

# FDA's New Question- Based ANDA Review Program

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# Outline

- Introduction and overview
- Current FDA CMC review: Quality by end product testing
- FDA's quality by design concepts
- New "Question-Based Review" concepts for generic drugs
- Summary

# FDA Goals for Question-Based Review

- “Requirement” beginning January 2007
- Conforms with the risk-based approach for cGMPs and product assessment
- Increased focus on formulation and manufacturing process
- Increased efficiency in the FDA review process

# ICH Submission Format for NDAs/ANDAs

## ■ CTD

- Module 1: Administrative Information
- Module 2: Quality Overall Summary and Clinical Summary
  - For ANDA's, we stress on M4Q: Summary of Critical CMC Elements
- Module 3: Quality
  - Body of Data; Detailed CMC Submission
- Module 4: Non-clinical
- Module 5: Clinical (Bioequivalence)

# Question-based Review: Quality Overall Summary is Key to Efficiency

- Single application format
  - Common Technical Document Format preferably eCTD
- Electronic Quality Overall Summary that will
  - ***directly address the OGD's questions***
  - ***result in a better understanding of sponsors' rationale for decisions and therefore, less misunderstandings***
  - ***reduce reviewers' time spent in fact finding and summarizing ANDA elements***

# QbR-QOS based CMC Review

Sponsor's  
QOS

+

Reviewer's  
Assessment

=

CMC  
Review

No Sponsor's  
QOS

=

?

# CMC Review under QbR-QoS

ANDA Application:  
Electronic QOS (Module 2)  
+ Body of Data (Module 3)

Reviewer evaluates application to assess

- Identity, strength, stability, purity, and quality
- sponsor's identification and control of critical formulation and process variables
- Specifications

Reviewer assesses if sponsor's QOS is an acceptable summary of Module 3

Reviewer inserts critical assessment into QOS, and, if necessary, edits QOS:

- Deletes superfluous information from QOS
- Add missing essential information into QOS from the body of data

Reviewer determines the level of risk associated  
with the manufacture and design of the product

Quality Review under  
QbR for Generic Drugs

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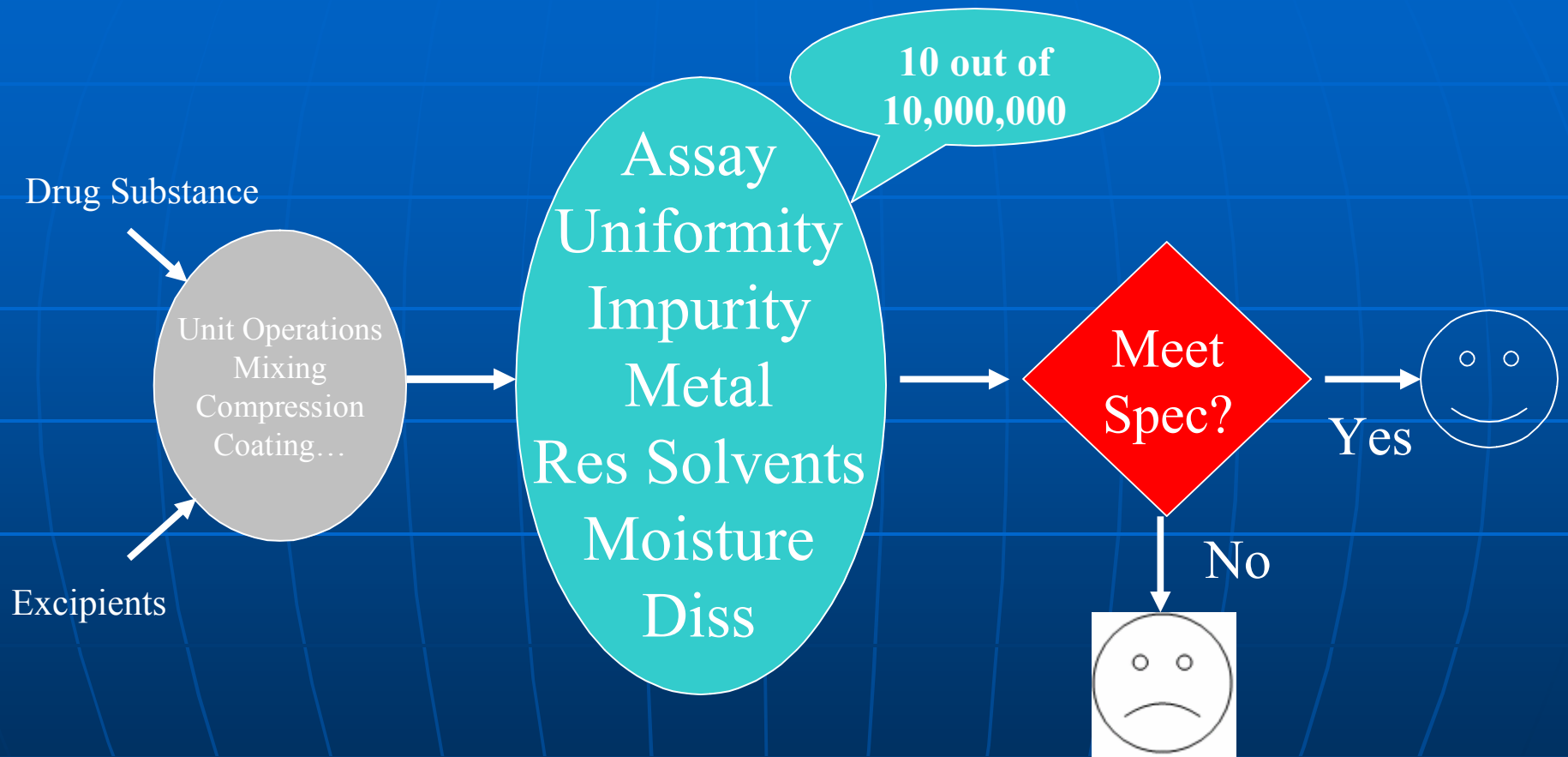
# FDA's Current CMC Review Perspective

