POLICY AND PROCEDURES

OFFICE OF PHARMACEUTICAL QUALITY

Applying ICH Q8(R2), Q9, and Q10 Principles to Chemistry, Manufacturing, and Controls Review

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PURPOSE

- This MAPP outlines and clarifies how product quality reviewers in the Office of Pharmaceutical Quality (OPQ) should apply the recommendations in the ICH Q8(R2), Q9, and Q10 guidances to industry.

BACKGROUND

- The International Council on Harmonisation (ICH) "Q8(R2) Pharmaceutical Development," published November 20, 2009, provides information on how to present knowledge gained when applying scientific approaches and quality risk management for developing and manufacturing a product. The annex in ICH Q8(R2) further clarifies key concepts outlined in the original guidance published in June 2006 and describes the principles of quality by design (QbD). Some of the information described in ICH Q8(R2) represents the minimum amount of information the applicant should provide in an application. "Enhanced" or QbD approaches as described in ICH Q8(R2) are encouraged.

- ICH "Q9 Quality Risk Management," published in June 1, 2006, provides information regarding systematic approaches to quality risk management.

- ICH "Q10 Pharmaceutical Quality System," published in April 7, 2009, establishes a new ICH tripartite model for an effective quality management system for the pharmaceutical industry. The model is referred to as the pharmaceutical quality system.

- The number of new drug applications (NDAs), investigational new drug applications (INDs), abbreviated new drug applications (ANDAs), and biologics license applications (BLAs) and their supplements containing QbD approaches has increased. Because of this increase, the Center recognizes the need for reviewers to consistently implement the ICH guidances in their reviews.

POLICY

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

RESPONSIBILITIES AND PROCEDURES

- Reviewers should ensure that applications contain at least the minimum information on pharmaceutical development described by ICH Q8(R2) as "At a minimum, those aspects of drug substances, excipients, container closure systems, and manufacturing processes that are critical to product quality should be determined and control strategies justified."

    - Namely, applications should include the following minimal elements delineated in the ICH Q8(R2) Annex:

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

    - Additionally, based on the ICH Q8(R2) parent document (page 3) 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

- As needed, the reviewer should confer with CMC subject matter experts and members of the extended review team (e.g., medical officer, pharmacology/ toxicology reviewer) to establish the relevance of CMC information that supports the drug's safety, efficacy, and performance.

- Applications can include information on enhanced knowledge of the product and process, which can be used to support more flexible regulatory approaches.

    - Reviewers should determine whether an application includes sufficient enhanced knowledge that demonstrates the applicant's understanding of material attributes, manufacturing processes, and controls for product quality to support the proposed flexible regulatory approaches. Examples of flexible regulatory approaches are as follows:

        - Manufacturing process improvements without regulatory notification (e.g., movement within a design space).
        - Approaches to reduce post-approval submissions through submission of change protocols (e.g., as described in 21 CFR 314.70(e), 21 CFR 601.12(e) or "Comparability Protocols for Human Drugs and Biologics – Chemistry, Manufacturing, and Controls Information," April 2016).
        - In-process tests in lieu of end product testing, including real time release testing approaches (e.g., "PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance," September 2004).
        - Mathematical models (e.g., multivariate models) as surrogates for traditional end product testing.

    - Reviewers should ensure, in situations when real time release testing is proposed, that the associated methodology is included in the specifications for an attribute that is indirectly controlled (e.g., through in-process testing or surrogate model).

- ICH Q9 provides a systematic approach to quality risk management. The risk assessments are usually the basis for the control strategy and those submitted in the application can justify the proposed flexible regulatory approaches.

- The reviewer should evaluate each risk assessment presented in an application.

- The reviewer should take a scientific and risk-based approach when reviewing the application:

    - The reviewer should evaluate the risks to product quality and the ability of the control strategy to suitably control the risks. The reviewer may choose to

conduct an independent formal risk assessment using the tools provided in ICH Q9 to aid with this evaluation.
- The extent of the review should be determined by the importance of the process or material being reviewed and the severity of its potential effect on product quality.
- As outlined in ICH Q10, the manufacturer's quality system is an important part of ensuring continued product quality. The reviewer should collaborate with the investigator and compliance officer, as needed, regarding potential risks in the manufacturing process if potential risks are discovered during the course of the review. This information is helpful during an inspection.

REFERENCES

- Guidance for Industry, "Q8(R2) Pharmaceutical Development" (Nov 2009) http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073507.pdf

- Guidance for Industry, "Q9 Quality Risk Management" (June 2006) http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073511.pdf

- Guidance for Industry, "Q 10 Pharmaceutical Quality Systems" (April 2009) http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073517.pdf

- Guidance for Industry, "Q8, Q9, and Q10 Questions and Answers (R4)" (November 2011) http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM210822.pdf

DEFINITIONS

- Quality Target Product Profile (QTPP): A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product.

- Critical Quality Attributes (CQA): A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

- Quality by Design (QbD): A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and

process control based on sound science and quality risk management.

- Design Space: The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory postapproval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval.

- Control Strategy: A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components; facility and equipment operating conditions; in-process controls; finished product specifications; and the associated methods and frequency of monitoring and control.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
2/7/2011	Initial	N/A
5/18/2016	N/A	Administrative updates to reflect OPQ reorganization
1/21/2022	N/A	Recertification. No changes.