Contains Nonbinding Recommendations

Draft Guidance on Methylphenidate Hydrochloride

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Active Ingredient: Methylphenidate hydrochloride

Dosage Form; Route: Extended release tablet; oral

Recommended Studies: Two studies

1. Type of study: Fasting
   Design: Single-dose, two-treatment, four-period, two-sequence, fully replicated crossover in-vivo
   Strength: 54 mg
   Subjects: Males and nonpregnant females, general population.
   Additional comments: If an applicant intends to develop a higher strength (i.e. 72 mg), use the Reference Standard listed in the Orange Book for the in vivo bioequivalence study.

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2. Type of study: Fed
   Design: Single-dose, two-treatment, four-period, two-sequence, fully replicated crossover in-vivo
   Strength: 54 mg
   Subjects: Males and nonpregnant females, general population.
   Additional Comments: None.

Analytes to measure (in appropriate biological fluid): Methylphenidate in plasma

Bioequivalence based on (90% CI): Methylphenidate
Refer to Additional Comments below for more guidance regarding bioequivalence.

Waiver request of in-vivo testing: 18 mg, 27 mg, and 36 mg based on (i) acceptable bioequivalence studies on the 54 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 on the FDA-Recommended Dissolution Methods web site, available to the public at the following location: 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 products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

In addition to the method above, for modified release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted in the application. Agitation speeds may have to 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. Specifications will be determined upon review of the data submitted in the application.

Due to a concern of dose dumping of drug from this drug product when taken with alcohol, the Agency currently requests that additional dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 900 mL, 0.1 N HCl, USP Apparatus II (paddle) @50 rpm, with or without alcohol;

Test 1: 12 units tested according to the proposed method (with 0.1N 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

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

Both test and RLD products must be tested accordingly and data must be provided on individual unit, means, range and %CV on all strengths.

Additional comments regarding the bioequivalence study:

1. Additional Bioequivalence Metrics – Partial AUCs

The Concerta® Tablet labeling indicates that Concerta® (methylphenidate hydrochloride) extended-release tablet is an extended-release formulation of methylphenidate with a bi-modal release profile. Each Concerta® tablet is comprised of an immediate-release component and an extended-release component, thus providing an immediate release of methylphenidate and a second extended release of methylphenidate.

Thus, Concerta® is a multiphasic modified-release formulation designed to release a bolus of methylphenidate followed by slower delivery later in the day. According to the FDA-approved

labeling for this product, clinical studies showed statistically significant improvement in behavioral assessment scores throughout 12 hours, relative to placebo, following administration of a single morning dose. As this multiphasic modified-release dosage form is designed to achieve both rapid onset of activity and sustained activity with a duration of 12 hours, FDA suggests that additional bioequivalence metrics may be appropriate to ensure that a generic (test) version is therapeutically equivalent to the corresponding reference product. Thus, for Concerta® the following three partial AUC (pAUC) metrics are proposed in addition to the traditional ($AUC_{0-\infty}$ and C_{max}) metrics:

- AUC_{0-T1} should compare test & reference systemic exposure responsible for early onset of response during the early part of the once-daily dosing interval;
- AUC_{T1-T2} should compare test & reference systemic exposure responsible for sustaining the response in the middle of the once-daily dosing interval. For the children taking this medication, this would correspond to the early afternoon time to ensure the completion of the school day after lunch; and
- AUC_{T2-T3} should compare test & reference systemic exposure responsible for maintenance of the response in late stage of the once-daily dosing interval. For the children taking this medication, this would correspond to the late afternoon time to ensure the completion of homework and other after-school activities.

The 90% confidence intervals of the geometric mean test/reference (T/R) ratios for the above five C_{max} and AUC metrics (C_{max}, AUC_{0-T1}, AUC_{T1-T2}, AUC_{T2-T3}, $AUC_{0-\infty}$) should fall within the limits of 80.00-125.00%.

The sampling time (T1) for the first pAUC is based on time at which 90-95% of subjects are likely to achieve optimal early onset of response. Because the rate of initial methylphenidate absorption is associated with the rate of early onset of response, the sampling time "T1" is determined based on T_{max} of the immediate-release portion of the formulation. T_{max} is a pharmacokinetic parameter associated with rate of response. T2 is based on the school hours and T_{max} of the extended-release portion of the formulation. T3 is based on the efficacy duration claim of Concerta® from the pivotal clinical studies.

