

Draft Guidance on Morphine Sulfate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Recommended studies: Two studies

1. Type of study: Fasting

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

Strength: 100 mg

Subjects: Healthy males and non-pregnant, non-lactating females, general population.

Additional Comments:

A naltrexone blockade should be used to reduce the risk of 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 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-way crossover in-vivo

Strength: 100 mg

Subjects: Healthy males and non-pregnant, non-lactating females, general population.

Additional Comments: See comments above.

Analytes to measure (in appropriate biological fluid): Morphine and its active metabolite, Morphine-6-glucuronide, in plasma

Bioequivalence based on (90% CI): Morphine

Waiver request of in-vivo testing: 15 mg, 30 mg, and 60 mg based on (i) acceptable bioequivalence studies on the 100 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths.

Evaluating the Abuse-Deterrence: Since the FDA has determined that the reference listed drug for morphine sulfate extended release tablets has abuse-deterrent properties (as described in section 9.2 of the approved Full Prescribing Information), the sponsor of a proposed generic version of the reference listed drug should refer to the draft guidance, “*General*

Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products for Industry,” regarding the studies that should be conducted to demonstrate that the proposed generic product is no less abuse-deterrent than the reference listed drug with respect to all potential routes of abuse.

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the **FDA-Recommended Dissolution Methods website** available to the public at the following location: <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Conduct comparative dissolution testing on 12 dosage units 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 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.

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: 900 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.