FDA’s Question-based Review (QbR): A Risk-based Pharmaceutical Quality Assessment Tool

Jennifer A. Maguire, Ph.D., OGD
Sharmista Chatterjee, Ph.D., ONDQA
CDER, FDA

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Discussion Points

• Why, What QbR?

• Sample Current QbR Questions

• Lessons Learned

• Next Steps
What is Quality?

“Our customers tell us we have a Quality problem, and we turn to our specs and our tolerances to see if they’re ‘right.’ ...Customers aren’t interested in our specs. They are interested in the answer to one simple question: Did the product do what I expected it to do? If the answer is yes, then it’s a quality product. If the answer is no, then it isn’t. At that point, our specs and tolerances aren’t ‘wrong.’ They’re just irrelevant!”
Where we were (2005)...

• Quality by end product testing
  – Limited or no development data
  – Little or no scrutiny on
    • Product design
    • Process design and scale-up

• Product specifications by test data from one/three batches
  – Little or no mechanistic understanding
  – “Overly conservative specifications”
    • Justify = Tighten
Genesis of Question-based Review (QbR)

  - Enhance and modernize regulatory processes
  - Improve overall pharmaceutical quality
  - Encourage risk-based approach that focus industry and agency’s attention on critical areas
- The ever increasing workload at OGD

(2005) Receipts of ANDAs

- ANDAs
- Employees

QbR as a Platform for Quality by Design (QbD)

• “The QbR will transform the CMC review into a modern, science and risk-based pharmaceutical quality assessment that incorporates and implements the concepts and principles of the FDA’s Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach and Process Analytical Technology initiatives.” per OGD website*

• It was OGD’s first step toward providing the generic industry with a platform for sharing, justifying and building quality into generic drugs.

What is Question-based Review (QbR)?

• A general framework for a science and risk-based assessment of product quality
  – Implemented by OGD for the CMC evaluation of ANDAs in 2007
  – QbR-QOS contains answers to standard questions and a summary of the Body of Data

• Asks the important scientific and regulatory review questions to
  – Comprehensively assess critical formulation and manufacturing process variables
  – Set regulatory specifications relevant to quality and product performance
  – Determine the level of risk associated with the design and manufacture of the product
A little more about QbR

• OGD’s QbR was designed with the expectation that ANDA applications would be organized according to the Common Technical Document (CTD), a submission format adopted by multiple regulatory bodies including the FDA. (ICH M4Q)

• Generic applicants are strongly recommended to submit their ANDAs in the electronic CTD format to facilitate the implementation of the QbR and to avoid undue delays in the approval of their applications.
ICH Common Technical Document

2.3 QOS
Summary of Critical CMC Elements

3.2 Body of Data
Detailed CMC Submission Package

Drug Substance (2.3.S / 3.2.S)

- General Information (2.3.S.1 / 3.2.S.1)
- Manufacture (2.3.S.2 / 3.2.S.2)
- Characterization (2.3.S.3 / 3.2.S.3)
- Control of Drug Substance (2.3.S.4 / 3.2.S.4)
- Reference Standards (2.3.S.5 / 3.2.S.5)
- Container Closure System (2.3.S.6 / 3.2.S.6)
- Stability (2.3.S.7 / 3.2.S.7)
Drug Product (2.3.P / 3.2.P)

- Description & Composition of the Drug Product (2.3.P.1 / 3.2.P.1)
- Pharmaceutical Development (2.3.P.2 / 3.2.P.2)
- Manufacture (2.3.P.3 / 3.2.P.3)
- Control of Excipients (2.3.P.4 / 3.2.P.4)
- Control of Drug Product (2.3.P.5 / 3.2.P.5)
- Reference Standards and Materials (2.3.P.6 / 3.2.P.6)
- Container Closure System (2.3.P.7 / 3.2.P.7)
- Stability (2.3.P.8 / 3.2.P.8)
Example: QbR-QOS

2.3.P.4 Control of Excipients

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

Compendial Excipients:
The following compendial excipients listed below do not exert critical functional roles in controlling the rate of MK release. Controls on these excipients will be based upon specifications defined by the USP/NF.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Manufacturer</th>
<th>Complies with USP/NF Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sugar Spheres NF, 25/30 mesh*</td>
<td>Sugar Inc.</td>
<td>Yes</td>
</tr>
<tr>
<td>Triethyl Citrate NF</td>
<td>Plasticizer Inc.</td>
<td>Yes</td>
</tr>
<tr>
<td>Butylated Hydroxyanisole NF</td>
<td>Antioxidant Inc.</td>
<td>Yes</td>
</tr>
<tr>
<td>Purified Water USP</td>
<td>In-House</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* The particle size of sugar spheres will comply with the labeled nominal size range of 25/30 mesh. This will ensure the sugar spheres have a uniform surface area for the manufacture of CR pellets which is critical for ensuring a uniform and reproducible MK drug release profile (see section 2.3.P.2.2).