Fasting Study: Log-transformed AUC_{0-3}, AUC_{3-7}, AUC_{7-12}, $AUC_{0-\infty}$, and C_{max}, where AUC_{0-3} is the area under the plasma-concentration vs. time curve from 0 to 3 hours, AUC_{3-7} is area under the curve from 3 to 7 hours; AUC_{7-12} is area under the curve from 7 to 12 hours; $AUC_{0-\infty}$ is area under the curve from 0 to infinity, and C_{max} is the maximum plasma concentration. The pAUCs, AUC_{0-3}, AUC_{3-7}, and AUC_{7-12} have been determined to be the most appropriate parameters for evaluation of the drug bioavailability responsible for the quick onset and sustained maintenance of the clinical response throughout the duration of drug effect. These three pAUCs replace the usual AUC_{0-t}, and together with the other bioequivalence parameters, $AUC_{0-\infty}$ and C_{max}, will ensure that the pharmacokinetic profiles and clinical effects of test and reference products are sufficiently similar.

Fed Study: Log-transformed AUC_{0-4}, AUC_{4-8}, AUC_{8-12}, $AUC_{0-\infty}$, and C_{max}, where AUC_{0-4} is the area under the plasma-concentration vs. time curve from 0 to 4 hours, AUC_{4-8} is area under the curve from 4 to 8 hours; AUC_{8-12} is area under the curve from 8 to 12 hours; $AUC_{0-\infty}$ is area under the curve from 0 to infinity, and C_{max} is the maximum plasma concentration. The pAUCs,

AUC_{0-4}, AUC_{4-8}, and AUC_{8-12} have been determined to be the most appropriate parameters for evaluation of the drug bioavailability responsible for the quick onset and sustained maintenance of the clinical response throughout the duration of drug effect. These three pAUCs replace the usual AUC_{0-t}, and together with the other bioequivalence parameters, $AUC_{0-\infty}$ and C_{max}, will ensure that the pharmacokinetic profiles and clinical effects of test and reference products are sufficiently similar.

The reasons for selecting 3 hours and 4 hours, respectively, for the early onset pAUCs in fasting and fed studies are as follows:

- For the immediate-release portion of the formulation, T_{max} is about 2 hours in fasting subjects;
- Food prolongs the T_{max} of immediate-release methylphenidate by about 1 hour;
- The IR methylphenidate T_{max} standard deviation is about 0.5 hour;
- For T_{max}, two standard deviations = 1.0;
- Generally, approximately 95% of observations fall within two standard deviations of the mean;

Thus, since the T_{max} from the immediate-release portion of this formulation is about 2 hours under fasting conditions and 3 hours under fed conditions, pAUCs calculated to 0-3 hours in a fasting BE study and 0-4 hours in a fed BE study should capture the responses of 95% of the subjects. This should provide assurance that a test and reference product will be therapeutically equivalent over the early part of the daily dosing interval, corresponding to onset of response.

The reasons for selecting 7 and 8 hours for the middle pAUCs in the fasting and fed studies, respectively, are based on the T_{max} values of extended-release portion of this formulation and school hours. This will ensure similar drug exposures during the remaining school hours after early onset of response. The reason for selecting 12 hours for the late pAUCs in both the fasting and fed studies is due to the labelled efficacy duration (i.e., 12 hours). AUC_{3-7} and AUC_{7-12} in the fasting state, and AUC_{4-8} and AUC_{8-12} in the fed state should ensure that two products are therapeutically equivalent over the later part of the daily dosing interval, corresponding to the duration of the sustained response.

2. Statistical Analysis of Pharmacokinetic Data – subject-by-formulation interaction variance

To ensure the switchability between Concerta® and generic products, a subject-by-formulation test for each PK metric is recommended in addition to the establishment of average bioequivalence based on the PK metrics identified in the previous section.
The procedure to calculate the point estimate for subject-by-formulation interaction variance can be found in APPENDIX G of the FDA 2001 bioequivalence statistical guidance[1], but is also reproduced in this recommendation in **Steps 1-3**.

[1] Guidance for Industry: Statistical Approaches to Establishing Bioequivalence, January 2001. Accessible from: http://www.fda.gov/downloads/Drugs/Guidances/UCM070244.pdf

Step 1. Define new variables using the logarithm-transformed pharmacokinetic parameters ($AUC_{0\text{-}3}$, $AUC_{3\text{-}7}$, $AUC_{7\text{-}12}$, $AUC_{0\text{-}\infty}$, and C_{max} for the fasting study; $AUC_{0\text{-}4}$, $AUC_{4\text{-}8}$, $AUC_{8\text{-}12}$, $AUC_{0\text{-}\infty}$, and C_{max} for the fed study).

