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Draft Guidance on Zolpidem Tartrate

August 2026

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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:	Zolpidem tartrate
Dosage Form:	Tablet, extended release
Route:	Oral
Strengths:	6.25 mg | 12.5 mg
Reference Listed Drug:	NDA 021774
Recommended Studies:	Two in vivo bioequivalence studies with pharmacokinetic endpoints

1. Class of study: Bioequivalence
   Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 12.5 mg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Safety recommendations:
   - Exclude geriatric subjects due to increased risk of impaired motor/cognitive performance and unusual sensitivity to sedative/hypnotic drugs.
   - Subjects should be evaluated prior to discharge for cognitive impairment such as drowsiness and instructed not to drive or operate machinery until their cognitive function returns to baseline level.

2. Class of study: Bioequivalence
   Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 12.5 mg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Safety recommendations: See recommendations under Study #1.

Analyte to measure: Zolpidem in plasma

Bioequivalence based on (90% CI): Zolpidem

1. For the fasting study, the following pharmacokinetic parameters will be evaluated for bioequivalence based on 90% CI: Log-transformed area under the concentration (AUC) time curve from hour 0 to hour 1.5 ($AUC_{0\text{-}1.5h}$), AUC from hour 1.5 to the last measurable time point ($AUC_{1.5h\text{-}t}$), AUC from hour 0 extrapolated to infinite time ($AUC_{0\text{-}\infty}$), and maximum concentration (Cmax). $AUC_{0\text{-}1.5h}$ and $AUC_{1.5h\text{-}t}$ have been identified as the most appropriate pharmacokinetic parameters for characterizing the sleep onset and sleep maintenance phases, respectively.

2. For the fed study, the following pharmacokinetic parameters will be evaluated for bioequivalence based on 90% CI: Log-transformed $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and C_{max}.

Bioequivalence of additional strength: Bioequivalence of the 6.25 mg strength to the corresponding reference listed drug (RLD)[1] strength may be demonstrated based on principles laid out in the guidance for industry *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application*.[a]

Dissolution test method and sampling times: For modified release drug products, applicants should develop specific discriminating dissolution methods. Alternatively, applicants may use the dissolution method set forth in any related official United States Pharmacopeia (USP) drug product monograph, or in the FDA's database, http://www.accessdata.fda.gov/scripts/cder/dissolution/, provided that applicants submit adequate dissolution data supporting the discriminating ability of such a method. If a new dissolution method is developed, submit the dissolution method development and validation report with the complete information/data supporting the proposed method. Conduct comparative dissolution testing on 12 dosage units for each strength of the test product and RLD. Specifications will be determined upon review of the abbreviated new drug application.

[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*.

In addition to the method above, submit dissolution profiles on 12 dosage units for each strength of the test product and RLD generated using USP Apparatus 1 at 100 rpm and/or Apparatus 2 at 50 rpm in at least three dissolution media (e.g., pH 1.2, 4.5 and 6.8 buffer). Agitation speeds may be increased if appropriate. It is acceptable to add a small amount of surfactant if necessary. Include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released to provide assurance against premature release of drug (dose dumping) from the formulation.

Document History: Recommended October 2011; Revised August 2026

[a] We update guidances periodically. For the most recent version of a guidance, refer to the FDA guidance webpage at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.