The compendial excipient, ethylcellulose, exerts a critical functional role in controlling the rate of MK release. Furthermore, during product development, studies evaluating varying grades of ethylcellulose indicated that viscosity significantly impacted the rate of MK release through the CR membrane (see section 2.3.P.2.2). Therefore, to ensure a consistent MK release profile, as well as a consistent spray coating process, more stringent specifications than those defined by the USP/NF will be imposed, including controls on viscosity and degree of substitution.

Example QbR-QOS:
QbR Uses QOS for Regulatory Assessment

• Quality Overall Summary (Module 2.3):
  – 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
QbR is the Backbone of our Review Template

2.3.P.4  Control of Excipients [name, dosage form]
What are the specifications for the inactive ingredients and are they suitable for their intended function?
Firm’s Response: This can be adopted from the QbR-QOS provided from the firm.

Reviewer’s Comment:

2.3.P.5  Control of Drug Product [name, dosage form]
What is the drug product specification? Does it include all the critical drug product attributes?
Firm’s Response: This can be adopted from the QbR-QOS provided from the firm.

Reviewer’s Comment:

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?
Firm’s Response: This can be adopted from the QbR-QOS provided from the firm.

Reviewer’s Comment:
The QbR System facilitates a science and risk-based review of formulation and manufacturing variables. It helps applicants recognize what OGD considers critical and directs industry toward product and process understanding. It enables a consistent, comprehensive approach to the evaluation and serves dual purposes for both Applicants and FDA Reviewers.
Sample Current QbR-QOS Questions
ICH Q8 and Pharmaceutical Development

*Pharmaceutical development is a learning process*

- Describe both success and failures in product development
  - Quality by Design (QbD)

- Information from pharmaceutical development studies can be a basis for risk management (using Q9)

- How is the risk identified?
  - Critical formulation and process parameters are generally identified through an assessment of the extent to which their variation can impact the quality of the drug product
2.3.P.2 Pharmaceutical Development (1)

• 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?

• 2.3.P.2.1.2 Excipients
  – What evidence supports compatibility between the excipients and the drug substance?
2.3.P.2 Pharmaceutical Development (2)

• 2.3.P.2.2 Drug Product
  – What attributes should the drug product possess?
  – How was the drug 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?
Process Development Expectations (1)

• Demonstrate process understanding to show ability to scale up the process and execute it consistently.

  – Failing to identify critical process parameters (CPP) and the critical process steps indicates lack of understanding.

  – Unidentified critical steps or process parameters may be indicative of a poorly controlled manufacturing process and considered higher risk.
Process Development Expectations (2)

• Impact of raw material attributes and process parameters on in-process materials and end product.

• How much of this knowledge is translated in building effective control strategy?
  – To move the controls (upstream) to each stage of manufacturing instead of focusing mainly towards the final stage(s) of manufacturing.
2.3.P.2 Pharmaceutical Development

• 2.3.P.2.3 Manufacturing Process Development
  – 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?
Fundamental Questions

Will the product design ensure desired performance?

Will the applicant be able to scale-up to commercial size; and ensure comparable quality to bio batch(es)?

Will the applicant be able to manufacture the product with defined quality parameters over time?
Where we are…

• QbR
• Guidance
  – Q8R2 Pharmaceutical Development (Nov 2009)
  – Q9 Quality Risk Management (June 2006)
  – Q8, Q9 and Q10 Questions and Answers (May 2010)
  – MAPP 5016.1: Applying ICH Q8(R2), Q9, and Q10 Principles to CMC Review (Feb 2011)
• Example Pharmaceutical Development Reports
  – QbD for MR dosage forms (Dec 2011)
  – QbD for IR dosage forms (April 2012)
• Justify = Justify
Where we are...

- Encourage a QbD approach using science, regulations, and risk assessment
- Expect applicants to convey better product and process understanding
MaPP 5016.1

All applications should include the following minimal elements from ICHQ8(R2) Annex:

• Quality target product profile (QTPP).
• Critical quality attributes (CQAs) of the drug product.
• CMAs of the drug substance and excipients.
• Selection of an appropriate manufacturing process.
• Control strategy.
MaPP 5016.1

All applications should contain the following:

• Information that conveys an **understanding of the development** of the drug product and its manufacturing process.

• **Identification of those aspects** of drug substances, excipients, container closure systems, and manufacturing processes **that are critical** to product quality that support the safety and efficacy of the drug product.

