Question-based Review for ANDAs

Chi-wan Chen, Ph.D.
Executive Director, Pfizer
Member, FDA Alumni Association

DIA China, Beijing, China
May 15-18, 2011

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Disclosures

- I am currently an employee of Pfizer, Inc. I am Executive Director, Global CMC
- I worked at the U.S. Food and Drug Administration (FDA) in 1986-2008. I was Deputy Director, Office of New Drug Quality Assessment, CDER.
- The following are my views and not necessarily the views of the Food and Drug Administration Alumni Association (FDAAA), or FDA, or Pfizer
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Outline*

- Introduction to Question-based Review (QbR)
  - What, when, why, and how
- Questions in Model QbR-Quality Overall Summary (QOS) for IR tablet
- Questions in Model QbR-Quality Overall Summary (QOS) for ER capsule
- Commonly cited deficiencies in ANDAs
- QbR lessons learned
- Summary
- Appendix: Example commonly cited deficiencies related to drug substance in ANDAs

* This presentation is based on publications and representations by Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. FDA

Question-based Review (QbR) – What is it?

- Question-based review (QbR) is a science- and risk-based approach to the Chemistry, Manufacturing, and Controls (CMC) evaluation of an Abbreviated New Drug Application (ANDA) to ensure product quality
- QbR contains the important scientific and regulatory review questions that captures key aspects of
  - Drug substance, excipients, formulation, process design, manufacture, control, container closure system, reference materials, and stability

QbR Development and Implementation Timeline

- Sep 2004 – FDA CGMP initiative and initiation of QbR
- Jan 2005 – QbR questions and review template drafted
- Aug 2005 – QbR White Paper posted on FDA website
- Jan 2006 – Model QbR-Quality Overall Summary (QOS) for IR tablet published
- Mar 2006 – Model QbR-QOS for ER capsule published
- Sep 2006 – First QbR ANDA approval
- Jan 2007 – Full implementation of QbR evaluation
- May 2010 – 100% ANDAs submitted with QbR-QOS, with few exceptions

Drivers and Purposes for QbR

- Drivers
  - Discrepancy between the objectives of FDA's CGMP for the 21st Century Initiative and current CMC review practices in Office of Generic Drugs (OGD)
  - Limited resources with increasing review workload in OGD
- Purposes
  - To transform OGD's CMC review into a modern, science and risk-based pharmaceutical quality assessment that incorporates and implements the concepts and principles of the 21st Century Initiative
  - To enable effective allocation of limited review resources

Objectives of QbR

- To assure product quality through design and performance-based specifications
- To facilitate continuous improvement and reduce CMC supplements through risk assessment
- To enhance the quality of reviews through standardized review questions
- To reduce CMC review time when applicants submit a quality overall summary that addresses the QbR

Ensuring Product Quality

- QbR questions encouraged open communication
  - Product design and development information
- Pharmaceutical Development P.2*
  - Justifying the applicant's choices of critical quality attributes (CQAs) and critical process parameters (CPPs)
  - Experimental design linking CQAs to CPPs
  - Demonstrating rationale for individual unit operations, specifications, or process parameters
  - Data from pilot batches of failing or suboptimal formulations or processes
  - Analysis of the issues and problems
  - Pathway to the optimized formulation and process

* FDA MaPP 5016.1, Feb 2011, states, “Reviewers should ensure that applications contain at least the minimum information on pharmaceutical development described by ICH Q8(R2)”

Increasing Quality, Transparency, and Consistency of Reviews

- Increased transparency for both FDA and industry
  - Facilitating communications
- Increased the quality of CMC reviews
  - Shifting the focus of the review to areas that are most likely to affect product quality
- Increased review consistency

Reducing Review Time

- Increased the amount of material covered in the CMC review
  - Time for the initial CMC review is marginally longer
- Reduced number of review cycles
  - When the applicant demonstrates process and product understanding
- Significantly decreased the time spent by CMC reviewer transcribing and summarizing information
  - Impacted by the quality of ANDAs

Advantages of QbR

- Questions guide industry to
  - Recognize issues OGD generally considers critical
  - Direct industry toward quality by design (QbD)
- Questions guide reviewers to
  - Prepare a consistent and comprehensive assessment of the ANDA
  - Assess critical formulation & manufacturing variables
- Questions inform readers of the review
  - How QbD was used in the ANDA
  - The basis for a risk assessment

