Oral Drug Products Administered Via Enteral Feeding Tube: In Vitro Testing and Labeling Recommendations

Guidance for Industry

DRAFT GUIDANCE

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Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Devices and Radiological Health (CDRH)

June 2021
Pharmaceutical Quality/CMC

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Oral Drug Products Administered Via Enteral Feeding Tube: In Vitro Testing and Labeling Recommendations Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations regarding in vitro testing of oral drug products, other than solutions, administered via enteral feeding tube (hereinafter *enteral tube*). These products represent a wide range of oral dosage forms including, but not limited to, granules, pellets, powders, suspensions, capsules, and tablets. The recommendations for in vitro testing apply to products that are subject to the following and submitted under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and 21 CFR parts 312 and 314:[2]

- New drug applications (NDAs) (original or supplemental) where applicants are seeking and/or revising enteral tube administration instructions and related information in labeling

- Abbreviated new drug applications (ANDAs) where the reference listed drug (RLD) contains enteral tube administration instructions and related information in labeling

- Investigational new drug applications where the investigational drug product is administered or planned for administration via enteral tube

[1] This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research in cooperation with the Center for Devices and Radiological Health at the Food and Drug Administration.

[2] The principles and recommendations in this guidance 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 labeling instructions for administration via enteral tube. Applicants seeking licensure for these products are encouraged to contact the Agency regarding their development plans.

Specifically, the guidance covers:

- In vitro testing recommendations to ensure oral drug product quality and, as applicable, bioequivalence to the RLD when evaluating a drug product's suitability for administration via enteral tube

- Appropriate content and format for submission of in vitro testing results regarding administration via enteral tube

- Recommendations on how to incorporate information about administration via enteral tube in drug product labeling when supported by in vitro testing results[3]

The guidance does **not** cover recommendations involving:

- Oral solutions, which do not present the same risk of forming occlusions when administered via enteral tube as other oral dosage forms containing solid or insoluble components

- Clinical study design to support enteral tube administration

- Physical characteristics of enteral tubes (e.g., connector design), which are covered in the guidance for industry *Safety Considerations to Mitigate the Risks of Misconnections with Small-bore Connectors Intended for Enteral Applications* (February 2015)[4]

Providing recommendations for in vitro testing of oral drug products administered via enteral tube will support the development of clear, product-specific enteral tube administration instructions in labeling for administration to patients unable to ingest oral drug products. The goal is to establish applicable in vitro methodology and provide information in drug product labeling for safe and effective administration of oral drug products through enteral tubes.

Applicants[5] are encouraged to discuss testing approaches that differ from those recommended in this guidance with the applicable review or assessment staff before conducting the studies.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless

[3] The recommendations in this guidance are limited to applicants for drug products seeking or bearing labeling instructions for administration via enteral tube. As of the time of publication of this guidance, no nonprescription drug product is labeled for administration via enteral tube. Therefore, with respect to nonprescription drug products, only those applicants seeking such labeling statements should follow the recommendations for in vitro testing to evaluate the drug products' suitability to be administered via enteral tube.

[4] 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.

[5] For the purposes of this guidance, the term *applicant* includes *application holder*, *manufacturer*, and *sponsor*.

specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

Enteral tubes are critical for patients who are unable to swallow oral dosage forms because of medical conditions or therapies that may compromise swallowing or the function of the proximal gastrointestinal system (e.g., feeding disorders, severe intellectual disabilities, neurological disorders, cancers). These patients rely on enteral tubes for their nutrition and drug treatment needs. This need spans patient care settings from intensive care units and other acute care settings to chronic residential care facilities and patients' homes. Enteral tube feeding at home is becoming widespread, with an estimated patient prevalence of 1,385 per 1 million U.S. inhabitants (Mundi et al. 2017). It is essential that each drug product administered via enteral tube is delivered in a manner that preserves the correct dose and the drug's expected safety and effectiveness profile, including any labeled **modified-release**[6] characteristics, and does not compromise the integrity of the tube. Although some FDA-approved drug products include instructions for enteral tube administration in their labeling, the administration instructions and in vitro testing to support administration via enteral tube are not sufficiently widespread or consistent (Ren et al. 2017).

Enteral tubes differ in tube diameter (inner and outer), tube composition, inner tube geometry, tube length, port number, connector type, port geometry (closed versus open distal tip), and number and location of eyes. Enteral tubes are composed of a variety of materials, including polyurethane, polyvinylchloride, and silicone. Table 1 summarizes common enteral tube types and their typical size ranges. In general, enteral tube size is designated by the diameter of the outer tube in French (Fr) units. Some enteral tubes can be inserted through the nose and are intended for short-term use, typically less than 4 weeks. Enteral tubes for chronic use (greater than 4 weeks) are placed percutaneously into the stomach or jejunum using an open surgical, endoscopic, or radioimaging technique.

