Contains Nonbinding Recommendations

Draft Guidance on Capsaicin

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Patch; topical

Recommended Studies: Three studies

1. Type of study: Bioequivalence study with clinical endpoint
   Design: Randomized, double-blind, parallel, controlled in vivo
   Strength: 8%
   Subjects: Males and non-pregnant, non-lactating females with postherpetic neuralgia (PHN)

   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*.
   - Specific recommendations relating to the bioequivalence study with clinical endpoint are provided below.

   Analytes to measure (in appropriate biological fluid): Not applicable

   Bioequivalence based on (90% CI): Clinical endpoint

   Waiver request of in vivo testing: Not applicable

   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 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: https://www.accessdata.fda.gov/scripts/cder/dissolution/.

2. Type of study: Adhesion study
Design: Single-dose, two-treatment, two period crossover in vivo
Strength: 8%
Subjects: Males and non-pregnant, non-lactating females, general population

Additional comments:

- 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 adhesion study.

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3. Type of study: Skin irritation and sensitization study
Design: Randomized, evaluator-blinded, within-subject repeat in vivo
Strength: Vehicle TDS and positive control (TDS containing active pharmaceutical ingredient should not be used in this study due to safety concerns)
Subjects: Males and non-pregnant, non-lactating females, general population

Additional comments:

- All test articles (i.e., vehicle TDS[1], positive control of low irritancy[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 product.

- Sequential TDS applications should be made to the same application site for 1 hour (the intended duration of wear) daily for a total of 21 consecutive days during the induction phase. The challenge phase should involve a single 48-hour application of the vehicle TDS.

- 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 regarding the bioequivalence study with clinical endpoint:

- The test TDS should have a design that can be safely cut to a smaller size.

[1] The 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.
[2] Safety concerns preclude the use of comparative studies with the test and reference products, therefore, the test product can be evaluated by testing a vehicle TDS versus a positive control TDS that produces mild irritation (e.g., ≤ 0.1% sodium lauryl sulfate).
[3] 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.

- The Office of Generic Drugs recommends conducting a bioequivalence study with a clinical endpoint in the treatment of PHN. Subjects should be randomized to receive a capsaicin topical TDS test product, the reference product, or control applied as one whole TDS applied to the affected area for a single 60-minute treatment. A low-concentration capsaicin TDS causing a perceptible local sensation should be used as a control rather than placebo to maintain the integrity of the double-blind design. Prior to application of the TDS containing the study drug, subjects should receive a single 60-minute application with a topical local anesthetic on the area of pain. The primary endpoint is the change in pain from baseline to 2, 8 and 12 weeks after application of the TDS in the self-evaluation of pain measured in mm on the Visual Analog Scale (VAS).

- Inclusion Criteria (the applicant may add additional criteria):
  a. Males and non-pregnant, non-lactating females aged 18 to 90 years with PHN with at least 3 months since vesicle crusting and VAS $\geq$ 45 mm
  b. On a stable regimen of chronic pain medication for at least 21 days prior to study enrollment and willing to maintain medications at the same stable dose(s) and schedule throughout the study

- Exclusion Criteria (the applicant may add additional criteria):
  a. Pregnant or lactating female
  b. Vesicle crusting < 3 months prior to randomization
  c. Non-intact or damaged skin within the area to be treated, e.g., eczema, psoriasis, exudative dermatitis, infected lesion, burn or wound
  d. Current use oral opioid exceeding a total daily dose of morphine 60mg/day or equivalent
  e. Current use of parenteral opioid at any dose
  f. History of substance abuse
  g. Lack of an effective rescue medication strategy for the subject, such as unwillingness to use opioid analgesics during treatment or high tolerance to opioids precluding the ability to relieve treatment-associated discomfort
  h. Use within 21 days prior to randomization of any topically applied pain medication (e.g., non-steroidal anti-inflammatory drugs (NSAIDs), menthol, methyl salicylate, local anesthetics, steroids or capsaicin products)
  i. Current use of class I (e.g., tocainide and mexiletine) or class III (e.g., amiodarone, bretylium, sotalol, dofetilide) antiarrhythmic drugs
  j. Medical history of methemoglobinemia or glucose-6-phosphate dehydrogenase deficiencies
  k. Medical history of uncontrolled hypertension or diabetes mellitus
  l. Severe cardiac, renal or hepatic impairment
  m. Clinically significant abnormal electrocardiogram at screening
  n. Significant pain of an etiology other than PHN (e.g., spinal stenosis, fibromyalgia or arthritis)
  o. Any implanted medical device for the treatment of neuropathic pain (e.g., spinal cord stimulator, intrathecal pump or peripheral nerve stimulator)

p. Known allergy or hypersensitivity to capsaicin, local anesthetics, adhesives or any excipient in the test product, reference product or topical anesthetic
q. Severe systemic disease (e.g., cancer, severe acute infection)
r. Use within 7 days prior to randomization of any topical agent on the affected site

