Overview of Quality-Related Controlled Correspondence (CC)

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SBIA Generic Drug Forum – April 10, 2024

Outline

- Changes in GDUFA III
- Types of OPQ CC
- OPQ Disciplines
- Best Practices
- FAQs for OPQ CC

Learning Objectives

- Outline changes in GDUFA III
- Describe types of quality-related CC reviewed by the Office of Pharmaceutical Quality (OPQ)
- Provide helpful information for submitting quality-related controlled correspondences

Controlled Correspondence Definition

Level I

- Prior to ANDA submission
- After a PSG Teleconference
- After issuance of a CRL or tentative approval
- After ANDA approval
- Concerning post-approval submission requirements

Level II

- Clinical content
- Covered Product Authorization
- Alternative bioequivalence approaches
- Input from another office or center

Clarification of Ambiguity

- Commitment Letter: Ambiguity in the controlled correspondence response "means the controlled correspondence response or a critical portion of it, merits further clarification"
- Requests to Clarify Ambiguities in FDA's Controlled Correspondence Response should be submitted within 7 days of the Agency's response.
- No new questions or re-phrasing of questions
- No new information

What is different in GDUFA III?

- Under the GDUFA III, correspondence seeking regulatory and/or scientific advice after the following can be submitted as a CC;
  - issuance of a Complete Response Letter (CRL)
  - tentative approval
  - ANDA approval

Previously under GDUFA II these were considered general correspondence.

- Response for Clarity of Ambiguities will be within 21 days of request receipt (submit request within 7 days)

OPQ Sub-disciplines responding to CCs

Office of Product Quality Assessment I & II

Drug product questions e.g., formulation, specifications, stability testing, container-closure, dissolution, in vitro-in vivo correlation

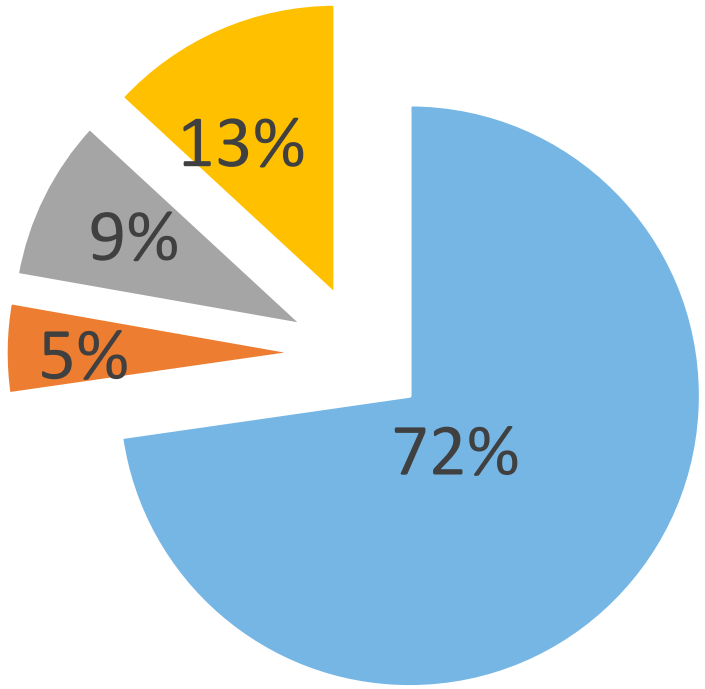
Office of Product Quality Assessment III

Drug Substance questions e.g., starting material, polymorphs) new API source, API sameness

Office of Pharmaceutical Manufacturing Assessment

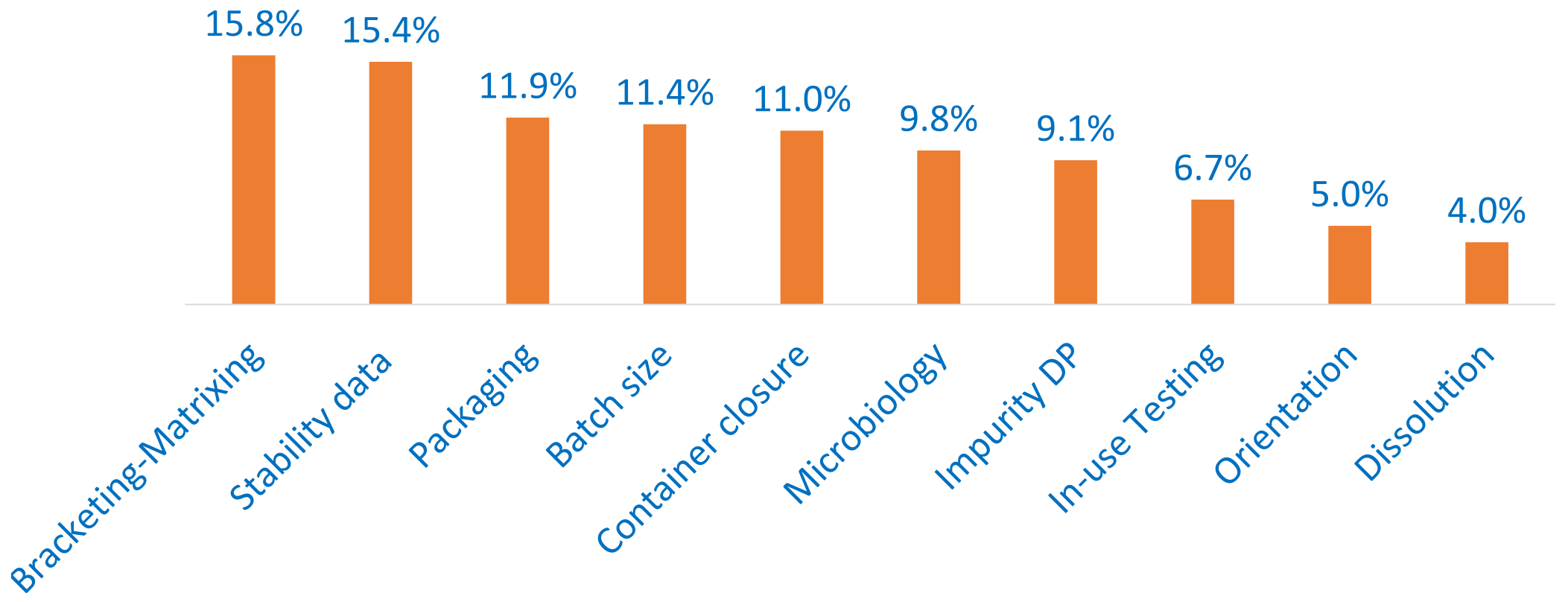
Manufacturing questions e.g., batch size, manufacturing process, sterile manufacture, bacterial endotoxin specifications

