stability
- Improved Scale Up Efficiency/Speed
- Standardize Ways of Working
- Engaging Science in Profitable Ways
- Improvement in Collaboration between Business Units and Enhanced Work Practices

"The Business Benefits of Quality by Design", T. Kourti and B. Davis, Pharmaceutical Engineering, July/Aug 2012, 32(4), 1-10.

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Industry Perspective on "The Future of QbD"

- *"QbD will become the norm"*
- *"The value of QbD principles is clear and will continue to be integrated into the product development processes."*
- *"QbD is already expanding its scope into new paradigms such as RTRT, continuous quality verification, analytical QbD, lean stability approaches and others. We expect this trend to continue."*
- *"QbD will continue to grow and become more embedded as it is applied more in production we will get better at it. We will use more prior knowledge and more risk-based approaches."*

"The Business Benefits of Quality by Design", T. Kourti and B. Davis, Pharmaceutical Engineering, July/Aug 2012, 32(4), 1-10.

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State of QbD

- The science and risk based approaches in QbD are being embraced by most innovator pharma companies for development
  - Often, the enhanced knowledge is not used to justify "regulatory flexibility" in the application
  - Experience has proven to improve product quality, process robustness and operational costs
- Some other companies starting to adopt QbD, including some generics and biotech companies
- Limited application of QbD and PAT concepts into Real Time Release Testing approaches or advanced manufacturing control

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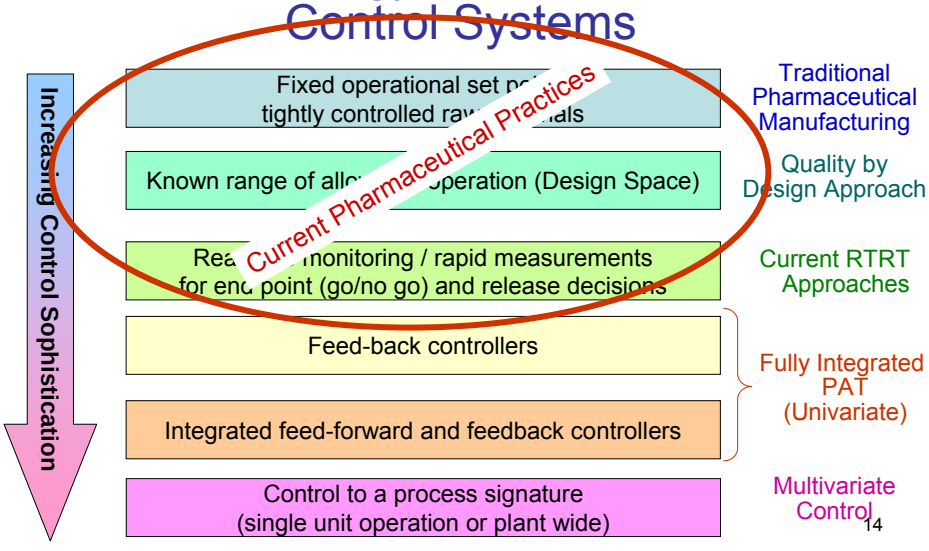
Technology Opportunities – Control Systems



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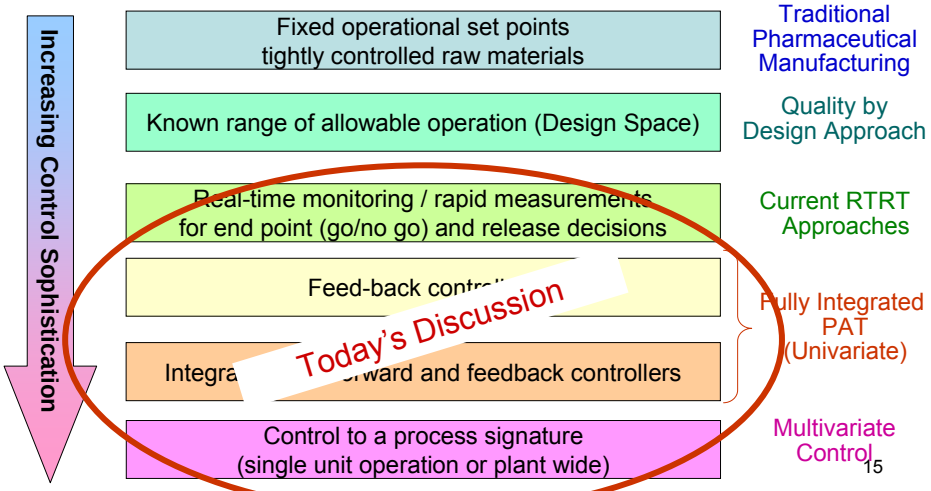
Technology Opportunities – Control Systems



Real Time Release Testing

- 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
  - Typically include a valid combination of measured material attributes and process controls

    ICH Q8(R2)

