Contains Nonbinding Recommendations

Draft Guidance on Buprenorphine

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Solution, extended release; subcutaneous

Recommended Study: One study

1. Type of Study: Bioequivalence study with pharmacokinetic endpoints
   Design: Single-dose, randomized, parallel, in vivo
   Strength: 300 mg/1.5 mL
   Subjects: Males and non-pregnant, non-lactating females with moderate or severe opioid use disorder (OUD), 18 to 65 years old
   Additional comments:
   - Buprenorphine extended-release injection, for subcutaneous use is under a Risk Evaluation and Mitigation Strategy (REMS) program with Elements to Assure Safe Use (ETASU) to mitigate the risk of serious harm or death with intravenous self-administration. All pertinent elements of the REMS must be incorporated into the protocol and informed consent in the bioequivalence study.
   - The patients with moderate to severe OUD should have initiated treatment with a transmucosal buprenorphine containing product, followed by a dose adjustment for a minimum of 7 days. The applicant can employ a washout before the dose of buprenorphine extended-release injection, for subcutaneous use.
   - During the washout period, subjects should be closely monitored by an experienced healthcare professional for signs and symptoms of opioid withdrawal. Nonopioid rescue medications to treat the signs and symptoms of withdrawal may be used as clinically appropriate.
   - It is important that patients not use any other buprenorphine-containing product, either therapeutically or illicitly after administration of buprenorphine extended-release injection, for subcutaneous use.

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

Bioequivalence based on (90% CI): Buprenorphine

The confidence intervals of the geometric mean test/reference (T/R) ratios for the metrics (C_{max}, $AUC_{0\text{-}tlast}$, and $AUC_{3week\text{-}4week}$) should fall within the limits of 80.00-125.00%, where C_{max} is the maximum plasma concentration, $AUC_{0\text{-}tlast}$ is the area under the curve from 0 to the last sampling time point, and $AUC_{3week\text{-}4week}$ is the area under the plasma concentration time curve from 3

weeks to 4 weeks. The applicant should submit time to maximum concentration (T_{max}) as supportive data.

Waiver request of in vivo testing: 100 mg/0.5 mL strength based on: (i) an acceptable bioequivalence study on the 300 mg/1.5 mL strength (ii) acceptable in vitro dissolution testing across all strengths and (iii) proportional similarity of the formulations across all strengths.

The formulation of test and reference products should be qualitatively (Q1) and quantitatively (Q2) the same per CFR 21 314.94 (a)(9)(iii).

Dissolution test method and sampling times: Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specification will be determined upon review of the abbreviated new drug application.