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Draft Guidance on Bupivacaine; Meloxicam

October 2025

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Active Ingredients:	Bupivacaine; Meloxicam
Dosage Form:	Solution, extended release
Route:	Periarticular
Strengths:	60 mg/2.3 mL (29.25 mg/mL); 1.8 mg/2.3 mL (0.88 mg/mL), 200 mg/7 mL (29.25 mg/mL); 6 mg/7 mL (0.88 mg/mL), 300 mg/10.5 mL (29.25 mg/mL); 9 mg/10.5 mL (0.88 mg/mL), 400 mg/14 mL (29.25 mg/mL); 12 mg/14 mL (0.88 mg/mL)
Recommended Study:	One in vivo bioequivalence study with pharmacokinetic endpoints

1. Type of study: In vivo bioequivalence study with pharmacokinetic endpoints
   Design: Single-dose, randomized, parallel in vivo study
   Strengths: 60 mg/2.3 mL (29.35 mg/mL); 1.8/2.3 mL (0.88 mg/mL), or 200 mg/7 mL (29.25 mg/mL); 6 mg/7 mL (0.88 mg/mL), or 300 mg/10.5 mL (29.25 mg/mL); 9 mg/10.5 mL (0.88 mg/mL), or 400 mg/14 mL (29.25 mg/mL); 12 mg/14 mL (0.88 mg/mL)
   Dose: Single dose of 60 mg bupivacaine and 1.8 mg meloxicam (2.3 mL)[1] via subcutaneous injection
   Subjects: Healthy males, non-pregnant and non-lactating females

[1] The prospective applicant may use partial of any one of the strengths to deliver this dose (i.e., 60 mg bupivacaine; 1.8 mg meloxicam in 2.3 mL drug product) for the bioequivalence study.

Additional comments:

a. Delivered via local subcutaneous injection. A moving needle technique may be used for administration.
b. Exclude subjects with abnormal liver function tests and monitor liver function during the study.
c. Females of reproductive potential should use effective contraception during the study and for one week after the last dose.
d. The co-packaged syringe should be used for the administration. Additional needle that is not co-packaged may be needed for subcutaneous injection.

Analytes to measure: Bupivacaine and meloxicam in plasma

Bioequivalence based on (90% CI): Bupivacaine and meloxicam

Waiver request of additional strengths: Any strength that is not studied in vivo based on (i) acceptable bioequivalence study on the strength(s) 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 on the FDA-Recommended Dissolution Methods website, 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 the test product and reference listed drug (RLD). Specifications will be determined upon review of the abbreviated new drug application (ANDA).

Additional information:

Formulation:
The proposed test product should be qualitatively (Q1)[2] and quantitatively (Q2)[3] the same as the RLD for all strengths. To support Q1 sameness, comparative characterization data on triethylene glycol poly(orthoester) in the drug product from a minimum of three exhibit batches[4] of the test product and three batches of the reference standard (RS) product should be provided. Comparative characterization data should include, but is not limited to:

- Polymer composition, structure, viscosity, molecular weight and molecular weight polydispersity, and glass transition temperature

[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.
[4] The manufacturing process for the exhibit batches should be reflective of the manufacturing process to be utilized for commercial batches. The three batches of test product should be manufactured from a minimum of three different batches of drug substance, excipients, and container/closure system.

In addition, to support quality assessment of the test product, provide characterization from at least three batches of raw triethylene glycol poly(orthoester):

- Polymer composition, structure, viscosity, molecular weight and molecular weight polydispersity, and glass transition temperature
- Contents of the individual hydrolytic products after complete hydrolysis of triethylene glycol poly(orthoester)

Additional characterization data on the triethylene glycol poly(orthoester) polymer may be requested during the assessment of the ANDA.

Device:
The RLD is presented as a kit that contains a vial of drug, one or two Luer-lock syringes, a vented vial spike, one or two Luer Lock cone-shaped applicators, and one or two syringe tip caps. The device components are the syringe(s), the vented vial spike, the applicator(s), and the tip cap(s).

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 device including:

- Tapered blunt applicator and compatible tip cap
- Vented needleless vial access (i.e., vial adapter or vial spike)

User interface assessment:
An 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 FDA guidance for industry on *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, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.