

**Draft Guidance on Elexacaftor, Ivacaftor, Tezacaftor; Ivacaftor  
December 2025**

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<b>Active Ingredients:</b>	Elexacaftor, Ivacaftor, Tezacaftor; Ivacaftor
<b>Dosage Form:</b>	Granules
<b>Route:</b>	Oral
<b>Strengths:</b>	80 mg, 60 mg, 40 mg; 59.5 mg and 100 mg, 75 mg, 50 mg; 75 mg
<b>Recommended Studies:</b>	Four in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Fasting  
Design: Single-dose, two-treatment, two-period crossover in vivo  
Strength: 100 mg, 75 mg, 50 mg (Elexacaftor, Ivacaftor, Tezacaftor)  
Subjects: Healthy males and non-pregnant, non-lactating females  
Additional comments:
  - Exclude subjects with abnormal liver function tests due to risk of drug-induced liver injury and liver failure. Monitor liver function tests during the study.
  - Mix granules with 5 mL of applesauce.
  - AUC(0-72h) may be used in place of AUC(0-t) for comparing the extent of absorption, due to the long half-life of elexacaftor and tezacaftor. Ensure adequate washout periods between treatments in the crossover study. Alternatively, a parallel study design may be considered.
2. Type of study: Fed  
Design: Single-dose, two-treatment, two-period crossover in vivo  
Strength: 100 mg, 75 mg, 50 mg (Elexacaftor, Ivacaftor, Tezacaftor)  
Subjects: Healthy males and non-pregnant, non-lactating females  
Additional comments: See comments above.

**Analytes to measure:** Elexacaftor, ivacaftor, and tezacaftor in plasma

**Bioequivalence based on (90% CI):** Elexacaftor, ivacaftor, and tezacaftor

3. Type of study: Fasting  
Design: Single-dose, two-treatment, two-period crossover in vivo  
Strength: 75 mg (Ivacaftor)  
Subjects: Healthy males and non-pregnant, non-lactating females  
Additional comments: Mix granules with 5 mL of applesauce. Conduct bioequivalence study according to the administration instructions in the reference product labeling.

For the ivacaftor studies, applicants may cross reference approved applications, e.g., abbreviated new drug application (ANDA) or new drug application, for the single entity of 75 mg ivacaftor granules as the basis of submission for this co-packaged product.

4. Type of study: Fed  
Design: Single-dose, two-treatment, two-period crossover in vivo  
Strength: 75 mg (Ivacaftor)  
Subjects: Healthy males and non-pregnant, non-lactating females  
Additional comments: See comments above.

**Analyte to measure:** Ivacaftor in plasma

**Bioequivalence based on (90% CI):** Ivacaftor

**Waiver request of in vivo testing:** 80 mg; 60 mg; 40 mg (elexacaftor, ivacaftor, tezacaftor) strength based on (i) acceptable bioequivalence studies on the 100 mg, 75 mg, 50 mg (elexacaftor, ivacaftor, tezacaftor) strength, (ii) acceptable in vitro dissolution testing of both strengths, and (iii) proportional similarity of the formulations between both strengths

59.5 mg (ivacaftor) strength based on (i) acceptable bioequivalence studies on the 75 mg (ivacaftor granules) strength, (ii) acceptable in vitro dissolution testing of both strengths, and (iii) proportional similarity of the formulations between both strengths

**Dissolution test method and sampling times:** The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Conduct comparative dissolution testing on 12 dosage units for each of both strengths of the test product and RLD<sup>1</sup>. Specifications will be determined upon review of the ANDA.

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**Document History:** Recommended December 2025

**Unique Agency Identifier:** PSG\_217660

<sup>1</sup> If the RLD is not available, refer to the most recent version of the guidance for industry *Referencing Approved Drug Products in ANDA Submissions*.