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Draft – Not for Implementation

Draft Guidance on Dextroamphetamine

November 2023

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

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:	Dextroamphetamine
Dosage Form:	System
Route:	Transdermal
Strengths:	4.5 mg/9 hr, 9 mg/9 hr, 13.5 mg/9 hr, 18 mg/9 hr
Recommended Studies:	One in vivo bioequivalence study with pharmacokinetic endpoints, one in vivo adhesion study, and one in vivo skin irritation study

1. Type of study: Bioequivalence study with pharmacokinetic endpoints
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 18 mg/9 hr
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments:
   a. 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 *systems*, *patches* or *extended release films*.
   b. Unless otherwise justified, the dextroamphetamine TDS should be applied to the same anatomical site on all subjects, selected from among those recommended for dosing in the approved labeling for the reference standard, and worn for 9 hours. Applicants should randomize subjects to receive either the test or reference standard 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.
   c. 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.

d. The applicant should follow FDA's current thinking in the most recent version of the FDA guidance for industry on *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*[a] for the design and conduct of the pharmacokinetic bioequivalence study.

Analyte to measure: Dextroamphetamine in plasma

Bioequivalence based on (90% CI): Dextroamphetamine

- The confidence intervals of the geometric mean test/reference (T/R) ratios for the metrics (C_{max}, $AUC_{2\text{-}9}$, $AUC_{0\text{-}tlast}$, and $AUC_{0\text{-}\infty}$) should fall within the limits of 80.00% - 125.00%, where $AUC_{2\text{-}9}$ 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 4.5 mg/9 hr, 9 mg/9 hr, 13.5 mg/9 hr strength of the TDS may be considered for a waiver of in vivo bioequivalence testing based on (i) an acceptable bioequivalence study with the 18 mg/9 hr strength, (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 18 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 listed drug (RLD) compared to the 18 mg/9 hr strength of the RLD.

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 dissolution testing on 12 dosage units each of all strengths of the test product and reference standard. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

2. Type of study: Adhesion study
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 18 mg/9 hr
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments:
   a. 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.
   b. The applicant should follow FDA's current thinking in the most recent version of the FDA guidance for industry on *Assessing Adhesion With Transdermal and Topical Delivery Systems for ANDAs*[a] for the design and conduct of the independent adhesion study or the combined study to evaluate both pharmacokinetic bioequivalence and adhesion.

3. Type of study: Skin irritation study
Design: Randomized, evaluator-blinded, within-subject repeat design in vivo
Strength: 4.5 mg/9 hr (Administered as one-half of the test and one-half of the lowest strength of the reference standard)
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments:
   a. All test articles (i.e., 4.5 mg/9 hr administered as one-half of the test[1], and one-half of the lowest strength of the reference standard, optional vehicle TDS[2] and optional negative control[3]) should be applied simultaneously to each subject at different positions on an application site recommended in the approved labeling for the reference standard.
   b. Sequential TDS applications should be made to the same application site every 24 hours for a total of 21 consecutive days.
   c. The applicant should follow FDA's current thinking in the most recent version of the FDA guidance for industry on *Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs*[a] for the design and conduct of the skin irritation study.

[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 ingredients
[3] An example of the optional negative control is an occlusion cover or device with normal saline applied on a polyester pad under the cover or within the device chamber.

Additional comments related 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.

1. 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.

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

3. Exclusion criteria (the applicant may add additional criteria):
    a. History of sensitivity to dextroamphetamine, other amphetamine products, 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, peripheral vasculopathy, Raynaud's phenomenon, or any other medical history that would put the subject at increased risk according to the Investigator
    c. History of narcotic abuse, drug abuse, or alcoholism
    d. Within 14 days of dosing, use of monoamine oxidase inhibitors

4. A listing of the prescription and over-the-counter drug products that are prohibited during the study should be provided, such as:
    a. Central nervous system stimulants other than test product and reference standard
    b. Monoamine oxidase inhibitors (MAOIs)
    c. Antihypertensives and pressor agents
    d. Drugs that affect the serotonergic neurotransmitter systems such as MAOIs, selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort.
    e. Cytochrome P450 2D6 (CYP2D6) inhibitors
    f. Urinary alkalizing agents and acidifying agents

Additional information:

Device:
The RLD is a transdermal delivery system and a drug-device combination product.

FDA recommends that prospective applicants examine the external critical design attributes, and the external operating principles of the RLD device when designing the test device.

User interface assessment:
An ANDA for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.[a]

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