POLICY

OFFICE OF GENERIC DRUGS

Using Four-Part Harmony in OGD-Related Assessment Communications[1]

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PURPOSE

- This MAPP describes how Office of Generic Drugs (OGD) assessors can follow the principles of Four-Part Harmony[2] to enhance the clarity of OGD-related communications. This MAPP applies to OGD-related communications that are sent to applicants[3] during assessments across the product life cycle. These communications include, but are not limited to, complete response letters, discipline review letters, and information requests.

  This MAPP applies to the following OGD Offices and Divisions:

  - Office of Bioequivalence
  - Office of Regulatory Operations, Division of Filing Review

[1] This MAPP is a companion to the Office of Pharmaceutical Quality (OPQ) MAPP 5016.8 Rev. 1 *Using Four-Part Harmony in Quality-Related Assessment Communications*.

[2] Four-Part Harmony is a format recommendation adopted by several Food and Drug Administration 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.
- MAPP 5016.8 Rev. 1 *Using Four-Part Harmony in Quality-Related Assessment Communications*.

[3] For the purposes of this MAPP, the term *applicants* refers to sponsors, submitters, and holders of abbreviated new drug applications (ANDAs) and Drug Master Files (DMFs).

- Office of Regulatory Operations, Division of Labeling Review
- Office of Research and Standards
- Office of Safety and Clinical Evaluation

The attachment provides examples of OGD-related communications.

BACKGROUND

- Four-Part Harmony is intended to ensure that assessors draft clear OGD-related communications to applicants and to ensure that OGD requests information from applicants that is appropriate to address a question or issue raised in a marketing application in an efficient manner. These principles may help applicants provide the necessary information to adequately respond to questions or issues raised during the assessment of their application by the Food and Drug Administration (FDA or Agency).

POLICY

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

  (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 method validation report provided in Module 3.2.S.4.3 titled, 'Analytical Method Validation Assay'").

  (2) **What is the issue?** Identify missing information or explain the problem with the submitted information and why it's a problem.

  (3) **What is needed?** Request the additional information needed to address the issue 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, scientific principles, or clinical or nonclinical data that support the request for information or revision.

- Based on the nature and extent of the issue, assessors may combine, omit,[4] or reorder the elements.

- Assessors will not use mandatory language such as *shall, must, required,* or *requirement* when referring to recommendations from guidance documents.[5] Instead, assessors will use words such as *should* or *recommend*. Assessors may use mandatory language, as applicable, when referring to regulatory or statutory requirements and will include a reference to the Code of Federal Regulations or a specific statute (e.g., the Federal Food, Drug, and Cosmetic Act).

- If the applicant's response to the OGD-related communication does not resolve the issue, assessors should consider rephrasing the OGD-related communication to clarify the basis for the request. This may help applicants provide adequate information to address the issue.

- Assessors will use language that clearly indicates the rationale for the requested information or revision.

- When citing a statutory or regulatory provision, it is sufficient to list the source (e.g., "…which is required per 21 CFR [insert specific regulatory cite]"). When citing a scientific principle as the basis for the request, assessors will specify the principle (e.g., "in accordance with [insert scientific principle]").[6]

RESPONSIBILITIES

- **OGD assessors** will follow the principles of Four-Part Harmony when drafting OGD-related communications.

[4] Omissions are only appropriate under limited circumstances (e.g., when using templated language).
[5] In general, guidance documents 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. In limited cases, a guidance document may implement a statutory provision that directs FDA to specify certain binding requirements through guidance. See, e.g., the guidance for industry *Providing Regulatory Submissions in Electronic Format – Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act* (December 2014).
[6] Except as described above, when citing or referencing FDA guidances, OGD disciplines must treat guidance documents as nonbinding. For example, a statement such as, "Per [Title] Guidance, the data provided is insufficient" should not be used. Instead, a statement such as, "As discussed in [Title] Guidance, the Agency interprets [regulatory cite] to require [insert regulatory requirement]. Your ANDA does not contain [insert regulatory requirement], nor does it provide any justification on why the data provided otherwise meets the requirement in [regulatory cite]. Thus, the data provided is insufficient."

