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Draft – Not for Implementation

Draft Guidance on Diclofenac Sodium

October 2022

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Active Ingredient: Diclofenac sodium

Dosage Form; Route: Gel; topical

Recommended Studies: Two options: (1) two in vitro bioequivalence studies, one in vivo bioequivalence study with pharmacokinetic endpoints, and other characterization tests or (2) one in vivo study with pharmacokinetic endpoints and one in vivo study with clinical endpoint

I. Option 1: Two in vitro bioequivalence studies, one in vivo bioequivalence study with pharmacokinetic endpoints, and other characterization tests

To demonstrate bioequivalence for diclofenac sodium topical gel, 1% using a combination of in vitro studies and an in vivo study with pharmacokinetic endpoints, the following criteria should be met:

1. The test product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference standard that may significantly affect the local or systemic availability of the active ingredient. For example, if the test product and reference standard are qualitatively (Q1) and quantitatively (Q2) the same, as defined in the most recent version of the FDA guidance for industry on *ANDA Submissions – Refuse-to-Receive Standards*[a], and the criteria below are also satisfied, the bioequivalence of the test product may be established using a characterization-based bioequivalence approach.

2. The test product and reference standard should have the same physicochemical and structural (Q3) attributes, based upon acceptable comparative Q3 characterization tests with a minimum of three batches of the test product and three batches (as available) of

the reference standard. The test product and reference standard batches should ideally represent the product at different ages throughout its shelf life. Refer to the most recent version of the FDA guidance for industry on *Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs*[a] for additional information regarding comparative Q3 characterization tests. The comparison of the test product and reference standard should include characterizations of the following Q3 attributes

a. Characterization of visual appearance and texture
b. Characterization of phase states and structural organization of matter
    - Microscopic examination with representative high-resolution microscopic images at multiple magnifications
    - Analysis of globule size distribution
c. Characterization of rheological behavior which may be characterized using a rheometer that is appropriate for monitoring the non-Newtonian flow behavior of semi-solid dosage forms. The following evaluations are recommended:
    - A characterization of shear stress vs. shear rate and viscosity vs. shear rate. At minimum, this should consist of numerical viscosity data at three shear rates (low, medium, and high).
    - A complete flow curve across the range of attainable shear rates, until low or high shear plateaus are identified.
    - Yield stress values should be reported if the material tested exhibits plastic flow behavior.
    - The linear viscoelastic response (storage and loss modulus vs. frequency) should be measured and reported. Any non-linear viscosity behavior over a range of shear rates should also be investigated, measured and reported.
d. Characterization of pH
e. Characterization of specific gravity
f. Characterization of any other potentially relevant Q3 attributes

3. The test product and reference standard should have an equivalent rate of diclofenac sodium based upon an acceptable in vitro release test (IVRT) bioequivalence study comparing a minimum of one batch each of the test product and reference standard using an appropriately validated IVRT method.

    Type of study: Bioequivalence study with IVRT endpoint
    Design: Single-dose, two-treatment, parallel, multiple-replicate per treatment group study design using an occluded pseudo-infinite dose, in vitro
    Strength: 1%
    Test system: A synthetic membrane in a diffusion cell system
    Analyte to measure: Diclofenac in receptor solution
    Equivalence based on: Diclofenac (IVRT endpoint: drug release rate)
    Additional comments: Refer to the most recent version of the FDA guidance for industry on *In Vitro Release Test Studies for Topical Drug Products Submitted in ANDAs*[a] for additional information regarding the development, validation, conduct and analysis of acceptable IVRT methods/studies. The batches of test

product and reference standard evaluated in the IVRT bioequivalence study should be included among those for which the Q3 attributes are characterized.

4. The test product and reference standard should have an equivalent rate and extent of diclofenac permeation through excised human skin based upon an acceptable in vitro permeation test (IVPT) bioequivalence study comparing a minimum of one batch each of the test product and reference standard using an appropriately validated IVPT method.

   Type of study: Bioequivalence study with IVPT endpoints
   Design: Single-dose, two-treatment, parallel, multiple-replicate per treatment group study design using an unoccluded finite dose, in vitro
   Strength: 1%
   Test system: Barrier-competent human skin from male and/or female donors of at least 18 years of age in a diffusion cell system
   Analyte to measure: Diclofenac in receptor solution
   Equivalence based on: Diclofenac (IVPT endpoints: total cumulative amount (AMT) and maximum flux (J_{max}))
   Additional comments: Refer to the most recent version of the FDA guidance for industry on *In Vitro Permeation Test Studies for Topical Drug Products Submitted in ANDAs*[a] for additional information regarding the development, validation, conduct and analysis of acceptable IVPT methods/studies. The batches of test product and reference standard evaluated in the IVPT bioequivalence study should be the same as those evaluated in the IVRT bioequivalence study.

