Question-based Review (QbR) and Submissions: CDER's Perspective

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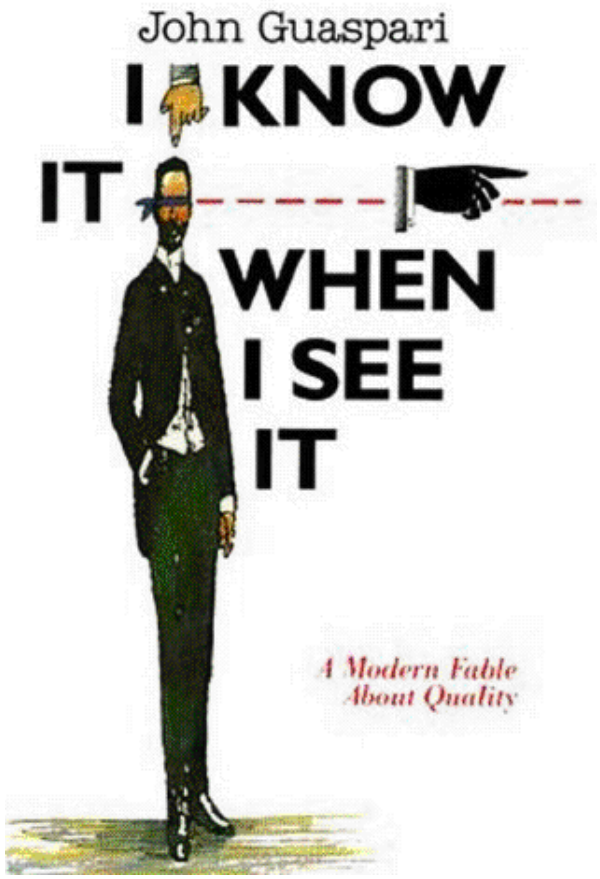
This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Outline for Today

- Brief background and introduction to QbR-QOS
- Current draft questions for drug product
- Insight into what regulators are looking for

What is Quality?

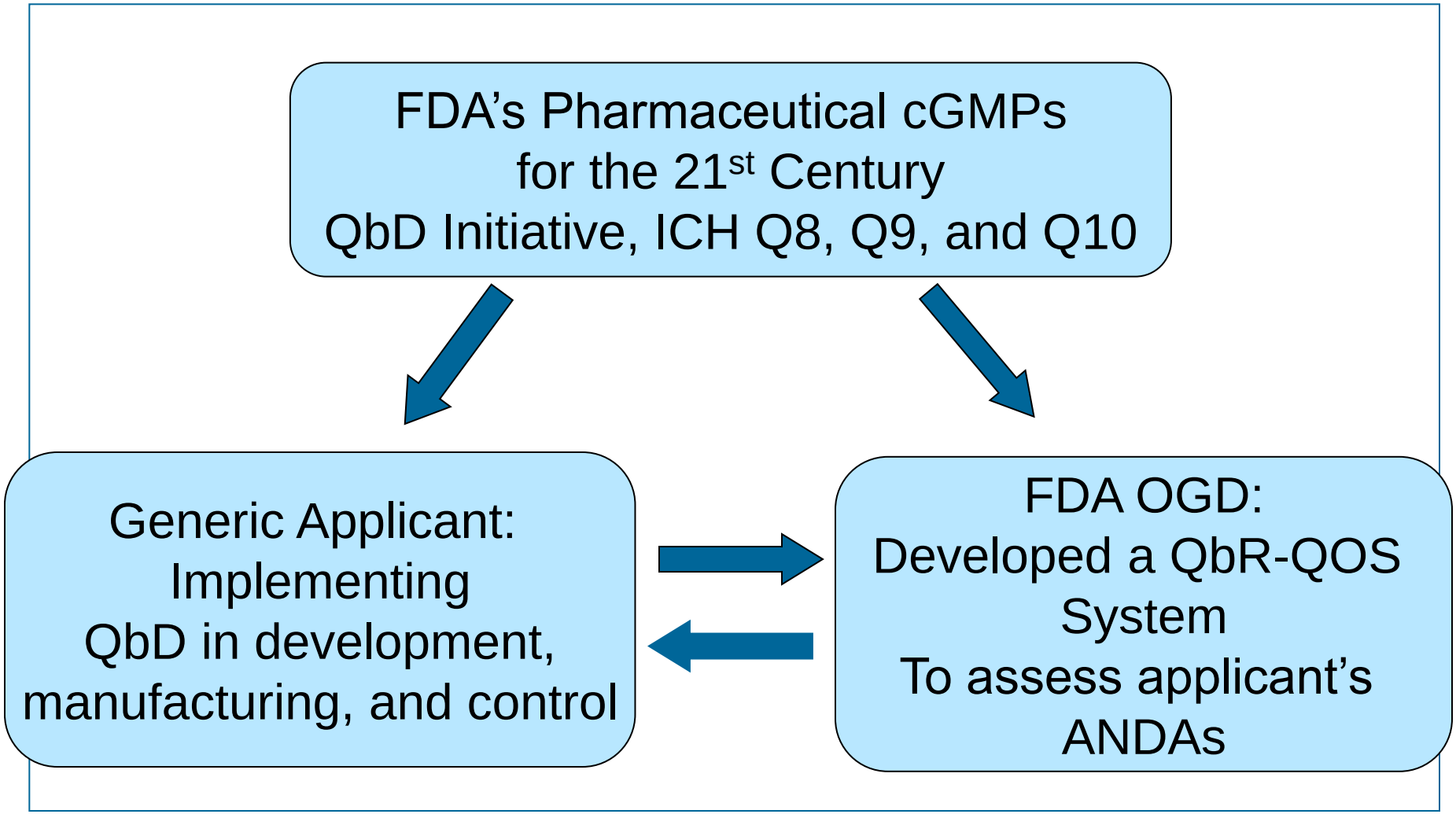
"Our customers tell us we have a Quality problem, and we turn to our specs and our tolerances to see if they're 'right.' …Customers aren't interested in our specs. They are interested in the answer to one simple question: **'Did the product do what I expected it to do?'** If the answer is **yes, then 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 to three batches
  - Little or no mechanistic understanding
  - "Overly conservative specifications"
    - Justify = **Tighten**