Table 1. Types and Characteristics of Enteral Tubes

Type	Outer Tube Diameter (Fr*,**)
Nasogastric	5-18
Nasoduodenal	3.5-12
Nasojejunal	3.5-12
Gastrostomy	12-30
Gastrojejunal	12-22
Jejunostomy	12-18

* Fr = French

** 3 Fr = 1 millimeter

Clinical data suggest enteral tube occlusions and clogs occur in 23 to 35 percent of cases during routine use (Bourgault et al. 2003; Dandeles and Lodolce 2011; Blumenstein et al. 2014). The

[6] Terms that appear in bold type upon first use are defined in the Glossary.

risks of enteral tube occlusion increase under a number of conditions, including, but not limited to, the following (Bourgault et al. 2003; Shipley et al. 2016):

- Presence of insoluble ingredients
- Aggregation in **dispersion media**
- Selection of an inappropriate vehicle to serve as the dispersion media[7]
- Inadequate flushing of the enteral tube before and after drug product administration
- Inadequate drug product dispersion before administration
- Larger particle size
- Drug product-enteral tube interactions
- Departures from drug product labeling or enteral tube instructions

The Agency recognizes the need for consistent in vitro testing to ensure safe and effective delivery of drug products that may be administered via enteral tube and to identify drug products that cannot be administered through an enteral tube without altering the safety and effectiveness profile of the drug product or compromising the integrity of the tube.

III. IN VITRO TESTING RECOMMENDATIONS TO EVALUATE DRUG PRODUCT SUITABILITY FOR ADMINISTRATION VIA ENTERAL TUBE

Given the inherent challenges of administering oral drug products via enteral tubes, it is critical that in vitro testing to evaluate drug product suitability for enteral tube administration be completed before the initiation of any clinical studies intended to support enteral tube administration claims in labeling. Performing controlled in vitro testing before the initiation of clinical studies will aid in developing appropriate administration instructions for clinical studies and potentially identify drug product-specific risks associated with enteral tube administration.

The in vitro testing recommended in this guidance should be performed for oral drug products other than solutions by: (1) applicants for new drugs, whether by original or supplemental application, seeking to add labeling instructions for administration via enteral tube; and (2) applicants for generic drugs where the RLD labeling includes instructions for administration via enteral tube. The results of in vitro testing to support the use of enteral tube administration should be submitted to the Agency as part of original or supplemental drug applications in which enteral tube administration labeling claims are sought. Completion of the recommended testing should demonstrate whether or not a drug product is suitable for enteral tube administration. More evidence may be needed to demonstrate suitability and/or compatibility for administration via enteral tube for a solid oral dosage form known to contain insoluble components than for an oral drug product that completely dissolves in the directed dispersion media.

Applicants seeking labeling instructions for administration via enteral tube should consider multiple factors when determining how to perform in vitro enteral tube administration testing during drug product development including:

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

- The active pharmaceutical ingredient's (API's) site of absorption from the gastrointestinal tract

- Whether the drug has a narrow **therapeutic index**

- Whether the drug product is a **delayed-release** or **extended-release** dosage form[8]

- The aqueous solubility of the API and inactive ingredients

- Whether the API or inactive ingredients may adhere to the enteral tube material (Jory et al. 2017)

The Agency recommends applicants consider the following test development recommendations and test types when conducting testing to demonstrate that oral drug products are suitable for administration via enteral tube. The data generated from the following studies should be included in a report to support enteral tube administration as a valid alternative method of drug product delivery.[9]

A. In Vitro Testing Development Considerations

The following testing recommendations are based on an expectation that the drug product will be prepared for in vitro testing in the same manner as it will be prepared for administration via enteral tube to a patient in planned clinical studies, or prepared as described in labeling submitted for approval, as applicable.

1. Selection of Enteral Tubes

If an applicant intends to recommend multiple tube types (e.g., nasogastric (NG), gastrostomy (G)) or sizes (e.g., Fr 10-16) for administration of its drug product, the recommended testing should, at minimum, be performed with the smallest intended enteral tube size for each type of material or design (see section III.B.4., Particle Size Distribution Study, for testing data that may be helpful in the selection of tube size). For example, if an applicant intends the labeling to include instructions for drug product administration with both NG (Fr 8 and above) and G tubes (Fr 12 and above), NG tubes should be tested at Fr 8 and G tubes should be tested at Fr 12.

