Improving Regulation of Drug Product Quality

Where do we go from here?

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Office of Pharmaceutical Science
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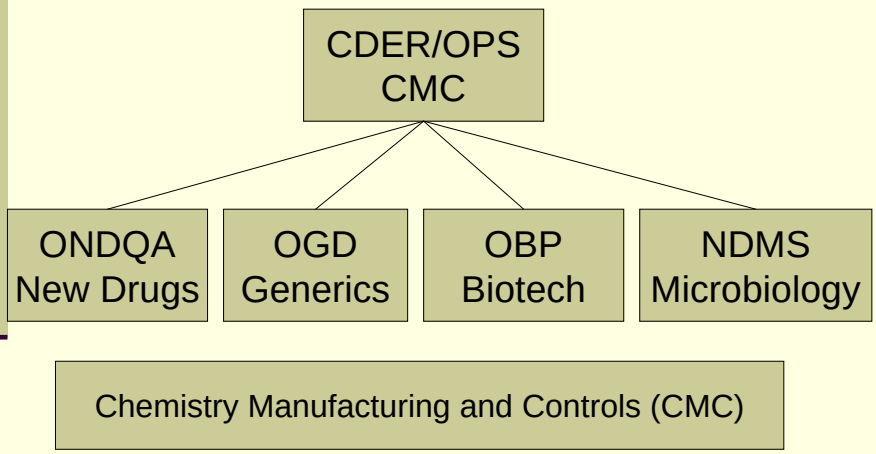
Office of Pharmaceutical Science (OPS) and CMC review programs



Still Looking For:

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

Janet Woodcock

October 5,2005

Realizations

- Industry needs better understanding of business case for – not just concepts of QbD
  - Need to see beyond “Regulatory Flexibility”
- FDA and industry need to determine the barriers/questions to implementation and ensure have appropriate answers
  - Expanded use of Pilot Programs can help
- FDA and industry need to identify science gaps and how to fill them
  - Can we get to “Clinically Relevant” attribute specifications?
- FDA needs to ensure better “guidances”
- All of us need to work with each other – collaboration to learn from each other
  - Can we borrow from other industries?

Assessment

- The Agency is committed to making the new paradigm work and we look forward to working with stakeholders to accomplish that end
- The Industry and others should understand the progress that is being made by the various assessment programs and how this progress affects them now and in future implementation
- The Industry and others are aware that they can come to the Agency to be better prepared to implement principles of QbD and to be better prepared to address the challenges of implementation

Question Based Review

- Implemented (mostly)
- Successful
- Can this be improved?
- Can this solution work in other programs other than OGD?

QbD Pilot(s)

- ONDQA Pilot is a success story
  - Variety of applications
  - Provides a foundation for future application review
  - Progress with applications outside the pilot
- We need to assure continuing progress

QbD Pilot(s)

- OBP Pilot is beginning
  - Planned with criteria and metrics
  - Untilizes QbD priciples in the most “complex” technical area
- Assure success through industry participation!

Risk Management

- Area ripe for improvement
  - Principles are highly developed
  - Tools are available
  - Under utilized in pharmaceutical industry
  - Highly successful approach in other industries
  - Successful when applied
- These tools can progress QbD
- Potential to solve quality of supplier problem

Keep progress moving

- Biotech Lifecycle
  - Risk Based Change Control
  - Multivariate Statistical Process Control
- Generic's
  - Enhance the team approach to review
  - Refine Pharmaceutical Equivalence
  - Refine Qbr

