Future of Question-based Review and Regulatory Submissions

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CMC Regulatory Submissions – The future is now!

• Functional
  – Electronic
  – Structured
  – Searchable

• Flexible
  – Dosage-form specific
  – Facilitate OPQ Team Quality Assessment

• High Quality
CMC Regulatory Submissions – The future is now!

• Lifecycle
  – Submission, Product, Sites
  – Delineation of Established Conditions

• Risk & Science Based

• Knowledge Management
  – Not just data…
  – Cohesive
  – Comprehensive & Concise?
  – Experience and Prior Knowledge Sharing
  – Gain Knowledge - Update Risks, Controls, etc.
Pharmaceutical cGMPs for the 21st Century — A Risk-Based Approach: Second Progress Report and Implementation Plan

- Encourage the early adoption of new technology advances...
- Facilitate modern quality management techniques, including implementation of quality systems approaches...
- Encourage implementation of risk based approaches that focus industry and Agency attention on critical areas.
- Ensure that regulatory review, compliance and inspection policies are based on state-of-the-art pharmaceutical science.
- Enhance the consistency and coordination…by further integrating enhanced quality systems approaches into the Agency’s business processes and regulatory policies concerning review and inspection activities.
Sharing The Load…

• FDA can…
  – Provide Transparency & Clear Expectations
    • Template
    • Guidance
    • Workshops

• Industry can…
  – Provide High Quality Submissions
  – Provide Feedback / Lessons Learned
  – Openness to “try something new”
Office of Pharmaceutical Quality (OPQ)

Mission
The Office of Pharmaceutical Quality assures that quality medicines are available to the American public

Vision
The Office of Pharmaceutical Quality will be a global benchmark for regulation of pharmaceutical quality
Benefits of OPQ

• One Quality Voice
  – Review/Inspection/Monitoring (Surveillance)
• Clear Communication with Stakeholders
• Use of Similar Quality and Risk language
• Common Quality Standards
• Lifecycle & Knowledge Management
• Team Based Quality Assessment
• Risk Based Decisions
• Science / Expertise Driven
• Effective Quality Assessment
How is QbR a step in the right direction?
How is QbR a step in the right direction?

• Clear Communication
• Use of Similar Language
• Common Quality Standards
  – Consistent with the current quality-by-design (QbD) paradigm
  – Congruent with risk management approaches
  – Encourages justification for choices made throughout the development and manufacture
  – Increases transparency in the applicant’s thought processes
How is QbR a step in the right direction?
Benefits to Reviewers

• Team Based Quality Assessment
• Risk Based Decisions
• Effective Quality Assessment
  • Guides reviewers for consistent and comprehensive quality evaluation
  • Includes **level of risk** associated with design and manufacture of the product
  • Provides **consistency** among the submissions
  • Leads to more focused and **efficient** review
How is QbR a step in the right direction?

Benefits to Applicants

- Clear Communication with Stakeholders
- Effective Quality Assessment
- Common Quality Standards
  - Standardizes submission expectations
  - Provides clear expectations
  - Provides an opportunity to address critical questions about the product’s design, failure risk, and manufacturing controls from both a performance and patient usability perspective.
  - Reduces in questions from the reviewers during the review cycles
  - Use as an internal communication tool (e.g., reg. affairs with development, etc.)
Using QbR Approaches for NDA Review – FDA Pilot
QbR for Review of New Drug Applications (NDA)

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

• Develop a QbR based review template for both NDA and ANDA
  – Supports implementation of integrated team based review within OPQ (Office of Pharmaceutical Quality)
QbR for NDAs

• Initial Steps – OPS TAG (Technical Advisory Group) team set up
  – Included expert QbR users from Generic Drug Chemistry and review staff from ONDQA (Office of New Drug Quality Assessment) to explore feasibility of implementation of QbR for NDA review
  – Develop one set of overarching QbR questions that apply to both new and generic drug products
Lessons Learned – QbR Review of NDAs

- Led to a more focused, faster review
- Proved useful as a standardized review tool
- Enhanced consistency
- Differentiated the applicant’s response from the reviewer’s evaluation

- 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
Lessons Learned – QbR Review of NDAs

• Developed a single set of high level questions that address the critical development aspects across various dosage forms & applicable for new and generic drug substance and drug products

• Additional review tools developed:
  – A Quality Checklist – “flag” high risk or noteworthy aspects of an application
  – QbR Companion Documents - Contains additional details for each QbR question, e.g.,
    – What the applicant should provide for each question
    – Points of Consideration for Reviewers
QbR – NEXT STEPS

• Refine questions based on reviewer and industry feedback - Revised DS and DP QbR Questions