Enteral tubes may be made with different materials (e.g., polyvinylchloride, silicone, polyurethane) and different designs (e.g., various numbers of ports and/or eyes, retention

[8] The term *modified-release* is defined in United States Pharmacopeia (USP) General Chapter <1151> *Pharmaceutical Dosage Forms*. "Modified-release is a term used when the rate and/or time of release of the drug substance is altered as compared to what would be observed or anticipated for an immediate-release product. Two modified-release profiles, delayed-release and extended-release, are recognized."

[9] The studies described in this guidance may be suitable for inclusion in various sections of the electronic common technical document, depending on the context of the submission. Therefore, the Agency recommends inclusion of a summary report in Module 2, with a link to the full testing report. See also the Appendix of this guidance for test report format.

balloons, open or closed distal end). Such differences may affect the inner tube diameter and/or flow of material through the tubes (Kurien et al. 2015). For in vitro testing, applicants should consider the material and design of the various enteral tubes that may be used for drug product administration, and test a representative selection of tubes to ensure complete delivery of the drug product in the recovery test. FDA recommends that applicants test at least three different enteral tube configurations for all tube types proposed in the labeling and provide justification for the enteral tubes selected for testing. Note that for G tubes, at least one tube should be tested with an inflated balloon configuration.

2. Dispersion Media and Dispersion Preparation

Various dispersion media such as purified water, apple juice, milk, and liquid nutritional supplements may be used as vehicles for oral drug product administration and to flush enteral tubes. The properties of the dispersion media may vary between brands or formulations. Variations may include pH, concentration, ingredients, and preparation method, among others. Therefore, applicants should consider the different types and properties of the vehicles that may be used for drug product administration and evaluate the risk due to potential variations in the dispersion media used. This analysis should form part of the basis for justifying the administration conditions, including dispersion media. Detailed instructions describing how the drug product is prepared for enteral tube administration should be documented including:

- Dispersion medium (e.g., type of water such as purified water (including distilled water and water for injection); type of liquid food; brand of juice)[10]
- Volume and temperature of the dispersion medium
- Holding/**soaking time** between dispersion and administration through the enteral tube
- Number of potential administrations through the tube based on proposed administration instructions (e.g., once per day, every four hours)
- Details regarding the preparation and dispersion method of the drug product (e.g., crush, suspend, dissolve, shaking method), including any equipment used in preparation or dispersion
- The pH of the medium before and after dispersion
- **Flush volume** used before and after drug product administration
- Tube and syringe used (e.g., brand item number, material, brand, inner and outer tube diameter, with or without balloon (filled according to the tube manufacturer's instructions), number of eyes, length of the tube, syringe tip type)

[10] Tap water is not recommended as a dispersion medium in the laboratory setting due to its variability as described in this guidance.

- **Holding position of the tube** and **holding position of the syringe** (e.g., horizontal, vertical)

- Method, analytical site, and testing dates for each of the tests

The pH for different types of water (e.g., distilled, sterile, and other types of bottled water) may vary between 5.5 to 8.5. When water is used as the dispersion medium, particularly for modified-release dosage forms or for products containing pH-sensitive coating excipients, the pH within the preparation container, oral syringe, or enteral tube might adversely affect the integrity of the **enteric coating** or dissolution of drug products. Therefore, in these cases, we recommend testing using water with different pH values (e.g., pH 5.5, 7.0, 8.5) for in vitro enteral tube studies even if labeling will specify a particular type of water. Similarly, when juice is used as the dispersion medium, multiple types of juice should be studied, even if labeling will specify a particular type of juice.

3. In Vitro Method Development

Development of in vitro methods should follow a risk-based process. In vitro testing conditions should be justified based on the drug product formulation and its proposed method of administration. For example, successful testing on the smallest tubing diameter recommended for use in the drug product labeling would obviate the need to perform testing through tubing with larger diameters. Likewise, performing the testing at the initial (time zero) and final time points proposed before administration (e.g., holding/soaking time) would also reduce the need for testing holding/soaking time points that fall between those two extremes. Applicants should also consider the dose strengths of their drug products to select the formulation at highest risk of forming occlusions for testing and should provide their rationale.

The following is a general overview of the in vitro testing method recommendations:

- The enteral tube should be prepared according to the tube manufacturer’s instructions (e.g., flushing the tube or inflating the balloon).

- The drug product (e.g., granules from capsule, tablet (crushed or not)) should be prepared in the dispersion medium (e.g., purified water, apple juice, or milk), and rotated gently until the drug product is completely dispersed with no particles visible that are large relative to the tube inner diameter.

