U.S. FOOD & DRUG ADMINISTRATION

Submitting a Successful Controlled Correspondence for Quality-Related Questions

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Learning Objectives

- To describe types of quality-related controlled correspondences reviewed by the Office of Pharmaceutical Quality (OPQ)
- To provide helpful information for submitting quality-related controlled correspondences

Controlled Correspondence Levels

Two Levels of Controlled Correspondences (CCs):

- Level 1 (60 days) – Most OPQ CCs
- Level 2 (120 days) – OPQ CCs which need a consult (from another center, office, or sub-office)

Refer to Generic Drug User Fee Act Reauthorization Performance Goals and Program Enhancements fiscal years 2022-2027 (GDUFA III)

OPQ Sub-disciplines

- **Drug Product Quality** (e.g., formulation, specifications, testing) reviewed by *Office of Lifecycle Drug Products*
- **Drug Substance** (e.g., starting material, polymorphs) reviewed by *Office of New Drug Products, Division of Lifecycle Active Pharmaceutical Ingredient*
- **Biopharmaceutics** (e.g., dissolution, in vitro-in vivo correlation) reviewed by *Office of New Drug Products, Division of Biopharmaceutics*

OPQ Sub-disciplines (continued)

- **Microbiology** (e.g., sterile manufacture, bacterial endotoxin specifications) reviewed by *Office of Pharmaceutical Manufacturing Assessment, Division of Microbiology Assessment*
- **Process and Facilities** (e.g., batch size, manufacturing process) reviewed by *Office of Pharmaceutical Manufacturing Assessment, Division of Pharmaceutical Manufacturing*

Submission Considerations

Pre-submission and Post-Approval CC:
Questions should be submitted separately for each OPQ sub-discipline, where possible (e.g., drug substance, drug product, and microbiology).

Post Complete Response Letter (CRL) CC:
All quality-related questions should be submitted in a single CC.

Submission Considerations

Quality-related questions should be in separate CC from non-quality-related questions.

Separate questions that require review by more than one discipline. For example, in post-approval CCs, quality questions on batch size, amount of stability data, etc. should be separated from questions on in-vivo testing where possible.

Successful CC Submission

- Contains concise and complete question(s) with appropriate supporting information
- Resolve Q1/Q2 formulation issues before submitting the CC for quality
- Verify that a new guidance has not been published on the topic
- Refer to FDA's guidance for industry, Questions and Answers on Quality Related Controlled Correspondence to determine if the answer is already posted there

Issues with Quality-Related CCs

Not enough background information

- Not including the proposed commercial batch size for questions about exhibit batch size
- Not clarifying if common blend is used for questions on bracketing
- Not providing necessary product information which is needed to answer the question (e.g., if product is Q1/Q2 with the RLD)

Issues with Quality-Related CCs

Too much information

- Lengthy and detailed information – emphasis of the CC should be on key information only and not extraneous data that do not support the request
- Complete study reports are not appropriate for a CC. Summary of data should be submitted

Issues with Quality-Related CCs

Lack of clarity

Question phrased so that it is difficult to understand or a specific question is not included

Too general

Questions related to post-approval changes (not related to specific ANDA) without providing the dosage form

Examples of Quality-Related CCs

Change in container closure system

- Ampule to vial, or vice versa
- Different size container from RLD
- Composition changes: Glass vial to plastic or vice versa

In general, container-closure changes are acceptable with justification and supporting data.

Examples of Quality-Related CCs

Number of exhibit batches to be 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

Examples of Quality-Related CCs

Device Questions

- OPQ reviews specifications, performance data and manufacturing quality control information (e.g., testing of different components, essential performance requirements (EPRs), stability requirements)
- OGD's Office of Research and Standards reviews questions on differences between the user interface of a proposed generic drug-device combination product as compared to the RLD

Examples of Quality-Related CCs

Discontinued Reference Listed Drug (RLD) / Reference Standard (RS)

- In most cases, when RLD is discontinued, RS can be used for physicochemical comparison studies.
- If RLD and RS are both discontinued, a CC should be submitted to OGD/Orange Book to assign a new RS which should be used for physicochemical comparison.

Refer to FDA guidance for industry, Referencing Approved Drug Products in ANDA Submissions

General Considerations

Specific questions that may not be answered in a CC

- Acceptability of a specification or in-process control
- Acceptability of overage in drug product

General guidance will be provided in CC response, but we may not be able to respond to specific limits and overage amounts. These will be assessed after submission during the ANDA review based on the totality of the information presented in the application.

Clarification of Ambiguity

- Clarification of ambiguities in the CC Response (submitted within 7 days after response)
- No new questions or re-phrasing of questions
- No new information

Inquiry or Controlled Correspondence

- 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.

Best Practices

- FDA will apply all available guidances (as applicable) to each situation. Therefore, it is in your best interest to do the same and provide scientific justification if variance from the guidance is requested.

- Reliance on historic trends may seem to be a sound approach for justification, however, if the regulatory science has moved beyond the understanding of that particular subject at that particular time, the significance of those earlier outcomes will be greatly diminished.

Challenge Question #1

Separate controlled correspondences should be submitted for different OPQ sub-disciplines for:

A. Pre-submission questions

B. Post-approval questions

C. Post-CRL questions

D. A and B

Challenge Question #2

Which of the following statements is TRUE?

A. If the RLD/RS is discontinued, another approved ANDA can be used for comparison

B. A follow-up question can be asked in request for clarification of ambiguity

C. A concise question and appropriate amount of information should be provided in the CC

Summary

- Provide appropriate information and clear and concise question(s) in the CC
- Submit separate CCs for different OPQ sub-disciplines (except for post-CRL CCs) and for OPQ and OGD
- Clarification of ambiguity in response should be submitted in 7 days and not contain any new information.

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

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