Quality of QbR ANDAs

- Main concern with OGD reviewers
  - Data in QbR-QOS differs from body of data (Module 3) = major deficiency
  - Response with inadequate supporting data
- Areas for improvement
  - Material compatibility data
    - Compatibility can not be justified by product stability data or physical observation
  - Incomplete justification
    - in-process material attribute range
    - Proposed product specifications
  - Process development and scale-up data
  - Scalability and robustness
  - In-process control
  - Drug product quality heavily relies on final product testing
  - QbR-QOS
    - Summary of Module 3 and not vice-versa

QbR Communication

- White Paper on Question-Based Review for CMC Evaluations of ANDAs (announced August 2005) http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM120971
- QbR Frequently Asked Questions
  - Available on QbR webpage at above link
- Lawrence Yu, et. al., "U.S. FDA question-based review for generic drugs: A new pharmaceutical quality assessment system," *Journal of Generic Medicines*, Vol 4, 239-248, 2007
- Aloka Srinivasan and Robert Iser, "FDA Office of Generic Drugs Question-based Review initiative: An update – past, present, and next steps," *Journal of Validation Technology,* Spring, 2009
- David Skanchy, "Question-Based Review: An FDA reviewer's perspective," *Pharmaceutical Technology,* October, 2009

- Model QbR-Quality Overall Summary (QOS) – IR Tablet (25 pages)*

- Model QbR-Quality Overall Summary (QOS) – ER Capsule (36 pages)*

* Posted by Office of Generic Drugs in 2006; available on QbR webpage: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM120971

Model QbR-QOS – IR Tablet

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, pKa, polymorphism, aqueous solubility (as function of pH), hygroscopicity, melting points, and partition coefficient?

2.3.S.2 Manufacturer

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

2.3.S.3 Characterization

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

Model QbR-QOS – IR Tablet (cont)

2.3.S.4 Control of Drug Substance

- What is the drug substance specification? Does it include all the critical drug substance attributes that affect the manufacturing and quality of the drug product?
- For each test in the specification, is the analytical method(s) suitable for its intended use and, if necessary, validated? What is the justification for the acceptance criterion?

2.3.S.5 Reference Standards

- How were the primary reference standards certified?

2.3.S.6 Container Closure System

- What container closure is used for packaging and storage of the drug substance?

2.3.S.7 Stability

- What drug substance stability studies support the retest or expiration date and storage conditions for the drug substance?

Model QbR-QOS – IR Tablet (cont)

2.3.P Drug Product

2.3.P.1 Description and Composition of the Drug Product

- What are the components and composition of the final product? What is the function of each excipient?
- Does any excipient exceed the IIG limit for this route of administration?
- Do the differences between this formulation and the RLD present potential concerns with respect to therapeutic equivalence

2.3.P.2 Pharmaceutical Development

2.3.P.2.1 Components of the Drug Product

2.3.P.2.1.1 Drug Substance

- Which properties or physical chemical characteristics of the drug substance affect drug product development, manufacture, or performance?

Model QbR-QOS – IR Tablet (cont)

2.3.P.2.1.2 Excipients

- What evidence supports compatibility between the excipients and the drug substance?

2.3.P.2.2 Drug Product

- What attributes should the drug product possess?
- 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?

2.3.P.2.4 Container Closure System

- What specific container closure attributes are necessary to ensure product quality?

2.3.P.3 Manufacture

- Who manufactures the drug product?
- What are the unit operations in the drug product manufacturing process?
- What is the reconciliation of the exhibit batch?

Model QbR-QOS – IR Tablet (cont)

- Does the batch formula accurately reflect the drug product composition? If not, what are the differences and the justifications?
- What are the in-process tests and controls that ensure each step is successful?
- What is the difference in size between commercial scale and exhibit batches? Does the equipment use the same design and operating principles?

2.3.P.4 Control of Excipients

- What are the specifications for the inactive ingredients and are they suitable for their intended function?

2.3.P.5 Control of Drug Product

- What is the drug product specification? Does it include all the critical drug product attributes?
- For each test in the specification, is the analytical method(s) suitable for its intended use and, if necessary, validated? What is the justification for the acceptance criterion?

Model QbR-QOS – IR Tablet (cont)

2.3.P.6 Reference Standards and Materials

- How were the primary reference standards certified?

2.3.P.7 Container Closure System

- What container closures are proposed for packaging and storage of the drug product?
- Has the container closure system been qualified as safe for use with this dosage form?

2.3.P.8 Drug Product Stability

- What are the specifications for stability studies, including justification of acceptance criteria that differ from the drug product release specification?
- What drug product stability studies support the proposed shelf life and storage conditions?
- What is the post-approval stability protocol?