- The drug product dispersion should be transferred into an oral syringe, the oral syringe (or funnel, if applicable) should be connected to the enteral tube, and the dispersion should be passed through the enteral tube into a collection container. After administration of the dispersion using the enteral tube, the enteral tube and syringe should be flushed with a specified amount of the dispersion medium.

B. Testing Type Recommendations

The type and extent of testing should be a risk-based decision focused on the characteristics of the individual drug product. For example, if additional procedures are needed during testing to demonstrate that the drug product can be delivered by enteral tube, the applicant should provide a detailed description of these procedures.

There are additional testing considerations for modified-release dosage forms. In vitro testing of modified-release products should demonstrate that preparation of the drug product for administration via enteral tube does not adversely affect the drug content assay or release characteristics (e.g., dissolution), where appropriate.

These testing recommendations do not replace conventional drug product quality characterization studies or in vivo bioequivalence studies for the drug product that are typically conducted.

1. Recovery Testing

The purpose of recovery testing is to determine the percentage of a dose of a drug that successfully passes through an enteral tube when the drug product is prepared and administered as specified or proposed in the product labeling. Recovery testing should be performed to support enteral tube administration. Applicants should determine the percentage of drug recovered at the tube exit relative to the initial dose of the drug product using a validated analytical method. The study should be conducted using an adequate number of samples and justification for the selected sample size should be provided. The tube and syringe should be examined visually, and any aggregation, buildup, clogging, or other observations should be recorded. The percentage of drug recovered at the tube exit relative to the initial dose should meet appropriate drug product release specifications for new drugs. For generic drugs, the percentage should be calculated as described in section III.C.2., Additional Considerations for ANDA Submissions. Applicants should provide video or photographs of the contents of the syringe and tube before, during, and after testing.

If a drug product will be administered multiple times in a 24-hour period, applicants should mimic the directed dosing regimen and record drug recovery after each individual administration (i.e., the same tube should be used for sequential administrations of the drug product).

If the dispersion medium is water, recovery testing should be performed with material recovered from the enteral tube using water with different pH values (e.g., pH 5.5, 7.0, 8.5) and various soaking times to support the intended delivery time. The pH values of the drug product dispersion should be measured upon initial dispersion and after delivery through the enteral tube.

2. Sedimentation Volume and Redispersibility Testing

Sedimentation volume and redispersibility testing should be performed to assess the sedimentation potential of a drug product within an enteral tube to support enteral tube administration. Insoluble components of a drug product have the potential for sedimentation that

may increase the risk of clogging. For convenience, instead of an enteral tube, a syringe can be used for this test. To test sedimentation volume, the syringe should be loaded with drug product dispersion and allowed to settle. Applicants should record the sedimentation volume and duration of test (e.g., holding/soaking time). Markings on the syringe can be used for the measurement.

Redispersibility of the drug product dispersion should be evaluated to determine if settled solids can be redispersed for administration (e.g., by shaking after the maximum directed soaking time). The syringe that was used for the sedimentation volume test above should be used to test redispersibility. Applicants should provide a qualitative description of the test product (e.g., particle aggregation and particles adhering to the syringe walls). Representative photographs of the syringe contents should be taken at various intervals throughout the testing process.

Sedimentation volume and redispersibility tests performed during product development or included as part of routine testing of the drug product (e.g., for oral suspensions) may be sufficient to serve as the sedimentation volume and redispersibility tests recommended in this guidance to support enteral tube administration.

3. In-Use Stability in Designated Dispersion Media

When labeling instructions for administration via enteral tube specify an in-use holding/soaking time before administration via enteral tube, in vitro testing as described in this guidance should include in-use stability testing through this in-use period.[11] Applicants should perform in-use stability testing in the proposed dispersion media to demonstrate that the drug product dispersion, when prepared for enteral tube administration, is chemically and physically stable (i.e., as indicated by the dissolution profile) throughout the specified soaking time at the recommended or proposed storage conditions. Chemical stability of the drug product dispersion under proposed storage conditions for enteral tube administration should be monitored at predetermined time intervals. The drug content and degradation products of the API should be determined using a stability-indicating method or methods. The results of the stability studies should provide assurance for the stability of the drug product dispersion during the proposed soaking period.

For extended holding times before administration of over 4 hours at room temperature or over 24 hours under refrigeration, applicants should include microbiological studies in support of the proposed storage conditions. For microbial testing and acceptance criteria for non-sterile aqueous drug products for oral use, see United States Pharmacopeia (USP) General Chapter <1111> *Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use*, USP General Chapter <61> *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests*, and USP General Chapter <62> *Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms*.

