

Draft Guidance on Menthol; Methyl Salicylate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Patch; topical

Recommended Studies: Three studies

1. Type of study: Bioequivalence study with pharmacokinetic endpoints
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 3%; 10% (Dose: Four whole 7 cm x 10 cm topical delivery systems (TDS) applied simultaneously over an 8-hour period, or two whole 10 cm x 14 cm TDS applied simultaneously over an 8-hour period)
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments:
 - In this document, this dosage form is referred to as a TDS and includes products that may be described elsewhere or known as *patches*.
 - Unless otherwise justified, the menthol; methyl salicylate TDS should be applied to the same anatomical site on all subjects and worn for 8 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. A smaller number of TDS may be used, provided the plasma concentrations of menthol and methyl salicylate are quantifiable, so as to adequately characterize the pharmacokinetic profile of menthol and methyl salicylate for the assessment of bioequivalence.
 - A sampling time at 24 hour post-dose should be included in the bioequivalence study. The frequency of sampling should adequately cover the absorption, distribution and elimination phase of the drug.
 - 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 placement of a TDS on irritated skin may affect the pharmacokinetics and because these TDS are intended to be irritating, it is recommended that the TDS for the second period of the pharmacokinetic study be applied to the same anatomical area but at different sites than those of the first period.
- 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): Menthol, methyl salicylate and salicylic acid in plasma

Bioequivalence based on (90% CI): Menthol and Methyl salicylate*

*If methyl salicylate cannot be measured in the blood for a sufficient time (at least 4 half-lives) to ascertain the elimination rate constant [and therefore the Area Under the Curve until infinite time (AUC_{inf})], the metabolite salicylic acid may be evaluated for its C_{max} and AUC parameters (log normally distributed) using two one-sided tests by comparing the 90% confidence intervals.

Waiver request of in vivo testing: The 10 cm x 14 cm strength TDS may be considered for a waiver of in vivo bioequivalence testing based on (i) an acceptable bioequivalence study with the 7 cm x 10 cm strength TDS, (ii) acceptable in vitro dissolution testing of both strengths, and (iii) proportional similarity of the TDS formulation across both strengths.

NOTE: The strength of this TDS 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 reference product.

Dissolution test method and sampling times: Comparative dissolution testing should be conducted on 12 dosage units each, of both 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/>.

2. Type of study: Adhesion study

Design: Single-dose, two-treatment, two period crossover in vivo

Strength: 3%; 10% (Dose: One whole 10 cm x 14 cm TDS applied simultaneously over an 8-hour period)

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 and sensitization study

Design: Randomized, evaluator-blinded, within-subject repeat in vivo

Strength: 3%; 10% (Dose: One-fourth of a 7 cm x 10 cm TDS)

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

Additional comments:

- All test articles (i.e., one-fourth of the test product¹, one-fourth of the reference product, optional one-fourth of the vehicle TDS² and optional negative control³) should be applied simultaneously to each subject at different positions on an application site recommended for dosing in the approved labeling for the reference product.
- Sequential TDS applications should be made to the same application site every 24 hours, for a total of 21 consecutive days. The TDS applied on Day 21 should be removed on Day 22.
- There is insufficient information to determine whether it is safe to simultaneously apply two whole, active menthol; methyl Salicylate 3%; 10% TDS on the same subject during a 21-day skin irritation and sensitization study. Since the reference product has a matrix design that can be safely cut in quarters, one fourth of the reference 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 in quarters, and one fourth of the test product may be applied simultaneously with one fourth of a reference product (to separate skin sites). It would not be acceptable to manufacture a separate

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

batch of the test product in order to use a smaller TDS in this study. If the test product has a design that cannot be safely cut to a smaller size, and/or if a prospective applicant proposes study design different than what is recommended above, the prospective applicant may submit a pre-Abbreviated New Drug Application 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.