In Vitro Enteral Feeding Tube Studies: Scientific and Regulatory Perspectives

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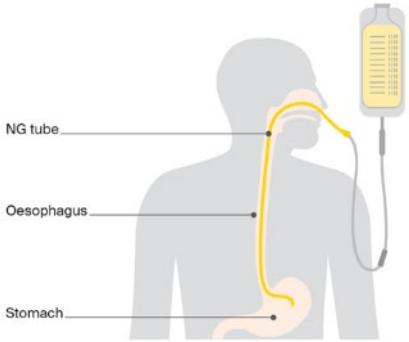
Everyone deserves
confidence in their *next* dose
of medicine.
Pharmaceutical quality
assures the
availability,
safety,
and efficacy
of *every* dose.

Background: Enteral Feeding Tubes

- Feeding tubes are critical for patients who are unable to swallow oral dosage forms
- These patients rely on feeding tubes for their drug treatment needs
- Feed tubes differ in:
  - ❑ Type (e.g., nasogastric, gastrostomy, nasojejunal, jejunostomy)
  - ❑ Material (e.g., polyurethane, polyvinylchloride, silicone)
  - ❑ Size (3.5 French – 30 French)
  - ❑ Design (e.g., number of ports and/or eyes; open or closed distal end, inflated balloon)



Background: Feeding Tube Clogging Risk

- Feeding tube clogs occur in 23 to 35 percent of cases during routine use (Bourgault et al. 2003; Dandeles and Lodolce 2011; Blumenstein et al. 2014)
  - Presence of insoluble ingredients
  - Aggregation in dispersion media
  - Selection of an inappropriate vehicle
  - Inadequate flushing of tubes
  - Large particle size
  - Drug product-tube interactions
  - Departures from drug product labeling on feeding tube instructions
- Feeding tube clogs lead to
  - Incomplete delivery of medicine
  - Removal and replacement of tube (for J and G, it is a surgical procedure)
  - Patient safety risks
  - Potential product recalls

Sources of In Vitro Feeding Tube Testing Recommendations

- Draft guidance "*Oral drug products administered via enteral feeding tube: in vitro testing and labeling recommendations*" (June 2021)
  - Provides overall framework for in vitro testing and labeling
  - Applies to NDAs, ANDAs, and INDs involving enteral tube administration
  - Focuses on oral dosage forms (excluding solutions)

- Product Specific Guidances (PSGs)
  - May provide product-specific in vitro feeding tube recommendations for ANDA development

In Vitro Feeding Tube Development Considerations

- Test with the smallest intended enteral tube size for each type of configuration (material or design)

- Perform testing at both 0- and for the maximum allowable holding time in accordance with the drug product labeling
    - When labeling specifies immediate administration after preparation, perform testing at 0 and 15-minute holding times
- Consider the dose strengths of their drug products to select the formulation at highest risk of forming occlusions for testing

Key In Vitro Enteral Feeding Tube Tests

- Recovery Testing
- Sedimentation Volume and Redispersibility Testing
- In-Use Stability in Designated Dispersion Media
- Particle Size Distribution Study
- Acid Resistance Testing

Recovery Testing

- Test at least three different enteral tube configurations for all tube types proposed in the labeling
- For G tubes, at least one tube should be tested with an inflated balloon configuration
- For products administered multiple times in 24 hours, use the same tube for sequential administrations and record recovery after each dose
- Perform testing at both 0- and for the maximum allowable holding time in accordance with the drug product labeling
    - When labeling specifies immediate administration after preparation, perform testing at 0 and 15-minute holding times
- For modified-release or pH-sensitive products, test water at multiple pH values (5.5, 7.0, 8.5) even if labeling specifies one type of water
- When juice is used as the dispersion medium, multiple types of juice should be studied even if labeling specifies a particular type of juice

Sedimentation Volume and Redispersibility Testing

- For convenience, instead of an enteral tube, a syringe can be used for this test
- The syringe that was used for the sedimentation volume test should be used to test redispersibility
- Sedimentation and redispersibility tests from product development or routine testing may be sufficient to support enteral tube administration

In-Use Stability in Designated Dispersion Media

- When labeling specifies an in-use holding time before enteral tube administration, perform in-use stability testing in the proposed dispersion media through this in-use period
- For extended holding times before administration of over 4 hours at room temperature or over 24 hours under refrigeration, conduct microbiological studies in support of the proposed storage conditions

Particle Size Distribution Study

- Recommended for modified-release dosage forms and other formulations where particle size may indicate a high risk for forming tube occlusions
- Determine the particle size of the drug suspension before and after delivery through the enteral tube using a validated method

Acid Resistance Testing

- Recommended for drug products with an enteric coating
- Performed under acidic conditions after the drug product is incubated in the dispersion medium and delivered through the enteral tube

