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Draft – Not for Implementation

Draft Guidance on Buprenorphine

February 2026

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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:	Buprenorphine
Dosage Form:	Solution, extended release
Route:	Subcutaneous
Strengths:	8 mg/0.16 mL (50 mg/mL), 16 mg/0.32 mL (50 mg/mL), 24 mg/0.48 mL (50 mg/mL), 32 mg/0.64 mL (50 mg/mL), 64 mg/0.18 mL (356 mg/mL), 96 mg/0.27 mL (356 mg/mL), 128 mg/0.36 mL (356 mg/mL)
Recommended Studies:	Two options: (1) two in vitro bioequivalence studies with supportive characterization studies, or (2) two in vivo bioequivalence studies with pharmacokinetic endpoints

I. Option 1: Two in vitro bioequivalence studies with supportive characterization studies

To be eligible for the bioequivalence studies recommended in this guidance, the test product[1] should be qualitatively (Q1)[2] and quantitatively (Q2)[3] the same as the reference listed drug (RLD).

[1] The manufacturing process for the exhibit batches should be reflective of the manufacturing process to be utilized for commercial batches.
[2] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD.
[3] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the RLD.

1. Type of study: Comparative in vitro drug release test (IVRT)
   Design: In vitro bioequivalence study on at least three batches of both test product and RS
   Strength: Any one of the strengths including 8 mg/0.16 mL, 16 mg/0.32 mL, 24 mg/0.48 mL, 32 mg/0.64 mL

2. Type of study: Comparative in vitro drug release test (IVRT)
   Design: In vitro bioequivalence study on at least three batches of both test product and RS
   Strength: Any one of the strengths including 64 mg/0.18 mL, 96 mg/0.27 mL, 128 mg/0.36 mL
   Additional comments: A properly developed and validated IVRT method that can detect potential formulation difference (e.g., phase structure variations resulting from differences in lipid ratios and lipid grades) and capture the complete release profile of buprenorphine should be provided. Equivalence in buprenorphine release should be established using a proper statistical method from test product and RS.

Supportive characterization studies:
Comparative physicochemical characterization of the weekly and monthly test products and the corresponding RS. The comparative studies should be performed on a minimum of three exhibit batches of the test product and three batches of the RS and should include:

a. Soybean phosphatidylcholine (as phosphatidylcholine) concentration and glycerol dioleate concentration
b. Specific gravity
c. Appearance
d. Viscosity
e. Water uptake kinetics in phosphate-buffer saline (PBS) (pH 7.4)[4]
f. Properties of liquid crystal depot fully hydrated in PBS, including appearance, phase structure[5], and rheological properties (complex viscosity and elastic modulus)
g. Time required to fully degrade liquid crystal depot in vitro

Additional comments:

- Liquid crystal depot can be formed in vitro by injection of the formulation into PBS.[6] The time required to reach full hydration can be informed by the water uptake kinetics study. For comparative characterization studies examining appearance, phase structure, and rheological properties, applicants should use fully hydrated depots to ensure assessment of the mature depot structure. However, for IVRT study, the applicants do not need to use fully hydrated depots since the depot will be exposed to a dissolution media during the test, which will naturally induce hydration as part of the release process.
- The degradation study may be combined with the IVRT or be conducted under a different experimental condition.

[4] Jenni Engstedt, René In 't Zandt, Justas Barauskas, Vitaly Kocherbitov. Swelling kinetics of mixtures of soybean phosphatidylcholine and glycerol dioleate. Colloids Surf B Biointerfaces. 2024 Jul:239:113955. doi: 10.1016/j.colsurfb.2024.113955.
[5] Fredrik Tiberg, Markus JohnssonMarija Jankunec, and Justas Barauskas, Phase Behavior, Functions, and Medical Applications of Soy Phosphatidylcholine and Diglyceride Lipid Compositions. Chem. Lett. 2012, 41, 10901092
[6] Jenni Engstedt, Martynas Talaikis, Justas Barauskas, Gediminas Niaura, Vitaly Kocherbitov. Hydration-induced lipid redistribution in swelling of controlled release liquid crystalline depots. Commun Chem. 2025 Oct 14;8(1):309. doi: 10.1038/s42004-025-01739-0.