• QbR questions for Terminally Sterilized & Aseptically Filtered products

• Lessons Learned from FDA Center for Veterinary Medicine QbR Submission and Review Templates

• Look at dosage form or unit operation specific considerations
QbR – NEXT STEPS

• Gain more QbR experience among CDER reviewers from use of QbR for review pilots (e.g. NDAs)

• Revise Internal Procedures and Training Guides

• Explore QbR-QOS for integrated review, as part of OPQ

• Continue dialog with external stakeholders (e.g., PhRMA, GPhA, etc.) and other regulatory agencies (e.g. EMA, PMDA, etc.)
2.3.S DRUG SUBSTANCE

2.3.S.1 Description and Composition

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, hygroscopcity, melting point(s), and partition coefficient?

2.3.S.2 Manufacture

2.3.S.2.1 Manufacturer

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?

2.3.S.2.2 Description of the Manufacturing Process and Controls

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

5. 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.
2.3.S DRUG SUBSTANCE

2.3.S.2.3 Control of Materials

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?

2.3.S.2.4 Control of Critical Steps and Intermediates

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) or tests, associated analytical procedures, and acceptance criteria for each control?

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

2.3.S.2.5 Process Validation and/or Evaluation

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

2.3.S.2.6 Process Development

13. What development and scale-up information supports the commercial process and control strategy?
2.3.S DRUG SUBSTANCE

2.3.S.3 Characterization
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?

2.3.S.4 Control of Drug Substance
16. What is the drug substance specification and what is the justification? Does the specification include all of the critical drug substance quality attributes?
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 your 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?

2.3.S.5 Reference Standards
20. How are the drug substance reference standards obtained, certified and/or qualified?

2.3.S.6 Container Closure
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?
Draft QbR – 2.3.S.7

2.3.S  DRUG SUBSTANCE

2.3.S.7 Stability

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 and any observed trends support your proposed retest period?

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

2.3.P.1 Description and Composition
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 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 Reference Listed Drug (RLD) formulation?

2.3.P.2 Pharmaceutical Development
4. For 505b(1) applications, what is the rationale for selecting the proposed dosage form for the drug product? For 505b(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 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 biopharmaceutical evaluations (i.e. disintegration, dissolution, diffusion, flux assay, etc.) were used during pharmaceutical development to ensure clinical performance?
2.3.P  DRUG PRODUCT

2.3.P.2.1 Components of the Drug Product

2.3.P.2.1.1 Drug Substance

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), 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 the validation or verification report(s).

2.3.P.2.1.2 Excipients

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

10. What is the rationale for the excipient selections?

2.3.P.2.2 Drug Product

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?
2.3.P DRUG PRODUCT

2.3.P.2.2 Drug Product

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?

2.3.P.2.3 Manufacturing Process Development

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 potentially high risk manufacturing unit operation:
   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.
2.3.P DRUG PRODUCT

2.3.P.2.4 Container Closure System

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 system(s), including bulk containers, qualified for suitability (protection, compatibility, safety, and performance)?

2.3.P.2.5 Microbiological Attributes

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

2.3.P.2.6 Compatibility

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)?
Draft QbR – 2.3.P.3

2.3.P DRUG PRODUCT

2.3.P.3 Manufacture

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 last FDA inspection of each facility involved and the result of the FDA inspection. Has the manufacturer addressed all the concerns raised at the FDA inspection?

23. What is the commercial batch formula and how does it differ from the registration batch formula? Please 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 the drug product 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?
2.3.P DRUG PRODUCT
2.3.P.4 Control of Excipients
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 consistency of the process and quality of the final drug product?

2.3.P.5 Control of 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 of the critical drug product quality attributes?
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 your 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?
2.3.P DRUG PRODUCT

2.3.P.6 Reference Standards or Materials
34. How are the drug product reference standards obtained, certified, and/or qualified?

2.3.P.7 Container Closure System
35. What container closure system(s) is proposed for commercial packaging of the drug product? What is the specification?

2.3.P.8 Stability
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 and data support the proposed shelf-life and storage conditions in the commercial container closure system? How does statistical evaluation of the stability data and any observed trends support your proposed shelf-life?
38. What is the post-approval stability protocol and other stability commitments for the drug product?
Beyond QbR...

The Future of Regulatory Submissions

• How to “package” the development history and control strategy?
  – What is the control strategy, what are the established conditions or “regulatory commitments”?

• How can we better present knowledge gained (not just data available) in Annual Reports and Supplements over product and submission Lifecycle?

• How best to communicate risks for overall Quality Assessment (API/DP/Mfg/Site)?
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