Contains Nonbinding Recommendations

Draft Guidance on Lidocaine

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Patch; topical

Recommended Studies: Three studies

1. Type of study: Bioequivalence (BE) study with pharmacokinetic (PK) endpoints
   Design: Single-dose, two-treatment, two-period crossover in vivo using three topical delivery systems (TDS) simultaneously
   Strength: 5%
   Subjects: Males and non-pregnant, non-lactating females, general population

   Additional comments:

   - In this document, this dosage form is referred to as a topical delivery system (TDS) and includes products that may be described elsewhere or known as *patches*.
   - Unless otherwise justified, three lidocaine TDS should be applied to the same anatomical site on all subjects and worn for 12 hours. Applicants should randomize subjects to receive either the test or reference listed drug (RLD) 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. A sampling time at 24-hour post-dose should be included in the BE study.
   - A validated analytical method with a lower limit of quantification (LLOQ) of 0.20 ng/mL is recommended to adequately measure lidocaine in plasma, to characterize the PK using three simultaneously applied lidocaine TDS. A smaller number of TDS units may be used simultaneously, if the resulting plasma concentrations of lidocaine are quantifiable and the PK profile of lidocaine can be adequately characterized for a BE assessment based on the 90% confidence interval criteria.
   - Contact of the TDS with the skin is essential for the in vivo performance of the TDS, and the PK 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 PK study. The PK samples should be collected and analyzed from all subjects at all sampling times regardless of the adhesion scores of the TDS. 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 PK BE study.

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

Bioequivalence based on (90% CI): Lidocaine

Waiver request of in vivo testing: Not applicable

NOTE: The strength of this topical dosage form is based upon the amount of drug in the TDS, expressed as a percentage based upon weight. A pharmaceutically equivalent drug product submitted in an ANDA should contain the same percentage of drug in the TDS, based upon weight.

The topical bioavailability of the drug from this drug product is influenced by the active surface area of the TDS. A drug product submitted in an ANDA should have the same active surface area as the RLD product.

Dissolution test method and sampling times: Comparative dissolution testing should be conducted on 12 dosage units each, of the test and RLD 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: 5%
Subjects: Males and non-pregnant, non-lactating females, general population

Additional comments:

- The applicant may elect to evaluate the PK BE (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 BE, 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 PK BE and adhesion.

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3. Type of study: Skin irritation and sensitization study
Design: Randomized, evaluator-blinded, within-subject repeat in vivo
Strength: 5% (administered as one-fourth of the test and one-fourth of the reference)

Subjects: Males and non-pregnant, non-lactating females, general population

Additional comments:

- All test articles (i.e., one-fourth of the test TDS[1], one-fourth of the RLD 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 RLD product.
- Sequential TDS applications should be made to the same application site every 48-72 hours for a total of 21 consecutive days.
- There is insufficient information to determine whether it is safe to simultaneously apply two whole, lidocaine TDS on the same subject during a 21-day skin irritation and sensitization study. Since the RLD product has a matrix design that can be safely cut, one-fourth of the RLD product can be used for these studies. If the test product also has a design that can be safely cut to a smaller size, it should also be cut, and one-fourth of the test product may be applied simultaneously with one-fourth of a RLD product (to separate skin sites). It would not be acceptable to manufacture a separate batch of the test TDS in order to use a smaller TDS in this study. If the test TDS has a design that cannot be safely cut to a smaller size, and/or if a prospective applicant proposes a study design different than what is recommended above, the prospective applicant may submit a pre-ANDA meeting request to discuss the proposed approach.
- 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.

- Exclusion Criteria (the applicant may add additional criteria):
    a. Medical history of hepatic disease.
- A list of the prescription and over-the-counter drug products, procedures, and

[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 is an occlusion cover or device with normal saline applied on a polyester pad under the cover or within the device chamber.

activities that are prohibited during the study should be included in the protocol, such as:

a. Antiarrhythmic drugs