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Draft Guidance on Naltrexone

November 2023

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form: For suspension, extended release

Route: Intramuscular

Strength: 380 mg/vial

Recommended Study: One in vivo bioequivalence study with pharmacokinetic endpoints

1. Type of study: In vivo bioequivalence study with pharmacokinetic endpoints
   Design: Single-dose, parallel in vivo
   Strength: 380 mg/vial
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: None

Analyte to measure: Naltrexone in plasma

Bioequivalence based on (90% CI): Naltrexone

The 90% confidence intervals of the geometric mean test/reference (T/R) ratios for the metrics (C_{max}, AUC_{1-10}, AUC_{10-28}, and $AUC_{0-\infty}$) should fall within the limits of 80% - 125%.

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 each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

In addition to the method specified on the Dissolution Methods Website, conduct comparative dissolution testing on 12 dosage units of the test and reference products at a strength of 380 mg/vial (dose: 380 mg) with the following method:

Strength:	380 mg/vial (dose: 380 mg)
Medium:	Phosphate buffered saline with 0.02% Tween 20 and 0.02% sodium azide, pH 7.4 ± 0.05 (final osmolality should be 270 ± 20 mOsm)
Volume:	Add 200 mL of release medium to a 250 mL HDPE plastic bottle containing 600 ± 10 mg of microspheres (203 mg naltrexone) at room temperature
Temperature:	37 ± 0.3 ºC

Samples should be taken at frequent time intervals and should also include samples on Day 1, Day 7, Day 14, and Day 28.

Additional information:

Device:
The reference listed drug (RLD) is presented as a kit that consists of: (1) one vial of naltrexone powder; (2) one vial of diluent; (3) one syringe; (4) one 20-gauge 1-inch preparation needle with needle guard system; (5) two 20-gauge 1 1/2-inch needles with needle guard system; and (6) two 20-gauge 2-inch needles with needle guard system. The syringe and needles with needle guard system are the device constituent parts.

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

- Needle gauge and length
- Needle guard system

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]

Document History: Recommended August 2009; Revised February 2014, September 2015, November 2023

Unique Agency Identifier: PSG_021897

[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.