- The protocol should include a list of the prescription and over-the-counter drug products, procedures, and activities that are prohibited during the study, such as:
  a. Any new therapy for treatment of pain or changes to current therapy, e.g., oral, topical, or parenteral NSAIDs, aspirin or narcotic pain medication
  b. Topical product other than the assigned treatment (including moisturizers, sun screen, creams, ointments, lotions, and powders) applied on or near the treatment area

- The recommended primary endpoint of the study is the mean change from baseline to study weeks 2, 8 and 12 in the self-evaluation of pain by the VAS in mm.

- Application site reactions such as erythema, dryness, burning/stinging, erosion, edema, pain and itching should be recorded at each visit to allow a comparison between treatment groups. A descriptive analysis comparing the application site reactions for each treatment group is recommended. It is important to ensure that the test product is not worse than the reference product with regard to the expected and unexpected application site reactions.

- Adhesion data should be collected during the course of the study to document that adhesion of the products is adequate. Applicants may consider establishing criteria for using tape to reinforce any TDS that are lifting during the study.

- The applicant should consider FDA's current thinking in the guidance *Assessing Adhesion With Transdermal and Topical Delivery Systems for ANDAs* regarding the adhesion scale used to monitor TDs adhesion during the study.

- The protocol should clearly define the per-protocol (PP), modified intent-to-treat (mITT) and safety populations.
  a. The accepted PP population used for bioequivalence evaluation includes all randomized subjects who:
     i. Meet all inclusion/exclusion criteria.
     ii. Are dosed a pre-specified proportion of the scheduled doses (generally at least 75% and no more than 125%) of the assigned product for the specified duration of the study. The protocol should specify how compliance will be verified, (e.g., by the use of subject diaries).
     iii. Do not miss a pre-specified number of scheduled doses for more than pre-specified number of consecutive days.
     iv. Complete the evaluation within the designated visit window with no protocol violations that would affect the treatment evaluation.
  b. The mITT and safety populations include all randomized subjects who use at least one dose of product.

- Subjects who are discontinued early from the study due to lack of treatment effect should be included in the PP population using Last Observation Carried Forward (LOCF). Subjects whose condition worsens and who require alternate or supplemental therapy for the treatment of their condition during the treatment phase of the study should be discontinued, included in the mITT and PP population analyses using LOCF, and provided with effective treatment. Subjects discontinued early for other reasons should be excluded from the PP population, but included in the mITT population, using LOCF. Applicants should provide a pre-specified definition of lack of treatment effect.

- The start and stop calendar date (e.g., mm/dd/yyyy) and study day (e.g., Day X) of concomitant medication use should be provided in the data set in addition to the reason for the medication use. The Applicant should clearly note whether the medication was used prior to baseline visit, during the study, or both.

- If the study allows for the use of a rescue medication, the applicant should submit a data set that includes the date and time of each rescue medication use for each subject who used the rescue medication at any point during the study. The applicant should pre-specify rescue medication use (name, type, frequency, reason to use), maximum allowable amount of daily rescue medication use, and any limitations (e.g., cannot use rescue medication within pre-specified number of hours prior to primary endpoint evaluation) for rescue medication use during the study.

- All adverse events (AEs) should be reported, whether or not they are considered to be related to the treatment. The report of AEs should include date of onset, description of the AE, severity, relation to study medication, action taken, outcome and date of resolution. This information is needed to determine if the incidence and severity of adverse reactions is different between the test product and reference product.

- All pregnancies should be reported, including outcome information.

- If the inactive ingredients are different than those contained in the reference product or in significantly different amounts, then the applicant should clearly describe the differences and provide information to show that the differences will not affect the safety, efficacy, or systemic or local availability of the drug. Inactive ingredients used should provide adequate margins of safety for the proposed clinical exposure in the target population (e.g., 2 months and older).

- The method of randomization should be described in the protocol and the randomization schedule should be provided. It is recommended that an independent third party generate and hold the randomization code throughout the conduct of the study in order to minimize bias. The Applicant may generate the randomization code if not involved in the packaging and labeling of the study medication. A sealed copy of the randomization scheme should be retained at the study site and should be

available to FDA investigators at the time of site inspection to allow for verification of the treatment identity of each subject.

- A detailed description of the blinding procedure should be provided in the protocol. The packaging of the test, reference and control products should be similar in appearance to make differences in treatment less obvious to the subjects and to maintain adequate blinding of evaluators. When possible, neither the subject nor the investigator should be able to identify the treatment. The containers should not be opened by the subject at the study center.

