General Quality Considerations of Drug Products Labeled for Alternate Dosing Administration

Ravikanth Kona, PhD

Pharmaceutical Scientist
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

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Learning Objectives

- Understand general quality considerations of Drug Products Labeled for Alternate Dosing Administration
- Identify relevant FDA Guidances' along with general quality information for generic drug applications.
- Learn effective data submission for Products Labeled for Alternate Dosing Administration.

Outline

- Products labeled for alternate administration
- Quality information
- Case studies
- Challenge questions

Alternate Dosing Administration

- Alternate dosing administration refers to the method of delivering a drug or medication through a different route other than the standard or conventional one, in order to achieve the desired therapeutic effect.
- Types of alternate dosing administration:
  - ❖ Use of Soft food or liquid as vehicle
  - ❖ Enteral Feeding tube
  - ❖ Admixtures

Use of Liquids and/or Soft Foods as Vehicles

- Many commercial drug product dosage forms such as granules, pellets, powders, or tablets have drug product labeling which includes instructions for the optional use of soft foods or liquids as vehicles for their administration.

- Footnote 4

[4] This guidance does not address use of vehicles for the purpose of demonstrating bioequivalence in generic drug products. For abbreviated new drug applications (ANDAs), recommendations for in vivo bioequivalence studies involving administration with liquids or soft foods will continue to be communicated in the respective product-specific Agency guidance. With respect to ANDAs and the recommendations contained in this guidance, we note that immediate-release solid oral dosage forms generally are considered to be products for which formulation differences between generic products and their reference listed drug (RLD) would not impact administration with vehicles. The vehicle studies on the RLD would establish the compatibility of the active ingredient with the recommended vehicles, and need not be repeated in an ANDA unless there is a risk that the formulation of the ANDA product would have a different impact on dosing with vehicles. When needed, the in vitro approaches in this guidance could be used to confirm that the formulation of a generic product is compatible with the vehicles of administration in the RLD label. If FDA determined that in vivo data are needed to support use of a vehicle for a generic product, the Agency would describe such data in its recommended product-specific bioequivalence studies.

Commonly Used Soft Foods and Liquids With Their Approximate pH Range

	pH range
Apples (puree)	3.34 – 3.90
Apple juice	3.35 – 4.00
Applesauce	3.10 – 3.60
Baby food, unstrained	5.95 – 6.05
Bananas (puree)	4.5 – 5.2
Buttermilk	4.41 – 4.83
Carrots (puree)	5.88 – 6.40
Chocolate pudding[a]	5.5 – 6.0
Coconut milk	6.1 – 7.0
Cranberry juice	2.30 – 2.52
Drinking water [b]	6.5 – 8.5
Fruit jellies	3.0 – 3.5
Fruit jam	3.5 – 4.5
Grapefruit juice [c]	2.90 – 3.25
Honey [d]	3.70 – 4.20
Infant formula	5.7 – 6.0
Maple syrup [e]	4.6 – 5.15
Milk	6.4 – 6.8
Orange juice	3.30 – 4.19
Orange marmalade	3.00 – 3.33
Peanut butter	6.28
Pineapple juice	3.30 – 3.60
Rice pudding [a]	4 – 5
Soybean milk	7
Strawberries	3.00 – 3.90
Strawberry jam	3.00 – 3.40
Yogurt	4.4 – 5.0

Source: 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).

General Consideration for selection of Vehicle

- Compatibility and Suitability
- Impact of Vehicle on the drug product
- Palatability and Swallowability
- Repeated users or multiple use
- Vehicle mixtures via feeding tubes

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).