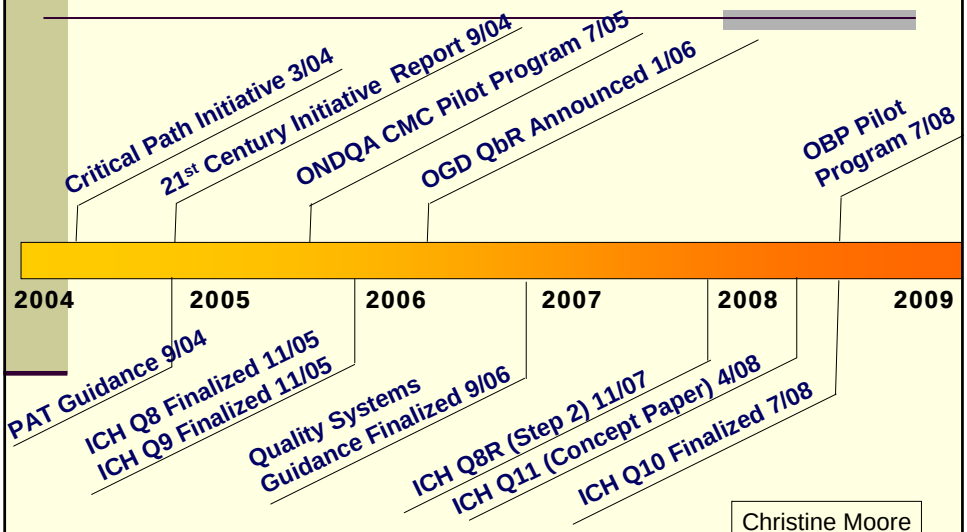
Keep Progress Moving

- ONDQA Design Space
  - Continue refinement of definition
  - Use visualization tools
    - Design space
    - Multivariate interactions
    - Demonstration of control
  - Risk management to mitigate uncertainty
  - Define real time release

Improve Interactions

- More review field interactions
  - Reviewers on inspection
  - Highly trained investigators
    - Pharmaceutical Inspectorate
- More industry meetings
  - During development
  - After approval

Timeline of Quality Related Activities



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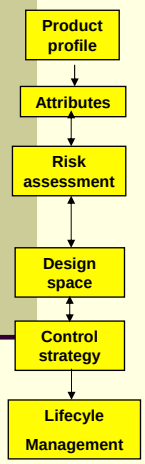
Example Approach (Q8R)



- Target the product profile
- Determine measurable product attributes which predict the product profile
- Link material attributes and process parameters to product attributes and perform risk assessment
- Document a design space for manufacturing
- Implement a control strategy
- Manage product lifecycle, including continual improvement

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Risk Assessment – FMEA

Environmentally Sensitive Crystalline Product

Category	Process Parameter	Severity S (1-5)	Occurrence O (1-5)	Detection D (1-5)	Risk priority number S*O*D	Criticality rank
Crystalliztn	Residual solvent	5	4	3	60	1
	Induction time	4	3	2	24	6
	Anti-solvent addition time	5	3	2	30	4
	Mixing	2	2	1	4	11
Isolation/ drying	Temperature during crystal drying	4	4	2	32	3
	Solids transfers	3	1	1	1	13
	Washing effectiveness	2	1	1	2	15
Handling/ storage	Relative humidity	5	3	3	45	2
	Inerting	4	2	3	24	6

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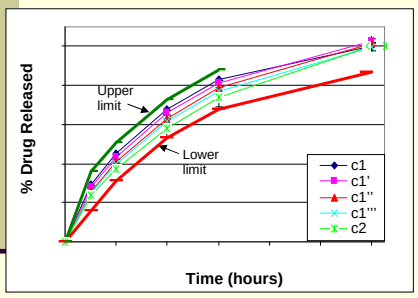
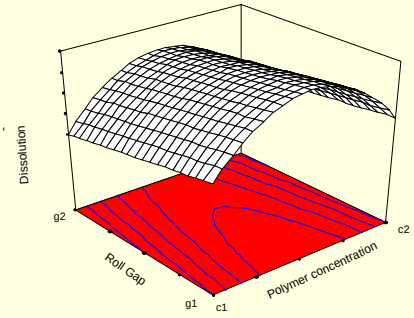
Design Space Example

