

Draft Guidance on Propofol

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

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| Active Ingredient: | Propofol |
| Dosage Form; Route: | Injectable; injection |
| Strength: | 10 mg/ mL |
| Recommended Study: | Two options: In vitro or In vivo studies |

I. In vitro option:

To qualify for the in vitro option for this drug product pursuant to 21 CFR 320.24 (b)(6), under which “any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence” may be acceptable for determining the bioavailability or bioequivalence (BE) of a drug product, all the following criteria should be met:

- i. The Test and Reference Listed Drug (RLD) formulations are qualitatively¹ and quantitatively² the same (Q1/Q2).
- ii. Acceptable comparative physicochemical characterization of the Test and RLD formulations. The comparative study should be performed on at least three exhibit lots of both Test and Reference products.³

Parameters to measure: Globule size distribution, viscosity profile as a function of applied shear, pH, zeta potential of the formulation and at physiological pH, osmolality, free acid concentration, and amount of propofol partitioned in the aqueous and oil phases.

The sponsor should also demonstrate that the test product is stable when diluted with 5% Dextrose Injection USP, according to label instructions. Comparative compatibility of the Test and Reference products should be demonstrated in Lactated Ringers Injection, USP and 5% Dextrose and 0.45% Sodium Chloride Injection, USP intravenous fluids. Globule size measurements and amount of propofol partitioned in the aqueous and oil phases along with other characterization tests may be used to support compatibility of the test product in the different intravenous fluids.

¹ Q₁ (qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference product.

² Q₂ (quantitative sameness) means that the concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the reference product.

³ All 3 exhibit batches should be at least 1/10 the size of the commercial batch and the manufacturing process used for the 3 exhibit batches should be reflective of the process used for the commercial batch.

Bioequivalence based on (95% upper confidence bound): Population bioequivalence (PBE) based on D50 and SPAN (alternatively harmonic intensity weighted average particle diameter and polydispersity index derived from cumulant analysis of the intensity size distribution) for the globule size distribution only (the other parameters do not require PBE analysis). The applicants should provide no less than 10 datasets from 3 batches each of the Test and Reference products to be used in the PBE analysis. Sponsors should compare the size parameter upon serial dilution (if applicable) of the Test and Reference products, and provide histograms of size distribution data of each diluted sample.

- iii. Acceptable comparative in vitro drug release rate tests from 12 units of each of the test and RLD formulations. The methodology used for in vitro drug release testing should be able to discriminate the effect of process variability in the production of the test formulation.

An in vivo pharmacokinetic bioequivalence study is requested for any generic propofol injection, 10 mg/mL that has a different inactive ingredient from the RLD⁴ or unacceptable data from in vitro comparative studies.

II. In vivo option:

Type of study: Fasting

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

Strength: 10 mg/mL

Dose rate: 30 mcg/kg/min

Subjects: Healthy males, non-pregnant and non-lactating females, general population 18 to 55 years of age

Additional comments: (1) Propofol should be administered as a slow intravenous infusion at a rate of 30 mcg/kg/min with monitoring and any necessary intervention by an anesthesiologist or nurse anesthetist throughout the infusion. Each subject should receive an infusion for 30 minutes. (2) Study subjects should have normal renal function (3) Please also conduct characterization studies described below.

Analytes to measure (in appropriate biological fluid): Propofol in plasma

Bioequivalence based on (90% CI): Propofol

Characterization studies: Globule size distribution, zeta potential profile and isoelectric point (if applicable), and amount of propofol and antimicrobial preservative partitioned in the aqueous and oil phases. The sponsor should also demonstrate that the test product is stable when diluted with 5% Dextrose Injection USP, according to label instructions. Comparative compatibility of

⁴ An in vivo pharmacokinetic bioequivalence study will also be requested for a test product which contains a different buffer, preservative or antioxidant.

the Test and Reference products should be demonstrated in Lactated Ringers Injection, USP and 5% Dextrose and 0.45% Sodium Chloride Injection, USP intravenous fluids. Globule size measurements and amount of propofol partitioned in the aqueous and oil phases along with other characterization tests may be used to support compatibility of the test product in the different intravenous fluids.

Dissolution test method and sampling times: Not applicable