POLICY

OFFICE OF PHARMACEUTICAL QUALITY

Responsibilities for the Assessment of In Vitro Testing for Oral Drug Products Administered Via Enteral Feeding Tube

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PURPOSE

- This Manual of Policies and Procedures (MAPP) defines the roles and responsibilities of the Office of Pharmaceutical Quality (OPQ),the Office of Generic Drugs (OGD) and the Office of New Drugs (OND) regarding the assessment[1] of in vitro testing of oral drug products[2] administered via an enteral feeding tube (hereinafter referred to as "enteral tube").[3] This MAPP also outlines collaborations associated with the development of enteral tube information in labeling.

- This MAPP pertains to the assessment of enteral tube information for oral drug products submitted as part of investigational new drug (IND) applications, new drug applications (NDAs), supplemental NDAs, abbreviated new drug applications (ANDAs), and supplemental ANDAs. Relevant dosage forms include, but are not limited to, the following:

    - Granules
    - Pellets
    - Powders

[1] The information included in this MAPP is relevant to assessors in the quality, bioequivalence, labeling, and project management disciplines.
[2] For the purposes of this MAPP, a reference to "drug products" includes drug products for oral administration subject to an application submitted under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) or relevant investigational new drug applications.
[3] This MAPP may also be relevant to products that are subject to biologics license applications that are developed or marketed as oral dosage forms other than solutions where the applicant is seeking to include labeling instructions for administration via enteral tube.

- Suspensions
- Capsules
- Tablets

- This MAPP does not apply to the assessment of:

  - Oral solutions[4]
  - Physical characteristics of the enteral tube (e.g., connector design)
  - Clinical studies to support enteral tube administration
  - Nonprescription drug products[5]

BACKGROUND

- In vitro testing plays a crucial role in ensuring the safe and effective delivery of oral drug products that are administered as dispersions via an enteral feeding tube. Consistency in the assessment of in vitro testing necessitates collaboration and effective communication between OPQ, OGD, and OND for verification of information stated in the labeling of oral drug products. This MAPP outlines the collaboration between OPQ, OGD, and OND pertaining to enteral tube information stated in the labeling of oral drug products administered via enteral tube.

- The draft guidance for industry *Oral Drug Products Administered Via Enteral Feeding Tube: In Vitro Testing and Labeling Recommendations* (June 2021)[6] provides recommendations for in vitro testing and labeling of oral drug products administered via enteral tube. This draft guidance outlines specific information on the recommendations for each of the in vitro tests and their correlation with risks and complications associated with oral drug product administration via enteral tube. This MAPP serves to complement the draft guidance for industry by delineating responsibilities for the assessment of in vitro tests and outlining the collaborations across various disciplines regarding relevant enteral tube-related information included in oral drug product labeling.

POLICY

- **For INDs and NDAs**, OPQ assessors from the Offices of Product Quality Assessment (OPQA) I and II will verify that the application or supplement includes in vitro testing to support a claim for administration of the drug product via enteral tube.

[4] Solutions do not present a risk of forming occlusions when administered via enteral tube.
[5] At this time, nonprescription drugs are not labeled for administration via enteral tube.
[6] When final, this guidance will represent FDA's current thinking on this topic. 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.

- OPQA I and II will collaborate with OND to verify that the language proposed in the NDA labeling[7] accurately reflects the information regarding enteral tube administration, based on in vitro testing.

- In cases where human factors information[8] is submitted, OPQA I and II will assist OND clinical staff and the Office of Surveillance Epidemiology (OSE)/Division of Medication Error Prevention and Analysis (DMEPA) with the assessment, if warranted.

- **For NDA supplements**, OPQ product assessors from OPQA I and II will coordinate with OND to verify that the language stated in the NDA labeling accurately reflects the information regarding enteral tube administration based on in vitro test data.

  - In cases where information on human factors studies is submitted, OPQA I and II will assist OND clinical staff and OSE/DMEPA with the assessment, if warranted.

- **For ANDAs and associated supplements**, OPQ assessors from OPQA I and II as well as staff from OGD will verify that the application or supplement includes comparative in vitro testing for the proposed generic drug product and the reference listed drug (RLD) or reference standard (RS)[9] to support a claim for administration via enteral tube.

  - OPQA I and II will collaborate with OGD to verify that the language stated in the ANDA labeling accurately reflects the information regarding enteral tube administration, based on in vitro testing.

RESPONSIBILITIES

- **OPQ/OPQA I and II Product Quality Assessors**

  (i) **For INDs, NDAs, and NDA supplements**:

  - Assess the adequacy of in vitro testing.

[7] Proposed labeling may include "Instructions for Use" (IFU) that are considered part of the drug product user interface. As such, additional data — such as data from human factors studies — could be used to inform the development of the IFU for a drug product. See guidance for industry *Instructions for Use — Patient Labeling for Human Prescription Drug and Biological Products — Content and Format* (July 2022). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https: //www.fda.gov/regulatory-information/search-fda- guidance-documents.

[8] The discussion of human factors considerations is beyond the scope of this MAPP. For additional information on development of the user interface and human factors considerations, see guidance for industry *Application of Human Factors Engineering Principles for Combination Products: Questions and Answers* (September 2023).

[9] The guidance for industry *Referencing Approved Drugs Products in ANDA Submissions* (October 2020) states that although the regulations do not require that an applicant use a particular product for in vitro testing, it is recommended that the reference standard also be used for in vitro testing.

- The following tests are applicable: recovery testing;[10] sedimentation volume and redispersibility testing; in-use stability in designated dispersion media; particle size distribution studies for suspensions; modified-release dosage forms and other formulations where particle size may indicate a high risk for forming tube occlusions; and acid resistance testing for drug products with an enteric coating.

