This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

**Active Ingredient:** Siponimod fumaric acid  
**Dosage Form; Route:** Tablet; oral  
**Recommended Studies:** Two studies

1. **Type of study:** Fasting  
**Design:** Single-dose, two-treatment, two-period crossover in vivo  
**Strength:** EQ 2 mg Base  
**Subjects:** Healthy males and non-pregnant, non-lactating females  
**Additional comments:** Exclude subjects with CYP2C9*3 allele, such as CYP2C9*1/*3, CYP2C9*2/*3, and CYP2C9*3/*3. Females of reproductive potential should use effective contraception during the study and ten days after the study. Do not use live attenuated vaccines during the study and for four weeks after the last dose of siponimod. Monitor for 6 hours after the first dose for signs and symptoms of bradycardia with hourly pulse and blood pressure measurement. Ensure an adequate washout period.
between treatments in the crossover study due to the long elimination half-life of siponimod. Alternatively, a parallel study design may be considered.

2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: EQ 2 mg Base
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: See comments above.

**Analyte to measure**: Siponimod in plasma

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

**Waiver request of in vivo testing**: EQ 0.25 mg Base strength based on (i) acceptable bioequivalence studies on the EQ 2 mg Base strength, (ii) proportional similarity of the formulations between both strengths, and (iii) acceptable in vitro dissolution testing of both strengths.

**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/](http://www.accessdata.fda.gov/scripts/cder/dissolution/). Conduct comparative dissolution testing on 12 dosage units for each of both strengths of the test and reference products. Specifications will be determined upon evaluation of the abbreviated new drug application.

**Unique Agency Identifier**: PSG_209884