

*Contains Nonbinding Recommendations*

*Draft – Not for Implementation*

## **Draft Guidance on Chlorhexidine Gluconate**

**May 2022**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

This guidance, which interprets the Agency’s regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA guidances means that something is suggested or recommended, but not required

This is a new draft product-specific guidance for industry on generic chlorhexidine gluconate.

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| <b>Active Ingredient:</b>   | Chlorhexidine gluconate  |
| <b>Dosage Form; Route:</b>  | Tablet; dental   |
| <b>Strength:</b>            | 2.5 mg   |
| <b>Recommended Studies:</b> | Two options: (1) one in vitro comparative drug release study with supportive characterization studies or (2) one in vivo bioequivalence study with clinical endpoint |

### **I. Option 1: One in vitro comparative drug release study with supportive characterization studies**

To qualify for the in vitro study recommended in this guidance, all of the following criteria should be met:

1. The test and Reference Listed Drug (RLD) formulations are qualitatively (Q1)<sup>1</sup> and quantitatively (Q2)<sup>2</sup> the same (Q1/Q2).
2. Acceptable comparative physicochemical characteristics of the test and Reference Standard (RS) products. The comparative study should be performed on at least three batches of both the test and RS products and should include:<sup>3</sup>
  - Type of gelatin
  - Degree of crosslinking of gelatin
  - Enzymatic degradation time of drug product
  - Dimensions and shape.

### **In vitro comparative drug release study:**

Type of study: Comparative in vitro drug release of chlorhexidine gluconate from the test and RS formulations.

Additional comments: The applicant is encouraged to develop and validate a protease-based method. The method should be able to capture the initial burst release phase and the sustained release phase.

## **II. Option 2: One in vivo bioequivalence study with clinical endpoint**

In vivo bioequivalence studies with clinical endpoint are requested for any generic chlorhexidine gluconate dental tablet product that has differences in inactive ingredient than the RLD, or differences in acceptable formulation characteristics that cannot meet the criteria described in Option 1.

Type of study: Bioequivalence study with clinical endpoint

Design: Randomized, double-blind, parallel, three-arm, placebo-controlled in vivo

Subjects: Male and non-pregnant, non-lactating female adults with chronic periodontitis

### **Additional comments regarding the bioequivalence study with clinical endpoint:**

1. FDA recommends conducting a bioequivalence study with clinical endpoint in the treatment of chronic adult periodontitis comparing the following treatments:
  - a. Scaling and root planing (S/RP) followed by subgingival application of generic chlorhexidine gluconate chip (chip), reference listed drug (RLD), or placebo chip at the Baseline (Day 1) visit and subgingival application of chip at the Month 3 (Day 90 ± 7) and the Month 6 (Day 180 ± 7) visits
  - b. Evaluate the primary endpoint at the Month 9 (Day 270 ± 14) visit

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<sup>1</sup> Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference product

<sup>2</sup> Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the reference product

<sup>3</sup> The manufacturing process for the exhibit batches should be reflective of the manufacturing process to be utilized for commercial batches.

2. Inclusion criteria:

- a. Male or female aged  $\geq 18$  years
- b. Minimum of 4 teeth with probing pocket depth (PPD) of 5 - 8 mm
- c. Target teeth with the following:
  - Must demonstrate bleeding on probing during the screening period.
  - Pockets not at adjacent tooth surface sites.
  - Not to have circumferential periodontal defects where the base of the pocket extended well beyond the proximal surface
  - Not to be malpositioned or crowned, if this in any way impedes accurate measurement of PPD or probing attachment level
  - No dental implant adjacent to the target tooth

3. Exclusion criteria:

- a. Female of childbearing potential who does not agree to utilize an adequate form of contraception throughout the study
- b. Patients having clinically significant or unstable disease conditions that potentially compromise healing potential such as cancer, diabetes, and immunocompromised status. Patients with type II diabetes (non-insulin-dependent diabetes) can be included if their conditions are considered stable and no medication changes occur during the 3 months prior to screening.
- c. Major recurrent aphthae
- d. Stomatitis or related pathoses
- e. Need for prophylactic antibiotics prior to dental treatment
- f. Oral local mechanical factors that could influence the outcome of the study
- g. Orthodontic appliances or any removable appliance that impinged on the tissues being assessed
- h. Soft or hard tissue tumors in the oral cavity
- i. Five or more caries lesions requiring immediate restorative treatment
- j. Severe generalized periodontal disease characterized by extensive tooth mobility and/or extensive alveolar bone loss involving 10 or more teeth
- k. Antimicrobial therapy within 30 days before entry into the study
- l. Hypersensitivity to chlorhexidine
- m. Within 6 months prior to baseline, any quadrant or maintenance S/RP, and/or periodontal surgical therapy
- n. Use within 1 month prior to baseline of any systemic or topical antibiotic.
- o. Use within 1 month prior to baseline of systemic or inhaled steroid medication.
- p. Use for at least 2 weeks within 1 month prior to baseline of any medication known to affect periodontal status (e.g., phenytoin, calcium antagonists, cyclosporine, warfarin, and nonsteroidal anti-inflammatory drugs) examination. Prophylactic use of aspirin ( $\geq 325$  mg daily) for cardiovascular indications is permitted.

