POLICY

OFFICE OF PHARMACEUTICAL QUALITY

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

Table of Contents

PURPOSE

This Manual of Policies and Procedures (MAPP) describes how the Office of Pharmaceutical Quality (OPQ) will address communication with the Office of Generic Drugs (OGD) and the Office of New Drugs (OND), where needed, 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 collaboration relating to the development of enteral tube information in labeling.

This MAPP applies 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:

[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.

- Granules
- Pellets
- Powders
- 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 helps to ensure the safe and effective delivery of oral drug products that are administered as dispersions via an enteral feeding tube. Consistency in assessment of in vitro testing necessitates collaboration and effective communication between OPQ, OGD, and OND to verify information proposed in the labeling of oral drug products. This MAPP outlines collaborations between OPQ, OGD, and OND pertaining to enteral tube information proposed 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 in vitro testing and labeling recommendations for oral drug products administered via enteral tube. The draft guidance details information on the recommendations for each of the in vitro tests and how these in vitro tests correlate with risks and complications associated with oral drug product administration via

[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 the 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.

enteral tube. This MAPP complements the draft guidance for industry by identifying responsibilities for the assessment of in vitro tests and outlining the collaborations across disciplines on relevant enteral tube-related information included in oral drug product labeling.

POLICY

- **For INDs and NDAs**, OPQ assessors from the Office of New Drug Products (ONDP) will verify that the application or supplement includes in vitro testing to support a claim for administration of the drug product via enteral tube.

  - ONDP will collaborate with OND to verify that the proposed NDA labeling[7] accurately reflects the information related to enteral tube administration based on in vitro testing.

  - In cases where human factors information[8] is submitted, ONDP 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 assessors from the Office of Lifecycle Drug Products (OLDP)/Division of Post-Marketing Activities I (DPMA I) and bioequivalence assessors from the ONDP/Division of Biopharmaceutics (DB) will coordinate with OND to verify that the proposed NDA labeling accurately reflects the information related to enteral tube administration based on in vitro test data.

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

- **For ANDAs and associated supplements**, OPQ assessors from the OLDP/Division of Post-Marketing Activities II (DPMA II) and OGD staff 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.

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

[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 the draft guidance for industry *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development* (February 2016). When final, this guidance will represent the FDA's current thinking on this topic.

[9] The Guidance for Industry "*Referencing Approved Drugs Products in ANDA Submissions*." (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.

- OLDP will collaborate with OGD to verify that the proposed ANDA labeling accurately reflects the information related to enteral tube administration based on in vitro testing.

RESPONSIBILITIES

OPQ/ONDP Product Quality Assessor

- Assesses the adequacy of in vitro testing for INDs and NDAs.
  - 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.

- Verifies 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 and NDAs.

- Communicates findings of in vitro tests to OND.

- Verifies, 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 proposed labeling or clinical protocol, as appropriate.

- Communicates with the Office of Program and Regulatory Operations (OPRO) about 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.

[10] Recovery testing should use the following conditions: (a) three different types (material or design) of tubes, (b) 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) different dispersion media properties (for modified-release products or products 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.

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

OPQ/OLDP Product Quality Assessor (Division of Post-Marketing Activities I):

- Assesses the adequacy of in vitro testing for NDA supplements.
  - 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; and acid resistance testing for drug products with an enteric coating.
- Verifies 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 products across NDA supplements**.**
- Communicates findings of in vitro tests to OND and OGD.
- Verifies, in collaboration with OND, whether adequate in vitro test data is submitted within the NDA, related supplemental NDA, or IND to support administration of the drug product via enteral tube as described in the proposed labeling or clinical study, as appropriate.
- Communicates with OPRO about 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.
- When human factors information is submitted, assists OND clinical staff and OSE/DMEPA with the assessment, if warranted.

OPQ/OLDP Product Quality Assessor (Pre-marketing Divisions):

- Assesses comparative in vitro testing data for the proposed generic product and the RLD or RS for ANDAs and associated supplements.
  - 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.
- Verifies that the language proposed in the RLD labeling (e.g., DOSAGE AND ADMINISTRATION section) is supported by in vitro test data.

- Performs 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 consensus.

OPQ/ONDP Biopharmaceutics Assessor (Division of Biopharmaceutics):

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

OGD Bioequivalence Assessor (Office of Bioequivalence):

- Assesses comparative in vitro testing data to verify bioequivalence[13] of the generic drug to the RLD or RS upon administration via enteral tube.

  - The following tests are applicable: recovery testing (statistical analysis and comparison to the RLD or RS based on data from one tube type/material);[14] 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.

- Office of Research and Standards will generate Product Specific Guidance to include in vitro feeding tube tests.

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 assessor and the OGD bioequivalence assessor to verify that in vitro test data: (a) demonstrate drug product suitability for administration via enteral tube and (b) support the proposed enteral tube information in the ANDA labeling (e.g., DOSAGE AND ADMINISTRATION section).[15]

[13] For pre-ANDA meetings, OGD's Office of Research and Standards will assess in vitro enteral tube studies for the purpose of demonstrating bioequivalence of the proposed generic product to the RLD. See also FN15.

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

[15] If clinical considerations are raised, the Division of Clinical Review within the Office of Safety and Clinical Evaluation within OGD may be consulted.

- Determines if inaccurate enteral tube information is identified in the NDA labeling (e.g., DOSAGE AND ADMINISTRATION section), and if inaccurate information is identified notifies OPQ or the OND clinical review team; and collaborates with each office to determine the best approach to address the issue.

OPQ/OPRO Regulatory Business Project Manager (RBPM):

- Sends timely information requests to the applicant.

REFERENCES

1. Draft guidance for industry *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development* (February 2016).[16]

2. Draft guidance for industry *Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments* (July 2018).[17]

3. Draft guidance for industry *Oral Drug Products Administered Via Enteral Feeding Tube: In Vitro Testing and Labeling Recommendations* (June 2021).[18]

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

EFFECTIVE DATE

This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
9/5/2023	Initial	N/A

[16] When final, this guidance will represent the FDA's current thinking on this topic.

[17] Ibid.

[18] Ibid.