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Draft – Not for Implementation

Draft Guidance on Ferric Maltol

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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 ferric maltol.

Active Ingredient: Ferric maltol

Dosage Form; Route: Capsule; oral

Recommended Studies: Two options

I. Option 1:

If the test product formulation is qualitatively (Q1)¹ and quantitatively (Q2)² the same as the reference listed drug (RLD) product formulation with respect to excipients, bioequivalence may be established by conducting in vitro dissolution testing.

¹ Q1 (qualitative sameness) means that the test product should contain the same excipients as the reference product.

² Q2 (quantitative sameness) means that the concentrations of the inactive ingredient(s) used in the test product are within $\pm 5\%$ of those used in the reference product.

Recommended study: In vitro dissolution testing

Apparatus: USP apparatus II (paddle)
Rotational speed: 75 rpm
Media: 0.1N HCl, pH 4.5 buffer, and pH 6.8 buffer
Volume: 900 mL
Temperature: 37°C ± 0.5°C

Bioequivalence based on: Acceptable comparative in vitro drug release tests should be provided for 12 dosage units for each of the test and reference products. A similarity factor (f₂) should be performed using mean profiles to assure comparable test and reference product drug release under a range of pH 1.2 to 6.8 conditions. The f₂ test comparing test versus reference in each media should be 50 or greater. Note that the f₂ test is not necessary when both test and reference dissolve 85% or more in 15 minutes or less. The methodology used for in vitro drug release testing should be able to discriminate the effect of formulation and manufacturing process variability in the production of the test formulation.

Waiver request of in vivo testing: Not applicable

II. Option 2:

If the test product formulation is not Q1/Q2 the same as the RLD with respect to excipients, bioequivalence should be established by conducting an in vivo bioequivalence study with clinical endpoints and in vitro dissolution testing.

Recommended studies: Bioequivalence study and in vitro dissolution testing

1. Type of study: Bioequivalence study with clinical endpoint
Design: Randomized, double blind, parallel, three arm, placebo-controlled in vivo
Strength: 30 mg iron
Subjects: Males and non-pregnant, non-lactating females, with quiescent inflammatory bowel disease and iron deficiency anemia
Additional comments: Specific recommendations are provided below.
2. Type of study: In vitro comparative multi-media dissolution studies
The same studies as recommended under Option 1.

Bioequivalence based on (90% CI): Primary efficacy endpoint with hemoglobin concentration (g/dL) from baseline to Week 4.

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 for each of the test and reference products. Specifications will be determined upon evaluation of the abbreviated new drug application.

Additional comments regarding in vivo bioequivalence study with the clinical endpoint:

1. Patients should receive the test product, reference product or placebo twice daily, taken 1 hour before or 2 hours after a meal.
2. Inclusion criteria (may add additional criteria as needed)
 - a. Male or nonpregnant, non-lactating females aged at least 18 years with quiescent inflammatory bowel disease (ulcerative colitis or Crohn's disease) and iron deficiency anemia
 - i. Quiescent ulcerative colitis is defined as a Simple Clinical Colitis Activity Index (SCCAI) score < 4 as measured at screening and randomization. Quiescent Crohn's disease is defined as Crohn's Disease Activity Index (CDAI) score < 220 as measured at screening
 - ii. Anemia is defined as hemoglobin ≥ 9.5 g/dL and < 12.0 g/dL for females and ≥ 9.5 g/dL and < 13.0 g/dL for males as measured at the screening
 - iii. Iron deficiency is defined as ferritin < 30 $\mu\text{g/L}$ as measured at screening
 - b. Patients receiving permitted immunosuppressants at screening must have been on a stable dose for at least 4 weeks prior to randomization
 - i. Permitted immunosuppressants include azathioprine, 6-mercaptopurine, tumor necrosis factor-alpha antagonists and corticosteroid doses \leq the equivalent of 25 mg/day prednisolone
3. Exclusion Criteria (may add additional criteria as needed)
 - a. Anemia due to any cause other than iron deficiency, including, but not limited to: severe malabsorption, immunosuppressant use
 - b. Receipt of:
 - i. Blood transfusion(s), intramuscular (IM) or intravenous (IV) administration of iron replacement products, or erythropoietin/erythropoiesis stimulating agents within the 12 weeks prior to randomization
 - ii. Oral iron replacement products or an immunosuppressant known to induce anemia (e.g., methotrexate, cyclosporin A and tacrolimus) within the 4 weeks prior to randomization
 - iii. Folic acid and/or vitamin B12 injections/infusions within 4 weeks prior to randomization unless the patient is on a stable treatment regimen for 12 weeks prior to randomization
 - c. Vitamin B12 concentration below the lower limit of normal as measured at screening
 - d. Folic acid deficiency as measured at screening

