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Draft Guidance on Oxycodone

November 2022

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

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 effects of the opioid. Administer the opioid antagonist in advance of opioid dosing to achieve adequate blockade of opioid receptors. The most common approach is to administer 50 mg of naltrexone 12 hours prior to study drug, at the time of study drug, and 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 opioid 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 labeling of the reference product. Otherwise, the study should be conducted in the fasting state as described above. See comments in Study 1.

4. Type of study: Fed, comparative nasal pharmacokinetic (PK) study with physically manipulated drug products, consistent with the recommendations in the most recent version of the FDA guidance for industry on *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*,[a] 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 population[1]
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., $AUC_{0-3\ hours}$ and $AUC_{0-4\ hours}$) 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.

[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.

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, applicants may provide justifications along with supporting evidence from in vitro and in vivo studies that the physically manipulated test product will not result in dose dumping or higher systemic exposure to oxycodone compared to the physically manipulated and orally ingested reference product.

Analyte to measure: Oxycodone in plasma

Bioequivalence based on (90% CI): Oxycodone

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

Additional strengths: Bioequivalence of the 9 mg, 13.5 mg, 18 mg, and 27 mg strengths to the corresponding reference product strengths may be demonstrated based on principles laid out in the most recent version of the FDA guidance for industry on *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*.[a]

Abuse deterrence evaluation: Refer to the most recent version of the FDA guidance for industry on *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*,[a] regarding the studies that should be conducted to demonstrate that the proposed generic product is no less abuse-deterrent than the reference product with respect to all potential routes of abuse. Consistent with the guidance, the potential applicants should consider, among other things, the following:

1. Including crushing of microspheres/beads/pellets by mortar and pestle in the evaluation of "most effective manipulation"
2. Using multiple capsules in physical manipulation study where it is feasible, and providing justification for the number of units used in a manipulation run
3. Including methanol and ethyl acetate in Level 3 solvents for determining extractability of opioid drug substance
4. 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: For modified release drug products, applicants should develop specific discriminating dissolution methods. Alternatively, applicants may use the dissolution method set forth in any related official United States Pharmacopeia (USP) drug product monograph, or in the FDA's database, http://www.accessdata.fda.gov/scripts/cder/dissolution/, provided that applicants submit adequate dissolution data supporting the discriminating ability of such a method. If a new dissolution method is developed, submit the dissolution method development and validation report with the complete information/data supporting the proposed method. Conduct comparative dissolution testing on 12 dosage units for each strength 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, submit dissolution profiles on 12 dosage units for each strength of the test and reference products generated using USP Apparatus 1 at 100 rpm and/or Apparatus 2 at 50 rpm in at least three dissolution media (e.g., pH 1.2, 4.5 and 6.8 buffer). Agitation speeds may 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 concerns of dose dumping of drug from this product when taken with alcohol, conduct additional dissolution testing on all strengths using various concentrations of ethanol in the dissolution medium as follows:

Testing conditions: 900 mL, 0.1N HCl, USP Apparatus 1 (basket) at 100 rpm, with or without alcohol

> 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

Conduct testing on both test and reference products accordingly, and provide data 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 with repeated administrations, particle size distribution testing, comparative dissolution testing, and sedimentation volume and redispersibility testing. For general procedures of in vitro feeding tube studies, refer to the most recent version of the FDA guidance for industry on *Oral Drug Products Administered Via Enteral Feeding Tube: In Vitro Testing and Labeling Recommendations*.[a]

Testing tubes: NG tube (8 French), G tube (12 French)

Testing strength: 36 mg

Dispersion media: Disperse the capsule contents in 15 mL of water with different pH values (e.g., pH 5.5, 7.0 and 8.5), milk and liquid nutritional supplement followed by flushing two more times, each with 10 mL of the same vehicle.

Incubation times: 0 minute and 15 minutes

Revision History: Recommended December 2016; Revised February 2018, September 2018, November 2022

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[a] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.