5. The test product and reference standard should demonstrate bioequivalence based upon an acceptable in vivo pharmacokinetic study with one batch each of the test product and reference standard.

   Type of study: Bioequivalence study with pharmacokinetic endpoints
   Design: Single-application, two-way crossover, in vivo
   Strength: 1%
   Subjects: Males and non-pregnant, non-lactating females, general population
   Analytes to measure: Diclofenac in plasma
   Equivalence based on: Diclofenac
   Additional comments: The study conditions such as the dose of the test product and reference standard, the site of dose application, etc. should be consistent across the study and the bioanalytical method should be sufficiently sensitive to be able to adequately characterize the pharmacokinetic profiles of the test product and reference standard. Refer to the most recent version of the FDA guidance for industry on *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*[a] for additional information regarding the analysis of the bioequivalence study with pharmacokinetic endpoints. The batches of test product and reference standard evaluated in the bioequivalence study with pharmacokinetic endpoints should be the same as those evaluated in the IVRT and IVPT bioequivalence studies.

II. Option 2: One in vivo study with pharmacokinetic endpoints and one in vivo study with clinical endpoint

1. Type of study: Bioequivalence study with pharmacokinetic endpoints
   Design: Single-application, two-way crossover, in vivo
   Strength: 1%
   Subjects: Males and non-pregnant, non-lactating females, general population
   Analytes to measure: Diclofenac in plasma
   Equivalence based on: Diclofenac
   Additional comments: The study conditions such as the dose of the test product and reference standard, the site of dose application, etc. should be consistent across the study and the bioanalytical method should be sufficiently sensitive to be able to adequately characterize the pharmacokinetic profiles of the test product and reference standard. Refer to the most recent version of the FDA guidance for industry on *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*[a] for additional information regarding the analysis of the bioequivalence study with pharmacokinetic endpoints.

2. Type of study: Bioequivalence study with clinical endpoint
   Design: Randomized, double blind, parallel, placebo controlled, in vivo
   Strength: 1%
   Subjects: Males and non-pregnant, non-lactating females with osteoarthritis of the knee
   Additional comments: Specific recommendations are provided below.

Additional comments regarding the bioequivalence study with clinical endpoint:

1. FDA recommends conducting a bioequivalence study with clinical endpoint in the treatment of osteoarthritis of the knee. Subjects are to be randomized to receive an approximately 4 gram dose of the test product, reference standard, or placebo (vehicle) applied to the arthritic knee. The study treatment is to be administered four times daily for 4 weeks or longer (see item 8). The primary endpoint is to be evaluated at the end of treatment.

2. Inclusion Criteria (the sponsor may add additional criteria):
   a. Males or non-pregnant, non-lactating females aged ≥ 35 years with a clinical diagnosis of osteoarthritis of the knee according to the American College of Rheumatology criteria, including all of the following criteria:
      - Symptoms for at least 6 months prior to screening
      - Knee (not referred) pain for 15 days of the preceding month (periarticular knee pain due to osteoarthritis and not due to other conditions such as bursitis, tendonitis, etc.)
      - The pain in the target knee required the use of nonsteroidal anti-inflammatory drugs (NSAID) or acetaminophen (topical or oral treatments)
   b. Had an X-ray of the target knee, taken no more than 1 year before baseline, showing evidence of osteoarthritis with Kellgren-Lawrence Grade 1-3 disease

c. After discontinuing all pain medications for at least 7 days, had at least moderate pain on movement for target knee, defined as a baseline score of ≥ 50 mm on a 0-100 mm Visual Analog Scale (VAS) immediately prior to randomization, AND a baseline Western Ontario McMaster Osteoarthritis (WOMAC) pain subscale of at least 9 immediately prior to randomization
d. Able to replace all current pain medications with acetaminophen for use as needed during the duration of the study [subjects should be able to withhold all rescue medication (e.g., acetaminophen) use for at least 24 hours prior to all WOMAC pain score assessments at study visits]

3. Exclusion Criteria (the sponsor may add additional criteria):
    a. Females who are pregnant, breast feeding, or who wish to become pregnant during the study period.
    b. X-ray showing evidence of osteoarthritis with Kellgren-Lawrence Grade 4 disease.
    c. History of osteoarthritis pain in the contralateral knee requiring medication within 1 year prior to screening.
    d. After discontinuing all pain medications for at least 7 days, had a baseline score of ≥ 20 mm on a 0-100 mm VAS for the contralateral knee immediately prior to randomization.
    e. History of secondary osteoarthritis, rheumatoid arthritis, chronic inflammatory disease (e.g., colitis) or fibromyalgia.
    f. History of asthma, hypertension, myocardial infarction, thrombotic events, stroke, congestive heart failure, impaired renal function or liver disease.
    g. History of gastrointestinal bleeding or peptic ulcer disease.
    h. Known allergy to aspirin or NSAID.
    i. Elevated transaminases at screening.
    j. Use of anticoagulants, ACE-inhibitors, cyclosporine, diuretics, lithium, or methotrexate within the past month prior to entry into the study.

