In-vitro Enteral (Nasogastric and Gastric) Feeding Tube Testing of Generic Drug Products: Case Studies

SBIA 2020: Advancing Innovative Science in Generic Drug Development Workshop

Session 4: In Vitro Feeding Tube Testing and GI Locally-Acting Products

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Learning Objectives

- Discuss Agency's challenges regarding assessment of in-vitro feeding tube testing data from generic drug products, and establishing their equivalency with the innovator product
- Understand relevance of Agency's recommendation on in-vitro enteral feeding tube tests
- Learn about efficient data submission for in-vitro feeding tube study, which may result in fewer review cycles

ANDA: Abbreviated New Drug Application (for generic drug products)

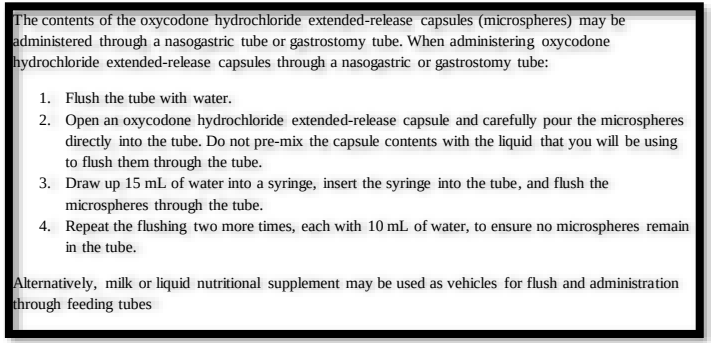
In-vitro Enteral Feeding Tube Testing

- ***Testing information/recommendations can be found in***
  - Reference Listed Drug (RLD) Package Insert/Prescribing Information (PI)
  - Product-Specific Guidance (PSG)

- ***PSGs- Comparative testing data should be provided***
  - Generic product vs Innovator (RLD)
  - Innovator product (RLD) data critical especially when clogging observed in generic product under one/more testing conditions

- ***Testing recommendations (risk-based)***
  - *Recovery – different tubing material/design, different pH, repeat tube administration*
  - *Sedimentation volume*
  - *Particle size distribution*
  - *Acid resistance*

Oxycodone Extended-release Capsules RLD PI

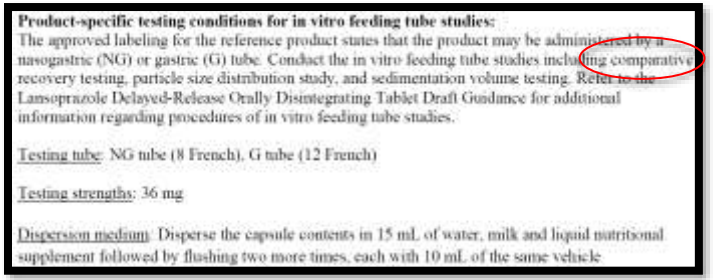


The contents of the oxycodone hydrochloride extended-release capsules (microspheres) may be administered through a nasogastric tube or gastrostomy tube. When administering oxycodone hydrochloride extended-release capsules through a nasogastric or gastrostomy tube:

1. Flush the tube with water.
2. Open an oxycodone hydrochloride extended-release capsule and carefully pour the microspheres directly into the tube. Do not pre-mix the capsule contents with the liquid that you will be using to flush them through the tube.
3. Draw up 15 mL of water into a syringe, insert the syringe into the tube, and flush the microspheres through the tube.
4. Repeat the flushing two more times, each with 10 mL of water, to ensure no microspheres remain in the tube.

Alternatively, milk or liquid nutritional supplement may be used as vehicles for flush and administration through feeding tubes

Oxycodone Extended-release Capsules PSG



Product-specific testing conditions for in vitro feeding tube studies:
The approved labeling for the reference product states that the product may be administered by a nasogastric (NG) or gastric (G) tube. Conduct the in vitro feeding tube studies including comparative recovery testing, particle size distribution study, and sedimentation volume testing. Refer to the Lansoprazole Delayed-Release Orally Disintegrating Tablet Draft Guidance for additional information regarding procedures of in vitro feeding tube studies.

