Draft Guidance on Lidocaine

August 2026

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form: System

Route: Topical

Strength: 10%

Reference Listed Drug: NDA 215029

Recommended Studies: One in vivo bioequivalence study with pharmacokinetic endpoints, one in vivo adhesion study, and one in vivo skin irritation study

1. Class of study: Bioequivalence
   Type of study: Bioequivalence study with pharmacokinetic endpoints
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 10%
   Dose: Two whole topical delivery systems (TDS) applied simultaneously over a 12-hour period
   Subjects: Healthy males and non-pregnant, non-lactating females
   Study design recommendations:
   - In this document, this dosage form is referred to as a TDS and includes products that may be described elsewhere or known as *systems* or *patches*.
   - Unless otherwise justified, two 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 drug product TDS 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 bioequivalence study with pharmacokinetic endpoints.

- A validated analytical method with a lower limit of quantification of 0.20 ng/mL is recommended to adequately measure lidocaine in plasma to characterize the pharmacokinetics using two simultaneously applied lidocaine TDS. A smaller number of TDS may be used simultaneously, if the resulting plasma concentrations of lidocaine are quantifiable and the pharmacokinetic profile of lidocaine can be adequately characterized for a bioequivalence 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 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 bioequivalence study with pharmacokinetic endpoints. 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, 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 refer to the guidance for industry *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*[a] for the design and conduct of the bioequivalence study with pharmacokinetic endpoints.
- 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 activities that are prohibited during the study should be included in the protocol, such as:
    a. Antiarrhythmic drugs

Analyte to measure: Lidocaine in plasma

Bioequivalence based on (90% CI): Lidocaine

In vitro drug release method and sampling times: In vitro release should be included for quality control. Provide an in vitro release method development report for the test product containing information and data that demonstrate the appropriateness of the selected in vitro release method[1] and sampling times, such as the discriminating ability to detect changes in critical quality attributes that could potentially impact drug product performance.

[1] Applicant-developed, United States Pharmacopeia (USP) drug product monograph, or Dissolution Methods database, https://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm

2. Class of study: Comparative clinical endpoint non-inferiority study
Type of study: Adhesion study
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 10%
Subjects: Healthy males and non-pregnant, non-lactating females
Study design recommendations:

- The applicant may elect to evaluate the 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 refer to the guidance for industry *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 bioequivalence and adhesion.
- Refer to study 1 for recommendations related to exclusion criteria and prohibited drug products, procedures, and activities during the study.

3. Class of study: Comparative clinical endpoint non-inferiority study
Type of study: Skin irritation study
Design: Randomized, evaluator-blinded, within-subject repeat design in vivo
Strength: 10% (administered as one-fourth of the test articles)
Subjects: Healthy males and non-pregnant, non-lactating females
Study design recommendations:

- All test articles (i.e., one-fourth of the 10% strength of both drug product TDS[2], optional vehicle TDS[3], and optional negative control[4]) should be applied simultaneously to each subject at different positions on the same anatomical site.
- Sequential TDS applications of each test article should be made to the same position every 48-72 hours for a total of 21 consecutive days.
- When evaluating the irritation potential only, applicants should compare the test articles in a minimum of 40 evaluable subjects, or a sufficient number of subjects to power the study at a level of 0.80 or higher, whichever is greater.
- If the test product contains an inactive ingredient that is not present in the reference listed drug (RLD) and is known to be sensitizing, or at a higher amount/concentration than previously used in an FDA-approved drug product with a similar context of use, FDA recommends conducting a combined irritation and sensitization study. FDA encourages applicants who have questions related to the need for a sensitization study for a proposed product (with a proposed formulation composition) to seek feedback through a controlled correspondence

[2] The test product evaluated should be the actual TDS to be marketed.
[3] 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.
[4] An example of the optional negative control treatment is an occlusive cover or device with normal saline applied on a polyester pad under the cover or within the device chamber.

or product development meeting.[5]

- There is insufficient information to determine whether it is safe to simultaneously apply two whole, active, 10% lidocaine TDS on the same subject during a 21-day skin irritation (and sensitization) study. Since the RLD has a matrix design that can be safely cut, the test product is anticipated to have a design that can also be safely cut to a smaller size. It would not be acceptable to manufacture a separate batch of the test product in order to use a smaller TDS in this study.
- The applicant should refer to the guidance for industry *Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs*[a] for the design and conduct of the skin irritation (and sensitization) study.
- Refer to study 1 for recommendations related to exclusion criteria and prohibited drug products, procedures, and activities during the study.

Formulation: 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 abbreviated new drug application (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.

Device: The RLD is presented as a TDS. The TDS is the drug-device combination product. FDA recommends that prospective applicants examine the size and shape and external critical design attributes 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 guidance for industry *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.[a]

Document History: Recommended August 2026

[a] We update guidances periodically. For the most recent version of a guidance, refer to the FDA guidance webpage at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[5] Applicants should refer to the guidance for industry *Controlled Correspondence Related to Generic Drug Development* and the guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* for additional information describing the procedures on how to clarify regulatory expectations regarding the applicants' individual drug development program.