Examples of RTRT Approaches

- On-line or in-line measurements and/or controls, for example
  - Tablet weight after compression
  - Particle size measurement after granulation or milling
  - Moisture measurement during drying
  - Blend uniformity
- Fast at-line measurements, for example
  - NIR for tablet assay
  - Disintegration in lieu of dissolution
- Models as surrogate for traditional release tests, for example
  - Multivariate model as a surrogate for dissolution
- Process signatures
  - *An evolving approach*

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Benefits of RTRT

- Provides for increased assurance of quality
  - More process data collected
- Provides increased manufacturing flexibility and efficiency
  - Shorter cycle time
  - Reduced inventory
  - Reduction in end product testing
  - Reduction in manufacturing cost
- Allows leveraging of enhanced process understanding
  - Potential for corrective actions to be implemented in real time

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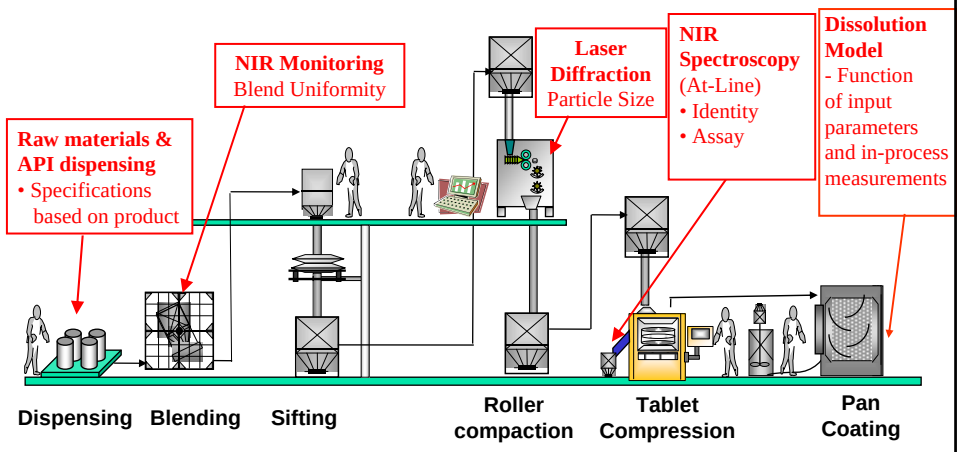
Example of An Unified Approach for RTRT



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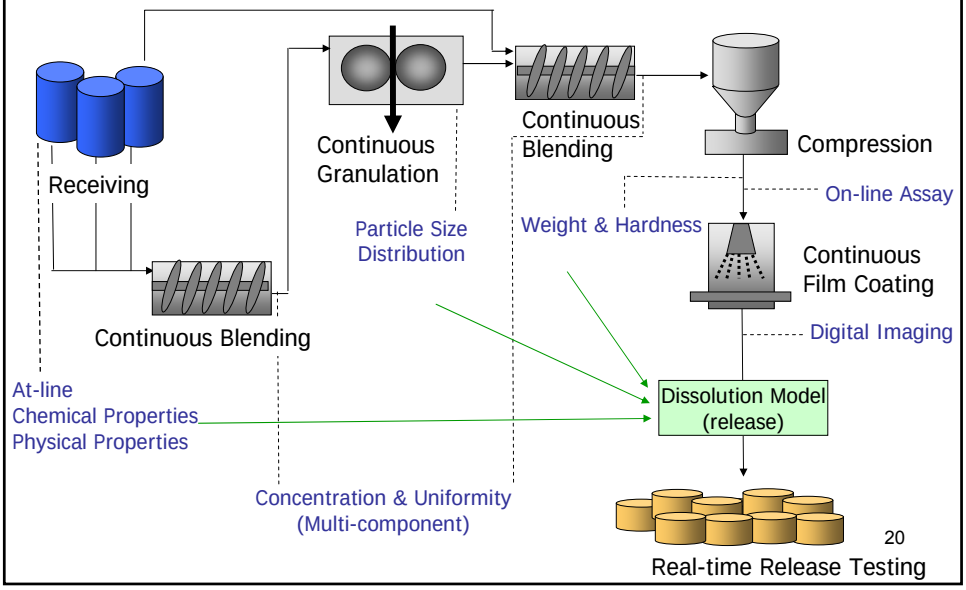
Conceptual Example for RTRT in Continuous Manufacturing



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Measurements vs. Controls

- Most QbD approaches to date have focused on greater process understanding to provide more robust manufacturing
- Most RTRT approaches to date have focused on in-process measurements to make release decisions
- Few examples of true PAT with integrated control have been proposed
  - Mostly unit operation specific
  - Some use of end-point determination (e.g., blending, drying)
  - Simple cases of feedback control (e.g., tableting, spray granulation)
  - Some examples of feed-forward control (e.g., based on excipient properties, in-process material attributes)