Effect of Polymer Concentration on Dissolution



Typical 2-dimensional analysis

Interaction Effect of Roll Gap and Polymer Concentration on Dissolution



Z: Dissolution
X: Polymer concentration
Y: Roll gap
Roll force fixed at f bar

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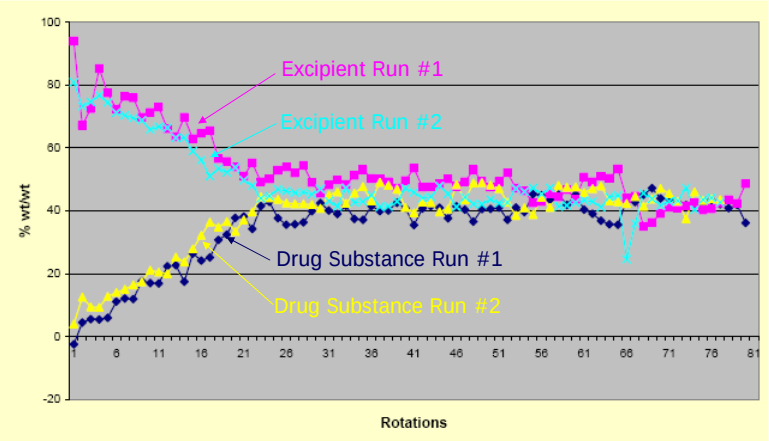
In Process Monitoring Example – Blending Step

On-line NIR Monitoring of Blend Uniformity



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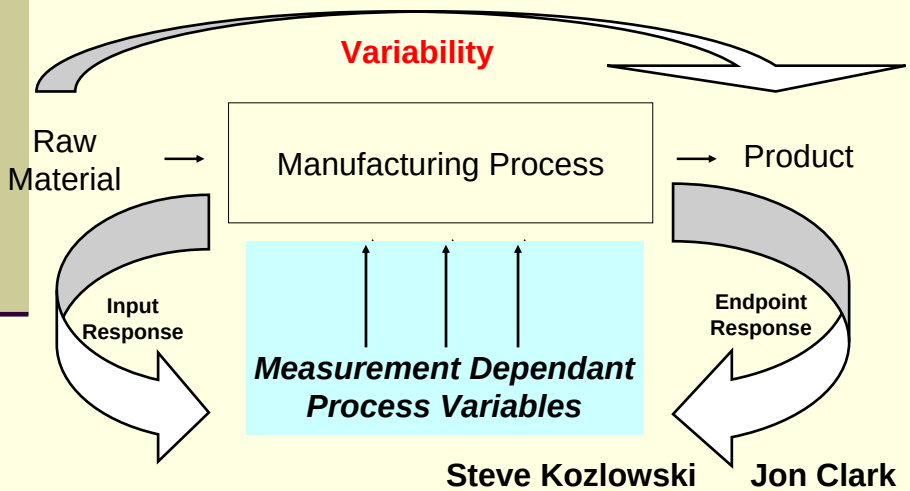
Manufacturing Process



Steve Kozlowski Jon Clark

Real Time Release

- Real-time release (RTR) is when all quality test results are obtained on-line/at-line during or immediately after manufacturing
- Manufacturing flexibility
  - Increased manufacturing efficiency
  - Measure and control in real-time
- Increased assurance of quality
  - Science based release criteria
  - More representative of process
- A more modern approach to manufacturing and controls

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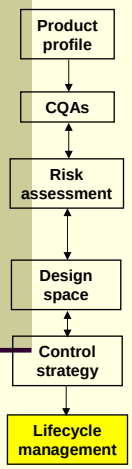
Lifecycle Management



Lifecycle Management deals with future:

- Change in manufacturing scale
- Process enhancements
- Analytical enhancements
- Site transfers
- Outsourcing of manufacturing
- Transfer of product ownership

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Lifecycle Management – Points to Consider

- Risk management
  - Use development information as starting point
  - Update as experience gained
- Process tracking and trending
  - Statistical process control
  - Adjust trends before they become problems
- Knowledge management
- Model maintenance and updating