- e. Contraindications for treatment with iron preparations (e.g., hemochromatosis, chronic hemolytic disease, sideroblastic anemia, thalassemia, or lead intoxication induced anemia)
 - f. Serum creatinine >2.0 mg/dL (176 µmol/L) as measured at screening
 - g. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels ≥ 5 times the upper limit of normal (ULN) at screening
4. The protocol should include a list of the prescription and over-the-counter drug products, procedures, and activities that are prohibited during the period indicated prior to and during the study, such as:
 - a. Iron preparations other than study medication
 - b. Blood transfusions
 - c. Erythropoietin/erythropoiesis stimulating agents
 - d. Vitamin B12 (oral vitamin B12 is allowed at any time during the study provided the treatment regimen is stable for 12 weeks prior to randomization and remains stable through Week 4)
 - e. Folic acid (oral folic acid is allowed at any time during the study provided the treatment regimen is stable for 12 weeks prior to randomization and remains stable through Week 4)
 - f. Initiation of immunosuppressant therapy or increases to existing dosing regimen (subjects receiving permitted immunosuppressants may have their doses adjusted down as necessary during the study)
 5. A screening period up to 14 days prior to randomization for patients with ulcerative colitis and up to 7 days for patients with Crohn's disease is recommended to assess study eligibility and baseline measures.
 6. The recommended primary endpoint is the mean change in hemoglobin concentration (g/dL) from Baseline to Week 4.
 7. Mean changes in iron parameters such as transferrin saturation (TSAT) and ferritin at Baseline and at Week 4 for the test and RLD products should be compared and reported.
 8. Patients should be discontinued from the study for hemoglobin ≤ 8.5 g/dL, SCCAI score ≥ 5 for patients with ulcerative colitis, or CDAI score ≥ 320 for subjects with Crohn's disease.

9. 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. Subject has ulcerative colitis or Crohn's disease
 - j. SCCAI or CDAI score
 - k. Name of planned treatment
 - l. Name of actual treatment
 - m. Safety population flag (yes/no)
 - n. Reason for exclusion from safety population
 - o. Modified Intent-to-Treat (mITT) population flag (yes/no)
 - p. Reason for exclusion from mITT population
 - q. Per Protocol (PP) population flag (yes/no)
 - r. Reason for exclusion from PP population
 - s. Randomized population flag (yes/no)
 - t. Date/time of first exposure to treatment
 - u. Date/time of last exposure to treatment
 - v. End of study date
 - w. End of study status
 - x. Subject required additional treatment due to unsatisfactory treatment response (yes/no)
 - y. Hemoglobin concentration at Baseline
 - z. Hemoglobin concentration at Week 4
 - aa. Ferritin concentration at screening
 - bb. Ferritin concentration at Week 4
 - cc. TSAT concentration at screening
 - dd. TSAT concentration at Week 4
 - ee. Compliance rate (%)
 - ff. Patient missed the pre-specified number of scheduled doses for more than pre-specified number of consecutive days (yes/no)
 - gg. Adverse event(s) reported (yes/no)
 - hh. Concomitant medication (yes/no)

10. Provide the basic data structure (BDS) dataset with records per subject, per analysis timepoint, 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. Name of planned treatment

- f. Name of actual treatment
 - 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)
 - n. Hemoglobin concentration
 - o. Ferritin concentration
 - p. TSAT concentration
 - q. Additional treatment required during the visit (yes/no)
 - r. Adverse event reported during the visit (yes/no)
 - s. Concomitant medication during the visit (yes/no)
11. Refer to the product-specific guidance on adapalene; benzoyl peroxide topical gel, 0.3%; 2.5% entitled *Guidance on Adapalene; Benzoyl Peroxide* for a recommended approach to statistical analysis and study design for bioequivalence studies with clinical endpoints.
12. Study data should be submitted in a standardized format. Refer to the study data standards published at www.fda.gov³.

Unique Agency Identifier: PSG_212320

³ Study Data Standards Resources: <https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources>