

Contains Nonbinding Recommendations
Draft – Not for Implementation
Draft Guidance on Morphine Sulfate
August 2024

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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:	Morphine sulfate
Dosage Form:	Capsule, extended release
Route:	Oral
Strengths:	10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 100 mg, 130 mg, 150 mg, 200 mg
Recommended Studies:	Three in vivo bioequivalence studies with pharmacokinetic endpoints
1.	Type of study: Fasting Design: Single-dose, two-treatment, two-period crossover in vivo Strength: 100 mg Subjects: Healthy males and non-pregnant, non-lactating females Additional comments: Use an opioid antagonist (e.g., naltrexone) to mitigate safety risk of the opioid (e.g., respiratory depression) in healthy subjects. Administer the opioid antagonist in advance of dosing the study drug and as appropriate thereafter (e.g., within 12 hours post dose) to adequately block opioid induced pharmacological effects based on the opioid antagonist and opioid product's effective duration. Monitor vital signs (e.g., pulse oximetry and continuous respiratory monitoring) during the study and implement standards and practice for detection and management of respiratory depression.
2.	Type of study: Fed Design: Single-dose, two-treatment, two-period crossover in vivo Strength: 100 mg Subjects: Healthy males and non-pregnant, non-lactating females Additional comments: See comments above.

3. Type of study: Fasting, sprinkle in applesauce
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 100 mg
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments: See comments above.

Analytes to measure: Morphine and its active metabolite, morphine-6-glucuronide, in plasma

Bioequivalence based on (90% CI): Morphine

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 area under the curve and maximum concentration.

Additional strengths: Bioequivalence of the 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 130 mg, 150 mg, and 200 mg strengths to the corresponding reference product strengths may be demonstrated based on the acceptable bioequivalence studies on the 100 mg strength and principles laid out in the most recent version of the FDA guidance for industry on *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application*.^a

Dissolution test method and sampling times: For modified release drug products, applicants should develop specific discriminating dissolution methods. Alternatively, applicants may use the dissolution method set forth in any related official United States Pharmacopeia (USP) drug product monograph, or in the FDA's database, <http://www.accessdata.fda.gov/scripts/cder/dissolution/>, provided that applicants submit adequate dissolution data supporting the discriminating ability of such a method. If a new dissolution method is developed, submit the dissolution method development and validation report with the complete information/data supporting the proposed method. Conduct comparative dissolution testing on 12 dosage units for each strength of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

In addition to the method above, submit dissolution profiles on 12 dosage units for each strength of the test and reference products generated using USP Apparatus 1 at 100 rpm and/or Apparatus 2 at 50 rpm in at least three dissolution media (e.g., pH 1.2, 4.5 and 6.8 buffer). Agitation speeds may be increased if appropriate. It is acceptable to add a small amount of surfactant if necessary. Include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released to provide assurance against premature release of drug (dose dumping) from the formulation.

Alcohol dose dumping studies: Due to concerns of dose dumping of drug from this product when taken with alcohol, conduct additional dissolution testing on all strengths using various concentrations of ethanol in the dissolution medium as follows:

Testing conditions: 900 mL, 0.1N HCl, USP Apparatus 1 (basket) at 100 rpm, with or without alcohol

Test 1: 12 units tested according to the proposed method (with 0.1N HCl), with data collected every 15 minutes for a total of 2 hours

Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Conduct testing on both test and reference products accordingly, and provide data on individual unit, means, range and %CV.

Product-specific testing conditions for in vitro feeding tube studies: The approved labeling for the reference product states that the product may be administered by a gastric (G) tube (16 French). Conduct the in vitro feeding tube studies including comparative recovery testing, particle size distribution, comparative dissolution testing, and sedimentation volume and redispersibility testing. For general procedures of in vitro feeding tube studies, refer to the most recent version of the FDA guidance for industry on *Oral Drug Products Administered Via Enteral Feeding Tube: In Vitro Testing and Labeling Recommendations*.^a

Testing tube: G tube (16 French)

Testing strength: 100 mg

Dispersion medium: 10 mL water with different pH values (e.g., pH 5.5, 7.0 and 8.5)

Comparative dissolution testing: After collection of the drug suspension at the feeding tube exit, perform comparative dissolution testing using the USP dissolution method: Stage 1 of 500 mL 0.1 N HCl for 1 hour and Stage 2 of 500 mL pH 7.5 phosphate buffer for 8 hours using USP Apparatus 1 (basket) at 100 rpm, maintained at a temperature of $37 \pm 0.5^{\circ}\text{C}$. Analyze the amount of morphine released at 1, 4, 6, and 9 hours.

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^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>.