Methods for Assessing Impact of a Vehicle on Product Quality Attributes

- Analytical Method
  - Assay of drug substance in the proposed vehicle should be developed and validated.
  - The source of analytical interferences should be determined, if needed.
- Assessment of the Drug Substance in the "Mixture"
  - Integrity
  - Potency
  - Stability
  - Homogeneity (dose uniformity)

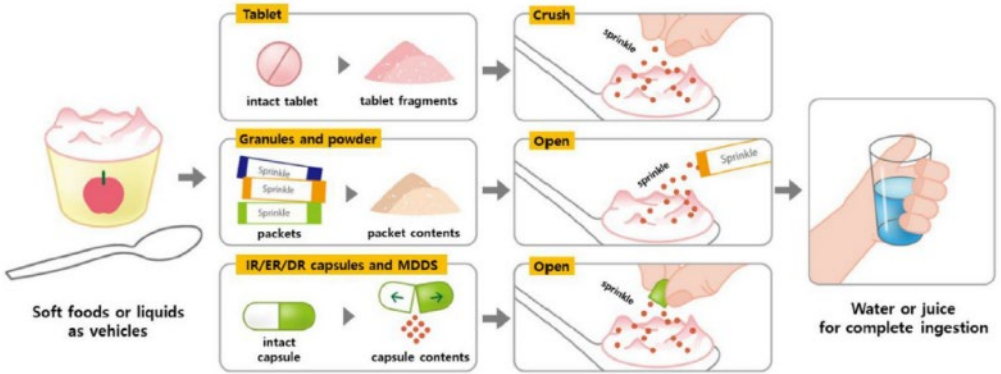
Once combined, the drug product and vehicle mixture should be ingested immediately (or as directed in the labeling) to avoid dosing errors or inadvertent dosing, and inadvertent contamination of the drug product-vehicle mixture. When the labeling calls for immediate use of the mixture, such use should be adequately supported by product quality assessments that are carried out at pre-determined times over two hours after preparation of the mixture. The two-hour assessment period is considered to provide the necessary time window to ensure physical and chemical stability of the drug product-vehicle mixture. Microbiological testing is not needed for the drug product-vehicle mixture if it is intended to be used within two hours because the risk of microbial proliferation to harmful levels is miminal. See section IV for recommended test methods.

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).

Drug Products Labeled for Sprinkle

*In the absence of availability of a dosage form that is appropriate for the targeted patient population (e.g., pediatric, geriatric), small amounts of liquids and/or soft foods as described in the FDA-approved product labeling can be used as a suitable vehicle(s) for oral administration and immediate ingestion of the specific drug product.**

- Sprinkle formulations are drug-containing pellets or granules that can be mixed with soft food before administration
- Intact – Granules, pellets, powders, coated mini-tablets or beads
- Manipulated – Crushing a tablet, emptying capsule contents, making serial dilutions, or mixing syrup into a vehicle.



Lee Han Sol *et.al,* Asian Journal of Pharmaceutical Sciences, Volume 15, Issue 3, May 2020, Pages 292-310

*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).

Quality Considerations for Sprinkle

- Maximum Bead Size for Drug Products Labeled for Sprinkle
  - Agency recommends a target bead size up to 2.5 mm with NMT10 percent variation over this size, to a maximum size of 2.8 mm.
  - Bead size determination in accordance with USP <786> or other appropriately validated methods.
  - For bead size greater than that recommended, justification should be provided.
- Enteral Feeding Tube Administration
  - All of the beads (uncrushed) be able to safely pass through the feeding tube and not cause tube occlusions.
  - *In-vitro* In-use tests.

Guidance for Industry "Size of Beads in Drug Products Labeled for Sprinkle" (May 2012).

Case Study: Generic Product was not tested per RLD Labeling

Immediate Release Capsules X USP (Sprinkle)

Labeling: *IR X capsules (sprinkle) may be swallowed whole or may be administered by carefully opening the capsule and sprinkling the entire contents on a small amount (teaspoon) of soft food.*

No comparability study with soft food to support RLD label

↓

Agency issued deficiency to address the label use

↓

- RLD PI recommends "Soft food"
- Cellulose acetate coated pellets (pH neutral).
- Not sensitive to Vehicle pH

