

Contains Nonbinding Recommendations

Draft Guidance on Morphine Sulfate

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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: Morphine Sulfate

Form/Route: Extended Release Capsule/Oral

Recommended studies: 3 studies

1. Type of study: Fasting
Design: Single-dose, two-way crossover in-vivo
Strength: 120 mg
Subjects: Healthy males and nonpregnant females, general population.
Additional Comments: A naltrexone blockade should be used to remove the risk of any opioid-related adverse events. Naltrexone should be administered well in advance of dosing to achieve adequate blockade of opioid receptors. A common approach is to administer 50 mg of naltrexone at the following times: (i) 12 hours prior to dosing, (ii) at the time of study drug dosing, and (iii) 12 hours after the last dose of study drug. Please 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-way crossover in-vivo
Strength: 120 mg
Subjects: Healthy males and nonpregnant females, general population.
Additional Comments: Please see comment above.

3. Type of study: Fasting Sprinkle in applesauce
Design: Single-dose, two-way crossover in-vivo
Strength: 120 mg
Subjects: Healthy males and nonpregnant females, general population.
Additional Comments: Please see comment above.

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

Bioequivalence based on (90% CI): Morphine

Please submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: (i) individual and mean

concentrations, (ii) individual and mean pharmacokinetic parameters, and (iii) geometric means and ratios of means for AUC and C_{max}.

Waiver request of in-vivo testing: Morphine Sulfate Extended Release Capsule, 30 mg, 45 mg, 60 mg, 75 mg and 90 mg based on (i) acceptable bioequivalence studies on the 120 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:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Please find the dissolution information for this product at this website. Please 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 application.

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. Please 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 a concern of dose dumping of drug from this drug product when taken with alcohol, the Agency currently requests that additional dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 1000 mL, 0.1 N HCl, USP apparatus 1 (Basket) @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

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