Genesis of QbR-QOS



What is QbR-QOS?

- Uses a question and answer format
- Is a general framework for a science and risk-based assessment of product quality*
  - QbR-QOS initiative started in 2005 in the Office of Generic Drugs (OGD)
  - Fully implemented for the CMC evaluation of ANDAs (Abbreviated New Drug Applications) in 2007
    - Included examples, Q&A, outreach
  - Currently being used by 100% of the generic industry for ANDA submissions

**Resources consulted for developing QbR-QOS included: review strategies used by Japanese Ministry of Health & Welfare, Health Canada and the Office of Clinical Pharmacology in CDER*

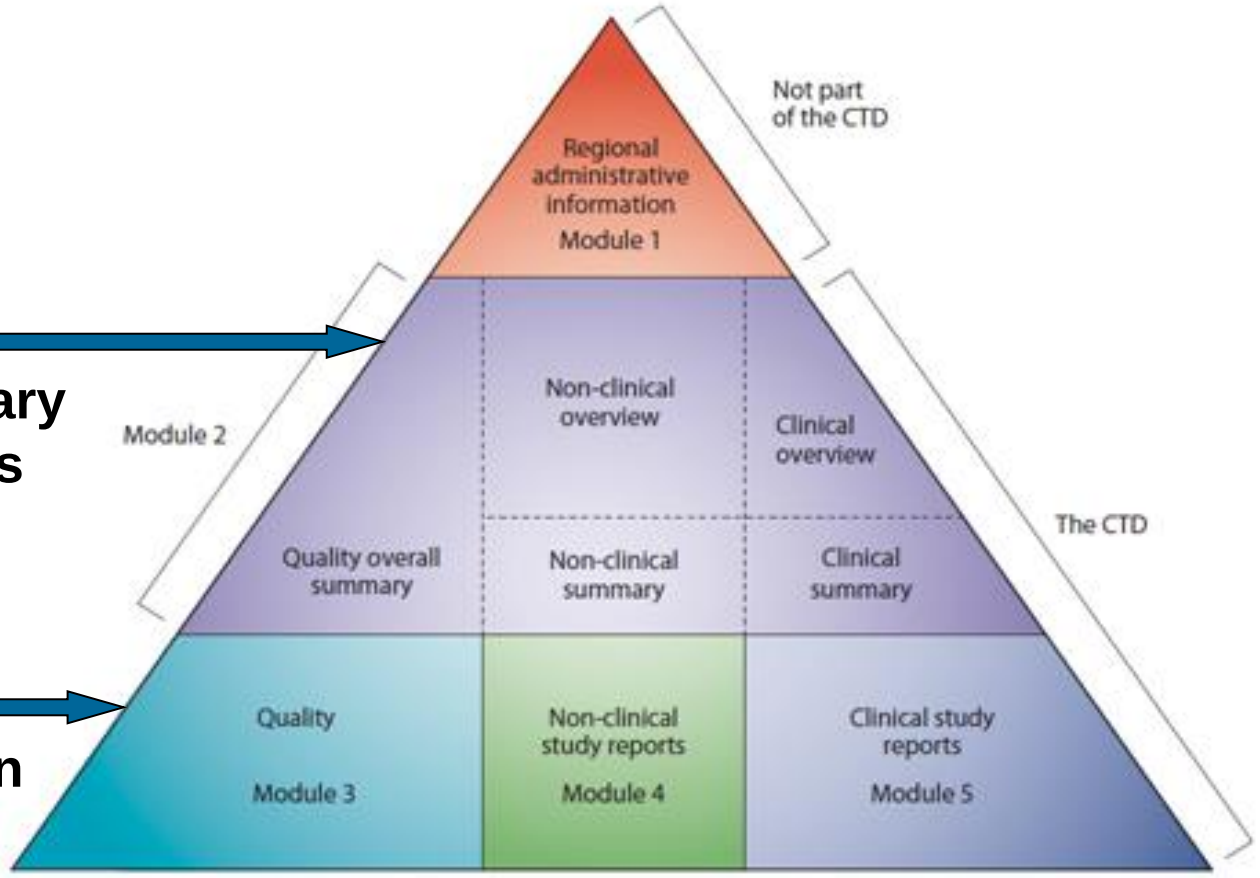
A little more about QbR…

- Contains answers to **important scientific and regulatory review questions**
  - Critical formulation and manufacturing variables
  - Specifications relevant to quality and performance
  - Risk of the design and manufacture
  - Control strategy
- Expectation that ANDA applications be **organized according to the Common Technical Document (CTD)**
  - Builds upon CTD QOS
  - Results in minimal change for applicants generating multi-region submissions
  - Encourages electronic submissions

