
POLICY

OFFICE OF PHARMACEUTICAL QUALITY
Using Four-Part Harmony in Quality-Related Assessment Communications

Table of Contents

PURPOSE	1
BACKGROUND	2
POLICY	2
RESPONSIBILITIES	4
REFERENCES	4
DEFINITIONS	4
EFFECTIVE DATE	5
CHANGE CONTROL TABLE	5
ATTACHMENT – Examples of Quality-Related Communications	6

PURPOSE

This MAPP describes how the Office of Pharmaceutical Quality (OPQ) product quality assessors can follow the principles of Four-Part Harmony¹ to enhance the clarity of quality-related communications.² This MAPP applies to quality-related communications that are sent

¹ Four-Part Harmony is a format recommendation adopted by several FDA centers. Efforts that align with or describe Four-Part Harmony include:

- The Prescription Drug User Fee Act VII goals letter titled “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027” available on the FDA website at <https://www.fda.gov/media/151712/download>.
- The Center for Biologics Evaluation and Research Standard Operating Procedure and Policy 8401.1 *Issuance of and Review of Responses to Information Request Communications to Pending Applications* available at <https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-procedures-sopps>.
- The guidance for industry and Food and Drug Administration staff *Developing and Responding to Deficiencies in Accordance with the Least Burdensome Provisions* (October 2022). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.
- The Medical Device User Fee Amendments V goals letter titled “MDUFA Performance Goals and Procedures, Fiscal Years 2023 Through 2027” available on the FDA website at <https://www.fda.gov/media/158308/download>.

² Quality-related communications include, but are not limited to, complete response letters, deficiency letters, discipline review letters, and information requests.

to applicants³ during assessments⁴ across the product life cycle. These communications identify deficiencies or request information during the assessment of submissions related to human drugs, including:

- Investigational new drug applications (INDs), new drug applications (NDAs), biologics license applications (BLAs), abbreviated new drug applications (ANDAs), and emergency use authorizations (EUAs), as well as drug master files (DMFs) that are referenced by INDs, NDAs, ANDAs, and other DMFs.
- Amendments and supplements to the applications listed above.
- Other submissions including, but not limited to, annual reports, postmarketing commitments, and submissions that involve intercenter consults with OPQ for drug quality assessment.

The attachment provides examples of quality-related communications.

BACKGROUND

- To promote efficient communication between assessment teams and applicants, FDA has committed to ensuring the use of Four-Part Harmony in quality-related communications.^{5,6} This commitment includes revising and publishing this MAPP and conducting internal training.⁷
- Four-Part Harmony is intended to ensure that assessors draft clear quality-related communications and provide a basis for each communication that is consistent with FDA's policy. This may help applicants provide adequate information to address identified quality issues.

POLICY

- Four-Part Harmony recommends that all quality-related communications address the following four essential components:

³ For the purposes of this MAPP, the term *applicants* refers to sponsors, submitters, and holders of INDs, NDAs, BLAs, ANDAs, and EUAs, as well as DMFs that are referenced in INDs, NDAs, ANDAs and other DMFs.

⁴ The Office of Pharmaceutical Quality generally uses the term *assessment* in place of *review*. *Assessment* means the process of both evaluating and analyzing submitted data and information to determine whether the application meets the requirements for approval and documenting that determination.

⁵ See the PDUFA VII goals letter.

⁶ In addition, assessors should apply the CDER Style Guide to quality-related communications.

⁷ The prior version of this MAPP (*Communication Guidelines for Quality-Related Information Requests and Deficiencies*) was internal to FDA.

- (1) **What was provided?** Acknowledge the information submitted by the applicant and provide a reference to relevant modules, sections, page numbers, or tables unless the part of the application being referenced is obvious from the description (e.g., “your proposed drug product specification”).
 - (2) **What is the issue?** Identify missing information or information that FDA considers inadequate.
 - (3) **What is needed?** Request additional information or recommend an alternative approach to address the issue.
 - (4) **Why is it needed?** State the basis for the information request or deficiency, and include:
 - a. The impact of the issue on the overall regulatory decision.
 - b. References to all or part of applicable regulations, statutes, guidances, and/or FDA-recognized consensus standards, as appropriate.
- Based on the nature and extent of the issue, assessors may combine, omit,⁸ or reorder the elements.
 - Quality-related communications should “request the minimum (i.e., least burdensome) amount of information necessary to adequately address the identified issue.”⁹
 - Assessors should not use mandatory language such as *shall*, *must*, *required*, or *requirement* when referring to recommendations from guidance documents or standards.¹⁰ Instead, assessors should use words such as *should* or *recommend*. Assessors may use mandatory language when referencing regulatory or statutory requirements in the Code of Federal Regulations or a specific statute (e.g., the Federal Food, Drug, & Cosmetic Act).
 - If the applicant’s response to the quality-related communication does not resolve the issue, assessors should consider rephrasing the quality-related communication to clarify the basis for the request. This may help applicants provide adequate information to address the issue.
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⁸ Omissions are only appropriate under limited circumstances (e.g., when using templated language).

⁹ See the guidance for industry and Food and Drug Administration staff *Developing and Responding to Deficiencies in Accordance with the Least Burdensome Provisions* (October 2022).

