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# Implementation of Quality-by-Design: Industry Perspective

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# Pharmaceutical Quality in the 21<sup>st</sup> Century

- Product Quality Initiative poised to take next steps into 21<sup>st</sup> century
- Will require movement onto unfamiliar ground for all of us
- Tremendous benefits to public, industry, regulators await
- We must be guided, as always, by rigorous science

*Source: Janet Woodcock, M.D., October 5, 2005*



# From a “Reactive” to a “Proactive” Decision System for Pharmaceutical Quality

- Reactive (examples)
  - Testing to document quality
  - Repeating deviation and out of specification investigations
  - *Prior Approval Supplement* for process optimization and continuous improvement efforts
  - Multiple CMC review cycles
  - Procrustean approach for demonstrating therapeutic equivalence of generic products
- Proactive (examples)
  - Quality by design and “real time release”
  - Right First Time
  - Process optimization and continuous improvement efforts within a facility’s quality system
  - Single CMC review cycle and risk-based specifications
  - QbD approaches for demonstrating therapeutic equivalence of generic products

**This is a journey and not a destination!**



Ajaz Hussain



# Quality by Design (QbD) Industry Perspectives

- Develop scientific understanding of critical process and product attributes
- Design controls and testing based on the limits of scientific understanding at development stage
- Utilize knowledge gained over the product's lifecycle to operate in an environment of continuous improvement

*Source: Janet Woodcock, M.D., October 5, 2005*



# What is Question-based Review?

- Question-based Review is a general framework for a science and risk-based assessment of product quality
- Question-based Review contains the important scientific and regulatory review questions to
  - Comprehensively assess critical manufacturing processes
  - Determine the level of risk associated with the manufacture and design of the product

Source: [www.fda.gov/cder](http://www.fda.gov/cder)



# CMC Review Under Question-based Review

- Questions guide reviewers to provide a consistent and comprehensive evaluation of the application
- Questions also alert the industry to what issues FDA generally considers critical in the evaluation of their applications
- The risk assessment component of the review provides for potential supplement reduction

Source: [www.fda.gov/cder](http://www.fda.gov/cder)



# Benefits of QbR

- Assure drug product quality
- Enhance review quality
- Reduction in review time
- Reduced post-approval supplements

[www.fda.gov/cder](http://www.fda.gov/cder)



# Design Space

- New drug development requires detailed understanding to achieve optimal bioavailability, safety, and efficacy.
- Generic drug development design is necessarily smaller and consequently restricted to produce equivalent products both pharmaceutically and therapeutically.
  - Plasma curves are pre-determined
  - Impurity profiles
  - Assay
  - Stability



# Generic QbD Principles

- API
  - Polymorphism
  - Particle size
  - Stability
- Excipients
  - Polymers to control release (proper selection)
  - Compatibility to API
  - Flow
  - Compression characteristics



# Generic QbD Principles

- Process
  - Compression ranges
  - Physical characteristics
  - Blend uniformity
- Finished product
  - Formulation Optimization
  - Stability
  - Drug Release
  - Packaging



# Example: CMC-API Selection Rationale/Process for Development

How do you know what questions to ask?

- What's the 1<sup>st</sup> API question you'd want the answer to if designing a product or in evaluating the appropriateness of the selected API attributes?
- The 2<sup>nd</sup>?, etc...
- The development scientist and the regulator are asking many of the same questions.

*Source: Ken Morris, July 20, 2004*



# Risk Based Development – CMC Questions

- Use sound scientific principles in the design of the product and Process
- Identify the critical attributes (CAs) for the raw materials
- Identify the process critical control points for the processes (PCCPs)
- Employ the proper analyses and PAT concepts for process understanding and control
- Tie it all together with the appropriate informatics to feed the information forward and backwards for QbD and continuous improvement and innovation = *reduced risk*
- Were the principles appropriately applied?
- How were the CA's identified and the formula designed?
- Ditto for the PCCP's
- What were the bases for analyses selection?
- What are the supporting data for all of the above?
- Product Development History

Source: Ken Morris, July 20, 2004



# Quality Overall Summary (QOS)

- Provides a source of the “answers”
  - Firms detail the logic associated with the development story
  - Reviewers do not need to track down information
- OGD placed example QOS documents on their website
  - Excellent resource for industry



# Generic Drug Development

- Product Development Reports are already being written
  - Often reviewed today during Pre-Approval Inspections by local field inspectors
  - Not previously apparent to OGD center reviews
- Inclusion in submission transfers information to the appropriate agency reviewer
  - Demonstrates QbD principles during initial review rather than just during Pre-Approval Inspections



# Current vs. QbD Desired State

- Companies often have information but it's not always in the filing
  - Reviewers must go through cycle of information requests and questions
  - Companies often have clear scientific rationales for choices but can not always share it
  - Reviewers must often “piece together” data and observations to discover the rationale for a spec, method, formula, process, etc.
  - Reviewers are left to analyzing data they often must extract out of the company
- Companies include needed data with filing and could share it prior to the filing
  - Companies include the data analysis to produce meaningful summaries and scientific rationales
  - Reviewers assess the rationales and summarized data presentations as satisfactory - or not



# PATENTS



# What Does QbD Deliver?

- Early development – CMC go/no go decisions with a higher level of certainty, i.e., reduced risk
- Late phase development – clear formulation and process design rationales
  - Control strategies based on understanding to reduce the risk
  - Facilitation of clear regulatory queries and logical responses
- Tech transfer – more realistic processes to transfer
  - Fewer “surprises”
  - Easier approval process and inspections

*Source: Ken Morris, July 20, 2004*



# QbD & Regulatory Flexibility

## IF

- Relevant (scientific) understanding (e.g., stability and bioavailability)
- Ability to predict quality / performance
- Confidence that product and process critical variables are controlled
  - With an appropriate ability to detect and prevent deviations
- High confidence in the value of regulatory specifications and process validation

## THEN

- First cycle CMC review more likely
- Process optimization possible without prior approval
- Risk-based Inspections feasible
  - Based on identification of critical product and process parameters

*Source: MAN SC Jul 04*



# Adoption of QbD delivers a new state:

- Product quality and performance achieved and assured by design of effective and efficient manufacturing processes
- Product specifications based on mechanistic understanding of how formulation and process factors impact product performance
- An ability to effect Continuous Improvement and Continuous “real time” assurance of quality

Source: FDA SC Jul 04



# Challenges

- QBR represents a significant change to the content of ANDA's
- Rapid implementation of the QBR system will be difficult
  - Requires change within industry as well as FDA
- Communication must improve
  - Requires change within industry as well as FDA
  - Feedback mechanism between industry and the agency regarding submission and scoring to allow applicants to learn and continuously improve.



# Final Thoughts

- The move to Question Based Reviews provides an opportunity for more efficient FDA evaluation of applications
- QBR is consistent with the Quality by Design paradigm and will help build quality into generic products rather than demonstrate (measuring) quality after manufacture
- The number of applications are anticipated to continue to increase in the next several years
- Industry is hopeful in the ability of QBR to contribute to improving the backlog at OGD