- Verify that the dissolution test results after delivery via combination of an oral syringe and an enteral tube conform to the acceptance criteria in the drug product specification for extended release[11] products across INDs, NDAs, and NDA supplements.

- Communicate the findings from in vitro tests to OND.

- Verify, in collaboration with OND and the Office of Translational Sciences (OTS)/Office of Clinical Pharmacology (OCP), whether adequate in vitro test data is submitted within the NDA, related supplement, or IND to support administration of the drug product via enteral tube as described in the language stated in the labeling or clinical study/protocol, as appropriate.

- Communicate with the Office of Program and Regulatory Operations (OPRO) regarding the need for an information request to be sent to the applicant[12] if in vitro test data have not been submitted or do not demonstrate drug product suitability for enteral tube administration.

- Assist OND clinical staff and OSE/DMEPA with the assessment when human factors information is submitted, if warranted.

(ii) **For ANDAs and associated supplements:**

- Assess comparative in vitro testing data for the proposed generic product and the RLD or RS in accordance with the applicable Product Specific Guidance, if available, for drug products administered via feeding tube. The following tests are applicable: recovery testing; sedimentation volume and redispersibility testing; in-use stability in designated dispersion media; particle size distribution studies for suspensions, modified-release dosage forms and other formulations where particle size may indicate a high risk for forming tube occlusions.

[10] Recovery testing should be conducted under the following conditions: (a) utilizing three different types (based on material or design) of tubes; (b) considering the number of potential administrations through the tube based on proposed administration instructions (e.g., once per day, or, if administered multiple times a day, mimicking the dosing instructions in the labeling for the drug product); and (c) employing various dispersion media properties (for modified-release products or those containing pH-sensitive excipients).

[11] Dissolution testing may also be appropriate for other dosage forms.

[12] For purposes of this MAPP, the term "applicant" includes application holders and sponsors.

- Verify that the language stated in the RLD labeling (e.g., DOSAGE AND ADMINISTRATION section) is supported by in vitro test data.

- Perform a discipline-specific assessment of the recovery and particle size distribution studies. If OPQ's conclusion for a recovery study differs from that of OGD's Office of Bioequivalence, the offices will work together to reach a consensus.

- Communicate with OPRO regarding the need for an information request to be sent to the applicant if in vitro test data have not been submitted or do not demonstrate drug product suitability for enteral tube administration.

- **OPQ/OPQA I and II Biopharmaceutics Assessor (Divisions of Product Quality Assessment VI and XII):**

  - Addresses consults from OTS/OCP, as needed, if OCP has questions regarding bioavailability/bioequivalence upon nasogastric (NG) tube administration.

- **OGD Bioequivalence Assessor (Office of Bioequivalence (OB)):**

  - Assesses comparative in vitro testing data to verify whether the generic drug, upon administration via enteral tube, is bioequivalent to the RLD or RS.
    - The following tests are applicable: recovery testing (statistical analysis and comparison to the RLD or RS based on data from one tube type/material);[13] particle size distribution (this is applicable to modified-release products only. A statistical analysis will be performed by the OGD bioequivalence assessor); acid resistance testing for drug products with an enteric coating; dissolution testing for extended-release products.

  - Performs a discipline-specific assessment of the recovery study. If OGD's conclusion for recovery studies differs from that of OPQ, both offices will work together to reach a consensus.

- **OGD Office of Research and Standards (ORS):**

  - Develops PSGs that include in vitro feeding tube information, as needed.
  - Coordinates with OGD/OB to update the PSGs as necessary to ensure consistency with the ANDA assessment of the in vitro feeding tube studies.
  - Assesses in vitro enteral tube studies for pre-ANDA meetings to demonstrate bioequivalence of the proposed generic product to the RLD.
  - Collaborates with OPQ on product quality concerns, if warranted.

[13] For example, the same type of tube that is used for acid resistance testing, dissolution testing, or particle size distribution studies.

- Provides responses to controlled correspondence questions for in vitro enteral tube, as appropriate.

- **OGD Labeling Assessor (Division of Labeling Review):**

  - Determines if the enteral tube information in the ANDA labeling aligns with the enteral tube information in the RLD labeling.

  - Coordinates with the OPQ product quality and OGD bioequivalence assessors to verify that in vitro test data: (a) demonstrate drug product suitability for administration via enteral tube and (b) support the stated enteral tube information in the ANDA labeling (e.g., DOSAGE AND ADMINISTRATION section).[14]

  - If made aware of inaccuracies in the enteral tube information in the RLD labeling (e.g., DOSAGE AND ADMINISTRATION section), notifies OPQ or the OND clinical review team; and collaborates with each office to determine the most effective approach to address the issue.

- **OPQ/OPRO Regulatory Business Project Manager (RBPM):**

  - Sends information requests to the applicant in a timely manner.

REFERENCES

1. Draft guidance for industry *Oral Drug Products Administered Via Enteral Feeding Tube: In Vitro Testing and Labeling Recommendations* (June 2021).[15]

2. Guidance for industry *Application of Human Factors Engineering Principles for Combination Products: Questions and Answers* (September 2023).

3. Guidance for industry *Instructions for Use — Patient Labeling for Human Prescription Drug and Biological Products — Content and Format* (July 2022).

4. Guidance for industry *Referencing Approved Drug Products in ANDA Submissions* (October 2020).

EFFECTIVE DATE

This MAPP is effective upon date of publication.

[14] If clinical considerations are raised, the Division of Clinical Review within the Office of Safety and Clinical Evaluation within OGD may be consulted.
[15] When final, this guidance will represent FDA's current thinking on this topic.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
9/5/2023	Initial	N/A
1/8/2026	Rev.1	1. Revisions made consistent with the 2024 OPQ reorganization. 2. Added a section on OGD/ORS responsibilities.