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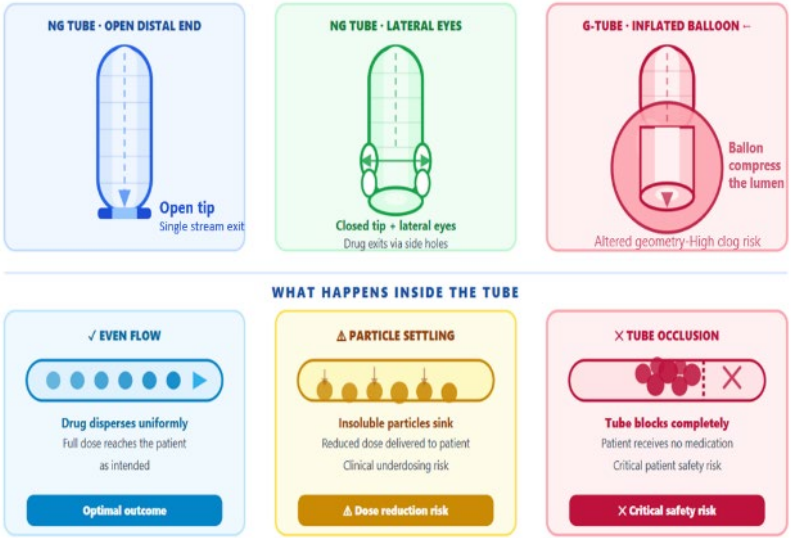
From Guidance to Practice: Common Industry Questions in Feeding Tube Studies

Where Industry Seeks Clarity: Recurring Themes in Feeding Tube CCs*

01	**Tube Selection and Configuration** Questions about number of tube configurations, materials, and designs required for testing	28%
02	**NG/G Tube Scope and Applicability** Questions about whether both NG and G tube types need to be studied or one can be omitted	22%
03	**Dispersion Medium / Water pH** Questions about acceptable water pH for dispersion medium and whether a single pH value is sufficient	20%
04	**Strength Selection** Questions about whether feeding tube studies can be limited to a single strength	18%
05	**Other / Miscellaneous** PSG vs. RLD labeling discrepancies, sample size, non-US tubes, sterility, and oral solution requirements	12%

*CC= Control correspondence

Tube selection: Can One Tube Represent Them All?



***AI-generated illustration intended for conceptual visualization only; does not represent actual device specifications or commercial device.**

Common Question from Industry

- We want to select one tube that represents the worst-case scenario for our product. We'll use that one tube for comparative testing between our generic and the RLD. Is that okay?
- Can we use an 8 French NG tube for our pediatric product?

FDA Position

- Minimum of 3 configurations for each tube type proposed in the labeling (e.g., NG and G tubes)
- Vary across 3 configurations, defined by materials (e.g., polyvinyl chloride, silicone, polyurethane) and/or designs (e.g., number of ports/eyes, open or closed distal end)
- For G tubes, at least one of the three configurations should be tested with an inflated balloon design
- For products with a pediatric indication for NG tube administration, a smaller tube size is recommended (e.g., 6 French NG tube) rather than the standard 8 French NG tube

Silence Is Not an Exemption: NG vs. G Tube Scope

Common assumption

“The RLD labeling refers to NG tubes when mentioning feeding tube administration. We will skip G-tube testing.”

FDA Position

Because the labeling does not specify a tube type, both NG and G tubes should be included in testing

Exemption

If labeling explicitly states “nasogastric tube only” then G tube testing may be waived.

Water pH -Do we need three pH values?

Common Questions from Industry

- When water is used as the dispersion medium, can we use a single unspecified pH water instead of testing at pH 5.5, 7.0, and 8.5?
- Is reporting the pH of water used during testing sufficient?

FDA Position

- For immediate release products without pH-sensitive coating: reporting water pH is sufficient
- For modified release or pH-sensitive coating products: testing at multiple pH values (5.5, 7.0, 8.5) is recommended

Which strength is the worst case?

Common Questions from Industry

Can we conduct feeding tube studies on only the highest strength and waive testing for lower strengths?
Is the worst-case strength sufficient to represent all strengths?

FDA Position

- Follow PSG recommendations for strength selection
- Testing on highest strength alone may be acceptable **if formulations are proportionally similar across all strengths** with scientific justification
- If lower strength contains disproportionately higher insoluble excipient load, lower strength should be tested

Key Takeaway

"What matters is not just which strength is highest — it is which strength poses the greatest risk of tube occlusion based on its insoluble excipient concentration in the final dispersion"

Miscellaneous but Meaningful: Notable Industry Questions

PSG vs. RLD Labeling Conflicts

When testing conditions differ between PSG and RLD labeling, which takes precedence?

Neither automatically wins — compare both, flag conflicts via CC, and let FDA decide.

Non-US Market Tubes

Can non-US tubes be used due to limited US supply?

US tubes preferred. If unavailable, justify scientifically in your ANDA and keep sourcing US tubes.

Sample Size Justification

Can replicates be reduced below 12 units?

No. 12 units each of test and reference standard are required per 2021 guidance. Reduction is not acceptable.

Oral Solution Requirements

Do oral solutions given via feeding tube require in vitro studies?

Generally, feeding tube studies are not recommended for oral solutions as they do not present the same risk of tube occlusion.

Closing the Loop: What the CCs Tells Us

What these questions tell us?

Industry seeks to minimize testing burden — FDA emphasizes risk-based, comprehensive testing.

How to get it right?

- Review 2021 FDA guidance thoroughly before designing studies
- Review the most current PSG and RLD labeling for your specific product
- Submit CC early if uncertainties exists
- Provide robust scientific justification for any deviations from PSG or RLD labeling
- Engage with FDA proactively rather than reactively

Key takeaways

"In Vitro Enteral Feeding Tube Studies" are not a checkbox — they are a patient safety commitment.

- 3 tube configurations required per tube type — material and design both matter.
- G-tube testing recommended unless explicitly excluded by labeling.
- Single pH water is acceptable for immediate release products — just report the pH.
- Worst case strength = highest insoluble excipient load, not necessarily the highest dose.

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Thank you!

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