- Quality by end product testing
  - Minimal evaluation of:
    - Product design
    - Process design and scale-up
- Product specifications by test data from one to three batches
  - Minimal or no mechanistic understanding
  - In most cases overly conservative specifications

# Current CMC Review Perspective

- Does not adjust review to the level of scientific understanding
  - All products (simple and complex) use the same approach
  - All products are subject to the same post-approval supplement requirements

# Quality by End Product Testing



# Outline

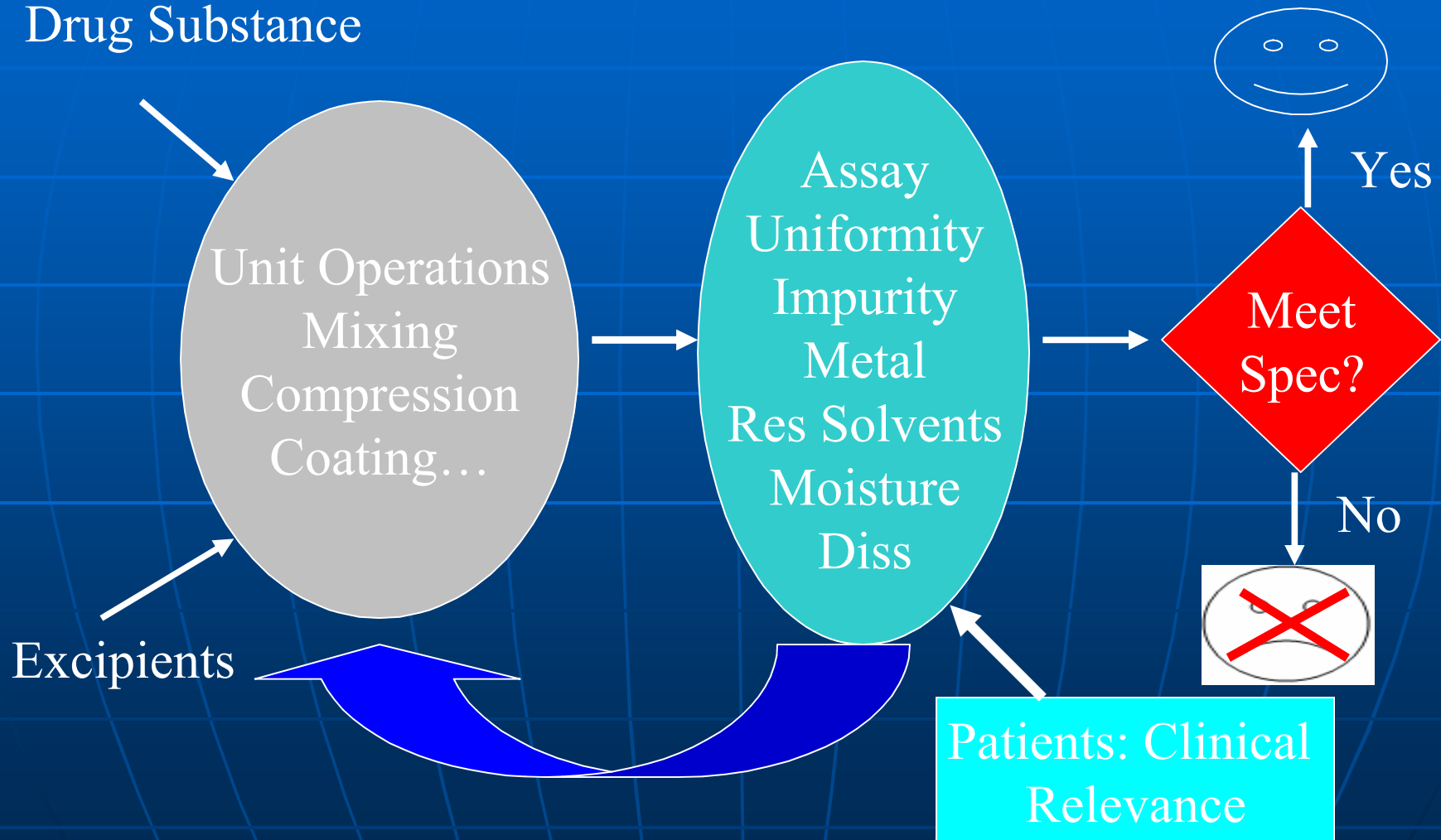
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# Pharmaceutical Quality

