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Draft Guidance on Doxepin Hydrochloride

October 2022

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Active Ingredient: Doxepin hydrochloride

Dosage Form; Route: Cream; topical

Recommended Studies: Two in vitro bioequivalence studies, one in vivo bioequivalence study with pharmacokinetic endpoints, and other characterization tests

To demonstrate bioequivalence for doxepin hydrochloride topical cream, 5% 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 doxepin hydrochloride release 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: 5%

Test system: A synthetic membrane in a diffusion cell system

Analytes to measure: Doxepin in receptor solution

Equivalence based on: Doxepin (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 doxepin 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: 5%
Test system: Barrier-competent human skin from male and/or female donors of at least 18 years of age in a diffusion cell system
Analytes to measure: Doxepin in receptor solution
Equivalence based on: Doxepin (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: In vivo pharmacokinetic study
Design: Single-application, two-way crossover study design
Strength: 5%
Subjects: Males and non-pregnant, non-lactating females, general population
Analytes to measure: Doxepin and its active metabolite nordoxepin in plasma
Equivalence based on: Doxepin
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 drug products. 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 pharmacokinetic bioequivalence study. The batches of test product and reference standard evaluated in the in vivo pharmacokinetic study should be the same as those evaluated in the IVRT and IVPT studies.

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: Not applicable

Applicants intending to propose an alternative approach by which to demonstrate bioequivalence should refer to the most recent version of the FDA guidance for industry on *Controlled Correspondence Related to Generic Drug Development*^a and the most recent version of the FDA guidance for industry on *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*^a for additional information describing the procedures on how to clarify regulatory expectations regarding your individual drug development program.

Revision History: Recommended November 2018; Revised November 2019, October 2022

Unique Agency Identifier: PSG_020126

^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>.