Testing tube: NG tube (8 French), G tube (12 French)

Testing strengths: 30 mg

Dispersion medium: Disperse the capsule contents in 15 mL of water, milk and liquid nutritional supplement followed by flushing two more times, each with 10 mL of the same vehicle

Most extensive test**. Case studies related to 'Recovery' test only**

Issues identified based on In-vitro Enteral Feeding Tube Testing data from generic drug products

I. *Tube clogging with generic product (ANDA), but not with innovator product (RLD)*
II. *Tube clogging behavior with generic product, varies with tubing material*
III. *Generic product testing was not performed per RLD PI or PSG*
IV. *Incomplete data submission*
V. *Miscellaneous issues*
VI. *Special cases: Generic product assessment was challenging due to unclear RLD information*

Case studies related to each of the above issue, are discussed henceforth.

***Note**: Case studies discussed here are for '**Recovery**' testing only. Case studies for Particle size distribution, Sedimentation and Acid resistance, are not included in this presentation.*

RLD: Reference Listed Drug; ANDA: Abbreviated New Drug Application; PI: Package Insert/Prescribing Information; PSG: Product-Specific Guidance

I. Tube clogging with generic product (ANDA), but not with innovator product (RLD)

Case#1: Clogging due to larger pellet size of generic product, compared to the innovator

Esomeprazole Magnesium Delayed-Release Capsules

Product-Specific Guidance- *Rev. Feb 2018*

- 8 French Nasogastric (NG) tube
- pH 8.5 (worst-case)
- 3 tubing materials (Polyvinylchloride or PVC, Silicone and Polyurethane)

Generic	Innovator
Complete tube clogging with PVC, Silicone and Polyurethane	No tube clogging observed

Larger pellet size of generic product compared to innovator product

FATAL FLAW

Reformulation

No blockage when reformulated with smaller core spheres

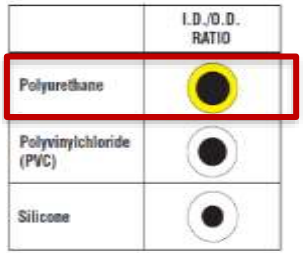
II. Tube clogging behavior with generic product, varies with tubing material

Case#1: Clogging with 6F PVC and 6F Silicone NG tubes, but not with 6F Polyurethane NG tubes

Esomeprazole Magnesium powder for Delayed-Release Oral Suspension

Worst case scenario: water pH 8.5, 15 min hold time

Both generic and innovator products → 100% recovery using 6F Polyurethane; No recovery using 6F PVC and 6F Silicone ← Confirmed by FDA labs



Particle size of generic not greater than innovator

To check material compatibility with PVC and Silicone, the following deficiency was sent:

'We noticed from your conclusions that both reference and test product failed to pass through the 6 Fr NG tube made with PVC and Silicone. We recommend you repeat the study with next higher size tubing like 8 Fr NG tube made with PVC and Silicone, using both the test and reference product. Please provide protocol, study report and associated images and videos for further review.'

No blockage observed using 8F PVC and 8F Silicone tubes - **Acceptable**

NG: Nasogastric; F: French; PVC: Polyvinyl Chloride

III. Generic product testing was not performed per RLD PI or PSG

Case#1: Testing not performed per PSG

Carglumic Acid Tablets for Oral Suspension

PSG recommends clinical dose of 100 mg/kg with 200 mg tablets

↓

ANDA sponsor study done at lower (< 100 mg/kg) clinical dose

↓

ANDA sponsor was asked to repeat study using clinical dose of 100 mg/kg
e.g., 30 tablets (6000 mg) dispersed in 75 mL considering average human weight of 60 kg

PI: Prescribing Information/Package insert; PSG: Product-Specific Guidance; ANDA: Abbreviated New Drug Application

III. Generic product testing was not performed per RLD PI or PSG

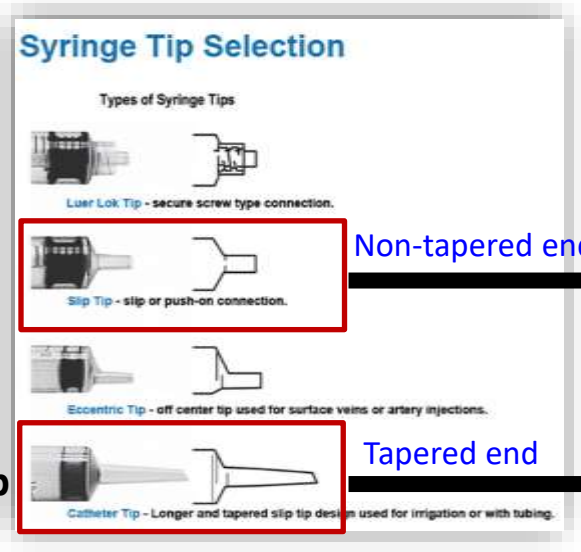
Case#2: Testing not performed per RLD PI

