

Draft Guidance on Morphine Sulfate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Active Ingredient: Morphine sulfate

Dosage Form; Route: Extended-release capsule; oral

Recommended Studies: Six studies

1. Type of study: Fasting
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 100 mg
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments: A naltrexone blockade should be used to reduce the risk of any opioid-related adverse events. Naltrexone should be administered well in advance of dosing to achieve adequate blockade of opioid receptors. The most common approach is to administer 50 mg – 100 mg of naltrexone at the following times: (1) 12 hours prior to dosing; (2) at the time of study drug dosing; and (3) 12 hours after the last dose of study drug. Consult with a physician who is an expert in the administration of opioids for an appropriate dose of narcotic antagonist.

2. Type of study: Fed
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 100 mg
Subjects: Males and non-pregnant, non-lactating females, general population
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: Males and non-pregnant, non-lactating females, general population
Additional comments: See comments above.

4. Type of study: Fasting
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 200 mg
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments: See comments above.

5. Type of study: Fed
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 200 mg
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments: See comments above.

6. Type of study: Fasting
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 10 mg
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments: See comments above.

Analytes to measure (in appropriate biological fluid): Morphine and morphine-6-glucuronide in plasma

Bioequivalence based on (90% CI): Morphine

Waiver request of in vivo testing: 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, and 80 mg strengths based on (i) acceptable bioequivalence studies on the 100 mg strength, (ii) acceptable in vitro dissolution testing for the 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, and 80 mg, and 100 mg strengths, and (iii) proportional similarity of formulations across 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, and 80 mg, and 100 mg strengths.

Waiver request of in vivo testing: 130 mg and 150 mg strengths based on (i) acceptable bioequivalence studies on the 200 mg strength, (ii) acceptable in vitro dissolution testing for the 130 mg, 150 mg, and 200 mg strengths, and (iii) proportional similarity of formulations across 130 mg, 150 mg, and 200 mg strengths.

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods web site, available to the public at the following location: <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

In addition to the method above, for modified release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted in the application. Agitation speeds may have to 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. Specifications will be determined upon review of the data submitted in the application.

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

Testing Conditions: 900 mL, 0.1 N HCl, apparatus 1 (basket) @ 100 rpm, with and without the alcohol (see below):

Test 1: 12 units tested according to the proposed method (with 0.1 N 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.

Both test and RLD products must be tested accordingly and data must be provided on individual unit, means, range and %CV on both strengths.

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 described below, and sedimentation volume testing. Refer to the Lansoprazole Delayed-Release Orally Disintegrating Tablet Draft Guidance for additional information regarding procedures of in vitro feeding tube studies.

Testing tube: G tube (16 French)

Testing strength: 10 mg, 100 mg, 200 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 I (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.