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Draft – Not for Implementation

Draft Guidance on Doxycycline Hyclate

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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.

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This is a new draft product-specific guidance for industry on generic doxycycline hyclate.

Active Ingredient:	Doxycycline hyclate
Dosage Form; Route:	System, extended release; periodontal
Recommended Studies:	Two options: (1) One in vitro drug release study with supportive characterization studies or (2) one in vivo bioequivalence study with clinical endpoints

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

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

1. The test and Reference Listed Drug (RLD) formulations are qualitatively (Q1)¹ and quantitatively (Q2)² the same (Q1/Q2).

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

² 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

2. Acceptable comparative physicochemical characterization 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:³
 - Viscosity of the polymeric formulation in the syringe A.
 - Viscosity and appearance of the reconstituted drug product.
 - Polylactic acid (PLA) characterization data including, but not limited to, molecular weight and weight distribution, polymer stereoisomer type. Additional PLA and drug product characterization data may be requested during the assessment of the ANDA.

In vitro bioequivalence study:

Acceptable comparative in vitro drug release of doxycycline hyclate from the test and RS formulations.

II. Option 2: One in vivo bioequivalence study with clinical endpoints

In vivo BE studies with clinical endpoint are requested for any generic doxycycline hyclate periodontal extended-release system 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.

1. Type of study: Bioequivalence study with clinical endpoint
Design: Randomized, double-blind (evaluator-blinded), parallel, three-arm, placebo-controlled in vivo
Strength: 50 mg
Subjects: Male and non-pregnant, non-lactating female adults with chronic periodontitis

Additional comments: Specific recommendations are provided below:

1. FDA recommends conducting a bioequivalence study with clinical endpoint in the treatment of chronic adult periodontitis comparing the test product of doxycycline dental product versus the RLD and placebo (vehicle) control. After initial dose (Day 0), subjects receive a second treatment 4 months after initial treatment (Day 120±7). The primary endpoint, gain in periodontal attachment level (PAL), is to be evaluated at Month 9 (Day 270 ± 14).
2. Inclusion criteria (the sponsor may add additional criteria):
 - a. Male or non-pregnant, non-lactating female aged ≥ 18 years in good general health (females of child-bearing potential should undergo screening for pregnancy prior to each application of study products and at the end of the study).
 - b. Chronic periodontitis: at least 4 teeth with probing pocket depth (PPD) of 5 mm or greater and bleeding on gentle probing.
3. Exclusion criteria (the sponsor may add additional criteria):

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

- a. Female of childbearing potential who does not agree to utilize an adequate form of contraception throughout the study
 - b. Severe generalized periodontal disease (e.g., substantial accumulation of subgingival calculus defined as 80% or greater surfaces of the dentition having detectable calculus)
 - c. Patients having clinically significant, unstable or chronic disease conditions that potentially compromise healing potential such as cancer, diabetes, cardiovascular diseases, connective tissue disease 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
 - d. A history of oral candidiasis
 - e. Stomatitis or related pathoses
 - f. Need for prophylactic antibiotics prior to dental treatment
 - g. Hypersensitivity to doxycycline hyclate or other tetracyclines
 - h. Within 2 months prior to the study, any scaling and root planing and/or periodontal surgical therapy
 - i. Antimicrobial therapy within 30 days prior to the study
 - j. Use of mouthwash with known antibacterial properties
 - k. Use of systemic or inhaled steroid medication within one month prior to the study
 - l. Use of sulfasalazine within 3 months prior to the study
 - m. Use for at least 2 weeks within 1 month prior to the study of any medication known to affect periodontal status (e.g., phenytoin, calcium antagonists, cyclosporine, warfarin, and nonsteroidal anti-inflammatory drugs) examination
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., Listerine, Plax, sanguinarine or hydrogen peroxide products) or dentifrices (e.g., triclosan or 0.454% stannous fluoride products)
 - b. Use of the following antibiotics: penicillin, amoxicillin, cephalosporins, other tetracyclines (e.g., minocycline), clindamycin, metronidazole, tinidazole, ornidazole and quinolone antibiotics
 - c. Use of non-steroidal anti-inflammatory drugs (NSAIDs) (except prophylactic doses of < 325 mg/day aspirin) within 2 weeks prior to the study
 - d. Systemic or inhaled steroids
 5. The application of study products should be performed at baseline (Day 0) visit. Retreatment with the same study treatment at baseline should be performed at month 4 (Day 120 ± 7). The treated pockets should be covered by a cyanoacrylate dental adhesive (e.g., Octyldent) and subjects should be instructed not to brush or floss during the 7 days until the dressing or adhesive are removed or degraded. If the dressing or adhesive are lost during the first 7 days, the investigator can replace them. At 1 week, they are removed from subjects. All subjects use one product out of the dressing and the adhesive for the study.
 6. The recommended primary endpoint is the within-subject average PAL gain from the baseline (Day 0) visit to Month 9 (Day 270 ± 14) visit in selected tooth sites. Four or five

sites qualified based on PPD are selected and their sites' PALs are measured for the assessment of the primary endpoint.

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 planned treatment
 - j. Name of actual treatment (exposure): test product, RLD, placebo control
 - k. Number of treatments (none, one, two)
 - l. Safety population flag (yes/no)
 - m. Reason for exclusion from safety population
 - n. Modified Intent-to-Treat (mITT) population flag (yes/no)
 - o. Reason for exclusion from mITT population
 - p. Per-Protocol (PP) population flag (yes/no)
 - q. Reason for exclusion from PP population
 - r. Randomized population flag (yes/no)
 - s. Date/time of first exposure to treatment
 - t. Date/time of last exposure to treatment
 - u. End of study date
 - v. End of study status
 - w. Subject required additional treatment due to unsatisfactory treatment response (yes/no)
 - x. Total number of teeth treated at Baseline (Day 1) visit with PPD \geq 5 mm and bleeding on gentle probing
 - y. Total number of teeth treated at Month 4 (Day 120) visit
 - z. Average periodontal attachment level (PAL) in selected pocket sites per subject at Baseline (Day 1) visit
 - aa. Average PAL per subject in selected pocket sites at Month 2 (Day 60) visit
 - bb. Average PAL per subject in selected pocket sites at Month 4 (Day 120) visit
 - cc. Average PAL per subjects in selected pocket sites at Month 9 (Day 270) visit
 - dd. Compliance rate (%)
 - ee. Concomitant medication (yes/no)
 - ff. 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
 - c. Name of actual treatment (exposure): test product, RLD, placebo control
 - g. Safety population flag (yes/no)
 - h. Modified ITT population flag (yes/no)
 - i. Per-Protocol (PP) population flag (yes/no)
 - j. Analysis date
 - k. Analysis visit
 - l. Study visit within the designated window (yes/no)
 - m. Analysis timepoint (e.g., hour 0, hour 2) (if applicable)
 - n. Number of teeth treated
 - o. PAL for each tooth treated
 - p. Average PAL in selected pocket sites per visit
 - q. Additional treatment required during the visit (yes/no)
 - r. Concomitant medication during this visit (yes/no)
 - s. Adverse event reported 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)^a 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.

Additional information:

Device:

The reference listed drug (RLD) product is presented as two prefilled syringes, which couple to form a mixing system, and a co-packaged blunt cannula. The two syringes and the cannula are device constituents used to administer the drug.

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 including the following characteristics:

- The external diameter of the cannula
- The length and flexibility of the cannula

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*.^b

Unique Agency Identifier: PSG_050751

^a 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>.

^b 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>.