

Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Simvastatin

October 2024

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

In general, FDA’s guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient:	Simvastatin
Dosage Form:	Tablet
Route:	Oral
Strengths:	5 mg, 10 mg, 20 mg, 40 mg, 80 mg
Recommended Study:	One in vivo bioequivalence study with pharmacokinetic endpoints

1. Type of study: Fasting
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 80 mg
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments: Females of reproductive potential should use effective contraception during the study. Applicants may consider using a reference-scaled average bioequivalence approach. If using this approach, provide evidence of high variability in the pharmacokinetic parameters (i.e., within-subject variability $\geq 30\%$) for the reference listed drug (RLD). For detailed information on this approach, refer to the most recent version of the FDA guidance for industry on *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*.^a

Analytes to measure: Simvastatin and its metabolite, beta-hydroxyacid in plasma

Submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C_{max}.

Bioequivalence based on (90% CI): Simvastatin

Waiver request of in vivo testing: 5 mg, 10 mg, 20 mg, 40 mg strengths based on (i) acceptable bioequivalence study on the 80 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all 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/>. Conduct comparative dissolution testing on 12 dosage units for each of all strengths of the test product and RLD.¹ Specifications will be determined upon review of the abbreviated new drug application.

Document History: Recommended May 2007; Finalized May 2008; Revised October 2024

Unique Agency Identifier: PSG_019766

^a For the most recent version of a guidance, check the FDA guidance website at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

¹ If the RLD is not available, refer to the most recent version of the FDA guidance for industry on *Referencing Approved Drug Products in ANDA Submissions*.