

Draft Guidance on Oxycodone

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Capsule, Extended Release; Oral

Recommended Studies: Three bioequivalence studies (1–3) and three in vivo abuse deterrence studies (4–6)

1. Type of study: Fasting
Design: Single-dose, two-treatment, two-period, crossover in vivo
Strength: 36 mg
Subjects: Males and non-pregnant, non-lactating females, general population
Additional Comments: Naltrexone or other opioid antagonist should be incorporated to block the pharmacodynamic (PD) effects of the opioid. The opioid antagonist should be administered well in advance of opioid 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-treatment, two-period, crossover in-vivo
Strength: 36 mg
Subjects: Males and non-pregnant, non-lactating females, general population
Additional Comments: See comments in Study 1.

3. Type of study: Fasting, sprinkle-in-applesauce
Design: Single-dose, two-treatment, two-period, crossover in-vivo
Strength: 36 mg
Subjects: Males and non-pregnant, non-lactating females, general population
Additional Comments: Administer the dose after sprinkling the entire contents of the capsule on a tablespoon of applesauce in accordance with the approved label of the reference listed drug (RLD). Otherwise, the study should be conducted in the fasting state as described above. See additional comments in Study 1.

4. Type of study: Fed, comparative nasal pharmacokinetic (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: 36 mg

Subjects: Non-dependent recreational opioid users, general population¹

Additional comments: See comments in Study 1. Take scientifically appropriate and ethical steps to protect human subjects. This should include 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 controlled substances such that participating in the study could make them vulnerable to relapse.² Pulverize test and reference products to a particle size range that is considered safe and tolerable for human insufflation studies. Characterize the formulation recovery, drug content, and particle size distribution of physically manipulated test and reference drug products used in the nasal 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., $AUC_{0-3 \text{ hours}}$ and $AUC_{0-4 \text{ hours}}$) as supporting data.

5. Type of study: Fasting, comparative oral PK study of chewed drug products

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

Strength: 36 mg

Subjects: Males and non-pregnant, non-lactating females, general population

Additional comments: See comments in Study 1. Patient-relevant chewing conditions that can discriminate between test and reference products’ ability of deterring chewing should be identified. Determine relevant PK parameters listed in Study 4.

6. Type of study: Fasting, comparative oral PK study with physically manipulated drug products

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

Strength: 36 mg

Subjects: Males and non-pregnant, non-lactating females, general population

Additional comments: See comments in Study 1. A suitable level of physical manipulation should be applied to both test and reference products to achieve a particle size range and drug 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 listed in Study 4. Alternatively, in lieu of conducting Study 6, the ANDA applicants may provide justifications along with supporting evidence from in vitro and in vivo studies that the

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

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.

physically manipulated test product will not result in dose dumping or a higher systemic exposure to oxycodone compared to the physically manipulated and orally ingested RLD.

Analytes to measure (in appropriate biological fluid): Oxycodone in plasma

Bioequivalence based on (90% CI): Oxycodone

Abuse deterrence based on (upper 95% CI): Oxycodone

Waiver request of in vivo testing: 9 mg, 13.5 mg, 18 mg and 27 mg, based on (i) acceptable bioequivalence studies on the 36 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths.

Abuse Deterrence Evaluation: Since the FDA has determined that the RLD for oxycodone extended-release capsules 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 ANDA applicants should consider, among other things, the following:

- (a) Including crushing of microspheres/beads/pellets by mortar and pestle in the evaluation of “most effective manipulation”
- (b) Using multiple capsules in physical manipulation study where it is feasible, and providing justification for the number of units used in a manipulation run
- (c) Including methanol and ethyl acetate in Level 3 solvents for determining extractability of opioid drug substance
- (d) Determining the drug content in manipulated drug products (e.g., cut, grated or milled) and quantifying the drug loss in samples prior to evaluating extractability

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 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 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, 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.

Alcohol dose dumping studies:

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 should be tested accordingly and data should be provided 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 nasogastric (NG) or gastric (G) tube. Conduct the in vitro feeding tube studies including comparative recovery testing, particle size distribution study, 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: NG tube (8 French), G tube (12 French)

Testing strengths: 36 mg

Dispersion medium: Disperse the capsule contents in 15 mL of water, milk and liquid nutritional supplement followed by flushing two more times, each with 10 mL of the same vehicle