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Draft Guidance on Birch Triterpenes

December 2025

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Active Ingredient:	Birch triterpenes
Dosage Form:	Gel
Route:	Topical
Strength:	10%
Recommended Studies:	Characterization studies to support active ingredient sameness, one in vitro bioequivalence study, and other characterization tests

Applicants intending to submit an abbreviated new drug application (ANDA) for this drug product are encouraged to seek feedback about their drug product development program by submitting a pre-ANDA product development meeting request to FDA. It is recommended to include the following information in the pre-ANDA meeting package: preliminary data on (1) active ingredient sameness characterization, (2) comparative physicochemical and structural (Q3) tests, (3) in vitro release test (IVRT) studies. Refer to 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.

Recommendations for demonstrating active ingredient sameness:

Birch triterpenes are a botanical active ingredient composed of a mixture of pentacyclic triterpenes. For a comprehensive characterization and demonstration of sameness between the test active ingredient and the active ingredient from the reference listed drug (RLD), FDA recommends that the prospective applicants develop and use properly validated orthogonal analytical methods to perform side-by-side comparative testing of the test active ingredient and the active ingredient from the RLD. A minimum of three batches of the test active ingredient and three batches of the active ingredient from the RLD should be characterized to assess the active

ingredient sameness. The active ingredient sameness can be established by evaluating the equivalence in the following:

1. Source of the naturally-occurring botanical raw material (BRM) – The BRM used to manufacture the proposed birch triterpenes should be equivalent to that used to manufacture the birch triterpene active ingredient for the RLD.

   The following two criteria should be assessed to ensure BRM identity:
   a. The same plant species: the BRM (birch bark) used to manufacture the proposed birch triterpenes should be collected from the same plant species, *Betula pendula* Roth, *Betula pubescens* Ehrh., or hybrids of both species, and from the same harvest regions.[1] They should be identified and authenticated using appropriate analytical methods (e.g. morphological identification and/or DNA barcoding).
   b. BRM assessment: the plant parts (outer bark) used as the BRM should be defined. The BRM should be collected following established good agricultural and collection practices (GACP) procedures to minimize variations in BRM and ensure the batch-to-batch consistency of the active ingredient. Refer to the most recent version of the FDA guidance for industry on *Botanical Drug Development*[a] for the Agency's current thinking on BRM quality control.

2. Active ingredient composition – The chemical composition of the test active ingredient and the active ingredient from the RLD should be analyzed using properly validated analytical methods. Any triterpenes with the levels at or higher than 0.1% should be reported and those major components with the levels at or higher than 0.3% should be identified and properly characterized. The test active ingredient should contain all major triterpene components identified in the active ingredient from the RLD. The levels of the individual major triterpene components (≥ 0.3%) and the total of all major components in the test active ingredient should be comparable to those of the active ingredient from the RLD. Any new major components identified in the test active ingredient that are not identified in the active ingredient from the RLD should be justified.

[1] Triterpene content may vary significantly across different regions. See: Holonec L, et al. "Evaluation of betulin and betulinic acid content in birch bark from different forestry areas of western Carpathians" *Not Bot Horti Agrobo* 2012, 40(2): 99-105. When the BRM is collected from different harvest regions, a justification should be provided to address why regional variation in the BRM does not affect the sameness of the extracted active ingredient compared to the active ingredient from the RLD. This justification may include, but is not limited to, regional variation analysis, extraction process robustness, and comparative analytical data.

Recommendations for demonstrating bioequivalence:

To demonstrate bioequivalence for birch triterpenes topical gel, 10% using in vitro studies, 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 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 RLD. The test product and RLD 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
        i. Microscopic examination with representative high-resolution microscopic images at multiple magnifications
        ii. Analysis of particle size distribution, if feasible
    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:
        i. 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).
        ii. A complete flow curve across the range of attainable shear rates, until low or high shear plateaus are identified.
        iii. Yield stress values should be reported if the material tested exhibits plastic flow behavior.
    d. Characterization of specific gravity
    e. Characterization of any other potentially relevant Q3 attributes

3. The test product and RLD should have an equivalent rate of drug release based upon an acceptable IVRT bioequivalence study comparing a minimum of one batch each of the test product and RLD 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: 10%
Test system: A synthetic membrane in a diffusion cell system
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. Measure appropriate analyte(s) during your IVRT method development studies and discuss them with the Agency during a prospective preANDA meeting. The batches of test product and RLD evaluated in the IVRT bioequivalence study should be included among those for which the Q3 attributes are characterized.

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[a] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents