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Draft Guidance on Berdazimer Sodium

November 2025

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Active Ingredient:	Berdazimer sodium
Dosage Form:	Gel
Route:	Topical
Strength:	EQ 10.3% Base
Recommended Studies:	Characterization studies to support active ingredient sameness, and one in vitro bioequivalence study and other characterization tests

Overview:
This draft guidance provides recommendations for the development of generic drug products for berdazimer sodium topical gel, EQ 10.3% Base. First, FDA provides recommendations for tests to support a demonstration of active ingredient sameness. Second, FDA provides recommendations for demonstrating bioequivalence of this drug product.

Recommendations for demonstrating active ingredient sameness:
Berdazimer sodium is a polymeric active ingredient consisting of a polysiloxane backbone with covalently bound N-diazeniumdiolate nitric oxide (NO) donors.[1] Even though the molecular mass and average molecular weight range cannot be determined because of its insoluble nature in aqueous and organic solvents, its polymeric composition and physicochemical properties can be characterized. The Agency recommends that 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 in the reference standard (RS). A minimum of three batches of the test active ingredient and the active ingredient extracted from three batches of the RS should be characterized to assess the active ingredient sameness. The active ingredient sameness can be established by evaluating the equivalence in the following:

1. Equivalence of chemical structure and composition

Generic drug applicants should define the chemical structure and composition of the test active ingredient using data obtained from the active ingredient manufacturing process and characterization on its constituent silane units. The molar ratios of monomers in the polymerization step should be controlled to provide the test active ingredient with a monomeric constituent composition consistent with the empirical molecular formula in the labeling.[2] In addition, applicants should characterize both the test active ingredient and the active ingredient in the RS to analyze individual constituent silane units for their structures and calculate the molar ratios between the constituent silane units. The structure and composition of the test active ingredient should be equivalent to that of the active ingredient in the RS.

2. Equivalence of physicochemical properties

Comparative physicochemical characterization of the test active ingredient and the active ingredient in the RS should be conducted using properly validated techniques adapted to account for the polymer's insolubility, where applicable, and should include:

a. Solid state ^{29}Si nuclear magnetic resonance (NMR) spectroscopy
b. Fourier transform infrared (FTIR) spectroscopy
c. X-ray powder diffraction (XRPD)
d. Differential scanning calorimetry (DSC)
e. Thermogravimetric analysis (TGA)
f. Scanning electron microscopy (SEM)
g. Optical property by polarized light microscopy

[1] Stasko N, McHale K, Hollenbach SJ, Martin M, Doxey R. "Nitric oxide-releasing macromolecule exhibits broad-spectrum antifungal activity and utility as a topical treatment for superficial fungal infections. Antimicrob Agents Chemother. 2018; 62(7), e01026-17.
[2] Comparative characterization is recommended to demonstrate active ingredient sameness including the relative ratios and any associated batch-to-batch ranges of each monomeric constituent in the polymeric material. Note that the ratios and molecular formula in the labeling are approximate and should be used as a reference.

Recommendations for demonstrating bioequivalence:
To demonstrate bioequivalence for berdazimer sodium topical gel, EQ 10.3% Base 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 RS that may significantly affect the local or systemic availability of the active ingredient. For example, if the test product and RS 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 RS 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 RS. The test product and RS 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 comparative Q3 characterization should be conducted with (1) the berdazimer sodium gel of the test product and RS and (2) the hydrogel of the test product and RS.

   The comparison of the berdazimer sodium gel of the test product and RS 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 particle size distributionof berdazimer sodium[3]
   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.
   d. Characterization of drying rate
   e. Characterization of specific gravity

[3] In addition to support equivalence of Q3 of the drug product, the particle size distribution of berdazimer sodium is also used to support equivalence of physicochemical properties of active ingredient

The comparison of the hydrogel of the test product and RS 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 particle size distribution, crystal habit, and polymorphic form of potassium phosphate
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.
d. Characterization of pH
e. Characterization of buffer capacity
f. Characterization of specific gravity

3. The test product and RS should have an equivalent rate of NO release based upon an appropriately validated method comparing a minimum of one batch each of the test product and RS. The applicant should develop a precise, sensitive and reproducible system that can be used to evaluate the release of NO from the test product and RS. Berdazimer sodium decomposition (measured as hMAP3-NONOate) should be compared following mixing of the berdazimer gel and the hydrogel in a 1:1 volume ratio.

    Type of study: Release study
    Design: Single-dose, two-treatment, parallel, multiple-replicate (e.g., six) per treatment group study design, in vitro
    Strength: EQ 10.3% Base
    Test system: A test system for mixing the berdazimer sodium gel and hydrogel
    Analyte to measure: Berdazimer sodium decomposition in the mixture of berdazimer sodium gel and hydrogel
    Equivalence based on: Berdazimer sodium decomposition, e.g., hMAP3-NONOate (drug release rate)

Additional comments: The applicant should design a system that allows for homogenous mixing of the berdazimer sodium gel and the hydrogel at 32 ºC. Samples can be obtained from the mixture and quenched at predetermined time intervals to capture berdazimer sodium decomposition (measured as hMAP3-NONOate). Data should be included to demonstrate that in the proposed system, berdazimer sodium decomposition is correlated with the release of NO for both the test product and RS. Method development data should be included to demonstrate that the proposed system results in a homogenous mixing of the berdazimer sodium gel and the hydrogel, selection of dose is adequate, samples drawn at prespecified timepoints are representative of the mixture, and the sampling volume/frequency are optimized to capture the decomposition of berdazimer sodium. Method validation should include data to support equipment qualification, sampling qualification, environmental control, linearity (e.g., berdazimer sodium decomposition vs log (time)), precision and reproducibility, discrimination sensitivity, specificity and selectivity, and robustness (temperature variation and mixing rate variation). Once the system has been developed and validated, such a system can be used for the comparative release study. The batches of test product and RS evaluated in the release study should be included among those for which the Q3 attributes are characterized.

Applicants with questions related to the implementation of the release study or 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 *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 the applicants' individual drug development program.

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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.