[11] See the ICH guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products* (November 2003) for additional information about in-use stability testing.

4. Particle Size Distribution Study

Particle size is a key attribute affecting the passage of a drug product through an enteral tube during administration. The particle size distribution study evaluates one mechanism by which a formulation could block the tube and predicts the risk of blockage. Particle size distribution studies should be conducted for modified-release dosage forms and other formulations where particle size may indicate a high risk for forming tube occlusions. Following the enteral tube preparation procedure outlined in section III.A.3., In Vitro Method Development, applicants should determine the particle size of the drug suspension before and after delivery through the enteral tube. Particle size should be determined using a validated method that is sufficiently reproducible and sensitive (e.g., laser diffraction method with the particle size data at the D10, D50, and D90 levels).

5. Acid Resistance Testing for Drug Products With an Enteric Coating

Acid resistance testing is used to ensure the integrity of the enteric coating of delayed-release dosage forms during administration via enteral tube.[12] Acid resistance testing should be performed on drug products with an enteric coating. The test should be performed under acidic conditions (pH 1.2 or 0.1 N HCl for 1–2 hour(s) per drug product release specification) after the drug product is incubated in the dispersion medium and delivered through the enteral tube. The percentage of drug released into the acidic medium should conform to the acceptance criteria set in the drug product specification. Applicants should consider the potential for degradation of the API if it is acid-labile.

6. Dissolution Testing for Extended-Release Drug Products

Dissolution testing should be performed for extended-release dosage forms to demonstrate that preparation and delivery via enteral tube does not affect the timing of drug release from the dosage form. Dissolution testing should be performed after administration through a combination of an oral syringe and an enteral tube in dissolution media specified in the drug product specification. The pH values of the drug product dispersion should be measured before and after delivery through the enteral tube. The amount of drug released into each recommended dispersion medium should also be quantitated after passing through the enteral tube. After collection of the drug product dispersion at the enteral tube exit, the particulates collected into a dissolution vessel should be transferred using the testing conditions specified in the drug product specification and the amount of drug released should be determined at time points per the drug product specification. The amount of drug released (after passage through the enteral tube) divided by the labeled content of the drug product and expressed as a percentage should conform to the acceptance criteria set in the drug product specification.

[12] A tablet that is enteric-coated would not likely be appropriate for enteral tube administration because crushing to disperse the drug would disrupt the function of the enteric coating, whereas a capsule containing enteric-coated beads may be suitable for enteral administration.

C. Data Submission for Drug Product Applications

In addition to the test results, applicants should submit test protocols and the analytical methods used for the in vitro enteral tube studies recommended in section III.B., Testing Type Recommendations. The test protocols should incorporate the recommendations in section III.A.2., Dispersion Media and Dispersion Preparation. Detailed method validation reports for the analytical techniques used should be submitted to demonstrate adequacy for the intended purpose. If the method validation reports for the analytical techniques used are provided elsewhere in the application, a link or reference to that location in the submission should be provided. Individual data, mean values, standard deviations, and coefficients of variation (CV %) for each test should be submitted. Test results should be submitted in the format described in the Appendix.

The tubing and syringe used for in vitro testing should be examined visually for any aggregation, adherence, or clogging, and the observations reported with supporting visual information (video and/or photographs). For recovery studies, applicants can provide videos that document the testing process and associated observations. If application of additional force to the syringe compared to that used for initial flushing with dispersion medium is needed during the testing to ensure complete recovery, it should be documented, and an explanation should be provided.

1. Additional Considerations for NDA Submissions

For NDAs, the in vitro testing recommendations provided in section III.B., Testing Type Recommendations, are intended as the initial step to demonstrate that a new drug product is suitable for administration via enteral tube. Clinical studies involving enteral tube administration of a new drug product are outside the scope of this guidance, but if applicable, generally should be conducted after the recommended in vitro studies demonstrate the suitability of a new drug product for enteral tube administration and the appropriate administration instructions have been established. For a new drug product seeking labeling instructions for administration via enteral tube, the proposed labeling statement in the DOSAGE AND ADMINISTRATION section should be developed based on, and be supported by, the results of enteral tube administration testing. To ensure adequate investigations, FDA encourages early communication with the review division to discuss in vitro testing and any clinical study protocol design. When submitting the in vitro test and any clinical study results, applicants should provide the enteral tube administration instructions, including the recommended enteral tube type, size, brand, part number, and the size of the oral syringe used. This information should be submitted at the time the claim for enteral tube administration is sought (e.g., in the original NDA submission, or in a supplement if clinically indicated).

