Question-based Review (QbR) under the Integrated Review Approach

Damaris Maldonado

Review Chemist

Office of Lifecycle Drug Products/ OPQ / CDER

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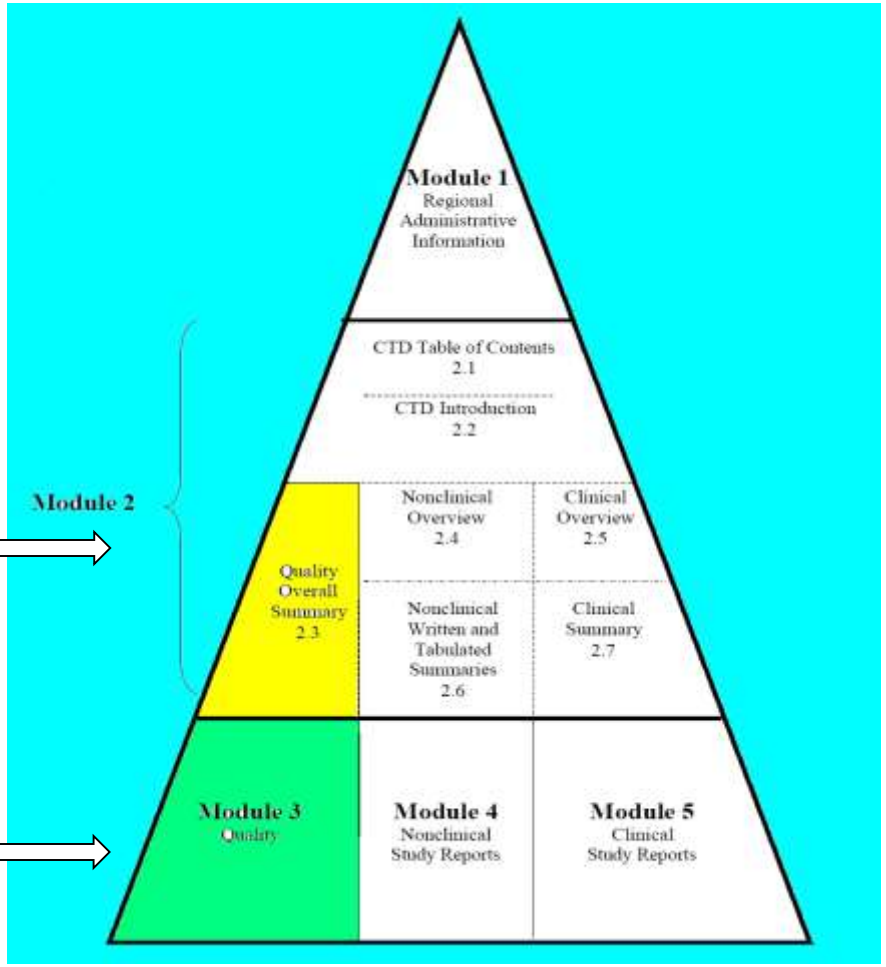
Outline

- Definition and Background of the Question based Review
- Benefits of QbR
- Update on current activities related to QbR from the CMC Review Perspective
- Integrated Quality Assessment
- Future of QbR and regulatory submissions

ICH Common Technical Document

QOS
Summary of Critical CMC Elements

Body of Data
Detailed CMC Submission Package



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Question based Review

- A general format that helps applicants convey aspects of the application (i.e., development history, control strategy and scale up plans) in Module 2 of ICH M4Q Common Technical Document
- Provides a summary of the chemistry, manufacturing and controls section of the application as promulgated in § 314.50(c)(2)(iv) and § 314.94(a)(11).

QbR Background

- Implemented in 2007
- Practical implementation of FDA's cGMPs for the 21st Century.
- Incorporates essential questions for ensuring drug product quality
- Revised to include questions that better capture quality-by-design (QbD) expectations

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- **WHY QbR?**

Why QbR

- **Focus industry and Agency attention on critical areas.**

- **Initiates a dialogue between Industry and the reviewer.**

Why QbR? (cont.)

- Timely communication of deficiencies or issues
- Enhanced ability to predict quality and performance

Why QbR? (cont.)

