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Draft Guidance on Isotretinoin

December 2025

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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: Isotretinoin

Dosage Form: Capsule

Route: Oral

Strengths: 8 mg, 16 mg, 20 mg, 24 mg, 28 mg, 32 mg

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: 32 mg
   Subjects: Healthy males
   Additional comments: Due to the known teratogenicity of isotretinoin, the study should be conducted in healthy males. Isotretinoin capsule is under a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU), which restricts its use. All pertinent elements of the REMS/ETASU must be incorporated into the protocol and informed consent.

2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 32 mg
   Subjects: Healthy males
   Additional comments: See comments above.

Analyte to measure: Isotretinoin in plasma

The plasma concentrations of isotretinoin should be corrected for baseline endogenous concentration by subtracting the mean pre-dose baseline value (average of at least three pre-dose values, e.g., -10, -2, and 0 hours). Any negative values obtained from baseline correction at time 0 hour should be designated as zero (0). Both baseline-corrected and uncorrected data should be submitted in the application.

Bioequivalence based on (90% CI): Baseline-corrected isotretinoin

Waiver request of in vivo testing: 8 mg, 16 mg, 20 mg, 24 mg, 28 mg strengths based on (i) acceptable bioequivalence studies on the 32 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all 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 each of all strengths of the test and reference listed drug (RLD).[1] Specifications will be determined upon review of the abbreviated new drug application.

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[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*.