2. Additional Considerations for ANDA Submissions

For ANDAs, the in vitro testing recommendations provided in section III.B., Testing Type Recommendations, are intended to demonstrate that a generic drug product is therapeutically equivalent to the RLD when administered according to the RLD product labeling enteral tube

administration instructions.[13] The enteral tube administration instructions provided in the DOSAGE AND ADMINISTRATION section of labeling for the RLD should guide development of the in vitro enteral tube administration testing procedures for the planned generic drug product. If the RLD is discontinued and the reference standard (RS) is being used for bioequivalence testing, the enteral tube administration instructions in the labeling of the RS should guide development of the in vitro enteral tube administration testing procedures.[14]

When performing the recommended in vitro testing to ensure bioequivalence to the RLD (or RS if the RLD is discontinued or otherwise unavailable) after administration via enteral tube, applicants should describe the testing conditions including: the number of units of the test and reference drug products used; enteral tube type, size, brand, and part number; and the size of the oral syringe used.

For comparative in vitro testing (e.g., recovery testing, acid resistance testing, and sedimentation testing), applicants should prepare the enteral tube studies based on the procedure outlined in the most current FDA-approved drug product labeling using 12 units each of the test (T) and reference (R) drug products dispersed in the dispersion medium for 0 minutes and for the maximum allowable holding/soaking incubation time in accordance with the drug product labeling, unless the testing conditions set forth in the relevant product-specific guidance for generic drug development state otherwise. All in vitro enteral tube tests should be performed on unexpired T and R batches of the drug product. When labeling instructions specify immediate administration after preparation, the Agency recommends performing comparative in vitro enteral tube testing at both 0- and 15-minute soaking times. For recovery testing, applicants should determine the percentage of drug recovered at the tube exit relative to the initial dose for both the T and R products using a validated analytical method. Applicants should calculate the T/R recovery ratio and the 90 percent confidence interval of the T/R recovery ratio.

This information should be provided in the original ANDA submission. For additional insight on the recommended in vitro testing reporting format, see the Bioequivalence Summary Tables for In Vitro Feeding Tube Testing.[15] Any recommendations for in vivo bioequivalence studies involving administration via enteral tube will be communicated in the respective product-specific guidance for generic drug development.[16]

[13] The regulations under 21 CFR 314.3 define *therapeutic equivalents* as follows: "approved drug products that are pharmaceutical equivalents for which bioequivalence has been demonstrated, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling."

[14] See the draft guidance for industry *Updating ANDA Labeling After the Marketing Application for the Reference Listed Drug Has Been Withdrawn* (July 2016). When final, this guidance will represent the FDA's current thinking on this topic.

[15] https://www.fda.gov/media/98853/download

[16] Product-specific guidances are published on the Product-Specific Guidances for Generic Drug Development web page at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.

IV. LABELING RECOMMENDATIONS

A. Oral Drug Product Recommended for Administration Via Enteral Tube

If there are adequate data that support administration of the drug product via enteral tube, the drug product labeling should include sufficient information to ensure that the health care provider, patient, and/or caregiver have the essential information to administer the drug product safely and effectively via enteral tube. The DOSAGE AND ADMINISTRATION section of labeling should include, as applicable:[17]

- Information on which dosage form(s) and strength(s) are suitable for administration via enteral tube.

- Recommended enteral tube characteristics, such as the following:

  – Type (e.g., NG, G)

  – Size range (expressed in French units)

  – Any other tube characteristic that affects passage of the drug product dispersion through the tube (e.g., material composition)

- Recommended drug product and enteral tube preparation instructions before administration. For example:

  – Dispersion media (e.g., type of water, milk, apple juice)

  – Details regarding the method of drug product dispersion (e.g., crush to a fine powder, suspend, dissolve, shaking method)

  – Volume of dispersion media and soaking time of drug product dispersion before administration

  – Preparation of the enteral tube (e.g., flushing the tube)

  – Other recommended preparation information (e.g., shaking the syringe immediately before administering the drug product dispersion, a physical description of the desired dispersion)

- Recommended administration instructions. These can include, but are not limited to:

  – Volume and rate of administration of the drug product dispersion for each strength (if different)

[17] See the guidance for industry *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (March 2010).

  - Holding positions of the syringe and tube during administration

  - Instructions regarding any residual drug product in the mixing container, syringe, or enteral tube

  - Information regarding the timing of administration, such as in relation to continuous enteral feeding or the appropriate interval prior to the administration of a different drug product.

- Instructions on maintenance of the enteral tube following administration (e.g., flushing of the tube)

- Instructions for storage of residual drug product dispersion during the in-use period, if applicable.