- Applicants should refer to 21 CFR 320.38, 320.63 and the guidance for industry *Handling and Retention of BA and BE Testing Samples*, regarding retention of study drug samples and 21 CFR 320.36 for requirements for maintenance of records of bioequivalence testing. In addition, the investigators should follow the procedures of 21 CFR 58 and ICH E6 *Good Clinical Practice: Consolidated Guideline* for retention of study records and data in order to conduct their studies in compliance with Good Laboratory Practices and Good Clinical Practices. Retention samples should be randomly selected from the drug supplies received for each shipment prior to dispensing to subjects. Retention samples should not be returned to the Applicant at any time.

- It is the applicant's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.

- A control arm is recommended to demonstrate that the test product and reference product are active and as a parameter that the study is sufficiently sensitive to detect differences between products.

- To establish bioequivalence for a continuous endpoint, it is recommended the following compound hypotheses be tested using the per protocol population:

  $H_O: \mu_T/\mu_R < \theta_1$ or $\mu_T/\mu_R > \theta_2$ versus $H_A: \theta_1 \leq \mu_T/\mu_R \leq \theta_2$

  where μ_T = mean of the primary endpoint for the test group, and
  μ_R = mean of the primary endpoint for the reference group

  The null hypothesis, H_O, is rejected with a type I error (α) of 0.05 (two one-sided tests) if the estimated 90% confidence interval for the ratio of the means between test and reference products (μ_T/μ_R) is contained within the interval $[\theta_1, \theta_2]$, where $\theta_1 = 0.80$ and $\theta_2 = 1.25$. Rejection of the null hypothesis supports the conclusion of equivalence of the two products.

- To establish sensitivity within the study for either a dichotomous or continuous primary endpoint, the test and reference products should both be statistically superior to the control. Conduct an appropriate two-sided inferential test with a type I error (α) of 0.05, using the mITT population.

- The protocol should include a section with fully detailed statistical analysis plan.

- Study data should be submitted in a standardized format. Applicants should refer to the study data standards published at www.fda.gov[4].

- Applicants should provide the Subject-Level Analysis Dataset (ADSL), one record per subject, using the following headings, if applicable:
  a. Study identifier
  b. Unique subject identifier
  c. Subject identifier for the study
  d. Study site identifier (if applicable)
  e. Age
  f. Age units (years)
  g. Sex
  h. Race
  i. Name of planned treatment
  j. Name of actual treatment
  k. Actual treatment (character)
  l. Safety population flag (yes/no)
  m. Reason for exclusion from safety population
  n. Modified Intent-to-Treat (mITT) population flag (yes/no)
  o. Reason for exclusion from mITT population
  p. Per-Protocol (PP) population flag (yes/no)
  q. Reason for exclusion from PP population
  r. Randomized population flag (yes/no)
  s. Date/time of first exposure to treatment
  t. Date/time of last exposure to treatment
  u. End of study date
  v. End of study status
  w. Subject required additional treatment due to unsatisfactory treatment response (yes/no)
  x. VAS (in mm) on Day 0 (baseline)
  y. VAS (in mm) on Week 2
  z. VAS (in mm) on Week 8
  aa. VAS (in mm) on Week 12
  bb. TDS removed due to strong skin irritation reaction (yes/no)
  cc. TDS reinforced with tape (yes/no)
  dd. Compliance rate (%)
  ee. Subject missed the pre-specified number of scheduled doses for more than pre-specified number of consecutive days (yes/no)
  ff. Concomitant medication (yes/no)
  gg. Adverse event(s) reported (yes/no)

[4] Study Data Standards for Submission to CDER and CBER available at: https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

- Applicants should provide basic data structure (BDS) dataset with records per subject, per visit, per analysis timepoint, using the following headings, if applicable:
    a. Study identifier
    b. Unique subject identifier
    c. Subject identifier for the study
    d. Study site identifier (if applicable)
    e. Name of planned treatment
    f. Name of actual treatment
    g. Safety population flag (yes/no)
    h. Modified ITT population flag (yes/no)
    i. Per-Protocol (PP) population flag (yes/no)
    j. Analysis date
    k. Analysis visit
    l. Study visit within the designated window (yes/no)
    m. Analysis timepoint (e.g., hour 0, hour 2) (if applicable)
    n. Evaluator: identity of evaluator
    o. VAS (in mm) at that visit (e.g., for Day 0 (baseline), Week 2, 8 or 12)
    p. Adhesion score at that visit
    q. Concomitant medication reported during this visit (yes/no)
    r. Additional treatment required during the visit (yes/no)
    s. Adverse event reported during this visit (yes/no)
    t. Laboratory testing during this visit (yes/no)