→

Soft food: Varying pH
Fruit jam, Banana puree, Rice pudding and Carrot puree

- Compatibility and Suitability
- Impact of vehicle
- Palatability and swallowability (neutral taste, pellet size meets guidance)
- Incubate up to 2 hr. in soft food

→

Testing:
- Integrity
- Potency
- Stability
- Homogeneity

Case Study: Unknown impurity in Generic product

Immediate Release Capsules Y

Label for Emergency Compounding of Oral Suspension from the 75 mg (Final Concentration 6 mg/mL). The label states that: *In the event that [redacted] for oral suspension is not available, the pharmacist may compound a suspension (6 mg/mL) from [redacted] 75 mg using one of these vehicles: Cherry Syrup (Humco®), Ora-Sweet® SF (sugar-free) (Paddock Laboratories), or simple syrup. Other vehicles have not been studied. This compounded suspension should not be used for convenience or when the FDA-approved [redacted] for oral suspension is commercially available.*

Store Condition per RLD PI:

- *In a refrigerator [2° to 8° C (36° to 46° F)]: Stable for 5 weeks when stored in a refrigerator.*
- *At room temperature [25° C (77° F)]: Stable for 5 days when stored at room temperature.*

Stability test data Unknown impurity when mixed with Cherry and Simple syrup exceeding ICH Identification Threshold (IT) limits

"Please provide identification and qualification information for this unknown impurity and justify your proposed limit of NMT 1.0% in the emergency compounding stability report. You may justify the limit based on the impurity level determined in the RLD product nearing expiration and confirm its same identity in both the ANDA and the RLD products."

Enteral Feeding Tube

- A feeding tube is a medical device used to provide nutrition or medication to patients who cannot obtain nutrition or medication by swallowing.

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

- Tube diameter
- Tube length
- Composition (polyurethane, polyvinylchloride, and silicone)
- Number of ports
- Connector type
- Port geometry (closed vs open distal tip)
- Eyes (number and location)

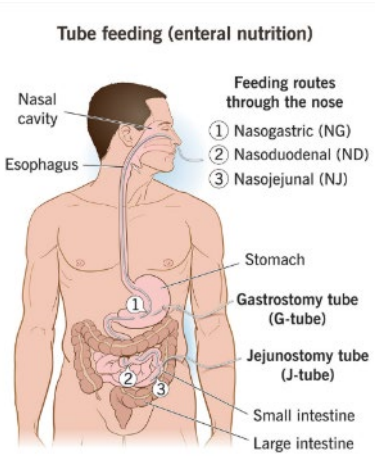
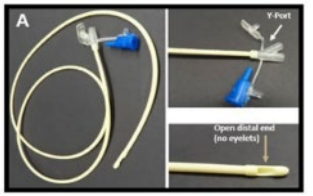
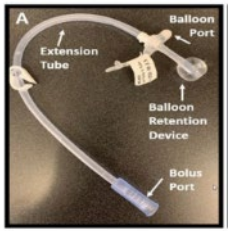


Image source: https://my.clevelandclinic.org/health/treatments/21098-tube-feeding--enteral-nutrition



A. Legacy NG-tube with Y-Port and open distal end



A. Legacy low-profile ('button') G-tube with bolus extension tubing attached

Image source: Wilson, S., Farabaugh, J., Liu, Y. et al. AAPS J 26, 43 (2024)

Variability associated with the insertion points, final site of drug release, are out of scope of the quality review.

Enteral Feeding Tube Testing (Risk-based)

Considerations for Generic Submissions

- Demonstrate that a generic drug product is therapeutically equivalent to the Reference Listed Drug (RLD) when administered according to the RLD product labeling.
- Instructions provided in the DOSAGE AND ADMINISTRATION section of labeling.
- Testing information – RLD Packaging Insert (PI) and Product Specific Guidance (PSG).
- 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.
- 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.