Clinically relevant information about dispersion media, preparation procedures, syringe characteristics, soaking times, and enteral tube characteristics that adversely affect drug delivery, if applicable, should be presented in the appropriate section(s) or subsection(s) of labeling (e.g., DOSAGE AND ADMINISTRATION section, WARNINGS AND PRECAUTIONS section, *Pharmacokinetics* subsection of the CLINICAL PHARMACOLOGY section).

If applicable, the DOSAGE AND ADMINISTRATION section should cross-reference the *Pharmacokinetics* subsection of the CLINICAL PHARMACOLOGY section of labeling, where a succinct summary of the relevant data (e.g., enteral tube characteristics, dispersion media or soaking times) that affect the pharmacokinetics of the drug product should be included.[18]

Provided below are examples of instructions for the preparation and administration of a drug product dispersion via enteral tube in the DOSAGE AND ADMINISTRATION section of labeling.

Example 1

To administer DRUG-X tablets (all strengths) via nasogastric tube (French size 8 or larger) follow these steps *[see Clinical Pharmacology (12.3)]*:

- Place one tablet in a catheter-tip syringe and draw up 20 mL of distilled water.

- Shake gently to allow for a quick dispersal.

- After the tablet has dispersed, swirl the catheter-tip syringe gently to keep the microgranules from settling, and immediately inject the mixture through the

[18] See the guidance for industry *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (December 2016).

nasogastric tube into the stomach. Do not save the water and microgranule mixture for later use.

- Refill the catheter-tip syringe with approximately 10 mL of distilled water, shake gently, and flush the tube.

- Refill the catheter-tip syringe again with 10 mL of distilled water, swirl gently, and administer.

Example 2

To administer DRUG-X capsules via nasogastric (French size 8 or larger) or gastrostomy tube (French size 12 or larger):

- Open the capsule and empty the entire contents of the capsule into a clean container with 30 mL of distilled water.

- Gently swirl the mixture in the container for 30 seconds or longer until all of the powder is uniformly dispersed in the liquid.

- After the capsule's contents have dispersed, draw up the mixture into a catheter tip syringe. Apply steady pressure to dispense the contents of the syringe into the nasogastric or gastrostomy tube within 15 minutes of preparation. Do not keep the mixture for later use.

- If residual drug remains in the syringe or tube, draw up 10 mL of distilled water into the syringe, swirl it around, and administer through the tube.

- Flush the tube with at least 10 mL of distilled water.

If applicable, FDA-approved patient labeling (e.g., Instructions for Use[19]) should include detailed patient-use instructions for the preparation, administration, handling, storage, and disposal of the drug product dispersion administered via enteral tube.[20]

[19] See the draft guidance for industry *Instructions for Use — Patient Labeling for Human Prescription Drug and Biological Products and Drug-Device and Biologic-Device Combination Products — Content and Format* (July 2019). When final, this guidance will represent the FDA's current thinking on this topic.

[20] The Instructions for Use 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 instructions for use for an NDA drug product. The discussion of human factors considerations is outside the scope of this guidance. For additional information on development of the user interface and human factors considerations, see the draft guidance for industry and FDA staff *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.

B. Oral Drug Product NOT Recommended for Administration Via Enteral Tube

If, in the development of an oral drug product intended for administration via enteral tube, testing identifies no successful method for preparation and administration of the drug product via enteral tube, then the DOSAGE AND ADMINISTRATION section of labeling should state this and provide a brief rationale, if appropriate. As applicable, relevant information supporting the recommendation against enteral tube administration should be succinctly summarized in other subsections or sections of labeling (e.g., DESCRIPTION section, *Pharmacokinetics* subsection of the CLINICAL PHARMACOLOGY section) and a cross-reference to that information should be provided in the recommendation.

Provided below are examples of statements recommending against administration of an oral drug product via enteral tube in the DOSAGE AND ADMINISTRATION section of labeling.

Example 1

Do not administer DRUG-Y via nasogastric, gastrostomy, or other enteral tubes because it may cause obstruction of enteral tubes.

Example 2

Do not administer DRUG-Y for Oral Suspension via nasogastric, gastrostomy, or other enteral tubes, because its chemical constituents may interact with the device material *[see Description (11)]*.

If applicable, FDA-approved patient labeling (e.g., Instructions for Use,[21] Medication Guide,[22] Patient Package Insert) should include patient-use instructions that the drug product should not be administered via enteral tube along with the reason why not.

[21] See footnote 19.

[22] 21 CFR part 208

GLOSSARY

Delayed-release: A formulation that achieves a delay in the release of the drug substance for some period of time after initial administration.