- **OGD concurring official**[7] will ensure that OGD-related communications follow the principles of Four-Part Harmony.

REFERENCES

- Generic Drug User Fee Amendments goals letter, "GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2023-2027."
- Prescription Drug User Fee Act goals letter, "PDUFA Reauthorization for Fiscal Years 2023 Through 2027."
- OPQ's MAPP 5016.8 Rev. 1, *Using Four-Part Harmony in Quality-Related Assessment Communications*, available at https://www.fda.gov/media/171613/download?attachment.

DEFINITIONS

- **Deficiency -** An outstanding issue that FDA identifies in a submission and communicates to the applicant.
- **OGD-related communication -** An OGD correspondence to an applicant or DMF holder that requests information or identifies deficiencies. These communications include, but are not limited to, the following:
  - **Complete Response Letter (CRL) -** A written communication to an applicant from FDA usually describing all the deficiencies that the Agency has identified in an abbreviated new drug application (ANDA) (including pending amendments) or a DMF that must be satisfactorily addressed before the ANDA can be approved. Refer to 21 CFR 314.110 for additional details.
  - **Discipline Review Letter (DRL) -** A letter used to convey 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 request (IR)** – A written communication to an applicant during an application assessment to request further information or a clarification of the information already provided that is needed or would be helpful to allow completion of the discipline assessment.
  - **Refuse to Receive Letter (RTR) -** A letter used to communicate to the applicant that the Agency has determined that an ANDA is not substantially complete. Refer to 21 CFR 314.101(d) for additional details.

[7] The OGD concurring official can be an OGD secondary assessor, division associate director/supervisor, division deputy director, or division director, as needed.

EFFECTIVE DATE

- This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
8/11/2022	Initial	CDER Internal MAPP
11/12/2025	Rev. 1	Updated to include all OGD-related communications and made MAPP external.

ATTACHMENT – Examples of OGD-related communications

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

Example 1

In your fasting bioequivalence study (study # XXXX), all pre-dose concentrations at 0-hour time point were set as 0.00 for the calculation of baseline adjusted AUC **(Element 1)**. However, this practice did not accurately reflect the baseline adjustment of the 0-hour samples **(Element 2)**. For each period, please calculate the baseline adjusted concentration of the 0-hour sample by subtracting the mean of three pre-dose concentrations (-1.00 hr, -0.50 hr and 0 hr) from the measured 0-hour sample concentration and submit the correct baseline adjusted dataset **(Element 3)**. This recalculation is necessary to accurately reflect the baseline adjusted concentration of the 0-hour samples. As noted in the Product-Specific Guidance on XXX Tablets (PSG), if baseline-adjusted concentration is negative, concentration should be set to zero (0.00). Please refer to PSG for details **(Element 4)**.

Example 2

In Module 5.3.5.4, your task analysis stated that "The Reference Listed Drug (RLD) requires the health care provider to pull back the plunger rod before depressing to overcome the initial force. The submitted drug product does not require the user to pull the plunger rod back." **(Element 1)**. In light of this design difference, it is not clear if your proposed product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling (**Element 2**).

1. Please provide the following information to show how your pre-filled syringe (PFS) design compares to the RLD PFS **(Element 3):**
    a. Explain in detail the unique difference in functionality in your proposed PFS design, which does not require the user to pull back the plunger rod to relieve any resistance, compared to the RLD PFS, which requires the user to pull the plunger back to relieve any resistance that may be present.
    b. Is your proposed PFS uniquely designed to have no resistance, unlike the RLD PFS? If not, please confirm that your proposed PFS has the same resistance created by the fluid contact path as the RLD PFS.

c. Is your proposed PFS uniquely designed such that it would not allow the user to push the barrel forward to relieve any resistance?
d. Provide a justification to show your drug product can be expected to have the same clinical effect and safety profile as the listed drug when administered to patients under the conditions specified in the labeling despite this difference.

