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Draft Guidance on Chlorhexidine Gluconate

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Active Ingredient: Chlorhexidine gluconate

Dosage Form: Solution

Route: Topical

Strength: 4%

Recommended Study: Request for waiver of in vivo bioequivalence study requirements

To qualify for a waiver of the in vivo bioequivalence study requirement under 21 CFR 320.22(b)(3), generic versions of chlorhexidine gluconate topical solution, 4% should contain the same active ingredient in the same concentration and dosage form as the reference standard and 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 a topical solution drug product that differs from the reference standard in inactive ingredients [as permitted by the chemistry, manufacturing, and controls regulations for abbreviated new drug applications (ANDAs), 21 CFR 314.94(a)(9)(v)], the regulation specifies that the applicant must identify and characterize the differences and provide information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

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.

Additional information:

Drug product:
In general, evidence to demonstrate that the formulation of the test product should not alter the local availability of chlorhexidine gluconate, compared to that from the reference standard, may be based upon a comparison of the formulation composition as well as relevant quality and performance attributes of the test product and reference standard formulations.

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], relevant quality and performance attributes should include appearance, pH, specific gravity, viscosity and any other potentially relevant physical and chemical properties, characterized for a minimum of three batches of the test and three batches (as available) of the reference standard. 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 characterization tests.

If the test product contains different inactive ingredients or other changes in the formulation compared to the reference standard, additional quality and performance characterizations should mitigate the risk that any differences between the test product and reference standard could affect the formulation interaction with the disease state that may be relevant to the safety or efficacy of the drug product.

Device:
The reference listed drug (RLD) has two presentations that are drug-device combination products:

- Bottle with co-packaged foaming dispensing pump with actuator
- Bottle with integrated foaming dispensing pump with actuator

The foaming dispensing pump with actuator are the device constituent parts, because it changes the drug from a solution to a foam as it delivers the drug to the user.

FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD devices when designing the test devices.

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 website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.