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System Dynamics

- For many systems, there is time dependency
  - Processing/reaction time for batch systems
  - Residence/transit time for continuous systems
- Effective controls rely on understanding relationships between process inputs and outputs **with time**
  - Sample size and sampling frequency considerations
- For continuous processes need to understand time dependency of flow and mixing
- For batch processes need to understand path dependence of unit operations
  - For some unit operations arriving at the same endpoint does not assure the same quality product
  - Often important physical or chemical attributes are not measured routinely but can affect downstream product performance

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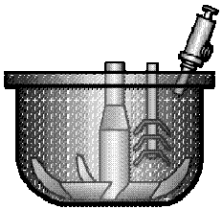
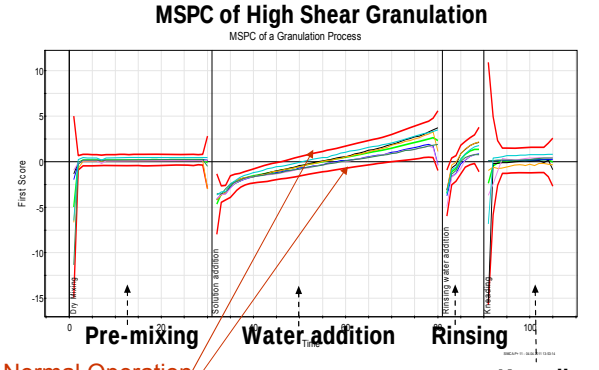
Multivariate Statistical Process Control (MSPC)

- 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

MSPC Example



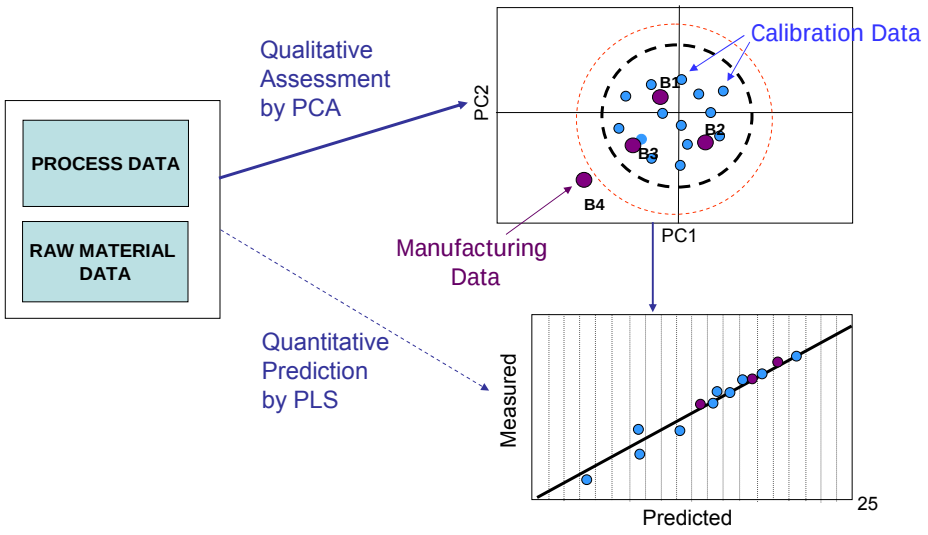
High Shear
Wet Granulator



Normal Operation
between red lines

- 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



Regulatory Experience with In-process Measurements

- ONDQA has approved the following NDA/sNDA submissions using in-process NIR based spectroscopy measurements:
  - Drying monitoring and end-point detection - 7
  - Blending monitoring/end-point detection - 9
- ONDQA has approved the following NDA/sNDA submissions for RTRT:
  - Online/at-line measurement of tablet content uniformity – 6
  - Models as surrogate for traditional release tests (e.g. dissolution, assay, particle size) - 4

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Regulatory Experience in Advanced Manufacturing Approaches

- Multiple companies active in continuous manufacturing for drug product and drug substance
  - At least 8 companies are active in the area
  - At this time, too few NDAs/sNDAs to give statistics
- Multiple companies using MSPC as part of their process monitoring or RTRT approaches

Future Opportunities for Advanced Manufacturing Approaches

- Regulatory Opportunities:
  - Clarifying expectations for verification and change of models used for RTRT and PAT (e.g., NIR models, surrogate models for dissolution)
  - A pathway for risk based assessment to ease post-approval change requirements
  - Increased International harmonization
- Emerging Technological Opportunities:
  - Multivariate statistical process control (MSPC)
  - Continuous manufacturing
  - Advanced control strategies
    - Complete process / plant-wide integrated process control
- Need more publically available examples

Conclusions

- Implementation of Quality by Design in the pharmaceutical industry has laid the groundwork for more advanced manufacturing approaches
- Currently many pharmaceutical companies are developing or have developed approaches for PAT, RTRT, MSPC and/or Continuous Manufacturing
- ONDQA is willing to discuss advanced manufacturing approaches with applicants prior to submission and as needed during the review process

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Thank you!

Questions, comments, concerns:
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