$= f$  (Drug Substance,  
Excipients, and  
Manufacturing)

# Quality by Design

Drug Substance



# What is Quality by Design?

- Quality should be built into the product; testing alone cannot be relied on to ensure product quality
- Pharmaceutical Quality by Design (QbD)
  - QbD means designing and developing a formulation and manufacturing processes to ensure predefined product quality by understanding and controlling formulation and manufacturing process variables that influence the quality of a drug product

# Target Product Quality Profile: Beginning the Drug Development with Final Attributes Defined

- Target product quality profile
  - Identity, strength/assay
  - Uniformity
  - Purity
  - Stability
  - Others
    - In vitro dissolution
    - Resuspendability
    - Etc.

# Two Parts of Pharmaceutical Development for Submission

- Product design
  - All products
- Process design
  - Complex products only
  - Optional for solution, IR tablet, and IR capsule

# Product Design Questions

- What attributes should the drug product possess?
- How was the product designed to have these attributes?
- Were alternative formulations or mechanisms investigated?

# Product Design Questions (cont'd)

- How were the excipients and their grades selected?
- How was the final formulation optimized?

# Process Design Questions

- Why was the manufacturing process selected for this drug product?
- How are the manufacturing steps (unit operations) related to the drug product quality?

# Process Design Questions (cont'd)

- How were the critical process parameters identified, monitored, and controlled?
- What is the scale-up experience with the unit operations in this process?

# Product/Process Development

- Product development reports are currently required by GMPs
- Some product/process development information already exists
- Most will not be adequate to fully satisfy QBR
- **May rely on prior knowledge in many cases**

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# Question-based Review

- A general framework for a risk-based assessment of product quality
- Contains the important scientific and regulatory review questions to
  - Comprehensively assess critical formulation and manufacturing process variables
  - Set regulatory quality standards
  - Determine the level of risk associated with the design and manufacture of the product

# QbR Principles

- Quality built in by design, development, and manufacture; confirmed by testing
- Risk-based approach maximizes economy of time, effort, and resources
- Utilizes the best practices of current review system and organization

# Submission Format Under QbR

- CTD
  - Module 1: Administrative Information
  - **Module 2: Quality Overall Summary and Clinical Summary**
    - Summary of Critical CMC Elements
  - **Module 3: Quality**
    - Body of Data; Detailed CMC Submission
  - Module 4: Non-clinical
  - Module 5: Clinical (Bioequivalence)

# QbR Relies on QOS for Regulatory Assessment

- Quality Overall Summary is the **key** element to QbR
- Quality Overall Summary will:
  - directly address OGD's routine questions
  - enhance FDA's understanding of sponsors' rationale for decisions and therefore, fewer misunderstandings
  - reduce reviewer time spent finding and summarizing ANDA elements

# **Guidance for Industry**

## **Organization of an ANDA**

**U.S. Department of Health and Human  
Services**

**Food and Drug Administration  
Center for Drug Evaluation and Research  
(CDER)**

**February 1999**

**OGD # 1**

**Revision 1**

# **Guidance for Industry**

**Providing Regulatory Submissions  
in Electronic Format – ANDAs**

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)**

**June 2002  
Electronic Submissions**

# Office of Generic Drugs

## ANDA Checklist for CTD or eCTD Format for Completeness and Acceptability of an Application for Filing

April 2006

**ANDA CHECKLIST FOR CTD or eCTD FORMAT  
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION  
FOR FILING**

For More Information on Submission of an ANDA in Electronic Common Technical Document

