Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Entrectinib

February 2026

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient: Entrectinib

Dosage Form: Pellets

Route: Oral

Strength: 50 mg/packet

Recommended Studies: Two in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 50 mg/packet at the administered dose of 200 mg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments:
   - Exclude subjects with abnormal liver function tests or with risk factors for prolonged QTc interval and Torsades de Pointes. Monitor electrocardiograms during the study. Females of reproductive potential should use effective contraception during the study and for at least 5 weeks after the last dose. Males with female partners of reproductive potential should use effective contraception during the study and for 3 months after the last dose.
   - Use a consistent administration method for test product and reference listed drug (RLD). Follow the administration instructions described in the RLD labeling.

2. Type of study: Fasting, in presence of an acid-reducing agent
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 50 mg/packet at the administered dose of 200 mg
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments:
    - A proton pump inhibitor (e.g., lansoprazole) is recommended for the selection of acid-reducing agents to compare gastric pH-dependent pharmacokinetics between the test and reference entrectinib products. The elevating effect of a proton pump inhibitor on gastric pH (e.g., mean pH over 24 hours, percentage of the time when the pH ≥4.0 in a 24-hour interval) is dependent on the individual proton pump inhibitor and its dose. Select a proton pump inhibitor that has minimal effect on pharmacokinetics of entrectinib via other interacting mechanisms and a dose that is expected to provide a near maximum effect on gastric acid suppression (i.e., pH elevation). Subjects should be pre-treated with a proton pump inhibitor for several days (e.g., 4 to 5 days) to reach its pharmacodynamic steady-state before administering the test product or RLD.
    - Other additional comments are the same as the fasting study above.

Analyte to measure: Entrectinib in plasma

Bioequivalence based on (90% CI): Entrectinib

Waiver request of in vivo testing of additional strength: Not applicable

Dissolution test method and sampling times: Dissolution test(s) should be included for quality control. 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.

Document History: Recommended February 2026

Unique Agency Identifier: PSG_218550

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