Assuming a four-period design with equal replication of the reference (R) and test (T) treatment arms in each sequence, each logarithm-transformed PK parameter is defined as Y_{ijkl} where:

i = 1, …s; indicates sequence
j = 1,…$n_{i;}$ indicates subject within sequence i
k = R,T; indicates treatment
l = 1,2; indicates replicate on treatment k for subjects within sequence i

The new variables are defined as:

$$I_{ij} = Y_{ijT\bullet} - Y_{ijR\bullet}$$
$$T_{ij} = Y_{ijT1} - Y_{ijT2}$$
$$R_{ij} = Y_{ijR1} - Y_{ijR2}$$

Where:

$$Y_{ijT\bullet} = \frac{1}{2}\left(Y_{ijT1} + Y_{ijT2}\right)$$
$$Y_{ijR\bullet} = \frac{1}{2}\left(Y_{ijR1} + Y_{ijR2}\right)$$

Step 2. Compute the formulation means and the variances of I_{ij}, T_{ij}, and R_{ij}, pooling across sequences.

These variance estimates are denoted as M_I, M_T, and M_R, respectively, where

$$\hat{\mu}_k = 1\big/_s \sum_{i=1}^{s} \overline{Y}_{i\cdot k\cdot}, \quad k = \text{R,T} \quad \text{and} \quad \hat{\Delta} = \hat{\mu}_T - \hat{\mu}_R$$
$$\overline{Y}_{i\cdot k\cdot} = \frac{1}{n_i} \sum_{j=1}^{s} \frac{1}{2} \sum_{l=1}^{2} Y_{ijkl}$$

$$M_I = \hat{\sigma}_I^{\,2} = \frac{1}{n_I}\sum_{i=1}^{s}\sum_{j=1}^{n_i}(I_{ij} - \bar{I}_i)^2$$

$$n_I = n_T = n_R = \left(\sum_{i=1}^{s} n_i\right) - s$$

$$M_T = \hat{\sigma}_{WT}^{\,2} = \frac{1}{2n_T}\sum_{i=1}^{s}\sum_{j=1}^{n_i}(T_{ij} - \bar{T}_i)^2$$

$$M_R = \hat{\sigma}_{WR}^{\,2} = \frac{1}{2n_R}\sum_{i=1}^{s}\sum_{j=1}^{n_i}(R_{ij} - \bar{R}_i)^2$$

Step 3. Estimate the subject-by-formulation interaction variance, $\hat{\sigma}_D^{\,2}$, by:

$$\hat{\sigma}_D^{\,2} = \hat{\sigma}_I^{\,2} - \frac{1}{2}\left(\hat{\sigma}_{WT}^{\,2} + \hat{\sigma}_{WR}^{\,2}\right) = M_I - \frac{1}{2}\left(M_T + M_R\right)$$

Step 4. Determine $H_{\hat{\sigma}_D^{\,2}}$, the 95% upper confidence bound for $\hat{\sigma}_D^{\,2}$.

The table below illustrates the construction of a (1-α) level upper confidence bound for $\hat{\sigma}_D^2$. Use α=0.05 for a 95% upper confidence bound. Note $n = \sum_{i=1}^{s} n_i$.

E_q= Point Estimate	H_q= Confidence Bound	$U_q=(H_q- E_q)^2$
$E_1 = M_I$	$H_1 = \frac{(n-s)\cdot M_I}{\chi^2_{\alpha,n-s}}$	U_1
$E_2 = -0.5\cdot M_T$	$H_2 = \frac{-0.5\cdot(n-s)\cdot M_T}{\chi^2_{1-\alpha,n-s}}$	U_2
$E_3 = -0.5\cdot M_R$	$H_3 = \frac{-0.5\cdot(n-s)\cdot M_R}{\chi^2_{1-\alpha,n-s}}$	U_3
	$H_{\sigma_D^2} = \sum E_q + \left(\sum U_q\right)^{1/2}$	

$H_{\sigma_D^2} = \sum E_q + \left(\sum U_q\right)^{1/2}$ is the upper 95% confidence bound for $\hat{\sigma}_D^2$. $\chi^2_{\alpha,n-s}$ is from the cumulative distribution function of the chi-square distribution with *n-s* degrees of freedom, i.e. $\Pr(\chi^2_{n-s} \le \chi^2_{\alpha,n-s}) = \alpha$. As per APPENDIX A in the FDA 2001 bioequivalence guidance, the recommended allowance for $\hat{\sigma}_D^2$ is 0.03.