• **Justifications for the control strategy.**
The QbR Experience in OGD

- The Positives -

- For Applicants:

  - Improved submission quality
  - Better connectivity between all parts of the submission
  - Development summary in QbR-QOS provides insight into sponsor’s rationale for product design and manufacturing choices
  - Creates a pathway for QbD by encouraging better product and process understanding
The QbR Experience in OGD

- The Positives -

• For the Office of Generic Drugs:
  – Focused review and product assessment
  – Clearly delineates scientific reviewer assessment from documentation
  – Justifications in QbR-QOS reduce the number of questions to sponsor
  – Common deficiencies are evident
Traditional versus QbR Submissions

Traditional

No PD
Assess spec
Summary
Body of Data

QbR
Assess QbD
Assess spec performance
Summary QbD
Body of Data QbD

Reviewer
Sponsor

Reviewer
Sponsor
The QbR Experience in OGD

- The Drawbacks -

- Still receive limited product and process development information to support development choices
- Applicants often provide responses to the QbR-QOS questions with no supporting information in Module 3
- Lack of clear rationale behind setting specifications
- Minimal justification of scale up process
- Yes/No and ‘Refer to DMF’ questions add little value
Recent Activities

• Efforts to harmonize approaches within CDER to ensuring drug product quality

• Working group is exploring the possibility of implementing a common QbR for both brand and generic drugs
  – An extremely collaborative effort
  – Areas of commonality outweigh those of dissimilarity
  – The QbR questions have been revised based on current expectations and lessons learned over the past six years
QbR for NDA Review

• Explore utilization of QbR approach for NDA review
  – Support adoption of a science and risk based review
  – Standardize review approach for both NDA and ANDA
  – Facilitate communication with all quality stakeholders

• Develop a QbR based review template for both NDA and ANDA
Initial Steps

• TAG (Technical Advisory Group) team set up including expert QbR users from OGD (Office of Generic Drugs) and review staff from ONDQA (Office of New Drug Quality Assessment) to explore feasibility of implementation of QbR for NDA review

• 3 recently approved NDA and 1 pending NDA were selected as a pilot

• Team review approach was implemented for each application

• During the review TAG team members did a gap analysis to identify QbR questions that warranted revision and also identify new questions.
Goals of the TAG Team

• One set of overarching questions that apply to both new and generic drug products

• High level questions that address the critical development aspects and manufacturing controls across various dosage forms
Overall Initial Assessment (1)

• The QbR Model:
  – Led to a more focused, faster review
  – Proved useful as a standardized review tool for ONDQA reviewers since ONDQA submissions are currently based on ICH CTD and include a QOS
  – Enhanced consistency
  – Differentiated the applicant’s response from the reviewer’s evaluation
  – Reviewers spend time only documenting critical scientific assessment with rationale
Overall Initial Assessment (2)

• Use of QbR questions that included risk assessment, QTPP, CQAs, critical properties of intermediates etc. contributed to:
  – Enhanced product and process understanding
  – Facilitated patient centric risk based evaluation
Outcome of Gap Analysis (1)

• Proposed a single Drug Product and Drug Substance QbR that is applicable for both NDA and ANDA
  – One set of overarching questions that apply to both new and generic drug substance and drug products
  – High level questions that address the critical development aspects across various dosage forms
  – Formatted based on ICH M4 QOS format, resulting in minimal change for applicants generating multi-ICH region dossiers
  – Minimized the number of questions while balancing the need for adequate inquiry to ensure drug product quality

• Current draft QbR includes 38 questions for drug product and 24 questions for drug substance
Outcome of Gap Analysis (2)

• Other documents created in addition to the QbR
  – A Quality Checklist
    • Captures initial QbR questions identified as “Yes/No” questions to highlight high risk or noteworthy aspects of an application
  – QbR Companion Documents (i.e., User Guides) for Drug Product and Drug Substance
    • Contains additional details for each QbR question, e.g.,
      – What the applicant should provide for each question
      – Points of Consideration for Reviewers

• ONDQA looking to pilot QbR in every review division
Sample Revised QbR Questions
What are the quality attributes of the finished product? Which quality attributes are considered critical quality attributes (CQAs)? For each CQA, what is the target and how is it justified?

Details in DRAFT Companion Document:
The following may be considered in response to this question:
• Relationship between the QA (quality attribute) and QTPP
• Adequacy of the proposed design target of the QA (preferably quantitative) that is supported by development data
• Risk-based justification to consider a QA as a CQA that is based on severity of harm with respect to clinical safety and/or efficacy and not on probability of occurrence
# Example Table to Document CQAs

<table>
<thead>
<tr>
<th>Quality Attribute</th>
<th>Is this a CQA?</th>
<th>QTPP Impacted</th>
<th>Design target</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assay</td>
<td>Yes</td>
<td>Dosage strength</td>
<td>90.0% to 110.0% of label claim</td>
<td>USP limits, Assay is related to dose delivered to patient; thus, for efficacy, needs to comply with the limits established for drug content.</td>
</tr>
<tr>
<td>Dissolution</td>
<td>Yes</td>
<td>Pharmacokinetic profile</td>
<td>&gt; 77% dissolved in 30 min</td>
<td>To comply with requirements of consistent in-vivo exposures</td>
</tr>
<tr>
<td>Water content</td>
<td>No</td>
<td></td>
<td></td>
<td>Drug substance A is not hygroscopic, hence no risk of water related adverse impact on quality</td>
</tr>
</tbody>
</table>
Design of Drug Product (2)

What aspects of the formulation were identified as potentially high risk?

