

**Draft Guidance on Citric Acid; Lactic Acid; Potassium Bitartrate**

**May 2023**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

In general, FDA’s guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

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**Active Ingredients:** Citric acid; Lactic acid; Potassium bitartrate

**Dosage Form; Route:** Gel; Vaginal

**Recommended Studies:** One in vitro sperm motility assay and other characterization tests

To demonstrate bioequivalence for citric acid; lactic acid; potassium bitartrate vaginal gel, 1%; 1.8%; 0.4%, 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*<sup>a</sup>, 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*<sup>a</sup> 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
- 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. Rheological behavior of the test product and reference standard should be assessed at 37°C based on the route of administration of this drug product. Characterization of rheological behavior of undiluted and diluted drug products (test product and reference standard) should be conducted in three comparative studies:
  - Rheological behavior of the undiluted drug products
  - Rheological behavior of the drug products diluted using simulated vaginal fluid at physiologically relevant ratios
  - Rheological behavior of the drug products diluted using simulated vaginal fluid combined with simulated semen fluid at physiologically relevant ratios

The rationale for the physiologically relevant ratios selected for rheological characterization data recommended above should be provided. The following evaluations are recommended for each of the above studies:

- 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 specific gravity
  - e. Characterization of pH
  - f. Characterization of buffering capacity including characterization of pH titration curves (and total acid titer, as applicable) of the proposed test product and reference standard under three separate study conditions:
    - Complete pH titration curves and total acid titer (acid neutralization value) of the drug product titrated with a regular base titrant (e.g., a sodium hydroxide solution)
    - Complete pH titration curves of the drug product diluted with simulated vaginal fluid at physiologically relevant ratio(s) titrated with a regular base titrant. The rationale for the physiologically relevant ratios selected for the study should be provided
    - Complete pH titration curves of the drug product titrated with simulated semen fluid
  - g. Characterization of any other potentially relevant Q3 attributes

3. The test product and reference standard should have equivalent performance ex vivo in a human sperm motility assay. A modified Sander-Cramer method (e.g., similar to Garg et al.<sup>1</sup> or Chakraborty et al.<sup>2</sup>) may be considered to determine the relevant controls of the study. Applicants should carefully consider and justify the study design (e.g., physiologically relevant ratio of the drug product: sperm sample) in the abbreviated new drug application (ANDA) submission. The batches of test product and reference standard evaluated in the sperm motility assay study should be included among those for which the Q3 attributes are characterized.

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*<sup>a</sup> and the most recent version of the FDA guidance for industry on *Formal Meetings between FDA and ANDA Applicants of Complex Products Under GDUFA*<sup>a</sup> for additional information describing the procedures on how to clarify regulatory expectations regarding your individual drug development program.

**Additional information:**

Device:

The reference listed drug (RLD) is presented in an assembly-required single-dose, prefilled, disposable vaginal applicator that is the device constituent.

FDA recommends that prospective applicants examine the size and shape, external critical design attributes, and external operating principles 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*.<sup>a</sup>

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<sup>a</sup> 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>.

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<sup>1</sup> Garg S, Anderson RA, Chany CJ 2nd, Waller DP, Diao XH, Vermani K, Zaneveld LJ. Properties of a new acid-buffering bioadhesive vaginal formulation (ACIDFORM). *Contraception*. 2001 Jul;64(1):67-75.

<sup>2</sup> Chakraborty D, Maity A, Jha T, Mondal NB. Spermicidal and contraceptive potential of desgalactotigonin: A prospective alternative of nonoxynol-9. *PLoS One*. 2014 Sep;9(9):e107164.