*Contains Nonbinding Recommendations*

**Draft Guidance on Acetaminophen; Benzhydrocodone Hydrochloride**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

**Dosage Form; Route:** Tablet; oral

**Recommended Studies:** Two studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover in vivo
   Strength: 325 mg; EQ 8.16 mg Base
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: Apadaz™ (acetaminophen; benzhydrocodone hydrochloride) is approved with a Risk Evaluation and Mitigation Strategy (REMS) with an Elements to Assure Safe Use (ETASU), which restricts its use. All pertinent elements of the REMS must be incorporated into the protocol and informed consent.

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2. Type of study: Fed
   Design: Single-dose, two-way crossover in vivo
   Strength: 325 mg; EQ 8.16 mg Base
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: See comments above

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**Analytes to measure (in appropriate biological fluid):** Acetaminophen and hydrocodone in plasma

**Bioequivalence based on (90% CI)**: Acetaminophen and hydrocodone

**Waiver request of in vivo testing:** 325 mg; EQ 4.08 mg Base and 325 mg; EQ 6.12 mg Base strengths based on (i) acceptable bioequivalence studies on the 325 mg; EQ 8.16 mg Base strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths

**Dissolution test method and sampling times:** The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods web site, available to the public at the following location: http://www.accessdata.fda.gov/scripts/cder/dissolution/. 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 abbreviated new drug application.