Esomeprazole Magnesium Delayed-Release Capsules

RLD PI recommends catheter tip syringe but ANDA sponsor used regular slip tip syringe

Common syringe tip types for injecting through tubing:

- Slip tip
- Catheter tip



Slip tip → Non-tapered end

Catheter tip → Tapered end

If pellet size is close to inner lumen size of the tip→ different clogging behavior based on choice of syringe

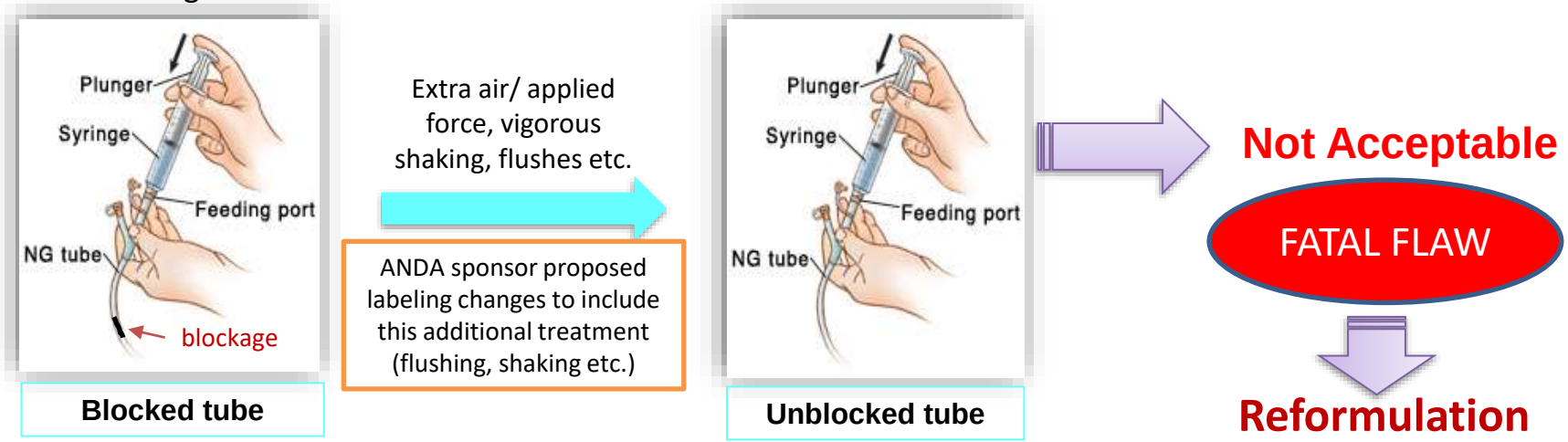
Image from https://www.vitalitymedical.com/blog/selecting-syringes-and-needles.html

III. Generic product testing was not performed per RLD PI or PSG

Case#3: Additional treatment to remove tube clogging with generic product

Esomeprazole Magnesium Delayed-Release Capsules

- *Test conditions*: water pH 8.5, 8F NG (polyurethane, PVC and silicone) tubes, catheter tip syringe
- Innovator product - No tube clogging irrespective of the tubing material
- Generic product – Pellets sticking to syringe wall and plunger, pellet aggregation and tube clogging with all three tubing materials



Images from https://www.saintlukeskc.org/health-library/your-childs-nasogastric-tube-flushing-tube

IV. Incomplete data submission

Case#1: Data with three tubing materials (e.g., Polyurethane, PVC, Silicone) not provided

For a product, PSG recommends recovery testing using 6F PVC, Polyurethane and Silicone NG tubes

- *ANDA sponsor provided in-vitro test data with 6F PVC tube*
- *6F Polyurethane and 6F Silicone tubes not available in the US market*
- *Sponsor provided data with 12F Polyurethane and 12F Silicone tubes*