4. The protocol should include a list of the prescription and over-the-counter drug products that are prohibited during the study, such as:
    a. Any other topical products applied to the target site
    b. Angiotensin-converting enzyme-inhibitors, anticoagulants, aspirin, cyclosporine, diuretics, lithium, methotrexate or oral NSAIDs
    c. Systemic corticosteroid or immunosuppressive drugs
    d. Systemic and topical pain medications other than acetaminophen

5. The Applicant should pre-specify rescue medication use (name, type, amount, frequency, reason for use), maximum allowable amount of daily rescue medication use, and any limitations such as subjects cannot use rescue medication within pre-specified number of hours (e.g., at least 24 hours) prior to all WOMAC pain score assessments in the study protocol.

6. Showering/bathing should be avoided for at least 1 hour after the application. Subjects should not apply moisturizer, sunscreen, make-up, cream, lotion, powder or any topical

product other than the assigned treatment to the treatment area. Subjects should be instructed to wash their hands after use, avoid exposure to sunlight, avoid the use of sunlamp, not use any type of bandage or occlusive dressing or heating pad on the treatment area, not allow the gel to come in contact with the eyes or mucous membranes, and not apply the gel to open skin wounds, infections, inflammations, or exfoliative dermatitis.

7. The recommended primary endpoint of the study is the mean change from baseline to Week 4 (or to the end of treatment as pre-specified) in the WOMAC pain score (pain score = 0 to 20), which is determined by the subject's responses to five questions (S1–S5) using a 5-point Likert scale (i.e., 'none'=0; 'mild'=1, 'moderate'=2; 'severe'=3; 'extreme'=4). The questions pertain to the amount of pain the subject is currently experiencing in the target knee [i.e., 'How much pain do you have' when 'Walking on a flat surface' (S1), 'Going up or down stairs' (S2), 'At night while in bed' (S3), 'Sitting or lying' (S4), 'Standing upright' (S5)].

8. Due to known significant placebo effect of this product, modifications to the recommended study design such as adding a placebo run-in period and increasing the treatment duration to increase assay sensitivity may be considered. All modifications to the study design must be pre-specified in the study protocol prior to unblinding of data and justification should be provided for the modifications.

9. Provide the subject-level analysis dataset, 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. Location of Treatment Area
    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 second 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. Baseline Kellgren-Lawrence grade of osteoarthritis on X-ray of the target knee
y. Immediately prior to randomization (baseline), pain on movement on a 0-100 mm VAS for target knee
z. Immediately prior to randomization (baseline), WOMAC pain score for target knee
aa. At the end of treatment WOMAC pain score for target knee
bb. Change from baseline to the end of treatment WOMAC pain score for target knee
cc. Compliance rate (%)
dd. Subject missed the pre-specified number of scheduled doses for more than pre-specified number of consecutive days (yes/no)
ee. Concomitant medication (yes/no)
ff. Adverse event(s) reported (yes/no)

10. Provide the basic data structure 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. PP population flag (yes/no)
    j. Analysis date
    k. Analysis visit
    l. Study visit within the designated window (yes/no)
    m. Pain on movement for target knee on a 0-100 mm VAS
    n. WOMAC pain score for target knee
    o. Additional treatment required during the visit (yes/no)
    p. Concomitant medication during the visit (yes/no)
    q. Adverse event reported during the visit (yes/no)
    r. Laboratory testing during this visit (yes/no)

11. Refer to the most recent version of the FDA product-specific guidance on *Adapalene; Benzoyl Peroxide Topical Gel* (NDA 207917)[b] for a recommended approach to statistical analysis and study design for bioequivalence studies with clinical endpoint.

12. Refer to the study data standards resources, https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.

Additional information:

Device:
The reference listed drug (RLD) product is presented in a tube and packaged in a box with a dosing card. The dosing card is the device constituent used to measure the correct dose for drug application to upper body sites and lower body sites.

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 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 web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.
[b] For the most recent version of a product-specific guidance, check the FDA product-specific guidance web page at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.