- Provides for an efficient review of low risk products and an in-depth review of more complex dosage forms and NTI drugs.
- Incorporates Quality by Design

Leveraging the Past For the Future

CDER's Office of Pharmaceutical Quality (OPQ)

- A single unit in CDER dedicated to drug product quality (new drugs, generic drugs and OTC drugs)
- Strategically organized to align review, inspection, and research functional areas

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CDER's OPQ

OPPQ

Office of Pharmaceutical Quality

Office of Program and Regulatory Operations

Office of Biotechnology Products

Office of New Drug Products

- ***API***
- ***Biopharm***

Office of Lifecycle Drug Products

- ***Post-Marketing (NDA) & ANDA***

Office of Process and Facilities

Office of Testing and Research

Office of Surveillance

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The Integrated Quality Assessment

Under OPQ a team-based approach is used to perform the quality assessment of an application based on risk management principles.

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The Integrated Quality Assessment

The team consists of:

- drug substance reviewers
- drug product reviewers
- process reviewers
- facility reviewers (including ORA investigators)
- other technical advisors as needed

Application Technical Lead (ATL)
- oversees the technical content

Business Process Manager (BPM)
- manages the process

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IQA Kick-Off Meetings

- Discuss Roles and Responsibilities
- Goal Dates Communicated
- Identified High Risk Areas are Shared in the Team
- Critical Issues Raised
- Plan for Inspections

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Team-based Integrated Quality Assessment

- Consolidated IQA Template
  - Contains:
    - Guiding questions for each discipline reviewer
    - Executive Summary
    - Initial and Final risk assessments
    - Consolidated comments from the review team

Team-based Integrated Quality Assessment

Examples of the Reviewer's Guiding Questions in P.2

- ***What physicochemical properties of the drug substance may impact drug product performance?***
- ***What evidence supports excipient-drug substance compatibility and, if applicable, excipient-excipient compatibility?***
- ***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?***

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Frequently Asked Questions

Question #1:

Is it mandatory to provide answers to all QbR questions?

Response:

No. QbR is a guide designed to aid in the preparation of the Quality Overall Summary.

Question #2:

Should we duplicate the response to the common questions related to the drug substance properties in Sections 2.3.S and 2.3.P?

Response: Yes. It facilitates the review of the drug substance specifications in sections S.4 as well as the review of the P.2 Development Report in light of the drug substance physicochemical properties.

Expectations - Case Studies

Product Development - Drug A Applicant A (Adequate)

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

Drug Substance Attributes	Conclusion/Remarks
Aqueous solubility (mg/mL) as function of pH	DS A shows pH dependent solubility. DS A was found to be highly soluble in OGD recommended dissolution media.
pH stability	Forced degradation data indicates that the drug substance is highly sensitive to alkali medium (0.1N NaOH).
Particle size distribution	Particle size distribution of the drug substance was observed in the range of 13 µm to 19 µm for d (0.5) and 39 µm to 45 µm for d (0.9).
Bulk density/Tapped density/ Flow ability	**Bulk density and Tapped density were observed in a range of 0.34 g/mL to 0.42 g/mL** **Values for HR and CI indicate very poor flow of the drug substance. Hence these properties may be critical for the manufacturing process.**
Polymorphism	DS A does not show polymorphism.
Hygroscopicity	**DS A is hygroscopic in nature. Precautions are required during drug product manufacture**
Melting point/range	Melts at about 230± 2°C with decomposition.
Specific Rotation	Between -19.4° and -22.0°
Photosensitivity	Non-photosensitive

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Applicant A (cont.)

Mechanical & Rheological Properties

- Hausner Ratio and CI indicate poor flow.
- Bulk density and tapped density were observed in the range of 0.34 g/ml to 0.42 g/ml

Hygroscopicity

- DS A is hygroscopic. Precautions are required during manufacture.

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Product Development - Drug A Applicant B (Inadequate)

- What are the physicochemical properties including physical description, melting range, pKa, UV absorption, potential isomerism?
  - Physical Description
  - Solubility
  - Polymorphism
  - Isomerism

Product Development - Drug B Applicant A (Adequate)

- **Polymorphic forms:** DS B exhibits polymorphism and the possible polymorphs are Form I, Form II, Form III, Form IV, Form V and Form VI.

