

Contains Nonbinding Recommendations

Draft Guidance on Nitroglycerin

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Nitroglycerin

Form/Route: Metered Spray/Sublingual

Recommended studies: 1 study

Type of study: Fasting

Design: Single-dose, two-way crossover in-vivo

Strength: 0.4 mg/spray x 2 sprays (0.8 mg dose)

Subjects: Healthy males and nonpregnant females, general population.

Additional Comments: (1) Product labeling states that the dose may be administered onto or under the tongue. Sublingual administration is recommended for the bioequivalence study. (2) Applicants may consider using a reference-scaled average bioequivalence approach for nitroglycerin. If using this approach, please provide evidence of high variability in the bioequivalence parameters of AUC and/or C_{max} (i.e., within-subject variability $\geq 30\%$). Please refer to the Bioequivalence Recommendations for Specific Products Guidance on Progesterone Capsules for additional information regarding this approach:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf>.

Analytes to measure (in appropriate biological fluid): Nitroglycerin and its active metabolites, 1,2-dinitroglycerin and 1,3-dinitroglycerin, in plasma.

Bioequivalence based on (90% CI): Nitroglycerin

Please 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}.

Waiver request of in-vivo testing: Not Applicable

Dissolution test method and sampling times: Not Applicable

Additional information: While comparative in vitro studies are not required, in vitro studies outlined in the 2002 Guidance for Industry, *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070575.pdf>) should be submitted for Chemistry, Manufacturing, and Controls evaluation.