ICH Common Technical Document

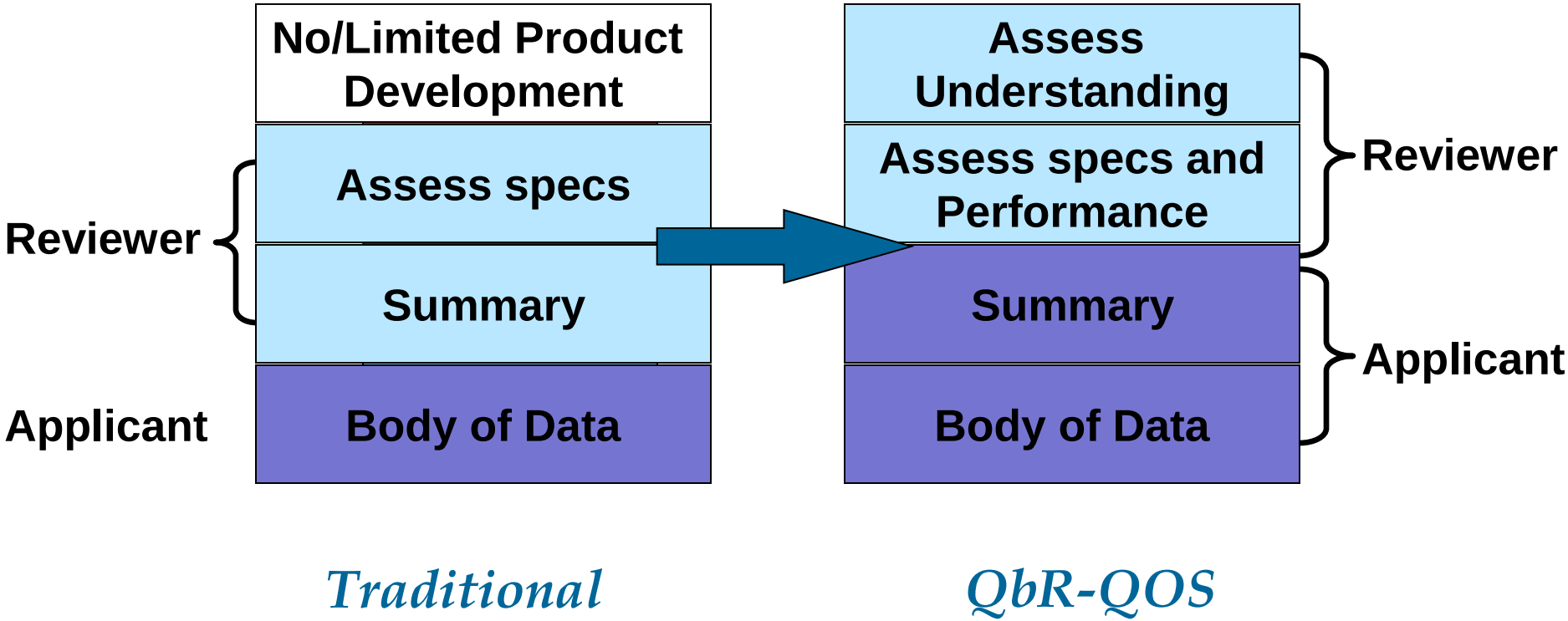
2.3 QOS
QbR answers and summary of critical CMC elements

3.2 Body of Data
Detailed CMC submission Package (No Change)



http://www.ich.org/products/ctd.html (M4Q: Quality)

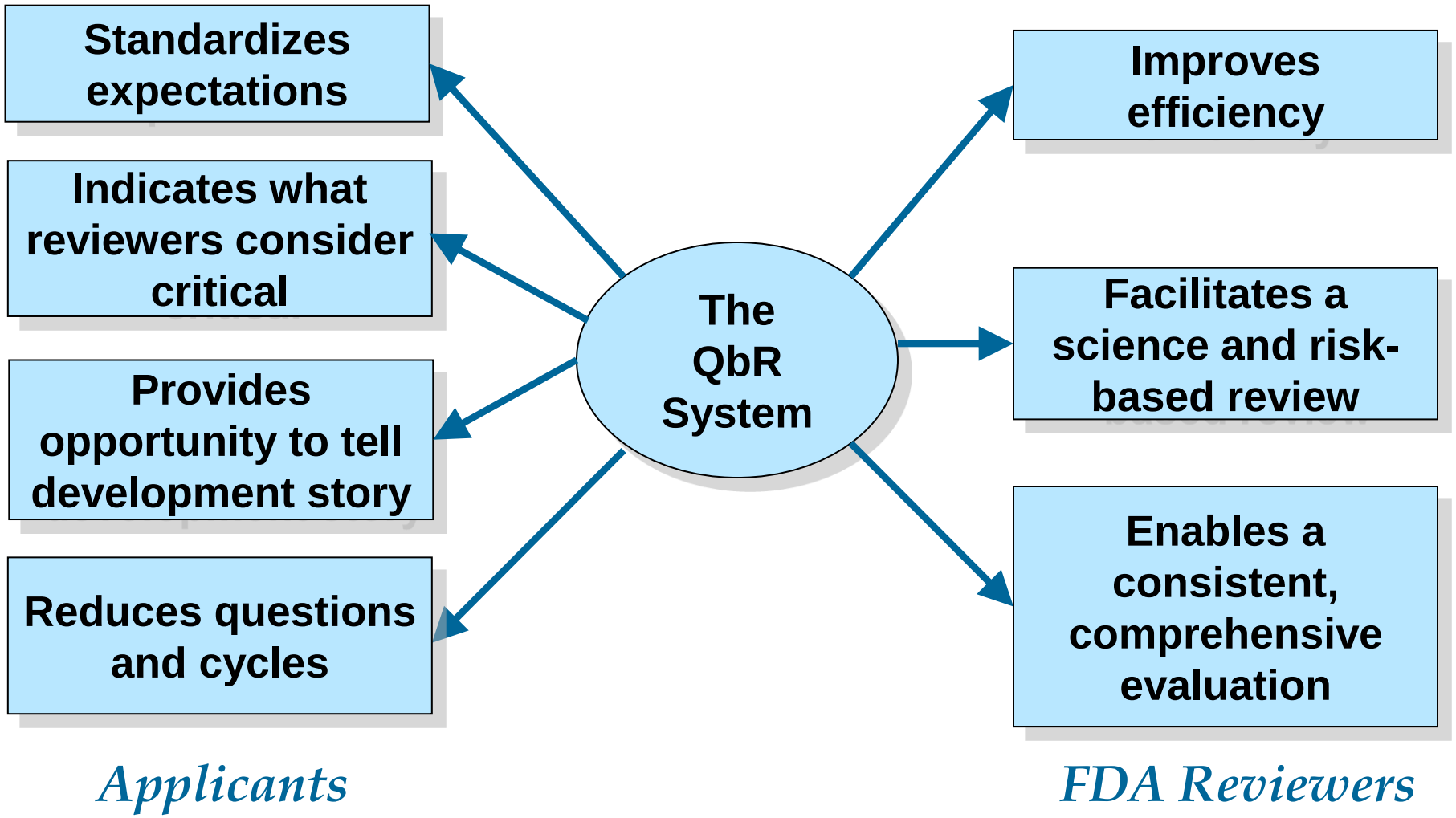
Traditional vs. QbR-QOS ANDA Submissions