Dispersion media: A qualified liquid substrate used to disperse a drug product for delivery through an enteral tube.

Enteric coating: A polymer barrier applied on drugs intended for oral administration that prevents their dissolution or disintegration in the gastric environment.

Extended-release: A formulation that makes the drug available over an extended period of time after ingestion. This allows a reduction in dosing frequency as compared to that presented by a conventional dosage form (e.g., a solution or an immediate-release dosage form).

Flush volume: A predetermined quantity of liquid used to purge an enteral tube before and/or after the administration of a drug product in the directed dispersion media.

Holding position of the syringe: The specific orientation (e.g., horizontal, vertical) at which a syringe must be maintained to ensure adequate administration of a drug product in the directed dispersion media.

Holding position of the tube: The specific orientation (e.g., horizontal, vertical) at which an enteral tube must be maintained to ensure adequate administration of a drug product in the directed dispersion media.

Modified-release: When the rate and/or time of release of the drug substance is altered as compared to what would be observed or anticipated for an immediate-release product. Two modified-release profiles, delayed-release and extended-release, are recognized.

Soaking time: A qualified duration of time that demonstrates adequate dispersion of an oral dosage form in the specified dispersion media.

Therapeutic index: A ratio of the median toxic dose to the median effective dose of a specific drug product.

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APPENDIX: RECOMMENDED REPORT FORMAT FOR SUBMISSION OF IN VITRO TESTING RESULTS TO SUPPORT ENTERAL TUBE ADMINISTRATION

Test Report Information

Complete test reports for nonclinical in vitro testing should include: the objective of the test, description of the test methods and procedures, predefined pass/fail criteria, test results, and discussion of conclusions.

A. Summary Table

To facilitate the assessment of submissions, FDA recommends that all submissions containing in vitro testing reports also include a tabular summary of the testing performed and results obtained, following the list in B. Test Reports.

B. Test Reports

Complete test reports should include clear, detailed descriptions of:

1. **Test performed**

2. **Test objectives**

3. **Test methods and procedures.** The following should be included:

    a. **Test sample information**

    The sample tested should be described.

    b. **Test sample size/selection**

    The report should provide a scientific rationale to support the number of samples tested. The test sample selection should consider both inter- and intra-lot variability (e.g., by examining multiple manufacturing lots if appropriate).

    c. **Test protocol**

    The test protocol should contain enough detail that an individual familiar with the testing will be able to interpret the purpose of the test, how the test was performed, and whether the test protocol and method are appropriate to evaluate the results of the testing. The test protocol should describe the test parameters, including an explanation of and rationale for critical test parameters. The test protocol should also include acceptance criteria with scientific or clinical justification for the relevancy of the acceptance criteria.

Inclusion of the test protocol is unnecessary if FDA-recognized consensus standards that include test methods are used during testing even when a Declaration of Conformity to the standard is not provided.[1] Instead, the report should include a full citation for the standard including the version, the extent to which the standard was followed, and any deviations from the standard. If the FDA-recognized consensus standard includes testing options (e.g., what to test, which test methods to use, performance limits to assess conformity), applicants should include explanations for the choices and selections made.

4. Predefined pass/fail criteria

The report should include all specifications or acceptance and rejection criteria used as well as a clinical or scientific justification for the specifications or acceptance and rejection criteria.

5. Test results

The report of test results should include:

a. Data points

The report should include all data points collected for the tests performed and a summary of the data (e.g., minimum, maximum, average, and standard deviation). Applicants should consider using consistent units throughout the testing. If data values are rounded, then the significant digit to which they were rounded should be specified.

b. Data analysis

Applicants should analyze the data, including any outlying points and anomalous results, and explain whether the data meet acceptance criteria. FDA recommends that applicants conduct data analyses for the test results using statistical analyses, when appropriate, and specify whether the acceptance criteria were met. If the data analysis demonstrates that the acceptance criteria were not met for either individual samples or entire sample populations, applicants should: discuss the potential reasons for test failure; determine if re-testing is appropriate; identify risk mitigation measure(s); and provide justification for why the testing results should be considered acceptable and supportive of the proposed labeling regarding administration via enteral tube.

[1] See the guidance for industry and FDA staff *Recognition and Withdrawal of Voluntary Consensus Standards* (September 2020). 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.

c. Protocol deviations

The report should describe any protocol deviations, the activities executed to determine the source of the deviation, and any effect on the test results and their interpretation.

6. Discussion of conclusions

Applicants should describe the conclusions drawn from the test results and the clinical significance of the conclusions.