POLICY AND PROCEDURES

OFFICE OF PHARMACEUTICAL SCIENCE

Chemistry Review of Question-based Review (QbR) Submissions

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PURPOSE

- This MAPP clarifies how drug substance and drug product reviewers in the Office of Pharmaceutical Science (OPS) should assess new drug applications (NDAs), abbreviated new drug applications (ANDAs), or Type II DMF submissions that follow a Question-based Review (QbR) format in conjunction with the International Conference on Harmonisation (ICH) guidance *M4Q: The CTD – Quality*, (ICH M4Q) Module 2.

- The MAPP may also be used as a guide for the assessment of submissions that do not follow the QbR format.

BACKGROUND

- QbR was developed for the assessment of generic drug applications (i.e., ANDAs) in response to FDA's initiative for Pharmaceutical cGMP's for the 21st Century. It uses QbR experiences from other CDER components (e.g., CDER MAPP 4000.4 *Clinical Pharmacology and Biopharmaceutics Review Template*), as well as other regulatory authorities (e.g., Health Canada) that use the quality overall summary (QOS) as a foundation for the primary chemistry review document.

- QbR is a general framework, recommended as a submission format by the draft guidance for industry *ANDA Submission - Content and Format of Abbreviated New Drug Applications*, for a science and risk-based assessment of product quality. It contains important scientific and regulatory review questions related to product and process design and understanding, product performance, and control strategy.

- The QbR format was fully implemented for assessment of ANDAs in 2007. Revised questions were developed in 2012 and 2014 to better capture quality-by-design (QbD) expectations, incorporating both internal and external stakeholder feedback (see Attachments 1 and 2).

- Although implemented for ANDAs, the QbR format could also be used as a basis for developing a structured QOS for NDAs.

- There are multiple benefits realized by using a QbR approach.

    - QbR provides a structured QOS submission format for applicants to provide a relevant, knowledge-rich summary of pertinent review aspects to allow for more effective assessment by regulators.

    - QbR reduces summarization and unnecessary documentation by the reviewer because the applicant-generated response to the QbR can be used as a starting point for the review document. This allows the reviewer to focus more effort on his/her assessment and to include relevant information from the applicant in the review document.

    - The QbR leads to a more focused assessment, shifting emphasis of assessment to areas that are most likely to affect product quality.

    - Use of QbR makes it easier for an independent reader to distinguish the reviewer's comments from information taken directly from the application.

    - Use of the QbR model provides support for a more efficient streamlined review for additional cycles.

    - The QbR model is based on a series of focused questions divided into three broad categories: (1) drug substance quality standard, (2) drug product quality standard, and (3) process understanding and plans for proposed scale-up of drug manufacturing. Therefore, it provides a framework for scientific collaboration, increased communication, and use of team-based review strategies.

- QbR questions follow the ICH M4Q common technical document (CTD) format and the questions relate to all pertinent sections of the application. The high-level questions apply uniformly to all dosage forms, yet allow applicants to include dosage form-specific details, as applicable. Additionally, the inclusion of questions on control strategy allows the applicant to present their overall control strategy, which is currently not co-located in the CTD format.

- The QbR model is not intended to replace the detailed supportive information in CTD Module 3 (found in 3.2 Body of Data per ICH M4Q). The QbR model only provides a format that helps applicants convey aspects of the application (e.g., development history, risk management, control strategy, and scale-up plans) in the QOS in CTD Module 2.

- Companion documents (see attachments 3 and 4) are available to help the reviewers clarify the information that should be provided by applicants in QbR submissions.

POLICY

- OPS drug substance and drug product reviewers will use a QbR review template when evaluating NDAs, ANDAs, and DMFs that are submitted using a QbR format.

- Although the QbR questions capture all of the important scientific and regulatory questions, upon review of a submission, the reviewer may still communicate with the applicant to ask additional questions (via the appropriate route: information request, complete response, easily correctable deficiency, etc.). For example, the reviewer may ask the applicant to clarify information or provide missing information.

- OPS drug substance and drug product review divisions may choose to use a QbR review template for applications that are not submitted in the QbR format.

RESPONSIBILITIES AND PROCEDURES

- Drug Substance and Drug Product Reviewers will:

    - Perform the assessment of submissions that include a QbR using the current version of the appropriate QbR review template.

    - Extract and deduce the applicant's response from the submission and include a brief summary in the review if a QbR is not provided in the submission.

    - Use the QbR companion documents as review guides to complete QbR reviews (see attachments 3 and 4). The companion documents provide examples of information that can be submitted to answer the QbR questions; however, the examples are for illustrative purposes only and should not be considered templates.

    - Read and consider all relevant information submitted by the applicant (e.g., QOS and body-of-data sections) while preparing the primary review; and be mindful that information submitted in the QOS (Module 2) should not contradict information provided in the body of data (Module 3).