Positive Aspects of QbR-QOS

- Consistent with the current quality-by-design (**QbD**) paradigm
- Congruent with **risk management** approaches
- Seeks **justification** for choices made throughout the development and manufacture of generic products
- Increases **transparency** in the thought processes of the applicants which helps to reduce deficiencies seeking clarification

Benefits of QbR



Current QbR-QOS Initiatives

- Develop a QbR-based review template with overarching questions **applicable to both new and generic drug products**
  - Standardize review approach for both NDA and ANDA
  - Support implementation of integrated team-based review within the future OPQ (Office of Pharmaceutical Quality)
  - Facilitate communication with all quality stakeholders
- Current draft QbR includes 38 questions for drug product and 24 questions for drug substance

Fundamental Review Questions

- *Will the product design ensure desired performance?*
- *Will the applicant be able to scale-up to commercial scale and ensure comparable quality to the bio batch(es)?*
- *Will the applicant be able to manufacture the product with defined quality parameters over time?*

OPS MAPP 5016.1: Applying ICH Q8(R2), Q9, and Q10 Principles to CMC Review

POLICY

- OPS CMC reviewers will consider ICH Q8(R2), Q9, and Q10 recommendations when reviewing applications that may or may not include QbD approaches.

OPS MAPP 5016.1: Applying ICH Q8(R2), Q9, and Q10 Principles to CMC Review

- Ensure that applications contain the following:
  - Quality target product profile (**QTPP**)
  - Critical quality attributes (**CQAs**)
  - 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
  - An **understanding** of the development of the drug product and its manufacturing process
  - **Control strategy** including justifications
- Evaluate each risk assessment
- Take a scientific and risk-based approach

Quality Target Product Profile (QTPP)

- 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?

What are we looking for?

- 505b(1): scientific and clinical rationale for the selected dosage form
- 505b(2) and 505(j): clinical, pharmacokinetic, drug release properties and physicochemical characterization of the RLD product
- QTPP considerations include but are not limited to:
  - Patient population
  - Dosage form and strength(s)
  - Route of administration and alternative methods of administration
  - Delivery system
  - Container closure system
  - Release or delivery of therapeutic moiety and attributes affecting pharmacokinetic characteristics
  - Quality attributes

Critical Quality Attributes (CQAs)

- 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?

What are we looking for?

- List of quality attributes relevant to the dosage form of the drug product
- Target for each quality attribute (preferably quantitative) that is supported by development data and scientifically justified
  - Defined early in development based on drug substance properties, dosing instructions, intended patient population and RLD characterization

What are we looking for?

