

Draft Guidance on Naloxone Hydrochloride

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Spray; nasal

Strengths: 2 mg/spray
4 mg/spray

Recommended Studies: Two options: In vivo or In vitro

I. In Vivo Option:

If the test (T) product is **not** qualitatively (Q1)¹ and quantitatively (Q2)² the same as the reference (R) product and the nasal spray device (e.g., the pump and actuator design) of the T product is appropriate for approval in an ANDA (as demonstrated by comparative analyses further described below), the following study is recommended to document bioequivalence (BE) of the T product to the R product:

Type of study: Fasting
Design: Single-dose, two-way crossover in vivo
Strength: 4 mg/spray x 1 spray (4 mg dose)
Subjects: Healthy males and non-pregnant females, general population.

Analytes to measure (in appropriate biological fluid): Naloxone in plasma.

Bioequivalence based on (90% CI): Naloxone

Additional comments regarding the BE study with PK endpoints: The following PK parameters will be evaluated: Log-transformed AUC_{0-t} , AUC_{0-inf} , and C_{max} . Applicants should submit partial AUC of early time points as supportive data to assess the onset of naloxone effect. Applicants should collect sufficient quantifiable PK samples to allow a comparison of exposure to naloxone between the T product and the R product within the initial 4 minutes, first 10 minutes, and 10-30 minutes after administration.

¹ Q₁ (qualitative sameness) means that the T product uses the same inactive ingredient(s) as the R product.

² Q₂ (quantitative sameness) means that concentrations of the inactive ingredient(s) used in the T product are within ± 5% of those used in the R product.

Waiver request of in vivo testing: 2 mg/spray strength, based on (i) acceptable bioequivalence study on the 4 mg/spray strength, and (ii) proportional similarity of the formulations across both strengths.

II. In Vitro Option:

If the T product formulation is Q1 and Q2 the same as the R product formulation, and the nasal spray device (e.g., the pump and actuator design) of the T is appropriate for approval in an ANDA (as demonstrated by comparative analyses further described below), BE can be established solely by in vitro performance tests. FDA recommends that applicants conduct the following in vitro BE studies for each strength on samples from each of three or more batches of the T product and three or more batches of the R product, with no fewer than 10 units from each batch.³ FDA recommends that three primary stability batches be also used to demonstrate in vitro BE. The batches should be prepared from three different batches of the same device (pump and actuator) components:

1. Single actuation content
2. Droplet size distribution by laser diffraction
3. Drug in small particles/droplets
4. Spray pattern
5. Plume geometry

Additional Comments: Refer to the product-specific guidance for Fluticasone Propionate Nasal Spray Metered⁴ for recommendations on design and equivalence criteria for the aforementioned in vitro BE studies, and general recommendations on the conduct of the in vitro BE studies and data submission.⁵

Waiver request of in vitro testing: Not Applicable

Dissolution test method and sampling times: Not Applicable

Additional Information:

Device:

Sponsors should refer to FDA's guidance entitled, *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (January 2017), which provides the Agency's current thinking on the identification and

³ If bioequivalence of the 4 mg/spray strength is acceptable, then drug in small particles/droplets and plume geometry BE tests may not be needed for the 2 mg/spray strength provided the 2 mg/spray product is manufactured without changing the actuator and metering valve or pump (other than diptube, due to different volumes of product or other factors) used in the 4 mg/spray product. With the exception of the reduced testing, the Agency recommends the same protocols and the acceptance criteria used to establish BE of the 4mg/spray product be used for the 2 mg/spray product.

⁴ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM461051.pdf>

⁵ Specific recommendations for in vitro BE testing at various life stages are not relevant for this product, given it is a single-use configuration.

assessment of any differences in the design of the user interface for a proposed generic drug-device combination product when compared to its RLD.

Early in product development and/or prior to the submission of an ANDA, FDA recommends applicants submit to OGD via controlled correspondence and/or a pre-ANDA meeting request, the results of the comparative analyses (e.g., comparative labeling analysis, comparative task analyses, physical comparison of the delivery device constituent part), including an overall assessment of any identified differences between the user interface of the T product when compared to the R product, as described in the guidance referenced above.