    - As applicable, group together QbR questions based on common topics (e.g., product development or container-closure system). For grouped questions, the reviewer(s) will include one summary of applicant submission information and

one reviewer assessment.

- Indicate "Not Applicable" for any QbR question that is not relevant to the drug product or drug substance being evaluated.

REFERENCES

ICH M4Q: The CTD - Quality
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073280.pdf

Guidance for Industry (DRAFT) ANDA Submissions - Content and Format of Abbreviated New Drug Applications
(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM400630.pdf)

EFFECTIVE DATE

This MAPP is effective upon date of publication.

ATTACHMENT 1: QbR QUESTIONS - DRUG SUBSTANCE

1. What are the nomenclature, molecular structure, molecular formula, CAS number, molecular weight, and pharmacological class of the drug?

2. What are the physical, chemical, biological and, if applicable, mechanical properties including physical description, pKa, chirality, polymorphism, aqueous solubility as a function of pH, hygroscopicity, melting point(s), and partition coefficient?

3. Who manufactures the drug substance? List each participant and facility involved in drug substance manufacturing/testing activities and clearly state their function. List the date of the last FDA inspection of each facility involved and the result of the inspection. Has the manufacturer addressed all concerns raised at the FDA inspection?

4. What is the flow diagram of the manufacturing process that shows all incoming materials, reagents, reaction conditions, and in process controls and, if appropriate, any reprocessing/reworking/alternative processes?

5. If applicable, what on-line/at-line/in-line monitoring technologies are proposed for routine commercial production that allows for real-time process monitoring and control. Provide a summary of how each technology was developed.

6. What is (are) the starting material(s) for the manufacturing process and how would changes in starting material quality and/or synthesis/source be controlled to minimize adverse effects on the drug substance quality?

7. What are the starting material specifications and how are they justified?

8. What are the specifications for reagents, solvents, catalysts, etc.? What are the critical attributes for these materials that impact the quality of the final drug substance?

9. What are the critical process parameters (CPPs) and how are they linked to drug substance quality?

10. What are the in-process controls (IPCs)/tests associated analytical methods and acceptance criteria for each control?

11. What are the specification(s) for the intermediate(s)?

12. What process validation and/or evaluation information is provided, if any?

13. What development and scale up information supports the commercial process and control strategy?

14. How is the drug substance structure characterized?

15. What are the potential impurities (e.g., related substances, degradants, inorganic impurities, residual solvents) in the drug substance? Which of these impurities are potentially genotoxic?

16. What is the drug substance specification and what is the justification? Does the specification include all of the drug substance critical quality attributes (CQAs)?

17. For each test in the specification, provide a summary of the analytical procedure(s) and, if applicable, a summary of the validation or verification report(s).

18. How do the batch analysis results compare to the proposed specification? Provide a summary of the batch analysis results.

19. What is the proposed control strategy for the drug substance manufactured at commercial scale? What are the residual risks upon implementation of the control strategy at commercial scale?

20. How are the drug substance reference standards obtained, certified, and/or qualified?

21. What container closure system(s) is proposed for commercial packaging of the drug substance and how is it suitable to ensure the quality of the drug substance during shipping and storage?

22. What are the stability acceptance criteria? If applicable, what is the justification for acceptance criteria that differ from the drug substance release specification?

23. What is the proposed retest period for the drug substance? What drug substance stability data support the proposed retest period and storage conditions in the commercial container closure system? How does statistical evaluation of the stability data, if any, and any observed trends support proposed retest period?

24. What are the post-approval stability protocols and other stability commitments for the drug substance?

ATTACHMENT 2: QbR QUESTIONS - DRUG PRODUCT (CHEMISTRY)

1. What is the description of the proposed commercial drug product? What are the components and composition of the final drug product as packaged and administered on both a per unit dose and %w/w basis? What is the function(s) of each excipient?

2. Does any excipient exceed the FDA inactive ingredient database (IID)[1] limit for this route of administration calculated based on maximum daily dose? If so, please justify.

3. If applicable, what are the differences between this formulation and the listed/reference listed drug (RLD) formulation?

4. For 505(b)(1) applications, what is the rationale for selecting the proposed dosage form for the drug product? For 505(b)(2) and 505(j) applications, what are the characteristics of the listed/reference listed drug product? What is the quality target product profile (QTPP) of the finished product based on the proposed indication and patient population? How is the QTPP justified?

5. What are the 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?

6. What is the approach for meeting the CQAs related to clinical performance? If applicable, what in vitro bio-performance evaluations (i.e., dissolution method, flux assay, etc.) were used during pharmaceutical development to ensure clinical performance?

7. What are the physical, chemical, biological and, if applicable, mechanical properties of the drug substance, including physical description, pKa, chirality, polymorphism, aqueous solubility (as a function of pH), hygroscopicity, melting point(s), and partition coefficient and, when available, BCS classification?