II. Option 2: Two in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Bioequivalence study with pharmacokinetic endpoints
   Design: Single-dose, randomized, parallel, in vivo
   Strength: Any one of the weekly strengths including 8 mg/0.16 mL, 16 mg/0.32 mL, 24 mg/0.48 mL, 32 mg/0.64 mL
   Dose: 8 mg, 16 mg, 24 mg, or 32 mg
   Subjects: Males and non-pregnant, non-lactating females with moderate or severe opioid use disorder (OUD), 18 to 65 years old

Additional comments:

1. Patients with moderate to severe OUD should be currently treated with a transmucosal buprenorphine-containing product. The applicant may employ a washout period before administration of buprenorphine extended release solution, for subcutaneous use.
2. Patients should be confined at the clinical unit during the washout period and until their OUD and withdrawal symptoms are appropriately managed. Patients should be closely monitored by a healthcare professional experienced in OUD management for signs and symptoms of opioid withdrawal and any adverse reactions to the study drug. An opioid withdrawal management protocol should be implemented. Non-opioid rescue medications should be readily available and may be administered as clinically appropriate to treat signs and symptoms of withdrawal.
3. Instruct patients to not use any other buprenorphine-containing product following the administration of buprenorphine extended release solution, for subcutaneous use.
4. Patients should be evaluated by a healthcare professional experienced in OUD management at the end of the study to determine an appropriate continuing treatment option based on individual benefits and risks.
5. Buprenorphine extended release solution, for subcutaneous use is approved 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.

Analyte to measure: Buprenorphine in plasma

Bioequivalence based on (90% CI): Buprenorphine

The 90% confidence intervals of the following pharmacokinetic parameters should meet the acceptable limits of [80.00-125.00]: Log-transformed C_{max}, AUC_{0-t}, and $AUC_{day5-day7}$, where C_{max} is the maximum plasma concentration, AUC_{0-t} is the area under the curve from 0 to the last sampling time point, and $AUC_{day5-day7}$ is the area under the plasma concentration time curve from Day 5 to Day 7. Note that the last sampling time point 't' equals the dosing interval of the product used in the in vivo pharmacokinetic study. The applicant should submit time to maximum concentration (T_{max}) and AUC_{inf} as supportive data.

2. Type of study: Bioequivalence study with pharmacokinetic endpoints
Design: Single-dose, randomized, parallel, in vivo
Strength: Any one of the monthly strengths including 64 mg/0.18 mL, 96 mg/0.27 mL, 128 mg/0.36 mL
Dose: Any one of the doses including 64 mg, 96 mg, 128 mg
Subjects: Males and non-pregnant, non-lactating females with moderate or severe opioid use disorder (OUD), 18 to 65 years old

Additional comments:

1. Patients with moderate to severe OUD should be currently treated with a transmucosal buprenorphine-containing product. The applicant may employ a washout period before administration of buprenorphine extended release solution, for subcutaneous use.
2. Patients should be confined at the clinical unit during the washout period and until their OUD and withdrawal symptoms are appropriately managed. Patients should be closely monitored by a healthcare professional experienced in OUD management for signs and symptoms of opioid withdrawal and any adverse reactions to the study drug. An opioid withdrawal management protocol should be implemented. Non-opioid rescue medications should be readily available and may be administered as clinically appropriate to treat signs and symptoms of withdrawal.
3. Instruct patients to not use any other buprenorphine-containing product following the administration of buprenorphine extended release solution, for subcutaneous use.
4. Patients should be evaluated by a healthcare professional experienced in OUD management at the end of the study to determine an appropriate continuing treatment option based on individual benefits and risks.
5. Buprenorphine extended release solution, for subcutaneous use is approved 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.

Analyte to measure: Buprenorphine in plasma

Bioequivalence based on (90% CI): Buprenorphine

The 90% confidence intervals of the following pharmacokinetic parameters should meet the acceptable limits of [80.00-125.00]: Log-transformed C_{max}, AUC_{0-t}, and $AUC_{week3-week4}$, where C_{max} is the maximum plasma concentration, AUC_{0-t} is the area under the curve from 0 to the last sampling time point, and $AUC_{week3-week4}$ is the area under the plasma concentration time curve from Week 3 to Week 4. Note that the last sampling time point 't' equals the dosing interval of the product used in the in vivo pharmacokinetic study. The applicant should submit time to maximum concentration (T_{max}) and AUC_{inf} as supportive data.

Waiver request of in vivo testing:
Any strength of weekly buprenorphine extended-release injection that is not studied in vivo based on (i) acceptable bioequivalence study on the weekly strength tested in vivo, and (ii) evidence supporting identical formulation composition across all strengths

Any strength of monthly buprenorphine extended-release injection that is not studied in vivo based on (i) acceptable bioequivalence study on the monthly strength tested in vivo, and (ii) evidence supporting identical formulation composition across all strengths

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 each of all strengths of the test and reference listed drug (RLD).[7] Specifications will be determined upon review of the abbreviated new drug application.

Additional information:

Device:
The RLD is presented as a kit that consists of (1) a prefilled syringe with a staked needle and an attached needle guard system and (2) a plunger rod. The syringe with the needle and the needle guard system are the device constituent parts. The plunger rod is a device component.

FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD device when designing the test devices including:

- Single-dose, fixed-dose, prefilled syringe format
- Needle gauge and length
- Needle guard system

User interface assessment:
An abbreviated new drug application (ANDA) for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the guidance for industry *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA.* [a]

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

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