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Draft Guidance on Sodium Phenylbutyrate

August 2026

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Active Ingredient:	Sodium phenylbutyrate
Dosage Form:	Powder
Route:	Oral
Strength:	3 gm/teaspoonful
Reference Listed Drug:	NDA 020573
Recommended Studies:	Two options: (I) One in vitro bioequivalence study or (II) one in vivo bioequivalence study with pharmacokinetic endpoints

Option I: One in vitro bioequivalence study:

Eligibility: If the test product formulation is qualitatively (Q1) and quantitatively (Q2) the same as the reference listed drug (RLD) in inactive ingredients and the active pharmaceutical ingredient is present in the same solid form as the RLD, bioequivalence may be established by conducting one in vitro comparative dissolution study.

1. Class of study: Bioequivalence
   Type of study: In vitro comparative dissolution study
   Comparative dissolution testing should be conducted using 12 dosage units for each of the test product and RLD in multiple media, including three compendial media covering the physiologically relevant gastrointestinal pH range (e.g., pH 1.2, 4.5, and 6.8) and the quality control medium (unless identical to the compendial media).

Provide a dissolution method development report for the test product containing information and data that demonstrate appropriateness of the selected dissolution method[1] and sampling times, such as the discriminating ability to detect changes in critical quality attributes that could potentially impact drug product performance.

Bioequivalence based on: Comparison of the mean dissolution profiles between the test product and the RLD across multiple media. Similarity can be concluded when both the test product and the RLD exhibit very rapid dissolution, defined as greater than 85% dissolved within 15 minutes in all tested media. When the very rapid dissolution criterion is not met, similarity should be demonstrated by an appropriate statistical comparison such as the f2 similarity factor.

Option II: One in vivo bioequivalence study with pharmacokinetic endpoints

1. Class of study: Bioequivalence
   Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 3 gm/teaspoonful
   Dose: 3 gm
   Subjects: Healthy males and non-pregnant, non-lactating females

Analyte to measure: Phenylbutyrate in plasma

Bioequivalence based on (90% CI): Phenylbutyrate

Recommendations for both Options:

Product-specific testing conditions for in vitro enteral tube studies: The approved labeling for the RLD states that the product may be administered via a nasogastric (NG) or gastrostomy (G) tube. Conduct the in vitro enteral tube studies below. For general procedures, refer to the guidance for industry *Oral Drug Products Administered Via Enteral Feeding Tube: In Vitro Testing and Labeling Recommendations*.

Testing tube: NG tube (6 French) and G tube (12 French)
Testing strength: 3 gm/teaspoonful
In vitro enteral feeding tube testing:

1. Comparative recovery testing
   - Three different configurations of 6 French NG tubes, defined by materials (e.g., polyvinylchloride, silicone, polyurethane) and/or designs (e.g., number of ports/eyes, open or closed distal end)
   - Three different configurations of 12 French G tubes
     - At least one G tube should be tested with an inflated balloon design
   - Repeated administration

[1] Applicant-developed, United States Pharmacopeia drug product monograph or Dissolution Methods database, https://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm

- Reporting the pH value of water
- Holding times of 0 and 15 minutes

2. Sedimentation volume and redispersibility testing
3. In-use stability in designated dispersion media (i.e., water)
4. Particle size distribution study

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