(eCTD) Format please go to: <http://www.fda.gov/cder/regulatory/ersr/ectd.htm>

\*For a Comprehensive Table of Contents Headings and Hierarchy please go to:

<http://www.fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf>

\*\* For more CTD and eCTD informational links see the final page of the ANDA Checklist

\*\*\* A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage <http://www.fda.gov/cder/ogd/>

ANDA #: \_\_\_\_\_ FIRM NAME: \_\_\_\_\_

PIV: \_\_\_\_\_ ELECTRONIC OR PAPER SUBMISSION: \_\_\_\_\_

RELATED APPLICATION(S): \_\_\_\_\_

First Generic Product Received? \_\_\_\_\_

DRUG NAME: \_\_\_\_\_

DOSAGE FORM: \_\_\_\_\_

Bio Assignments:		<input type="checkbox"/> Micro Review
<input type="checkbox"/> BPH	<input type="checkbox"/> BCE	
<input type="checkbox"/> BST	<input type="checkbox"/> BDI	

Random Queue:

Chem Team Leader: \_\_\_\_\_ PM: \_\_\_\_\_ Labeling Reviewer: \_\_\_\_\_

Letter Date:	Received Date:
Comments:	On Cards:
Therapeutic Code:	
Archival copy:	Sections
Review copy:	E-Media Disposition:
Not applicable to electronic sections	
PART 3 Combination Product Category	
<small>(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm</small>	

Reg. Support Reviewer	Recommendation:
Date	<input type="checkbox"/> FILE <input type="checkbox"/> REFUSE to RECEIVE
Supervisory Concurrence/Date: _____	Date: _____

# **Guidance for Industry**

## **Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications**

**Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)  
October 2005**

**\* Pay attention to M4Q: The CTD – Quality General**

# Manufacturing Process Assessment

- Three-tiered assessment of manufacturing
  - Tier 1 applies to all dosage forms
  - Tier 2 applies to dosage forms that are not solutions (equivalent to current practice)
  - Tier 3 applies to dosage forms that are not solutions, IR tablets, or IR capsules

# Post-approval Changes

- FDA envisions QbR to:
  - Draw conclusions about risk of proposed changes
    - Eliminate/downgrade regulatory burden for CMC supplements
  - Allow sponsors to execute manufacturing processes for which they have demonstrated process understanding
    - Facilitating continuous CMC improvement and innovation

# Proposed Risk-based Scoring System

- ANDA drugs: score
- Risk

NTI Drugs	+1
Complex dosage form	+1
Insufficient or missing PD reports	+1
Application of poor quality	+1

- Possible risk scores = 0, 1, 2, 3, or 4
- The review team proposes a final risk assessment score

# What post-approval waivers/ commitments are appropriate?

- Total risk score of 1 or less
  - Many CBE-0 and CBE-30 changes shifted to annual report
  - Possible to downgrade certain PAS changes to CBE/annual report
- Total risk score of more than 1
  - No change in supplement submission and review

# FDA's View of QbR Benefits

- High product quality
  - Quality by design
- Efficient and timely review
  - Quality overall summary
- Risk based reduction of supplements
- Science based specifications
  - Safety and efficacy, not process capability
- Consistency and transparency of review

# QbR Challenges and Questions

- How quickly will FDA change its expectations to conform with QbR?
- Will new types of deficiencies arise?
- Will review time decrease?
- Will FDA permit more post-approval changes to be implemented without prior approval?
- CTD/e-CTD format is essential

# Recommendations

- Plan for QbR submission at the time of product development
- Coordinate preparation of dossier with all relevant departments
- Obtain assistance from experts if needed
  - Poor quality QbR submissions will result in significant delay for approval

# Summary

- QbR will be 'required' in January 2007
- Plan your QbR submission at the product development stage
- Become familiar with FDA's new content/format guidance for ANDAs
- Seek assistance if needed
- Be prepared for some new questions from FDA

# CTD and eCTD

## Informational Links

Organization of the CTD

<http://www.fda.gov/cder/guidance/4539O.PDF>

eCTD Submissions

<http://www.fda.gov/cder/guidance/7087rev.pdf>

Drug Substance

<http://www.fda.gov/cder/guidance/3969DFT.pdf>

Drug Product

<http://www.fda.gov/cder/guidance/1215dft.pdf>

Pharmaceutical Development

<http://www.fda.gov/cder/guidance/6672dft.pdf>

CTD-Efficacy

<http://www.fda.gov/cder/guidance/4539E.pdf>

CTD-Quality

<http://www.fda.gov/cder/guidance/4539Q.PDF>

**Thank You !**