*Contains Nonbinding Recommendations*

**Draft Guidance on Mesalamine**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

**Active Ingredient:** Mesalamine

**Dosage Form; Route:** Extended release capsule; oral

**Recommended Studies** Four studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover design, in vivo
   Strength: 500 mg (Recommended dose: 2 × 500 mg capsules)
   Subjects: Normal healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study.
   Additional comments: Other study designs are acceptable if appropriate. Specific recommendations are provided below.

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2. Type of study: Fed
   Design: Single-dose, two-way crossover design, in vivo
   Strength: 500 mg (Recommended dose: 2 × 500 mg capsules)
   Subjects: Normal healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study.
   Additional comments: Other study designs are acceptable if appropriate. Specific recommendations are provided below.

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3. Type of study: Fasting sprinkle-in-applesauce or yogurt
   Design: Single-dose, two-way crossover design, in vivo
   Strength: 500 mg (Recommended dose: 2 × 500 mg capsules)
   Subjects: Normal healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study.
   Additional comments: Other study designs are acceptable if appropriate. Specific recommendations are provided below.

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**Analytes to measure (in appropriate biological fluid):** Mesalamine in plasma

**Bioequivalence based on (90% CI): Mesalamine**

**Additional comments regarding the BE study with PK endpoints:**

1) Applicants may consider using a reference-scaled average bioequivalence approach for mesalamine. If using this approach, the applicant should provide evidence of high variability in the bioequivalence parameters (i.e., within-subject variability $\geq$ 30%) for the reference product. For general information on this approach refer to the Progesterone Capsule Guidance for additional information regarding highly variable drugs.

2) For the fasting and sprinkle fasting studies, the following PK parameters will be evaluated: Log-transformed $AUC_{0-3}$, $AUC_{3-t}$, $AUC_{0-t}$, and $C_{max}$, where $AUC_{0-3}$ is the area under the plasma concentration vs. time curve from 0 to 3 hours, $AUC_{3-t}$ is the area under the plasma concentration vs. time curve from 3 to the last measurable time point, $AUC_{0-t}$ is the area under the curve from 0 hours to the last measurable time point, and $C_{max}$ is the maximum plasma concentration. Applicants should have extensive sampling points around $T_{max}$ to have accurate estimation of $C_{max}$ and $T_{max}$, and at least four non-zero measurements of concentration are recommended for each partial AUC.

3) For the fed study, the following PK parameters will be evaluated: Log-transformed $AUC_{0-t}$, and $C_{max}$. Please submit $AUC_{0-3}$ and $AUC_{3-t}$ data as supportive evidence of comparable therapeutic outcome.

4) As $AUC_{0-t}$ is recommended in place of $AUC_{0-\infty}$, the last sampling time point should be at least at 72 hours.

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4. Type of study: In vitro comparative dissolution study
Strength: 250 mg and 500 mg
Apparatus: USP 2 (paddles)
Speed: 100 rpm
Media: 0.1 N HCl and appropriate buffers at pH values of 4.5, 6.0, 6.5, 6.8, 7.2, 7.5
Volume: 900 mL
Temperature: 37ºC
Sampling times: 1, 2, 4, 6, 8, and 12 hours or as needed for profile comparison
Additional Comments: The applicant should use at least 12 dosage units per test. The f2 metric will be used to compare dissolution profiles.

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**Waiver request of in vivo testing:** Mesalamine extended release capsules, 250 mg, may be considered for a waiver of in vivo bioequivalence testing based on (1) acceptable bioequivalence studies on the 500 mg strength, (2) acceptable dissolution testing of the 250 mg and 500 mg strengths, and (3) proportional similarity in the formulations of the 250 mg and 500 mg strengths.

**Dissolution test method and sampling times:** The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods website, available to the public at the following location: http://www.accessdata.fda.gov/scripts/cder/dissolution/. Please 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 (ANDA).