NOT ACCEPTABLE

Agency's recommendations

- ✓ *12F is much larger than 6F. Suggest to find the next available size e.g., 8F in this case*
- ✓ *If possible, look into the global market*
- ✓ *You may use feeding tubes with **different materials** (Polyurethane, Polyvinylchloride, Silicone) OR **different designs** (e.g., number of ports and/or eyes in NG tube, open or closed distal end for NG tube, G tube with and without inflated balloon) e.g., 6F Polyurethane NG tube with 2 ports, 6F Polyurethane NG tube with 3 ports in this case*

It is ANDA sponsor's burden to justify choice of tube material/design used in the study

F: French; PVC: Polyvinyl Chloride

IV. Incomplete data submission

Examples	Agency's Recommendation
ALL tests in PSG not performed	Please follow all recommendations (no test is optional)
Missing details on materials and/or methods	Please provide details on materials used e.g., tube and syringe details. Provide details on method e.g., dispersion media, media volume, flushing volume and frequency, holding angle, holding time, etc. Provide explanation if additional pressure is needed to be applied during the testing to ensure complete recovery.
Testing with three different types of apple juice not provided	Please test in three different brands of apple juice. Enteric coating integrity is pH dependent. Apple juice properties may vary between brands e.g., pH, concentration etc.. Further, pH of apple juice may be different when reconstituted from frozen concentrate with different volume of water.

V. Miscellaneous issues

- Discrepancy in provided data (%recovery indicated no blockage, but video file showed tube blockage)
- Video submission not in required format (https://www.fda.gov/media/85816/download)
- No pictures, videos, observations and/or conclusions
- Pictures provided but not clear/fuzzy, to make any observations
- Non-specific analytical methods (UV method instead of HPLC) for analysis of drug

VI. Special case:

Generic product assessment was challenging due to unclear RLD information

Case#1: RLD PI includes NO information on feeding tube administration procedure

Sodium Polystyrene Sulfonate Suspension

RLD PI

The resin may be introduced into the stomach through a plastic tube and, if desired mixed with a diet appropriate for a patient in renal failure

No information on tube type (NG/G), size (in French), Dispersion volume, holding time, flushing volume etc.

Product-Specific Guidance (PSG): *Published July 2018*

- NG tube (8 French), G tube (12 French)
- Refers to *Lansoprazole Delayed-Release Orally Disintegrating Tablet Draft Guidance* for information on test procedure

NG: Nasogastric; G: Gastrostomy

VI. Special case:

Generic product assessment was challenging due to unclear RLD information

Case#2: RLD PI includes partial information on feeding tube administration procedure

Oxycodone Extended-release Capsules

RLD PI

*-**Includes**: Testing procedure, flushing volume, tube type (NG/G)*

*-**Does not include**: Tube size, water pH (5.5-8.5)*

Water pH critical since enteric coating contains myristic acid (converts to water soluble myristate at pH 8.5)

RLD PI

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Alternatively, milk or liquid nutritional supplement may be used as vehicles for flush and administration through feeding tubes

***Product-Specific Guidance**- Rev. Sept 2018*

- NG tube (8 French), G tube (12 French)
- Refers to 'Lansoprazole Delayed-Release Orally Disintegrating Tablet Draft Guidance' for procedures
  - Water with different pH e.g., pH 5.5, 7.0 and 8.5

VI. Special case:

Generic product assessment was challenging due to unclear RLD information

General Recommendations when RLD PI has insufficient information:

- ✓ *Always look for **Product-Specific Guidance** (PSG)*
- ✓ *For products wherein RLD PI contains incomplete information on feeding tube testing recommendation, and there is no PSG, Agency encourages use of 'Controlled Correspondence', through which the Sponsor can ask for Agency's recommendation.*

Summary and Conclusion

- Discussed case studies are based on challenges faced by the Agency, when assessing in-vitro feeding tube testing data in generic drug product applications (ANDA).
- The examples may help ANDA sponsors prepare efficient submissions, thereby reducing back and forth with the Agency, resulting in fewer review cycles

ANDA: Abbreviated New Drug Application

Challenge Question

The most prevalent issue faced by the Agency during ANDA assessment of in-vitro feeding tube data:

A. No pictures /videos provided

B. Did not follow recommendations in RLD PI/PSG

C. Lack of information on test materials and methods

D. Product not tested with three (NG) tubing materials/designs

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