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Draft Guidance on Tovorafenib

November 2025

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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: Tovorafenib

Dosage Form: For suspension

Route: Oral

Strength: 25 mg/mL

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: 25 mg/mL at a dose of 100 mg (4 mL)
   Subjects: Healthy males and healthy females not of reproductive potential
   Additional comments:
   - Exclude subjects with abnormal liver function tests. Males with female partners of reproductive potential should use effective contraception during the study and for 2 weeks after the last dose of the study. Subjects should be instructed to use appropriate sun protection during the study to prevent photosensitivity reactions.
   - $AUC_{(0\text{-}72h)}$ may be used in place of $AUC_{(0\text{-}t)}$ for comparing the extent of absorption, due to tovorafenib's long half-life. Ensure an adequate washout period 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: 25 mg/mL at a dose of 100 mg (4 mL)
Subjects: Healthy males and healthy females not of reproductive potential
Additional comments: See comments above.

Analyte to measure: Tovorafenib in plasma

Bioequivalence based on (90% CI): Tovorafenib

Waiver request of in vivo testing: Not applicable

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 each of the test product and reference listed drug (RLD).[1] Specifications will be determined upon review of the abbreviated new drug application (ANDA).

In vitro feeding tube studies:

The approved labeling for the RLD states that the product can be administered by a nasogastric (NG) or gastrostomy (G) tube after preparation. Refer to the most recent version of the guidance for industry *Oral Drug Products Administered Via Enteral Feeding Tube: In Vitro Testing and Labeling Recommendations*[a] for conducting the in vitro feeding tube studies including comparative recovery testing and sedimentation volume and redispersibility testing, in-use stability in designated dispersion media, and particle size distribution study.

1. Testing tube: NG tube (6 French) and G tube (12 French), each including
    - 3 different tube materials (e.g., polyvinylchloride, silicone, polyurethane) and/or designs (e.g., various numbers of ports and/or eyes, open or closed distal end, retention balloons)
        - At least one G tube should be tested with an inflated balloon design
    - Reporting of the pH value of the 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

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

Additional information:

Device:
The RLD is presented in a bottle co-packaged with a bottle adapter[2] and an oral syringe. The oral syringe is the device constituent part.

FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD devices when designing the test devices including:

- Volume markings
- Visibility and contrast of plunger gasket within the syringe

User interface assessment:
An ANDA for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the guidance for industry *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA.*[a]

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[a] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[2] See the most recent version of the Guidance for *Industry Restricted Delivery Systems: Flow Restrictors for Oral Liquid Drug Products Guidance for Industry*.