- **Identification by XRD:** The X-ray diffractogram of the test sample matches Form III working standard with respect to the 2θ values observed.

- **Observation:** The lead formulation was stressed for a period of 6 months under accelerated conditions and tested using XRPD. The study results did not show any change in polymorphic characteristics as evidenced from the 2θ angles presented .

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Product Development - Drug B Applicant B (Inadequate)

PHYSICOCHEMICAL CHARACTERISTICS

- Solubility
- Hygroscopicity
- Photostability
- Intrinsic dissolution rate
- Compression Properties

} Polymorphism??

- Excipient compatibility study

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Cocoa Butter Has Polymorphs!

FORM & MELTING POINT	DESCRIPTION & PROPERTIES
I 17.3˚C	**BOTH SOFT AND CRUMBLY WITH NOTICEABLE BLOOMING** Form I is produced by cooling melted chocolate rapidly (e.g. by putting it in the freezer). Form II is produced by cooling melted chocolate at 2˚C per minute. Form I crystals also gradually become Form II after a short time of freezing temperature storage.
II 23.3˚C	
III 25.5˚C	**BOTH FIRM, BUT DON'T GIVE A GOOD 'SNAP', & SHOW SOME BLOOMING** Form III is produced by cooling at 5-10˚C. Form II becomes Form III after storage at low temperatures above freezing. Form IV is produced by allowing melted chocolate to cool at room temperature; Form III also becomes Form IV after storage at room temperature for some time.
IV 27.3˚C	
V 33.8˚C	**SHINY, SMOOTH TEXTURE, GOOD 'SNAP', AND MELTS IN THE MOUTH** Formed by tempering chocolate slowly at room temperature. Most desirable!
VI 36.3˚C	**HARD AND MELTS SLOWLY IN THE MOUTH, SHOWS SOME BLOOMING** Can't be formed from melted chocolate - can only be formed after solid, tempered chocolate has rested for at least 4 months.

INCREASED STABILITY & DENSITY

Examples of polymorph/crystal transitions

- Ritonavir
- Rotigotine
- Irbesartan

Product Development
Drug Substance Attributes

- Solubility
- Stability
- Compaction, bulk and tapped density
- Particle size, shape, porosity
- Flow properties of the micronized drug substance
- Hygroscopicity
- Solid State Crystal Properties
- Melting Point
- Organoleptic Properties

Summary

- Applicant should show an understanding of:
  - The principles, materials, technology, scalability and potential sources of variation.
  - Potential interactions between the formulation and the process.

Future Direction: Lifecycle Management

Future Direction – Lifecycle Management

QbD =

Product Understanding	+	Process Understanding
• Product Design • Product Quality Attributes • Desired Product Performance • Product Specifications		• Process Design • Process Parameters • Process Performance • Process Controls

The Knowledge Base

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Lifecycle Management

- The integrated **Knowledge Base** allows for:
  - Greater parity in the regulatory oversight
  - Clearer identification of product risks
  - Application of uniform quality standards
  - Quickly addressing quality problems
  - Overall efficiency improvements

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Conclusion

The Goal is Drug Product Quality

- The Agency is committed to adapting and changing its organizational structure and processes to best respond to ongoing challenges
  - Increasing drug product complexity
  - New user fee requirements (GDUFA and BsUFA)
  - Increasing globalization of facilities
  - Drug Shortages
  - Drug Recalls

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References/Resources

OPQ Questions

CDER-OPQ-Inquiries@fda.hhs.gov

e-CTD Questions

esub@fda.hhs.gov

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Acknowledgements

- Susan Rosencrance
- Robert Iser

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References/Resources

- **MaPP 5015.10**

http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM423752.pdf

- **ICH M4Q: The CTD - Quality**

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073280.pdf

References/Resources

- **QbR questions for Terminally Sterilized & Aseptically Filtered products**

  http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm120971.htm

- **Guidance for Industry (DRAFT) ANDA Submissions - Content and Format of Abbreviated New Drug Applications**

  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM400630.pdf

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Thank you for your attention!

Questions?

surveymonkey.com/r/GDF-D1S6