Contains Nonbinding Recommendations

Draft Guidance on Methylphenidate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Film, extended release; transdermal

Recommended Studies: Three studies

1. Type of study: Bioequivalence study with pharmacokinetic endpoints
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 30 mg/9 hr
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments:
   - In this document, this dosage form is referred to as a transdermal delivery system (TDS) and includes products that may be described elsewhere or known as *patches* or *extended release films*.

   - Unless otherwise justified, the methylphenidate TDS should be applied to the same anatomical site on all subjects, as recommended for dosing in the approved labeling for the reference product and worn for 9 hours. Applicants should randomize subjects to receive either the test or reference product in a given study period. When possible, the TDS administered in the second study period should be applied to the same anatomical site as in the first study period, but on the contralateral side of the body.

   - Contact of the TDS with the skin is essential for the in vivo performance of the TDS, and the pharmacokinetics may be altered when a TDS loses its adherence to the skin. Therefore, the adhesion of each TDS should be monitored and recorded throughout the pharmacokinetic study. The applicant should prespecify their inclusion criteria for the statistical analysis of pharmacokinetic endpoints and perform their primary pharmacokinetic analysis on the per protocol population, however, pharmacokinetic samples should be collected and analyzed from all subjects at all sampling times regardless of the adhesion scores of the TDS and regardless of the inclusion criteria for the statistical analysis of pharmacokinetic endpoints. Provisions should be included in the study protocol to ensure that deliberate actions with the intent to re-apply a detached area of the TDS, to apply pressure to the TDS, or to reinforce TDS adhesion with the skin (e.g., overlays) are avoided throughout the study.

   - The applicant should follow FDA's current thinking in the guidance *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* for the design and conduct of the pharmacokinetic bioequivalence study.

Analytes to measure (in appropriate biological fluid): Methylphenidate in plasma, using an achiral assay for d- and l-methylphenidate

Bioequivalence based on (90% CI): Methylphenidate

- The confidence intervals of the geometric mean test/reference (T/R) ratios for the metrics (C_{max}, AUC_{2-9}, $AUC_{0-tlast}$, and $AUC_{0-\infty}$) should fall within the limits of 80-125%, where AUC_{2-9} is the area under the plasma concentration vs. time curve from 2 to 9 hours.

- Adequate pharmacokinetic samples are needed, particularly during the first 2-3 hours, to enable the evaluation of drug release into systemic circulation following TDS application.

Waiver request of in vivo testing: The 10 mg/9 hr, 15 mg/9 hr and 20 mg/9 hr strengths of the TDS may be considered for a waiver of in vivo bioequivalence testing based on (i) an acceptable bioequivalence study with the 30 mg/9 hr strength TDS, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the TDS formulation across all strengths.

NOTE: The proportional similarity of the TDS formulation across all strengths means i) that the amounts of active and inactive ingredients per unit of active surface area are identical for the different strengths of the test product, and ii) that the ratios of the active surface areas of each strength of the test product compared to the 30 mg/9 hr strength of the test product are the same as the corresponding ratios for the active surface areas of each strength of the reference product compared to the 30 mg/9 hr strength of the reference product.

Dissolution test method and sampling times: Comparative dissolution testing should be conducted on 12 dosage units each, of all strengths of the test and reference products. Information on a dissolution method for this drug product can be found on the FDA Dissolution Methods web site, accessible at: http://www.accessdata.fda.gov/scripts/cder/dissolution/.

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2. Type of study: Adhesion study
   Design: Single-dose, two-treatment, two period crossover in vivo
   Strength: 30 mg/9 hr
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments:
   - The applicant may elect to evaluate the pharmacokinetic bioequivalence (study 1) and the adhesion (study 2) in a single study with a combined purpose, or in independent studies. In either case, the studies should be adequately powered to evaluate the bioequivalence, and independently, the comparative assessment of adhesion.

- The applicant should follow FDA's current thinking in the guidance *Assessing Adhesion With Transdermal and Topical Delivery Systems for ANDAs* for the design and conduct of the independent adhesion study or the combined study to evaluate both pharmacokinetic bioequivalence and adhesion.

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3. Type of study: Skin irritation study
   Design: Randomized, evaluator-blinded, within-subject repeat in vivo
   Strength: 10 mg/9 hr
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments:
   - All test articles (i.e., 10 mg/9 hr test product[1], 10 mg/9 hr reference product, optional vehicle TDS[2], and optional negative control[3]) should be applied simultaneously to each subject at different positions on an application site recommended for dosing in the approved labeling for the reference TDS.

   - Sequential TDS applications should be made to the same application site every 48-72 hours[4], for a total of 21 consecutive days. A TDS applied on Day 19 should be removed on Day 22.

   - The applicant should follow FDA's current thinking in the guidance *Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs* for the design and conduct of the skin irritation and sensitization study.

Additional comments relating to all studies:

In addition to the recommendations in the general guidances referenced above, and the product specific recommendations related to the individual studies, the following product specific recommendations should be considered.

- Assess potential subjects for exclusion due to a family history of sudden death or ventricular arrhythmia, and monitor the subjects' blood pressure and heart rate at all visits.

[1] The test product evaluated should be the actual TDS to be marketed.
[2] The optional vehicle TDS should contain all of the inactive ingredients in the test product and be identical to the test product in every manner except for the absence of the active ingredient.
[3] An example of the optional negative control treatment is an occlusion type device with normal saline applied on a polyester pad under the cover or within the device chamber.
[4] This is different than the usual recommendation for applications of the TDS for the intended duration of wear. Studies involving 21 days of continuous daily application of this product have led to intolerable irritation. In general, less irritation has been observed with less frequent TDS applications (i.e., longer duration of wear). The 3-times-per-week application regimen is expected to result in a greater proportion of subjects completing the intended 21-day induction period in studies of this product.

- Inclusion Criteria (the applicant may add additional criteria):
  a. Subject has a normal screening echocardiogram; non-specific ST-T wave changes are acceptable

- Exclusion Criteria (the applicant may add additional criteria):
  a. History of sensitivity to methylphenidate or other components of the TDS
  b. History of severe depression, psychoses, bipolar disorder, mania, aggression, marked anxiety, agitation, tension, seizures, Tourette's Syndrome, motor tics, glaucoma, migraines, structural cardiac abnormalities, serious heart problems, hypertension, heart failure, myocardial infarction, ventricular arrhythmia, exertional chest pain, unexplained syncope
  c. History of narcotic abuse, drug abuse, or alcoholism
  d. Within 14 days of dosing, use of monoamine oxidase inhibitors

- Provide a listing of the prescription and over-the-counter drug products that are contraindicated during the study, such as:
  a. Central nervous system stimulants other than test and reference products
  b. Monoamine oxidase inhibitors
  c. Antihypertensives and pressor agents
  d. Coumarin anticoagulants, anticonvulsants (e.g., phenobarbital, phenytoin, primidone), clonidine, tricyclic drugs (e.g., imipramine, clomipramine, desipramine) and selective serotonin reuptake inhibitors