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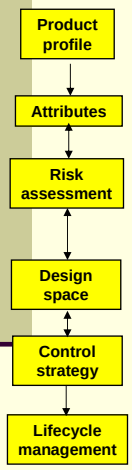
CMC Lessons Learned Summary



- More scientific information was shared
- Science and risk-based approaches including
  - Risk assessment
  - Design space
  - Tests for Product Attributes upstream at control points
  - On-line analyzers for intermediates
  - In-process testing, in lieu of end-product testing
- Risk-based regulatory decisions were enabled

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OBP Pilot Program

FR Notice July 2, 2008

- To define clinically relevant attributes for protein products (regulated by OBP) and link them to manufacturing processes
- To consider quality-by-design (QbD) approaches to unit operations in supplements (10) as well as original applications (5)
- To explore the use of protocols submitted under (21 CF 314.70(e) and 601.12(e))

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Expanded Change Protocols

- Discussion of measurable attributes (links to clinical performance)
- Discussion of Control Points and raw material attributes (links to measureable attributes, thus clinical performance)
- Risk Assessments and supporting documentation
- Description of the Design Space and supportive data
- Description of the Control Strategy (risk mitigation)
- **The Change Control plan**
  - Types of changes (change space)
  - Change Evaluation strategy
  - Risk management plans
  - Regulatory reporting mechanism
  - Quality system approaches