- Risk-based justification to identify the CQAs based on severity of harm to the patient with respect to clinical safety and/or efficacy and not on probability of occurrence

Quality Attribute of the Drug Product	Target	Is it a CQA?	Justification
Identification	Positive for drug substance X	Yes	
Assay	100% of label claim	Yes	
Content Uniformity (Weight Variation)	Conforms to USP <905>; AV < 15	Yes	

Risk Assessment

- What physicochemical properties of the drug substance may impact drug product performance?
- What aspects of the formulation were identified as potentially high risk to the drug product performance?
- What is the potential risk of each process step to impact the drug product CQAs and how is the risk level justified?

What are we looking for?

- Use risk assessment to focus development efforts
- Summary of risk assessment to rank or prioritize variables based on their potential effects on product CQAs
  - Include justifications!
- Source of prior knowledge as well as relevance to the current process should be clearly described

Drug Product CQAs	Eudragit L100-55 Level	SLS Level	HPMC 2208 Level	HPMC 2208 Viscosity	Magnesium Stearate Level	Opadry I Level (non-functional)
Tablet Size	Medium	Low	High	Low	Low	Low
Assay	Low	Low	Low	Low	Low	Low
Content Uniformity	Low	Low	Low	Low	Low	Low
Dissolution	High	High	High	High	Medium	Low

Product Understanding

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

- What is the rationale for the excipient selections?

Product Understanding (con't)

- 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?

- 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?

Product Understanding (con't)

- 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 support the formulation changes and link the development formulations to the proposed commercial formulation?

Process Understanding

- 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?
  c) What material attributes and process parameters 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?

What are we looking for?

- Provide a summary in a manner that allows the reviewer to follow the logical progression of the drug product development.
- For DOEs, show that the conclusion is statistically meaningful
- When no DOE is performed, clarify what 'significant' means and discuss how decisions regarding criticality were made

What are we looking for?

- For complex drug products, consider verification studies at larger scale
- Discuss theory, scale-up factors, first principles and/or other approaches used to adjust the process parameters across scale
- Summarize any studies and data to support changes to equipment design or operating principles
- Consider capacity utilization and run time affects on product quality and manufacturability

Control Strategy

- What is the specification for the…drug substance, excipients, drug product, container closure system?
- 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?
- If applicable, what online/at line/in line monitoring technologies are proposed for routine commercial production that allow for real-time process monitoring and control? Provide a summary of how each technology was developed.

Control Strategy (con't)

- 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?

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

What are we looking for?

- Answer conveys product and process understanding
- Proposed commercial control strategy is supported by development work
- For PAT, a description of the technology that is replacing a traditional method and how it will be implemented
  - Discussion of the impact on the overall control strategy
  - For a high impact technology (used for product release), provide:
    - Description of the instrument and its location
    - Development and validation of the calibration method
    - Summary of the model maintenance approach

What are we looking for?

- Should ensure the identity, strength, quality and purity of the drug substance and bioavailability of the drug product
- Residual risks (e.g., scale-up) should be identified

Summary

- QbR-QOS is a “new” quality assessment system that focuses on critical pharmaceutical quality attributes.
- It facilitates a modern, science- and risk-based pharmaceutical quality assessment review
- It is a pathway for demonstrating product and process understanding
- It increases transparency

Why we do this. . .

FOR INFORMATION ONLY

Draft QbR – 2.3.S.1-2

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/reworking/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.

Draft QbR – 2.3.S.2 con't

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?

Draft QbR – 2.3.S.3-6

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?

Draft QbR – 2.3.P.1-2

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 bioperformance evaluations (i.e. disintegration, dissolution, diffusion, flux assay, etc.) were used during pharmaceutical development to ensure clinical performance?

Draft QbR – 2.3.P.2 con't

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?

Draft QbR – 2.3.P.2 con't

2.3.P DRUG PRODUCT

2.3.P.2.2 Drug Product con't

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.

Draft QbR – 2.3.P.2 con't

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?

Draft QbR – 2.3.P.4-5

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?

Draft QbR – 2.3.P.6-8

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?