4. The protocol should include a list of the prescription and over-the-counter drug products that are prohibited during the study, such as:
  - a. Antibacterial oral rinses (e.g., Arestin, Listerine, Plax, sanguinarine or hydrogen peroxide products) or dentifrices (e.g., triclosan or 0.454% stannous fluoride products)
  - b. Systemic penicillin, amoxicillin (without clavulanate) or erythromycin for more than 14 consecutive days per treatment
  - c. Acute medical use of the following antibiotics: amoxicillin with clavulanate (e.g., Augmentin), cephalosporins, tetracyclines (including minocycline and doxycycline), clindamycin, metronidazole, tinidazole, ornidazole, ciprofloxacin, ofloxacin, and temafloxacin
  - d. Non-steroidal anti-inflammatory drugs (NSAIDs) (except prophylactic doses of  $\geq 325$  mg/day aspirin) for more than 14 consecutive days or more than 30 total days
  - e. Systemic or inhaled steroids
  
5. S/RP should be performed only at the Baseline (Day 1) visit. After a full mouth S/RP, the assigned study treatment should be applied to all sites with PD  $\geq 5$  mm up to 8 chips. Retreatment with the study treatment should be performed at the Month 3 (Day  $90 \pm 7$ ) and the Month 6 (Day  $180 \pm 7$ ) visits to all sites that were treated at baseline, as well as all new sites with PD  $\geq 5$  mm.
  
6. The recommended primary endpoint is the change of within-subject average PD from the Baseline (Day 1) visit to the Month 9 (study Day  $270 \pm 14$ ) visit.
  
7. Provide the Subject-Level Analysis Dataset (ADSL), one record per subject, using the following headings, if applicable:
  - a. Study identifier
  - b. Unique subject identifier
  - c. Subject identifier for the study
  - d. Study site identifier (if applicable)
  - e. Age
  - f. Age units (years)
  - g. Sex
  - h. Race
  - i. Name of Actual Treatment (exposure): test product, RLD, placebo control
  - j. Number of Treatments (none, one, two)
  - k. Completed the study (yes/no)
  - l. Reason for premature discontinuation of subject
  - m. Subject required additional treatment for periodontal disease due to unsatisfactory treatment response (yes/no)
  - n. Per Protocol (PP) population inclusion (yes/no)
  - o. Reason for exclusion from PP population
  - p. Modified Intent to Treat (mITT) population inclusion (yes/no)
  - q. Reason for exclusion from mITT population
  - r. Safety population inclusion (yes/no)
  - s. Reason for exclusion from safety population

- t. Total number of teeth treated at Baseline (Day 1) visit
  - u. Total number of teeth treated on Month 3 (Day 90) visit
  - v. Total number of teeth treated on Month 6 (Day 180) visit
  - w. Average pocket depth (PD) per subject at Baseline (Day 1) visit
  - x. Average PD per subject at Month 3 (Day 90) visit
  - y. Average PD per subject at Month 6 (Day 180) visit
  - z. Average PD per subjects at Month 9 (Day 270) visit
  - aa. Concomitant medication (yes/no)
  - bb. Adverse event(s) reported (yes/no)
8. Provide the basic data structure (BDS) dataset with records per subject, per visit, per analysis timepoint, using the following headers, if applicable:
- a. Study identifier
  - b. Unique subject identifier
  - c. Subject identifier for the study
  - d. Study site identifier (if applicable)
  - e. Name of planned treatment
  - f. Name of Actual Treatment (exposure): test product, RLD, placebo control
  - g. Analysis date
  - h. Analysis visit
  - i. Number of days since baseline visit
  - j. Evaluator: identity of evaluator
  - k. Number of teeth treated
  - l. PD for each tooth treated
  - m. Average PD per visit
  - n. Concomitant medication reported during this visit (yes/no)
  - o. Adverse event reported during this visit (yes/no)
  - p. Laboratory testing during this visit (yes/no)
9. Refer to the most recent version of the FDA product-specific guidance on *Adapalene; Benzoyl Peroxide Topical Gel* (NDA 207917)<sup>a</sup> for a recommended approach to statistical analysis and study design for bioequivalence studies with clinical endpoints.
10. Refer to the study data standards resources, <https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources>.

**Waiver request of in vivo testing:** Not applicable.

**Dissolution test method and sampling times:** The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

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**Unique Agency Identifier:** PSG\_020774

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<sup>a</sup> For the most recent version of a product-specific guidance, check the FDA product-specific guidance web page at <https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm>