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Draft Guidance on Trazodone Hydrochloride

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

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Active Ingredient: Trazodone hydrochloride

Dosage Form: Tablet, extended release

Route: Oral

Strengths: 150 mg, 300 mg

Recommended Study: Two options: (1) one in vivo bioequivalence study with pharmacokinetic endpoints or (2) alternative approach to establish bioequivalence

I. Option 1: One in vivo bioequivalence study with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 150 mg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: The 300 mg strength and a fed study are not recommended because of increased potential for QT prolongation.

Analyte to measure: Trazodone in plasma

Bioequivalence based on (90% CI): Trazodone

Additional strength: Bioequivalence of the 300 mg strength to the corresponding reference listed drug (RLD)[1] strength may be demonstrated based on principles laid out in the most recent version of the FDA guidance for industry on *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.

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.

Trazodone hydrochloride extended release tablets are scored. To ensure the performance of the split tablet, perform manual as well as mechanical splitting and conduct additional dissolution testing of split tablet portions versus the whole tablet for both test product and RLD.

Alcohol dose dumping studies: Due to concerns of dose dumping of drug from this product when taken with alcohol, conduct additional dissolution testing on all strengths using various concentrations of ethanol in the dissolution medium as follows:

Testing conditions: 900 mL, 0.1 N HCl, USP Apparatus 2 (paddle) at 100 rpm, with or without alcohol

> Test 1: 12 units tested according to the proposed method (with 0.1 N HCl) with data collected every 15 minutes for a total of 2 hours
>
> Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours
>
> Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

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

Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Conduct testing on both test product and RLD accordingly, and provide data on individual unit, means, range and %CV.

II. Option 2: Alternative approach to establish bioequivalence

Option 2 can be used when the RLD is listed in FDA's Approved Drug Products with Therapeutic Equivalence Evaluations' (the Orange Book) Discontinued Drug Product List (Discontinued Section) and there is no drug product listed in the Orange Book's Prescription Drug Product List (Active Section) that is, or can be, designated as a reference standard for the RLD. Applicants are recommended to discuss their development program with the FDA via the pre-abbreviated new drug application meeting pathway. For additional information, refer to the most recent versions of the FDA guidance for industry on *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*.[a] Conduct one in vivo study with pharmacokinetic endpoints using the trazodone hydrochloride immediate release 50 mg tablet three times daily and comparative pharmacokinetic analysis.

1. Type of study: Fasting
   Design: Two-treatment, two-period crossover in vivo
   Strength: 150 mg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments:
   - A fed study is not recommended because of increased potential for QT prolongation.
   - Ensure baseline fasting conditions are established and consistent fasting conditions maintained between each dose of the trazodone hydrochloride immediate release 50 mg tablet, e.g., a minimum of 4 h of fasting should be maintained before each dose. The tablet should be dosed in 8-hour intervals (e.g., 23:30 on Day 1, 7:30 and 15:30 on Day 2).[2] Ensure blood sampling characterizes complete drug exposure (e.g., sampling until 72 h from the first dose).
   - Applicants can submit questions pertaining to the selection of trazodone hydrochloride immediate release tablet 50 mg via a controlled correspondence. Refer to the most recent version of the FDA guidance for industry on *Controlled Correspondence Related to Generic Drug Development*.[a]

Analyte to measure: Trazodone in plasma

Bioequivalence based on (90% CI): Trazodone

[2] The dosing interval is recommended to match closely to the dosing interval used in publicly available literature.

Dissolution test method and sampling times: For this alternative bioequivalence approach, conduct the dissolution test for each strength of the test product. The testing should include the discriminating dissolution, multi-pH dissolution, and dissolution on split tablets utilizing the methods referenced in Option 1.

Alcohol dose dumping studies: For this alternative bioequivalence approach, conduct the alcohol dose dumping studies for each strength of the test product utilizing the conditions referenced in Option 1.

Method for Statistical Analysis Using the Alternative Approach to Establish Bioequivalence:

Step 1.

Obtain the point estimate of the log-transformed geometric mean ratio of trazodone immediate release 100 mg tablet (**C1)** vs. RLD extended release 300 mg tablet (**R**) (θ_{C1_R}), along with the mean squared error (MSE_{C1_R}), and degrees of freedom (df_{C1_R}), utilizing information available on trazodone following administration of **C1** every 8 hours (total of three doses daily) and a single dose of **R** under fasting conditions in healthy subjects (n=23) (i.e., Table 1 in Clinical Pharmacology and Biopharmaceutics Review(s) of new drug application 022411, Published Study). Because pharmacokinetics for trazodone is dose proportional, data of the Published Study can be extrapolated to understand the relative bioavailability for a single dose of trazodone hydrochloride extended release 150 mg tablet and 50 mg trazodone immediate release 50 mg every 8 hours (total of three doses daily).

Step 2.

Determine the relative bioavailability between a single dose of test product for trazodone hydrochloride extended release 150 mg tablet (**T**) and trazodone hydrochloride immediate release 50 mg tablet (**C2**) every 8 hours (total of three doses daily) from the study recommended in Option 2 (Option 2 Study).

Calculate the point estimate of the log-transformed geometric mean ratio of **T** vs. **C2** (θ_{T_C2}), along with the mean squared error (MSE_{T_C2}) and degrees of freedom (df_{T_C2}) from Option 2 Study.

Step 3.

If the studies in Step 1 and Step 2 (i.e., Published Study and Option 2 Study) satisfy the constancy assumption (e.g., Both studies are conducted in a similar manner, refer to Option 2), then the following approach similar to the literature[3] can be used to calculate the point estimate of the log-transformed geometric mean ratio of **T** vs. **R** (θ_{T_R}) and the 90% CI of θ_{T_R}.

An unbiased point estimator for θ_{T_R} can be calculated as

[3] J Biopharm Stat. 2004 Nov;14(4):857-67. doi: 10.1081/BIP-200035418. PMID: 15587968.

$$\hat{\theta}_{T\_R} = \hat{\theta}_{T\_C2} + \hat{\theta}_{C1\_R}\,, \qquad \textbf{\textit{Equation}}\ (\mathbf{1})$$

where

$\hat{\theta}_{T\_C2}$ = estimate of log-transformed geometric mean ratio of **T** vs. **C2** from Step 2,
$\hat{\theta}_{C1\_R}$ = estimate of log-transformed geometric mean ratio of **C1** vs. **R** from Step 1.

The following steps can be used to determine the 90% CI of θ_{T_R}:

1) Test the equality of intra-subject variances between **T** and **C2** ($\sigma^2_{T\_C2}$) and between **C1** and **R** ($\sigma^2_{C1\_R}$) using an F test.

   Calculate the 95% CI of $\sigma^2_{T\_C2}/\sigma^2_{C1\_R}$ as

$$\left[\frac{MSE_{T\_C2}/MSE_{C1\_R}}{F_{(0.975,\, df_{T\_C2},\, df_{C1\_R})}}, \frac{MSE_{T\_C2}/MSE_{C1\_R}}{F_{(0.025,\, df_{T\_C2},\, df_{C1\_R})}}\right].$$

2) If the 95% CI of $\sigma^2_{T\_C2}/\sigma^2_{C1\_R}$ contains 1, then calculate the 90% CI of θ_{T_R} under the homogeneous assumption; otherwise, calculate it under the heterogeneous assumption.

   a) Under the homogeneous assumption, the 90% CI of θ_{T_R} is calculated as

$$\hat{\theta}_{T\_R} \pm t_{(0.95,\, df_{T\_R})} \times SE_p\,,$$

   where $\hat{\theta}_{T\_R}$ is obtained from Equation **(1)**, and the standard error of $\hat{\theta}_{T\_R}$ and degrees of freedom under homogeneity (SE_p and df_{T_R}) can be calculated as

$$SE_p = \sqrt{MSE_p \times \frac{1}{2}\left(\frac{1}{n_{T\_C2,1}} + \frac{1}{n_{T\_C2,2}} + \frac{1}{n_{C1\_R,1}} + \frac{1}{n_{C1\_R,2}}\right)}\,,$$

$$df_{T\_R} = df_{T\_C2} + df_{C1\_R}\,,$$

   where

$$MSE_p = \frac{df_{T\_C2} \times MSE_{T\_C2} + df_{C1\_R} \times MSE_{C1\_R}}{df_{T\_C2} + df_{C1\_R}}$$

   is the pooled mean squared error,
   $n_{T\_C2,1}$ = number of subjects in sequence 1 from the study that compares **T** and **C2**,
   $n_{T\_C2,2}$ = number of subjects in sequence 2 from the study that compares **T** and **C2**,
   $n_{C1\_R,1}$ = number of subjects in sequence 1 from the study that compares **C1** and **R**,
   $n_{C1\_R,2}$ = number of subjects in sequence 2 from the study that compares **C1** and **R**.

b) Under the heterogeneous assumption, the 90% CI of θ_{T_R} is calculated as

$$\hat{\theta}_{T\_R} \pm t_{(0.95,\, df_{WS})} \times SE_{T\_R},$$

where $\hat{\theta}_{T\_R}$ is obtained from Equation **(1)**, the standard error of $\hat{\theta}_{T\_R}$ under heterogeneity (SE_{T_R}) is calculated as

$$SE_{T\_R} = \sqrt{{SE_{T\_C2}}^2 + {SE_{C1\_R}}^2},$$

and the degrees of freedom can be approximated using the Welch-Satterthwaite equation

$$df_{WS} \approx \frac{\left({SE_{T\_C2}}^2 + {SE_{C1\_R}}^2\right)^2}{\frac{{SE_{T\_C2}}^4}{df_{T\_C2}} + \frac{{SE_{C1\_R}}^4}{df_{C1\_R}}},$$

where

$$SE_{T\_C2} = \sqrt{MSE_{T\_C2} \times \frac{1}{2}\left(\frac{1}{n_{T\_C2,1}} + \frac{1}{n_{T\_C2,2}}\right)},$$

$$SE_{C1\_R} = \sqrt{MSE_{C1\_R} \times \frac{1}{2}\left(\frac{1}{n_{C1\_R,1}} + \frac{1}{n_{C1\_R,2}}\right)}.$$

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