Implementation of Quality-by-Design: Question-based Review

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Generic Drugs Hit Backlog At FDA
No Plans to Expand Review Capabilities

By Marc Kaufman
Washington Post Staff Writer

“…the Food and Drug Administration has a backlog of more than 800 applications to bring new generic products to the market - an all-time high.”

“Rep. Henry A. Waxman (D-Calif.), ‘This is the time for the FDA to be ramping up its generic reviews, not to be falling so badly behind.’"
Receipts of ANDAs

2001 2002 2003 2004 2005

ANDAs
Employees

0 200 400 600 800 1000
Receipts of Supplements (ANDAs)

- 2001: 2500
- 2002: 2500
- 2003: 3000
- 2004: 4000
The Desired State: A Mutual Goal of Industry, Society, and the Regulators

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

Pharmaceutical Quality in the 21st Century
Janet Woodcock, M.D.
Deputy Commissioner for Operations
Characteristics of Desired State

• Manufacturers have extensive knowledge about critical product and process parameters and quality attributes
• Manufacturers strive for continuous improvement
• FDA role: Initial verification, subsequent audit
• No manufacturing supplements needed

Pharmaceutical Quality in the 21st Century
Janet Woodcock, M.D.
Deputy Commissioner for Operations
Current CMC Review: Issues

• Quality by end product testing
  – Little or no scrutiny on product and process design

• Product specifications
  – Little or no mechanistic understanding
  – “Overly conservative and often irrelevant specifications”

• Does not adjust review to the level of scientific understanding
Quality by End Product Testing

Drug Substance

Unit Operations
Mixing
Compression
Coating

Excipients

Assay
Uniformity
Impurity
Metal
Res Solvents
Moisture
Diss

Meet Spec?

10/30 out of
10,000,000

Yes

No

CFR 314.70
Change Guidance

10/30 out of
10,000,000

CFR 314.70
Change Guidance
Why Question-based Review?

• Workload
  – Number of applications is quickly growing
  – Number of reviewers is slowly growing
  – Each application leads to supplements

• Quality
  – FDA cGMP Initiative; Pharmaceutical Quality in the 21st Century
  – Issues with current CMC review
Question-based Review

• Question-based Review is a new review system for a science and 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 specifications relevant to quality
    • Determine the level of risk associated with the manufacture and design of the product
Question-based Review System

- Quality by Design
- Novel Risk Assessment
- QbR Questions
- Quality Overall Summary
- Post Approval Changes
Question-based Review Incorporates Quality by Design to Assure Product Quality
What is Quality?

• Fitness for intended use
  – Free of contamination and reproducibly deliver the therapeutic benefit promised in the label to the consumer (Janet Woodcock)
  • Consumer expectation

• Pharmaceutical Quality
  \[ = f \text{ (drug substance, excipients, manufacturing)} \]
How Do You Judge Quality?

• Quality can be evaluated by in vivo or in vitro performance tests
  – In Vivo: PK, PD, Clinical
  – In Vitro: Assay, Uniformity, Purity, and/or Dissolution
How Does Quality Relate to Product Performance?

• Quality by design assures *in vitro* product performance

• *In vitro* product performance provides assurance of *in vivo* product performance
Quality by Design

- Drug Substance
- Unit Operations (Mixing, Compression, Coating...)
- Excipients
- PAT
- Assay Uniformity Purity Diss
- Always Meet Spec
- Clinical Relevance

Always Meet Spec
What is Quality by Design?

• Pharmaceutical Quality by Design (QbD)
  – QbD means designing and developing formulations and manufacturing processes to ensure predefined product quality

• Understanding and controlling formulation and manufacturing process variables affecting the quality of a drug product
Where Does Design of Quality Begin?

• Target product quality profile
  – Beginning drug development with the end in mind
  – What performance is needed to get clinical benefit and meet consumer expectation

• Pharmaceutical Quality

  \[ \text{Pharmaceutical Quality} = f \text{ (drug substance, excipients, manufacturing)} \]
What Does QbD Constitute?

• Define target product quality profile
  – The performance needed to get clinical benefit and meet consumer expectation
• Design and develop product and manufacturing process to meet target product quality profile
• Identify and control critical raw material attributes, process parameters, and sources of variability
• The process is monitored and adapted to produce consistent quality over time
Design Space

• Design Space
  – The multidimensional combination and interaction of input variables (e.g., Material attributes) and process parameters that have been demonstrated to provide assurance of quality

• Design of Experiments
  – A structured, organized method for determining the relationship
Design Space: Regulatory Challenges

Potential Design Space

10 Fold Generation

Design Space

Confirmation
QbD Questions Under QbR

• Define target product quality profile
  – What attributes should the drug product possess?

• Design and develop **product** and manufacturing process to meet target product quality profile
  – How was the product designed to have these attributes?
  – Were alternative formulations or mechanisms investigated?
  – How were the excipients and their grades selected?
  – How was the final formulation optimized?
QbD Questions Under QbR (Continued)

• Design and develop product and manufacturing process to meet target product quality profile
  – What are the unit operations in the drug product manufacturing process?
  – Why was the manufacturing process selected?
  – How are the unit operations related to the drug product quality?
QbD Questions Under QbR (Continued)

• Identify and control critical raw material attributes, process parameters, and sources of variability
  – Which properties or physicochemical characteristics of the drug substance affect drug product development, manufacture, or performance?
  – What evidence supports compatibility between the excipients and the drug substance?
  – How were the critical process parameters identified, monitored, and controlled?
QbD Questions Under QbR (Continued)

