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Draft – Not for Implementation

Draft Guidance on Buprenorphine Hydrochloride

August 2026

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Active Ingredient:	Buprenorphine hydrochloride
Dosage Form:	Tablet
Route:	Sublingual
Strengths:	EQ 2 mg Base | EQ 4 mg Base (FDA-2024-P-2909) | EQ 8 mg Base | EQ 12 mg Base (FDA-2024-P-2909)
Reference Listed Drug:	NDA 020732
Recommended Studies:	Two options: (I) One in vivo bioequivalence study with pharmacokinetic endpoints or (II) one in vivo bioequivalence study with pharmacokinetic endpoints for suitability petition strengths

Option I: One in vivo bioequivalence study with pharmacokinetic endpoints

1. Class of study: Bioequivalence
   Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: EQ 8 mg Base
   Subjects: Healthy males and non-pregnant, non-lactating females
   Safety recommendations:
   - Use an opioid antagonist (e.g., naltrexone) to mitigate safety risk of the opioid (e.g., respiratory depression) in healthy subjects. Administer the opioid antagonist in advance of dosing the study drug and as appropriate thereafter (e.g., within 12 hours post dose) to adequately block opioid induced pharmacological effects based on the opioid antagonist and opioid product's effective duration.

- Monitor vital signs (e.g., pulse oximetry and continuous respiratory monitoring) during the study and implement standards and practice for detection and management of respiratory depression.
- Buprenorphine hydrochloride tablet is under a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU), which restricts its use. All pertinent elements of the REMS/ETASU must be incorporated into the protocol and informed consent.

Study design recommendations:

- Hold the tablet under the tongue until tablet dissolves.
- $AUC_{(0\text{-}72h)}$ may be used in place of $AUC_{(0\text{-}t)}$ for comparing the extent of absorption, due to buprenorphine's long half-life. Ensure adequate washout periods between treatments in the crossover study.
- Alternatively, a parallel study design may be considered.

Analyte to measure: Buprenorphine in plasma

Bioequivalence based on (90% CI): Buprenorphine

Bioequivalence of additional strengths: Waiver request of in vivo testing of additional strengths of EQ 2 mg Base based on (i) an acceptable bioequivalence study on the EQ 8 mg Base strength, (ii) acceptable comparative in vitro dissolution studies between the additional strength and the EQ 8 mg Base strength using 12 units per strength, and (iii) proportional similarity of the formulations between both strengths

Option II: One in vivo bioequivalence study with pharmacokinetic endpoints for suitability petition strength

Eligibility: If an applicant intends to submit an abbreviated new drug application (ANDA) for both the reference listed drug (RLD) strengths of EQ 2 mg Base and EQ 8 mg Base and the suitability petition strengths of EQ 4 mg Base (FDA-2024-P-2909) and EQ 12 mg Base (FDA-2024-P-2909), conduct an in vivo bioequivalence study using the test product of EQ 12 mg Base strength and the reference standard of EQ 12 mg Base strength.

1. Class of study: Bioequivalence
   Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: EQ 12 mg Base
   Subjects: Healthy males and non-pregnant, non-lactating females
   Safety recommendations: See recommendations under Option I, Study#1.
   Study design recommendations: See recommendations under Option I, Study#1.

Analyte to measure: Buprenorphine in plasma

Bioequivalence based on (90% CI): Buprenorphine

Bioequivalence of additional strengths: Waiver request of in vivo testing of additional strengths of EQ 2 mg Base, EQ 4 mg Base, and EQ 8 mg Base based on (i) an acceptable bioequivalence study on the EQ 12 mg Base strength, (ii) acceptable comparative in vitro dissolution studies between the additional strength and the EQ 12 mg Base strength using 12 units per strength, and (iii) proportional similarity of the formulations across all strengths

If an applicant holds an approved ANDA for the EQ 2 mg Base and EQ 8 mg Base strengths, an applicant may request biowaivers of the EQ 4 mg Base and EQ 12 mg Base strengths. Provide adequate justification, including the manufacturing process, formulation proportionality, and comparable in vitro dissolution profiles across the strengths.

Recommendations for both Options:

Dissolution: Dissolution test(s) should be included for quality control and to support a waiver request of in vivo testing of additional strengths. For the quality control dissolution method, provide a dissolution method development report for the test product containing information and data that demonstrate appropriateness of the selected dissolution method[1] and sampling times, such as the discriminating ability to detect changes in critical quality attributes that could potentially impact drug product performance.

Document History: Recommended May 2010; Revised February 2014, August 2026

[1] Applicant-developed, United States Pharmacopeia drug product monograph or Dissolution Methods database, https://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm