

Draft Guidance on Morphine Sulfate; Naltrexone Hydrochloride

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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; Naltrexone hydrochloride
- Dosage Form; Route:** Capsule; extended release; oral
- Recommended Studies:** Three bioequivalence studies (1–3) and two in vivo abuse deterrence studies (4–5)

1. Type of study: Fasting

Design: Single-dose, two-treatment, two-period crossover in vivo

Strength: 60 mg/2.4 mg

Subjects: Males and non-pregnant non-lactating females, general population; subjects should have a history of morphine administration for therapeutic purposes at the study dose or higher that was well tolerated.

Additional Comments: Due to safety concerns, bioequivalence studies on the highest strength are not recommended. A naltrexone blockade is not recommended because the bioequivalence studies should also demonstrate minimal absorption of naltrexone following oral administration of the intact products. Appropriate safety monitoring for opioid-related adverse events should be included in the study protocol.

2. Type of study: Fed

Design: Single-dose, two-treatment, two-period crossover in vivo

Strength: 60 mg/2.4 mg

Subjects: Males and non-pregnant non-lactating females, general population; subjects should have a history of morphine administration for therapeutic purposes at the study dose or higher that was well tolerated.

Additional Comments: See comments in Study 1. Refer to the Amantadine Hydrochloride Tablet Guidance for additional information regarding fed studies.

3. Type of study: Fasting, sprinkle in applesauce

Design: Single-dose, two-treatment, two-period crossover in vivo

Strength: 60 mg/2.4 mg

Subjects: Males and non-pregnant non-lactating females, general population; subjects should have a history of morphine administration for therapeutic purposes at the study dose or higher that was well tolerated.

Additional Comments: See comments in Study 1. Fasting study, with capsule contents sprinkled over a spoonful of applesauce in accordance with the approved reference listed drug (RLD) labeling.

4. Type of study: Fasting, comparative oral pharmacokinetic (PK) study with physically manipulated drug products
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 60 mg/2.4 mg
Subjects: Males and non-pregnant non-lactating females, general population; subjects should have a history of morphine administration for therapeutic purposes at the study dose or higher that was well tolerated.
Additional Comments: A naltrexone blockade is not recommended because the PK-based abuse deterrence study for an opioid agonist/antagonist combination product should also evaluate the antagonist (i.e., naltrexone for the subject drug product) bioavailability from the physically manipulated products. Appropriate safety monitoring for opioid-related adverse events should be included in the study protocol. Take scientifically appropriate and ethical steps to protect human subjects, e.g., confirming an adequate naltrexone release from the physically manipulated test and reference products using appropriate in vitro approaches prior to conducting the in vivo oral PK study. A suitable level of physical manipulation should be applied to both test and reference products to achieve a particle size range and opioid/antagonist release that can discriminate between their ability to deter abuse. Characterize the formulation recovery, drug content, and particle size distribution of physically manipulated reference and test drug products used in the oral PK study using validated analytical procedures. Determine relevant PK parameters including maximum concentration (C_{max}), area-under-the-curve (AUC_{0-t} and $AUC_{0-\infty}$), and time to maximum concentration (T_{max}). Applicants should submit partial AUCs (e.g., $AUC_{0-2 \text{ hours}}$) as supportive data.
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5. Type of study: Fasting, comparative nasal PK study with physically manipulated drug products, consistent with the recommendations in FDA's guidance, "General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products," for tier 2 evaluation of abuse by insufflation as applicable
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 30 mg/1.2 mg
Subjects: Non-dependent recreational opioid users, general population¹
Additional Comments: See comments in Study 4. Pulverize test and reference products to a particle size range that is considered safe and tolerable for human insufflation studies. Take scientifically appropriate and ethical steps to protect human subjects. This should include confirming an adequate naltrexone release from the physically manipulated test and reference products using appropriate in vitro approaches prior to conducting the in vivo nasal PK study and ensuring that each subject is not physically dependent on opioids (e.g., through a naloxone challenge test) and has not been seeking or undergoing treatment for abuse of

¹ This means non-dependent recreational opioid users from the general population who have experience in the use of opioids for non-therapeutic purposes.

controlled substances such that participating in the study could make them vulnerable to relapse².

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

Bioequivalence based on (90% CI): Morphine

Abuse deterrence based on: Upper 95% confidence bound for morphine; lower 95% confidence bound for naltrexone (or 6- β -naltrexol)

Plasma naltrexone and 6- β -naltrexol concentrations may be low and highly variable following single administration of intact morphine sulfate/naltrexone hydrochloride capsules in the bioequivalence studies. Develop a method of adequate sensitivity to measure plasma naltrexone and 6- β -naltrexol concentrations. The PK profiles of naltrexone and 6- β -naltrexol in the bioequivalence studies should be submitted as supportive evidence of comparable therapeutic outcome.

For the in vivo abuse deterrence studies, if naltrexone can be reliably measured, the lower 95% confidence bound should be obtained for naltrexone while 6- β -naltrexol data should be submitted as supportive evidence to demonstrate that the proposed generic drug product is no less abuse deterrent. If naltrexone cannot be reliably measured, the lower 95% confidence bound should be obtained for 6- β -naltrexol.

Waiver request of in-vivo testing: 20 mg/0.8 mg, 30 mg/1.2 mg, 50 mg/2 mg, 80 mg/3.2 mg and 100 mg/4 mg based on (i) acceptable bioequivalence studies on the 60 mg/2.4 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity in the formulations across all strengths. Refer to the Mirtazapine Tablet Guidance for additional information regarding waivers of in-vivo testing.

Abuse Deterrence Evaluation: Since the FDA has determined that the RLD for morphine sulfate; naltrexone hydrochloride extended-release capsule (NDA 022321) has properties that are expected to deter abuse (as described in Section 9.2 of the approved Full Prescribing Information), you should refer to the guidance, “*General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*,” regarding the studies that should be conducted to demonstrate that the proposed generic product is no less abuse-deterrent than the RLD with respect to all potential routes of abuse. Consistent with the guidance, the potential Abbreviated New Drug Application (ANDA) applicants should consider, among other things, the following:

- a) Conducting all in vitro abuse deterrence studies using a bracketing design based on appropriate justification (e.g., extremes of the ratios of opioid to excipients contributing to abuse deterrence) or the highest strength based on compositional proportionality of the proposed generic formulations across all strengths.

² For criteria on evaluating substance dependence, refer to, for example, the latest version of *Diagnostic and Statistical Manual of Mental Disorders*, Arlington, VA, American Psychiatric Association.

- b) Ensuring that the formulation components containing morphine sulfate and naltrexone hydrochloride should not be physically distinguishable (i.e., color, size, shape) to allow physical separation.
- c) Including buffers near the neutral pH (e.g., pH 4.5 and 6.5) as additional Level 1 solvents.
- d) Determining the content of both morphine and naltrexone in manipulated drug products (e.g. cut, grated or milled) and quantify the drug loss in samples prior to evaluating extractability.

Dissolution test method and sampling times:

Note that a **Dissolution Methods Database** is available to the public at the OGD website <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Find the dissolution information for this product at this website. 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) and water at 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.

Alcohol dose dumping studies:

Due to a concern of dose dumping from this drug product when taken with alcohol, conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 500 mL, 0.1 N HCl, USP apparatus 2 (paddle) @50 rpm, with or without alcohol (see below):

- 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 morphine and naltrexone components of test and reference products of all strengths.