• The process is monitored and adapted to produce consistent quality over time
  – What are the in-process tests and/or controls that ensure each step is successful?
  – What is the scale-up experience with the unit operations in this process?
  – In the proposed scale up plan what operating parameters will be adjusted to ensure the product meets all in-process controls and final product specifications?
  – What evidence supports the plan to scale up the process to commercial scale?
Question-based Review
Uses Quality Overall Summary to Ensure Efficient CMC Assessment
Diagram of the ICH Common Technical Document

QOS
Summary of Critical CMC Elements

Body of Data
Detailed CMC Submission Package
ANDAs under QbR

- Encouraging all ANDAs be submitted in the CTD format and preferably electronic CTD to support Question-based Review

  - The 1999 and 2002 Guidances for Industry; Organization of an ANDA have been removed from the Regulatory Guidance page

  - The ANDA Checklist for Completeness and Acceptability of an Application for Filing can be found on the OGD web page (4/19/2006) [http://www.fda.gov/cder/ogd/]
QbR-QOS for ANDAs

**QOS for ANDA**
ANDA Sponsors' summary of critical CMC elements from the application that answers the QBR questions

**QOS**
Sponsors' summary of critical CMC elements in the CTD

**QbR**
Reviewer tool for ANDA Assessment
OGD Model QOS

- Model Quality Overall Summary for ER Product
  - http://www.fda.gov/cder/ogd/
    OGD_Model_Quality_Overall_Summary.pdf

- Model Quality Overall Summary for IR Product
  - http://www.fda.gov/cder/ogd/
    OGD_Model_QOS_IR_Product.pdf
Quality Review under QbR

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 prepares critical assessment using QOS
If necessary, reviewer edits QOS:
• Deletes superfluous information from QOS
• Rectify QOS by adding missing and essential information

Quality review under QbR for Generic Drugs
QbR Uses QOS for Regulatory Assessment

• Quality Overall Summary that will
  – directly address 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
Question-based Review Uses A Novel Risk-based Approach to Maximize Economy of Time, Effort, and Resources and to Facilitate Continuous Improvements
Risk-based Approach

- One goal of risk assessment is to allocate scarce reviewer resources to benefit the public
  - More emphasis on
    - Critical dose drugs (NTI)
    - “Complex” dosage forms/delivery systems
  - Less yet appropriate emphasis on
    - Solution products and Solid Oral IR Dosage Forms
  - Eliminating supplements for minor and most moderate and some major post-approval changes
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

• Draw conclusions about risk that will be useful in evaluating the need for post approval supplements
  – Eliminate/downgrade up to 80% of CMC supplements, and thus free up scarce resources

• Allow sponsors freedom to execute manufacturing processes for which they have demonstrated process understanding
  – Facilitating continuous CMC improvement and innovation
Proposed Risk-based Scoring System

<table>
<thead>
<tr>
<th>ANDA drugs</th>
<th>Risk score</th>
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<tbody>
<tr>
<td>NTI Drugs</td>
<td>+1</td>
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<tr>
<td>Complex dosage form</td>
<td>+1</td>
</tr>
<tr>
<td>Insufficient or missing PD reports</td>
<td>+1</td>
</tr>
<tr>
<td>Application of poor quality</td>
<td>+1</td>
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</tbody>
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- 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
Question-based Review Will be Implemented in 2007
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>2004</td>
<td>FDA’s cGMP Initiative and Initiation of QbR</td>
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<tr>
<td>1/2005</td>
<td>QbR Questions drafted</td>
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<tr>
<td>2/2005</td>
<td>GPhA Technical Advisory Committee Meeting</td>
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<tr>
<td>4/2005</td>
<td>PQRI and FDA Specification Workshop</td>
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<tr>
<td>6/2005</td>
<td>OGD GPhA Technical Advisory Committee Joint Meeting</td>
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<td>6/2005</td>
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<tr>
<td>8/2005</td>
<td>OGD QbR White Paper</td>
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<tr>
<td>10/2005</td>
<td>AAPS Quality Workshop</td>
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<tr>
<td>10/2005</td>
<td>GPhA Fall Technical Workshop</td>
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<tr>
<td>1/2006</td>
<td>ANDA Submission Checklist</td>
</tr>
<tr>
<td>1/2006</td>
<td>Example Quality Overall Summary</td>
</tr>
<tr>
<td>2/2006</td>
<td>GPhA Technical Advisory Committee Meeting</td>
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<tr>
<td>3/2006</td>
<td>OGD CMC Review Format and Example</td>
</tr>
<tr>
<td>5/2006</td>
<td>GPhA QbR Training</td>
</tr>
</tbody>
</table>
QbR ANDA Submission

- Five major generic companies have submitted QbR applications
- Almost all major generic companies are planning to submit QbR applications this year
Experience with Assessment of QbR ANDAs: Documentation Advantages

• Primary reviewer saves time
  – Summary of application
    • Facts finding
    • Tables & charts
    • Chemical structures
    • Specifications etc

• No transcriptional errors
Experience with Assessment of QbR ANDAs: Technical Advantages

• Enhanced product and review assessment
  – Critical formulation and manufacturing process variables identified and controlled in QbR-QOS

• Insight into sponsor’s development plans
  – Product & Process Design and Development
  – Directly address the OGD’s questions

• Better understanding of sponsors' rationale for decisions and therefore, less misunderstandings
Question-based Review: Conclusion

• High product quality
  – Quality by design
• Efficient and timely review
  – Quality Overall Summary
• Risk based reduction of supplements
  – Up to 80% for ANDAs
• Science based specifications
  – Safety and efficacy, not process capability
• Consistency and transparency of review
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