Model QbR-QOS – ER Capsule (Additional Questions to IR Model)

2.3.P.2.3 Manufacturing Process Development

This section is optional for a non-critical dose drug formulated in a solution or an immediate release dosage form

- Why was the manufacturing process described in 2.3.P.3 selected for this drug product?
- How are the manufacturing steps (unit operations) related to the drug product quality?
- How were the critical process parameters identified, monitored, and/or controlled?
- What is the scale-up experience with the unit operations in this process?

2.3.P.3 Manufacture

If the Product is a NTI Drug or a Non-Simple Dosage Form

- In the proposed scale-up plan what operating parameters will be adjusted to ensure the product meets all in-process and final product specifications?
- What evidence supports the plan to scale up the process to commercial scale?

OGD Articles on Common CMC Deficiencies

- FDA OGD published a series of articles that provide an overview of common deficiencies cited throughout the CMC section of ANDA entitled, "Common Deficiencies in Abbreviated New Drug Applications," Aloka Srinivasan, et. al., *Pharmaceutical Technology*
  - Part 1 – Drug Substance, Jan 2010 (see Appendix)
  - Part 2 – Description, Composition, and Excipients, Aug 2010
  - Part 3 – Control of the Drug Product and Stability, Feb 2011
- ANDA deficiencies persisted despite full adoption of QbR, said OGD at GPhA Workshop in Oct 2010

QbR Lessons Learned*

- The positives
  - Product & Process Development summary in QbR-QOS provides insight into applicant's rationale for product design and development of manufacturing process
  - Justifications in QbR-QOS reduce the number of questions to applicant
  - Critical parameters identified in QbR-QOS enhance product and review assessment
  - Electronic QbR-QOS reduces transcriptional errors and saves documentation time
- The negatives
  - Limited product and process development information
  - Applicants have provided response to the QbR-QOS questions with no supporting information in Module 3
  - Lack of clear minimal justification for scale up process

* A. Srinivasah, OGD, FDA/GPhA Technical Conference, Oct 2010

Summary

- QbR is FDA OGD's first step toward providing the generic industry with a platform for sharing information, justifying specifications, and building quality into generic drugs
- OGD has published Model QbR-QOS for IR and ER, Commonly Deficiencies in ANDAs, and other guides to facilitate QbR implementation
- As of May 2010, 100% ANDAs were submitted with QbR-QOS with few exceptions
- Justification in QbR-QOS reduces the number of questions to applicant and/or review cycles
- Critical parameters identified in QbR-QOS enhance quality of product and review assessment
- However, ANDA deficiencies persisted despite full adoption of QbR

Appendix

QbR – Commonly Cited Deficiencies in ANDAs

Examples of Commonly Cited DS-Related Deficiencies in ANDAs

- The DMF related to the drug substance is deficient, and the holder has been notified. Please do not respond until the DMF holder has responded to all the deficiencies.
- The general properties section (S.1) of the ANDA fails to contain all relevant information. Please provide hygroscopicity, solubility as a function of pH, and melting range for the drug substance.
- Please revise the characterization section (S.3) to include full International Union of Pure and Applied Chemistry (IUPAC) names, structures, and classification of the impurities as process related and/or degradation products
- Please tighten or justify the proposed limits for the specified impurities based on ICH Q3A on *Impurities in New Drug Substances* recommendations, taking into account maximum daily dose (MDD).

Examples of Commonly Cited DS-Related Deficiencies in ANDAs (cont)

- Please include a suitable test and justified criterion for water content of the drug substance.
- Please add a quantitative control of the counter-ion in your drug substance.
- Based on the chiral nature of the drug substance, please include a control for the relevant enantiomer and diastereomers.
- In view of the chiral nature of the drug substance, please include a chiral identity.
- We recommend a chiral assay of your drug substance, since it is prone to racemization on storage.
- As validated methods were transferred from the DMF holder, please provide verification data to demonstrate that the methods can be performed at the proposed facility.

Examples of Commonly Cited DS-Related Deficiencies in ANDAs (cont)

- Please provide a USP cross-over study for the assay method to demonstrate the proposed method is equivalent or better than the compendial method.
- We recommend that a chromatographic method be proposed for the analysis of drug substance assay.
- Please revised the certificate of analysis to report impurity results as discrete numerical values instead of as "conforms." If results are below the method limit of quantitation (LOQ), please report as less than LOQ; and if results are below the limits of detection (LOD), please report as less than LOD or "none detected."
- Please provide LOD and LOQ for all specified impurities and residual solvents.
- Please provide information on all impurity reference standards used, including lot number source of the standard, and purity.