Comparative in-vitro testing

- Recovery
- Sedimentation volume and Redispersibility
- In-use stability in designated dispersion media
- Particle Size Distribution (PSD) studies for suspensions, modified-release dosage forms and other formulations where particle size may indicate a high risk for forming tube occlusions
- Acid resistance testing for drug products with an enteric coating
- Dissolution of Extended-Release Dosage forms

Case Study: Incomplete Information

Immediate Release Tablet Z

Applicant provided data using one material
NG (8 F) - PVC
G (12 F) - PVC

Recommended NG tube (8Fr) and G tube (12Fr) sizes, using three different designs with different options such as different tubing materials, geometries, number and types of ports, etc.

Provided NG tube (8F) & G (12 F)
- PVC, Silicon, polyurethane
- Lengths & diameter
- Single and dual ports
- Closed & open tip
- lateral eyes

2.6 Administration Options

For adult patients who are unable to swallow whole tablets, [redacted] tablets (all strengths) may be crushed and mixed with applesauce immediately prior to use and administered orally. After the administration of a crushed [redacted] 15 mg or 20 mg tablet, the dose should be immediately followed by food. Administration with food is not required for the 2.5 mg or 10 mg tablets [see Clinical Pharmacology (12.3)].

Administration of [redacted] tablets via nasogastric (NG) tube or gastric feeding tube: After confirming gastric placement of the tube, [redacted] tablets (all strengths) may be crushed and suspended in 50 mL of water and administered via an NG tube or gastric feeding tube. Since [redacted] absorption is dependent on the site of drug release, avoid administration of [redacted] distal to the stomach which can result in reduced absorption and thereby, reduced drug exposure. After the administration of a crushed [redacted] 15 mg or 20 mg tablet, the dose should then be immediately followed by enteral feeding. Enteral feeding is not required following administration of the 2.5 mg or 10 mg tablets [see Clinical Pharmacology (12.3)].

Crushed [redacted] tablets (all strengths) are stable in water and in applesauce for up to 4 hours. An in vitro compatibility study indicated that there is no adsorption of [redacted] from a water suspension of a crushed [redacted] tablet to PVC or silicone nasogastric (NG) tubing.

*Per Draft Guidance for Industry "Oral Drug Products Administered Via Enteral Feeding Tube: In Vitro Testing and Labeling Recommendations" (June 2021). 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.*

Testing @ 0 & 4 h:
- Comparative recovery
- Sedimentation
- Particle Size Distribution

Case Study: Granule Build-up in Syringe in Delayed Release Capsules

Delayed Release Capsules A

Labeling: *Capsule can be opened and the intact pellets emptied into a syringe and delivered through the nasogastric tube*

8 F NG tubes (PVP, polyurethane and silicone), pH 8.5 after a 15 minute incubation time

- Granule build-up in polyurethane in ANDA
- No build-up in RLD

FDA Labs:
- Show large number of granules remained in syringe
- Low recovery for ANDA compared to RLD

- ANDA instructions for use are different from RLD labeling
- Cannot meet RLD label for alternate administration
- Recommended Reformulation

X

Product Specific Guidance
- NG Tube (8 F)
- pH 5.5, 7.0 and 8.5 (worst case)
- PVC, polyurethane and silicone

Reformulated to address sticking
- Hypromellose (overcoat)
- Talc (lubrication)

"After evaluation of the adherence issue, it is noted that surface characteristics and physicochemical properties of [redacted] product are related to the intrinsic behavior of the product design and manufacturing process. We recommend that you reformulate the drug product to address the propensity of the granule adherence to the syringe plunger and wall under alternative administration through NG feeding tube delivery. A new batch will be necessary with data (e.g., in process and release) meeting all the proposed specifications. Please provide available stability data under both accelerated and long-term storage."

Drug Product Administered as Admixtures

- A pharmaceutical admixture consists of a drug product mixed with an appropriate diluent in a suitable dosing/ delivery device for the purpose of parenteral infusion to the patient.

