Question-based Review: A New Quality Assessment System for Generic Drugs

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Quality by Design

FDA’s Pharmaceutical cGMP for the 21st Century QbD Initiative

Generic Sponsor: Implementing QbD in development and manufacturing

FDA Office of Generic Drugs: Developed a Question-based Review System that assesses sponsor’s QbD ANDAs
Office of Generic Drugs White Paper

Question-Based Review (QbR) for Generic Drugs:
An Enhanced Pharmaceutical Quality Assessment System

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Introduction

The Office of Generic Drugs (OGD) is developing a question-based review (QbR) for its Chemistry, Manufacturing, and Controls (CMC) evaluation of Abbreviated New Drug Applications (ANDAs) that is focused on critical pharmaceutical quality attributes. The QbR is a concrete and practical implementation of the underlying concepts and principles outlined by the FDA’s cGMPs for the 21st Century [1] and PAT [2] initiatives. It will transform the CMC review into a modern, science and risk-based pharmaceutical quality assessment. This white paper discusses 1) what QbR is, 2) why QbR is necessary, 3) how QbR was developed, and 4) what the benefits of QbR are.
**January 2006**

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


**MODULE 2**

**SUMMARIES**

<table>
<thead>
<tr>
<th>2.3</th>
<th>Quality Overall Summary (QOS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>E-Submission:</strong> PDF</td>
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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/](http://www.fda.gov/cder/ogd/)

**Question based Review (QbR)**

<table>
<thead>
<tr>
<th>2.3.S</th>
<th>Drug Substance (Active Pharmaceutical Ingredient)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.3.S.1</td>
<td>General Information</td>
</tr>
<tr>
<td>2.3.S.2</td>
<td>Manufacture</td>
</tr>
<tr>
<td>2.3.S.3</td>
<td>Characterization</td>
</tr>
<tr>
<td>2.3.S.4</td>
<td>Control of Drug Substance</td>
</tr>
<tr>
<td>2.3.S.5</td>
<td>Reference Standards or Materials</td>
</tr>
<tr>
<td>2.3.S.6</td>
<td>Container Closure System</td>
</tr>
<tr>
<td>2.3.S.7</td>
<td>Stability</td>
</tr>
</tbody>
</table>

**ACCEPTABLE**

[A]
Questions to be completed by ANDA Sponsors for the preparation of a QbR-Quality Overall Summary

2.3.S DRUG SUBSTANCE

2.3.S.1 General Information

What are the nomenclature, molecular structure, molecular formula, and molecular weight?
What are the physicochemical properties including physical description, \( \text{pK}_a \), polymorphism, aqueous solubility (as function of pH), hygroscopicity, melting points, and partition coefficient?

2.3.S.2 Manufacture

Who manufactures the drug substance?
How do the manufacturing processes and controls ensure consistent production of drug substance?

2.3.S.3 Characterization

How was the drug substance structure elucidated and characterized?
How were potential impurities identified and characterized?
QBR Principles

- Preserve the best practices of current review system and organization
- Quality built in by design, development, and manufacture and confirmed by testing
- Risk-based approach to maximize economy of time, effort, and resources
- Best available science and wide consultation to ensure high quality questions
QbR ANDA Submission

QbR ANDA Submissions in 2007 and 2008

% QbR ANDA

Time

Thank You!
QbR Questions Serve Dual Purposes

- **Questions guide reviewers**
  - A consistent and comprehensive evaluation of the application
  - Assess critical formulation and manufacturing process variables as well as control strategies

- **Questions guide industry**
  - Issues we generally consider critical
  - Direct industry toward quality by design
  - Prepare high quality QOS
ANDAs Under QbR

Quality Overall Summary that will
- address the QbR questions and guide reviewers through the application
- eliminate unnecessary copying of information such as composition, specification, and manufacturing process, etc., resulting in shorter review time

Product Development Report that will explain
- how drug substance properties and formulation variables affect the performance of the drug product
- how the sponsor identifies the critical manufacturing steps, determines operating parameters, selects in-process tests to control the process, and scales up the manufacturing process
Traditional CMC Review to QbR Assessment

Reviewer

Sponsor

Traditional

QbR

No PD Inf

Assess spec

Summary

Body of Data

Assess QbD

Assess spec performance

Summary QbD

Body of Data QbD
First 40 QbR Approvals

(QbR Approvals
(Median Approval Time = 13 M)

First 40 QbR approvals; not necessary suggesting that QbR reduce review time
Quality QbR Submissions

Biggest Concern of OGD Reviewers
- Data in QbR-QOS differs from data in rest of application
  - This is not acceptable! It will increase review time

Other Areas for Improvement
- Limited process development and scale-up data
- Limited material compatibility data
- Incomplete justification of proposed product specifications
- QbR-QOS should be a summary of Module 3 and not vice-versa
- ~40 pages
QbR Resources

- **Questions**
  - [http://www.fda.gov/cder/ogd/QbR_Summary_outline.htm](http://www.fda.gov/cder/ogd/QbR_Summary_outline.htm)

- **Examples (Model QOS)**
  - extended release capsule
  - immediate release tablet

- **Explanations (FAQ)**
Quality by Design is the Future

- **ANDAs need QbD**, particularly for complex dosage forms
- **QbD makes it clear to FDA how sponsors ensure product quality and equivalence**
- **Recent warning letter to an ANDA sponsor**
  - “you stated that your firm will continue releasing X because routine product testing of manufactured lots is sufficient proof that the process is validated. We disagree with your assessment. Product testing alone is not sufficient to assure that a process consistently produces a product with predetermined specifications”
Overview of QbD

1. Labeled Use
   - Safety and Efficacy

2. DEFINE Quality
   - Target Product Profile

3. DESIGN Formulation and Process

4. IDENTIFY Critical Material Attributes and Critical Process Parameters

5. CONTROL Materials and Process

TARGET → DESIGN → IMPLEMENTATION

QbD Resources

- ICH Q8 and Q8(R1)

- QbD: Product and Process Development, Understanding, and Control
  - http://www.springerlink.com/content/d426770m1p0860r1/fulltext.pdf

- QbD: Concepts for ANDAs
  - http://www.springerlink.com/content/a456mq78m36k98k7/fulltext.pdf
OGD example QbD for generic drugs
- OGD reviewers are developing an example QbD for generic drugs
- The example QbD for generic drugs will be shared with industry to seek industry feedback

QbR questions will be revised based on the example QbD for generic drugs
Question-based Review is a new quality assessment system that incorporates some underlying concepts and principles of quality by design.

Quality by Design is the future for generic drug development.

Future enhancement of Question-based Review intends to fully incorporate the elements of Quality by Design.