Details in DRAFT Companion Document:
The following may be considered in response to this question:
• Use of risk assessment approach to rank or prioritize formulation variables, in the intermediates and final products, based on their potential effects on product CQAs
• Any special considerations based on the product characteristics (for example: low dose formulations, extended release, phase separations)

Example presentation of formulation risks (show risk level in each cell as low, medium or high)

<table>
<thead>
<tr>
<th>Drug Product CQAs</th>
<th>Eudragit L100-55 Level</th>
<th>SLS Level</th>
<th>HPMC 2208 Level</th>
<th>HPMC 2208 Viscosity</th>
<th>Magnesium Stearate Level</th>
<th>Opadry I Level (non-functional)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablet Size</td>
<td>Medium</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Assay</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Content Uniformity</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Dissolution</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Medium</td>
<td>Low</td>
</tr>
</tbody>
</table>
**Evaluation of Control Strategy**

What is the proposed Control Strategy for the drug product manufactured at commercial scale? What are the residual risks upon implementation of the control strategy at commercial scale?

**Sample Control Strategy Table**

<table>
<thead>
<tr>
<th>Drug Product CQA</th>
<th>Incoming materials</th>
<th>Special environmental controls</th>
<th>Process parameter controls</th>
<th>In-process controls (measurements)</th>
<th>Release Testing</th>
<th>Residual risks or Potential failure modes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identity</td>
<td>ID testing on drug substance</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Tested at release</td>
<td>None</td>
</tr>
<tr>
<td>Assay</td>
<td>Drug substance purity</td>
<td>Manufacturing vessels and lines purged with nitrogen to reduce degradation</td>
<td>Blend Time Press Speed</td>
<td>In-process core tablet assay measured by NIR</td>
<td>None</td>
<td>Finished product having tablets with unacceptable assay</td>
</tr>
</tbody>
</table>
### Draft List of Noteworthy Elements

<table>
<thead>
<tr>
<th>#</th>
<th>Checklist</th>
<th>Yes</th>
<th>No</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Drug substance overage</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>End of Phase II/Pre-NDA Agreements</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Narrow Therapeutic Index drug?</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>USAN name assigned?</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Design space in terms of Formulation variables</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>Design space in terms of process variables</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>Analytical Procedures Design Space</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>Real Time Release Testing (RTRT) Proposals for regulatory flexibility</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>9.</td>
<td>Nanomaterials (e.g. drug substance, excipients, carriers etc)</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>10.</td>
<td>Non-compendial analytical procedures for drug products</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>11.</td>
<td>Botanical</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>12.</td>
<td>SPOTS (Special Products On-line Tracking System)</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>13.</td>
<td>Non-compendial analytical procedures for excipients</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>14.</td>
<td>Excipients of human or animal origin</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>15.</td>
<td>Novel excipients</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>16.</td>
<td>Process Analytical Technology (online/inline/at line) used for real time decisions</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>17.</td>
<td>Genotoxic structural alerts</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>18.</td>
<td>Citizen Petition and/or Control Correspondence Linked to the Application</td>
<td></td>
<td>x (closed)</td>
<td></td>
</tr>
<tr>
<td>19.</td>
<td>Hold times exceeding 30 days</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>20.</td>
<td>In-use stability studies</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>21.</td>
<td>Use of models for release including plans for model maintenance</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>22.</td>
<td>Comparability protocols</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>23.</td>
<td>Continuous Manufacturing</td>
<td></td>
<td>x</td>
<td></td>
</tr>
</tbody>
</table>
Summary

• QbR is a “new” quality assessment system that focuses on critical pharmaceutical quality attributes.
• It has transformed CMC review into a modern, science- and risk-based pharmaceutical quality assessment system
• It is a pathway for demonstrating product and process understanding
• Increased transparency
  – Facilitates risk-based communications
Where we are going...

• Revising QbR to further encourage QbD and to standardize approaches / expectations in the Office of Pharmaceutical Quality
  – Scientific justification
  – Risk Assessment
  – Understanding, understanding, understanding

• Companion documents to accompany revised QbR

• Considering additional QbR questions for complex dosage forms

• Standardizing submission quality
  – Acceptability of an Application for Filing Checklist

• Meetings / Workshops / Training