This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

In September 2015, FDA issued a draft product-specific guidance for industry on generic ledipasvir; sofosbuvir. We are now issuing revised draft guidance for industry that replaces the previously issued guidance.

Active Ingredients: Ledipasvir; Sofosbuvir
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: 90 mg; 400 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: Measure hepatitis B surface antigen and hepatitis B core antibody and exclude subjects with evidence of current or prior hepatitis B virus infection. Due to the potential risk of serious symptomatic bradycardia, exclude subjects who are taking amiodarone. Ensure an adequate washout period between treatments in the crossover study due to the long elimination half-life of ledipasvir. Alternatively, a parallel study design may be considered.
2. Type of study: Fed  
   Design: Single-dose, two-treatment, two-period crossover in vivo  
   Strength: 90 mg; 400 mg  
   Subjects: Males and non-pregnant, non-lactating females, general population  
   Additional comments: See comments above.

Analytes to measure: Ledipasvir and sofosbuvir in plasma

Bioequivalence based on (90% CI): Ledipasvir and sofosbuvir

Waiver request of in vivo testing: 45 mg; 200 mg based on (i) acceptable bioequivalence studies on the 90 mg; 400 mg 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 review of the abbreviated new drug application.

Revision History: Recommended September 2015; Revised May 2021

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