CC Topics in 2023



- Drug Product
- Drug Substance
- Manufacturing
- Post-approval

Top 10 Quality CC Subjects in 2023



Submission Best Practices

Pre-submission and Post-Approval CC:

- Questions should be submitted separately for each OPQ CC sub-discipline, where possible (e.g., drug substance, drug product, and manufacturing).

Post Complete Response Letter (CRL) CC:

- All quality-related questions should be submitted in a single CC.
- Include a copy of the CRL and the reference specific deficiency.

Tips for a successful quality related CC

- Contains concise and complete question(s) with appropriate supporting information
- Resolve Q1/Q2 formulation issues before submitting the CC
- Verify if a new guidance has been published on the topic where the information in the inquiry can be found. Click here for resource
- Refer to FDA Guidance for Industry, Questions and Answers on Quality Related Controlled Correspondence to determine if the answer is already posted

Questions that cannot be answered in a CC

- Acceptability of a specification, in-process control, or study plan
- Acceptability of API overage in final product
- Impurity clearance approach
- Adequacy of characterization studies
- Proprietary information from the RLD or other applications

External Inquiry vs CC

- Some inquiries sent to the OPQ inquiries mailbox or other Agency mailboxes may be eligible to be submitted as CCs.
- FDA will notify the inquirer and request that the question be submitted as a CC.

Frequently Submitted CC

Stability

How much stability data is needed for ANDA submission?

Provide **three** discrete batches and 6 months of accelerated data and 6 months of long-term data at the time of submission for all strengths of all dosage forms.

https://www.fda.gov/files/drugs/published/ANDAs--Stability-Testing-of-Drug-Substances-and-Products--Questions-and-Answers.pdf

Packaging of Exhibit Batches

How many batches should be fully packaged?

One exhibit batch should be completely packaged in marketing presentation. The other two batches can be partially packaged in sufficient quantities to comply with 21 CFR 211.166(a)(1-5) and 211.166(b).

Refer to FDA guidance for industry, ANDAs: Stability Testing of Drug Substances and Products, Questions and Answers (May 2014)

API Lots

How many lots of API can be used for exhibit batches?

A minimum of two lots of the drug substance should be used to manufacture the three primary batches of drug product.

However, for nasal aerosols and nasal sprays, use three different lots of drug substance.

https://www.fda.gov/files/drugs/published/ANDAs--Stability-Testing-of-Drug-Substances-and-Products--Questions-and-Answers.pdf

Conclusion

- Provide clear and concise information which is appropriate to the question(s).
- Separate CCs for different OPQ sub-disciplines (except for post-CRL CCs) and for Bioequivalence.
- Clarification of ambiguity should be submitted within 7 days and not contain any new information and response will be issued within 21 days.

Resources

- Guidance for Industry, Controlled Correspondence Related to Generic Drug Development (Draft) December, 2022 https://www.fda.gov/media/164111/download
- Guidance for Industry, Questions and Answers on Quality-Related Controlled Correspondence, September 2021 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/questions-and-answers-quality-related-controlled-correspondence-guidance-industry
- Questions and Answers on Quality-Related Controlled Correspondence, September 2021 https://www.fda.gov/drugs/pharmaceutical-quality-resources/questions-and-answers-quality-related-controlled-correspondence

Challenge Questions

Question #1

Under GDUFA III which of the following can be submitted as a Controlled Correspondence? Correspondence seeking regulatory and/or scientific advice after issuance of a:

A. Complete Response Letter (CRL)
B. Tentative approval
C. ANDA approval
D. All of the above

Question #2

Complete study reports are not appropriate for a CC.

A. True
B. False

Thank you

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