¹⁰ Guidance documents and standards describe FDA’s current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. Applicants can use an approach other than the one set forth in a guidance document if it complies with the relevant statutes and regulations.

RESPONSIBILITIES

OPQ primary quality assessors will follow the principles of Four-Part Harmony when drafting quality-related communications.

OPQ discipline-specific concurring officials¹¹ will ensure that quality-related communications follow the principles of Four-Part Harmony.

REFERENCES

- Center for Biologics Evaluation and Research Standard Operating Policy and Procedure 8401.1 *Issuance of and Review of Responses to Information Request Communications to Pending Applications* (October 2022)
 - Generic Drug User Fee Amendments goals letter, “GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2023-2027”
 - Guidance for industry and Food and Drug Administration staff *Developing and Responding to Deficiencies in Accordance with the Least Burdensome Provisions* (October 2022)
 - Medical Device User Fee Amendments goals letter “MDUFA Performance Goals and Procedures, Fiscal Years 2023 Through 2027”
 - Prescription Drug User Fee Act goals letter “PDUFA Reauthorization for Fiscal Years 2023 Through 2027”
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DEFINITIONS

- **Deficiency** – An outstanding issue that FDA identifies in a submission and communicates to the applicant, sponsor, or DMF holder.
- **Quality-related communication** – An FDA correspondence to an applicant, sponsor, or DMF holder that requests information or identifies deficiencies. These communications include, but are not limited to, the following:
 - **Complete response letters** - “usually describing all of the deficiencies that the agency has identified in” an NDA, ANDA, BLA, supplement, or a DMF that is referenced by an ANDA “that must be satisfactorily addressed before [an application or supplement] can be approved” (21 CFR 314.3, 21 CFR

¹¹ The OPQ discipline-specific concurring official can be an OPQ senior pharmaceutical quality assessor (or a designated secondary assessor), application technical lead, branch chief, or division director, as needed.

600.3(l), and the Generic Drug User Fee Amendment III goals letter,¹² see also 21 CFR 314.110 and 21 CFR 601.3).

- **Deficiency letters** - identifying deficiencies to a DMF holder for an inadequate DMF referenced by an IND, NDA, or another DMF.
- **Discipline review letters** - conveying preliminary thoughts on possible deficiencies found by a discipline assessor and/or assessment team for its portion of the pending application at the conclusion of the discipline assessment.
- **Information requests** - asking for further information or clarification that is needed for or would help with completion of the discipline assessment.

EFFECTIVE DATE

- This MAPP is effective September 22, 2023.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
9/22/17	Initial	n/a
9/22/2023	Rev. 1	Updated to fulfill PDUFA VII commitments.

¹² See Generic Drug User Fee Amendments III goals letter titled “GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2023-2027” available on the FDA website at <https://www.fda.gov/media/153631/download>.

ATTACHMENT – Examples of Quality-Related Communications

The following examples are intended to demonstrate the use of Four-Part Harmony in quality-related communications. These examples do not represent any particular aspect of technical assessment and are not inclusive of additional recommendations that Office of Pharmaceutical Quality suboffices may include in quality-related communications. For demonstration purposes, the Four-Part Harmony elements are labeled in parentheses and in bold print in each example. Assessors will not label the elements in quality-related communications that are sent to applicants.

Example 1

For your drug product, we acknowledge the X-month accelerated and Y-month long term stability data provided in section 3.2.P.8.3 (**element 1**). The provided stability data do not support the proposed shelf life, because insufficient long-term data were provided to support extrapolation to 2 years (**element 2**). Provide updated stability data to support your proposed shelf life; otherwise, revise your proposed shelf life (**element 3**). For more information, see International Council for Harmonisation (ICH) guidance for industry *Q1E Evaluation of Stability Data* (June 2004), including Appendix A, which provides recommendations for evaluating data to estimate a drug product's shelf life (**element 4**).¹

Example 2

The validation information for the sterilization of the equipment and components that directly contact the drug product provided in section 3.2.P.3.5 (**element 1**) corresponds to only one run (**element 2**). To validate the sterilization of the production loads, you should demonstrate the reproducibility of the process by submitting data from two additional successful sterilization runs from either the initial validation or the most recent requalification (**element 3**). For more information, refer to FDA guidance for industry *Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products* (November 1994) (**element 4**).

Example 3

In the supplement, you proposed new lower strengths for drug product XXX based on the approved higher strength (**element 1**). To comply with the requirements in 21 CFR 320.21, applicants must submit in vivo bioavailability data to support the approval of the newly proposed lower strengths, or applicants must submit a biowaiver request (**element 4**). However, we cannot locate the in vivo bioavailability data or a biowaiver request in your submission (**element 2**). Submit a biowaiver request with the supporting data and information in accordance with 21 CFR 320.22 for the proposed lower strengths under eCTD

¹ Do not include hyperlinks to specific guidance documents in communications. Rather, include the following language for the first reference to a guidance in communications to the applicants: "We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>."

section 1.12.15, Request for waiver of in vivo bioavailability studies, or provide in vivo bioavailability data (**element 3**).