8. What is the drug substance specification used to accept the incoming drug substance batches and how is it justified? For each test in the specification, provide a summary of the analytical procedure(s) and, if applicable, a summary of validation or verification report(s).

9. What evidence supports excipient-drug substance compatibility and if applicable, excipient-excipient compatibility?

10. What is the rationale for the excipient selections?

[1] To search for an ingredient, visit Web page http://www.accessdata.fda.gov/scripts/cder/iig/index.Cfm.

11. What aspects of the formulation were identified as potentially high risk to the drug product performance?

12. What formulation development studies were conducted? What attributes of the drug substance, excipients and in-process materials were identified as critical and how do they impact the drug product CQAs?

13. How does the proposed commercial formulation differ from the formulations used during bioequivalence and/or clinical studies? What is the rationale for the formulation change? What biopharmaceutics evaluations (comparative dissolution, bioequivalence studies, biowaivers, etc.) support the formulation changes and link the development formulations to the proposed commercial formulation?

14. What is the rationale for selecting this manufacturing process for the drug product?

15. What is the potential risk of each process step to impact the drug product CQAs and how is the risk level justified?

16. For each of the potentially high risk manufacturing unit operations:

    a) What input material attributes and process parameters were selected for study and what are the justifications for the selection?

    b) What process development studies were conducted? Provide a summary table listing batch size, process parameter ranges, equipment type and estimated use of capacity.

    c) What process parameters and material attributes were identified as critical and how do they impact the drug product CQAs?

    d) How were the process parameters adjusted across lab, pilot/registration and commercial scale? What are the justifications for any changes?

17. If applicable, what online/at-line/in-line monitoring technologies are proposed for routine commercial production that allows for real-time process monitoring and control? Provide a summary of how each technology was developed.

18. What specific container closure system attributes are necessary to ensure drug product integrity and performance through the intended shelf life? If applicable, what are the differences in the container closure system(s) between this product and the RLD?

19. How was the container closure systems(s) including bulk containers, qualified for suitability (protection, compatibility, safety and performance)?

20. When applicable, what microbiological attributes were evaluated on the finished product?

21. If applicable, what supportive data demonstrates the compatibility of the drug product with the means of administration (e.g., additives and/or diluents, other co-administered drugs, dosing device)?

22. Who manufactures the drug product? List each participant and facility involved in drug product manufacturing/testing activities and clearly state their function. List the date of the last FDA inspection of each facility involved and the result of the inspection. Has the manufacturer addressed all concerns raised at the FDA inspection?

23. What is the commercial batch formula and how does it differ from the registration batch formula? Provide justifications for any differences?

24. What is the flow diagram of the manufacturing process that shows all incoming materials, processing steps/unit operations, and in-process controls?

25. What is the detailed process description including process parameters, material attributes of raw materials and intermediates, equipment type, batch size, in-process controls including acceptance criteria and any proposed reprocessing?

26. What in-process sampling strategies and methods are used to monitor in-process material attributes that have a potential to affect quality?

27. What are the in-process test results for each process step of the registration batch(es)? What are the differences, if any, in the in-process controls for the registration batch(es) and the intended commercial batches? What are the justifications for these differences?

28. What are the excipient specifications and how are they justified? How do the proposed acceptance criteria for the material attributes of the excipients ensure the quality of the final drug product?

29. What is the drug product specification, what is the justification, and how is it linked to the product performance and patient safety? Does the specification include all the CQAs for the drug product?

30. For each test in the specification, provide a summary of the analytical procedure(s) and, if applicable, a summary of the validation or verification report(s).

31. How do the batch analysis results compare to the proposed specification? Provide a summary of the batch analysis results.

32. What are the drug product degradants? For each degradant, what is the structure, chemical name, origin, and mechanism of formation? How are the proposed limits justified and/or qualified for safety based on nonclinical studies? What is the control strategy for the potential drug product degradants?

33. 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?

34. How were the drug product reference standards obtained, certified and/or qualified?

35. What container closure system(s) is proposed for commercial packaging of the drug product? What is the specification?

36. What is the stability specification? If applicable, what is the justification for acceptance criteria that differ from the drug product release specification?

37. What is the proposed shelf life for the drug product? What drug product stability studies support the proposed shelf life and storage conditions in the container closure system? How does statistical evaluation of the stability data and any observed trends support the proposed shelf life?

38. What are the post-approval stability protocol and other stability commitments for the drug product?

ATTACHMENT 3: DRUG SUBSTANCE QbR REVIEW COMPANION DOCUMENT

The writable PDF companion document is attached to this MAPP. Click the paper clip icon, called "Attachments: View file attachments," on the left side of this PDF document. Then select the file called "QbR DS companion document."

ATTACHMENT 4: DRUG PRODUCT QbR REVIEW COMPANION DOCUMENT

The writable PDF companion document is attached to this MAPP. Click the paper clip icon, called "Attachments: View file attachments," on the left side of this PDF document. Then select the file called "QbR DP companion document."