We request a complete written response no later than [DATE] in order to continue our comparative analyses evaluation and our analysis of whether your proposed product will produce the same clinical effect and safety profile as the RLD under the conditions specified in the labeling. See the draft guidance for industry *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (January 2017) **(Element 4)**.

Example 3

Pharmacology/Toxicology has completed review of your toxicological assessment report (Annexure 1), submitted on [DATE], to address the safety of leachables in your proposed [insert drug product name] **(Element 1)**. Upon review, we have determined that the submitted information does not adequately address the safety of detected leachables at their maximum daily exposure (MDE) levels in your drug product. You provided a toxicological assessment for mutagenicity using ToxTree®, and you provided the in-silico prediction to address the general toxicity of the detected leachables. However, use of ToxTree® alone for mutagenicity evaluation and in-silico evaluation of general toxicity are not acceptable. Additionally, there are several leachables exceeding the analytical evaluation threshold (AET) that need to be identified **(Element 2)**. Therefore, your proposed container closure system for your [insert drug product name] product is not qualified for safety **(Element 4)**.

To resolve these deficiencies and qualify the safety of your proposed container closure system, we recommend the following **(Element 3)**:

- Identify leachables exceeding the AET with a chemical structure and/or CAS number for each leachable.
- Submit a general safety assessment (general toxicity, irritation/sensitization potential), considering the context of use of your proposed product, for all leachables with an MDE exceeding 5 mcg/day. You may submit full study reports or legible copies of published literature in your justification. If you use surrogate compounds or group compounds together to evaluate general safety, submit a rationale for your approach.

- Submit a mutagenicity assessment using approaches described in ICH M7(R2)[8] for all leachables with MDE exceeding 1.5 mcg/day.

Example 4

The following comments have been identified by the Division of Labeling Review (DLR) based on your submission(s) on [DATE]. Prior to final approval, the proposed labeling should be clear and precise (grammar, spelling, and formatting) for end users and should accurately reflect the Reference Listed Drug (RLD) information in accordance with applicable Federal law (e.g., 21 CFR 314.94(a)(8)). We also recommend reviewing official compendia and FDA policies (e.g., relevant guidance). **(Element 4)**.

1. CONTAINER LABEL **(Element 1)**
   a. Ensure the color scheme of your proposed drug product is well differentiated from your other related products **(Element 3)**. The currently proposed blue-green (Pantone 3237 C) for the 90 mg sachet label is the same as the 180 mg oral tablet label under ANDA XXXXX [insert drug product name], and the dark blue color (Pantone 2945 C) for the 360 mg sachet label is the same as the 90 mg oral tablet label **(Element 1)**. This may lead to look-alike similarity that could lead to product selection errors when stored in close proximity **(Element 2)**. Refer to the guidance for industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) **(Element 4)**.

2. MEDICATION GUIDE **(Element 1)**

The pronunciation of the nonproprietary name does not conform to the phonetic pronunciation in the current USP Dictionary of USAN and International Drug Names (i.e., (dee fer' a sir ox)) **(Element 2, 4)**. You should revise your proposed pronunciation to conform **(Element 3)**.

Example 5

In module 3.2.P.1 **(Element 1)**, inactive ingredient justification for oral liquid drug products should not be based on a listed percentage in the inactive ingredient database (IID) **(Element 2)**. Justify the calculated amount based on an amount-per-unit in the IID listing that corresponds to an oral dosage form (e.g., solid oral dosage form) **(Element 3)**. Refer to the guidance for industry *ANDA Submissions — Refuse-to-Receive Standards* (December 2016) for further information **(Element 4)**.

[8] See the ICH guidance for industry *M7(R2) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk* (July 2023).