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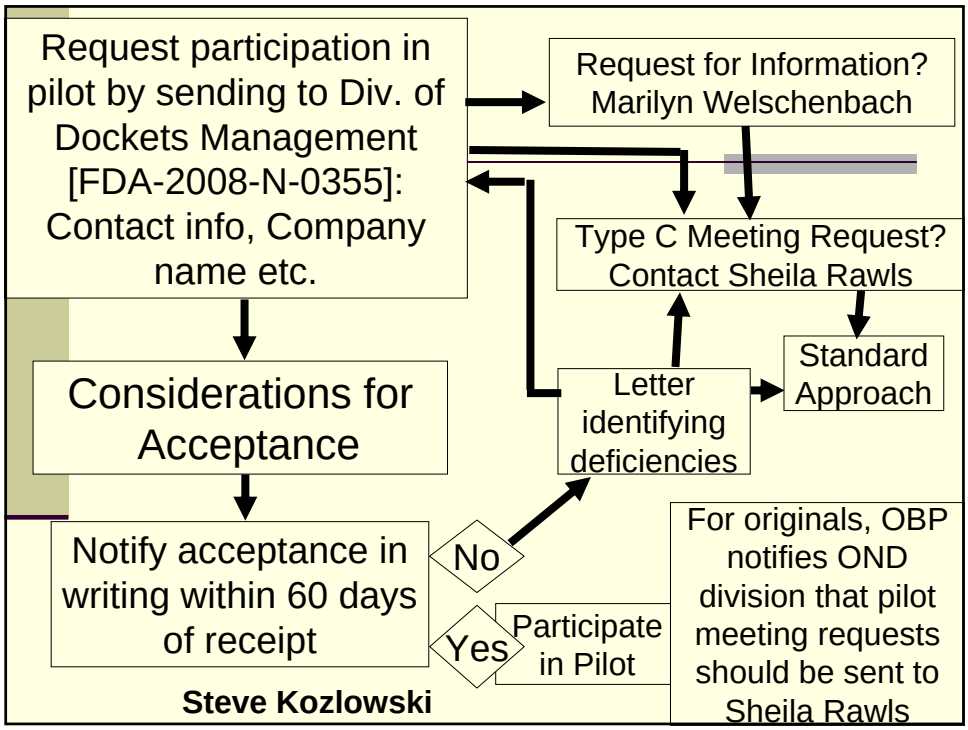
Request participation in pilot by sending to Div. of Dockets Management [FDA-2008-N-0355]: Contact info, Company name etc.
Request for Information? Marilyn Welschenbach
Type C Meeting Request? Contact Sheila Rawls
Standard Approach
Letter identifying deficiencies
Considerations for Acceptance
Notify acceptance in writing within 60 days of receipt
No
Yes
Participate in Pilot
For originals, OBP notifies OND division that pilot meeting requests should be sent to Sheila Rawls
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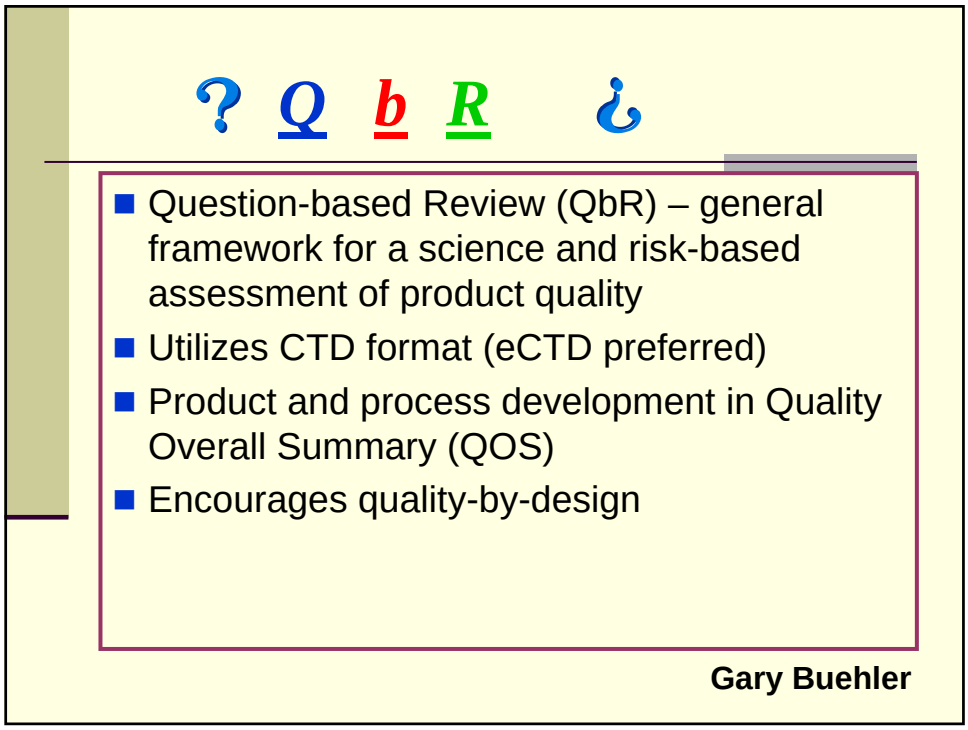
? Q b R ¿
Question-based Review (QbR) – general framework for a science and risk-based assessment of product quality
Utilizes CTD format (eCTD preferred)
Product and process development in Quality Overall Summary (QOS)
Encourages quality-by-design
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QbR Reviewer Experience

- ✓ Can use QbR-QOS as backbone of review
- ✓ Able to find justification for development decisions
- ✓ Critical parameters identified in QbR QOS and discussed the body of data
- ✓ Fewer questions to sponsors

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QbR Industry Experience

- FDA expectations better defined
- QbR questions have changed information gathering and data reporting during generic drug development
- Deficiencies are science-based and used to re-direct R&D activities for future ANDAs

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Future of QbR

First revision in 2009 based on reviewer and industry input

Reviewer concerns

- Apparent “cutting and pasting”
- Limited process development and scale-up
- Limited material compatibility data
- Incomplete justification for specifications
- QbR-QOS should be summary of Module 3

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What do we do about PAT?

- Can PAT be identified as a sampling issue?
  - Merely a method of control
  - Increases timeliness and number of samples
  - Decreases analysis time
- 21 CFR 211 has specific sampling requirements
  - Does this make it a field issue?
  - If so, can it be handled as a validation issue?
  - More on this tomorrow…

Thank you

- Say what you do
- Do what you say