*Contains Nonbinding Recommendations*

*Draft – Not for Implementation*

**Draft Guidance on Aspirin; Butalbital; Caffeine; Codeine Phosphate**

**October 2024**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

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**Active Ingredients:** Aspirin; Butalbital; Caffeine; Codeine phosphate

**Dosage Form:** Capsule

**Route:** Oral

**Strength:** 325 mg; 50 mg; 40 mg; 30 mg

**Recommended Study:** One in vivo bioequivalence study with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 325 mg; 50 mg; 40 mg; 30 mg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: Aspirin; butalbital; caffeine; codeine phosphate capsule is under a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU). All pertinent elements of the REMS/ETASU are recommended to be incorporated into the protocol and informed consent.

**Analytes to measure:** Butalbital and codeine in plasma

**Bioequivalence based on (90% CI)**: Butalbital and codeine

**Waiver request of in vivo testing:** Not applicable

**Dissolution test method and sampling times:** The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, http://www.accessdata.fda.gov/scripts/cder/dissolution. Conduct comparative dissolution testing on 12 dosage units for each of the test product and reference listed drug (RLD).[1] Specifications will be determined upon review of the abbreviated new drug application.

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**Document History:** Recommended December 2009; Finalized August 2017; Revised October 2024

**Unique Agency Identifier:** PSG_019429

[1] If the RLD is not available, refer to the most recent version of the FDA guidance for industry on *Referencing Approved Drug Products in ANDA Submissions.*