Q8(R2) Pharmaceutical Development, Section F Compatibility (2.6)

> The compatibility of the drug product with reconstitution diluents (e.g., precipitation, stability) should be addressed to provide appropriate and supportive information for the labelling. This information should cover the recommended in-use shelf life, at the recommended storage temperature and at the likely extremes of concentration. Similarly, admixture or dilution of products prior to administration (e.g., product added to large volume infusion containers) might need to be addressed.

Common diluents for IV administration:

- 0.9 % sodium chloride injection, USP (normal saline)
- 5 % dextrose injection, USP (D5W)
- Ringer's Injection, USP
- Lactated Ringer's Injection, USP

Case Study: Lyophilized Powder for Injection

Drug Product B for Injection

RLD ( ):
- Reconstitute for Injection with 4 mL of sterile WFI for subcutaneous administration, and
- Diluted suspension of for Injection with 0.9% sodium chloride injection or lactated ringer's injection for intravenous administration

Subcutaneous Administration

Suspension Stability Storage timelines	
Diluent	Storage Temperature/Duration
Room temperature (25°C / 77°F) Sterile Water for Injection, USP	Store at room temperature at 25°C (77°F) for up to 1 hour or refrigerated at 2°C to 8°C (36°F to 46°F) for up to 8 hours.
Cold (2°C to 8°C / 36°F to 46°F) Sterile Water for Injection, USP	Store refrigerated at 2°C to 8°C (36°F to 46°F) for up to 22 hours.

Reconstitution fluid	Volume	Container	Duration/Storage condition
Non refrigerated water	4.0 ml	Vial & Syringe	0 hr at RT
			1 hr at RT
			hr at 2°C to 8°C
Refrigerated wat	4.0 ml	Vial & Syringe	hr & 22 hr at 2°C to 8°C

Intravenous Administration

for injection reconstituted and diluted for intravenous administration may be stored at 25 C (77° F), but administration must be completed within 1 hour of reconstitution.

Reconstitution fluid	Volume	Container	Duration/Storage condition
0.9% Sodium Chloride	4.0 ml	Infusion bottle	0 hr & 1 hr at RT
Lactate Ringer's	4.0 ml	Infusion bottle	0 hr & 1 hr at RT

Appearance, pH, Color/clarity, Related substances, Assay, osmolality, visible particles

Challenge Question #1

Testing recommendations for in-vitro feeding tube studies include:

A. Recovery Testing

B. Sedimentation Volume and Redispersibility Testing

C. Particle Size Distribution Study

D. All of the above

Challenge Question #2

Which of the following statements is NOT true?

A. Sprinkle formulations are drug-containing pellets or granules that can be mixed with soft food before administration.

B. Comparability study with soft food to support RLD label is not a requirement.

C. Agency recommends a target bead size up to 2.5 mm with NMT10 percent variation over this size, to a maximum size of 2.8 mm.

D. Assessment of the Drug Substance in the “Mixture” includes integrity, potency, stability and homogeneity.

Summary

- Understand drug product quality considerations for dosage forms labeled for alternate administration
- Discussed several case studies along with quality information necessary to ensure drug product meets RLD labeling requirements
- Information provided help Sponsors submit effective data, resulting in fewer review cycles.

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  - Dr. Thomas Oliver, Division Director, DPQA I
  - Dr. Suhas Patankar, Supervisor, DPQA I
  - Dr. Kiet Nguyen, SPQA, DPQA I
- GDF 2025 Planning Committee

Resources

- Draft Guidance for Industry “Oral Drug Products Administered Via Enteral Feeding Tube: In Vitro Testing and Labeling Recommendations” (June 2021). https://www.fda.gov/media/149688/download
- Guidance for Industry “Size of Beads in Drug Products Labeled for Sprinkle” (May 2012). https://www.fda.gov/media/79676/download
- 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). https://www.fda.gov/media/114872/download
- ICH Q8 (R2) Pharmaceutical Development. https://www.fda.gov/media/71535/download

FDA U.S. FOOD & DRUG ADMINISTRATION

Questions?