Contains Nonbinding Recommendations

Draft Guidance on Sumatriptan Succinate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Powder; nasal

Strength: EQ 11 mg Base

Recommended Studies: In vitro and in vivo studies

FDA recommends the following in vitro or in vivo studies to establish bioequivalence (BE) of the test (T) and reference (R) nasal powders containing sumatriptan succinate.

In Vitro BE Studies

FDA recommends that prospective applicants conduct the following in vitro BE studies 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. FDA recommends that three primary stability batches be also used to demonstrate in vitro BE. The three batches of T product should be manufactured from, at minimum, three different batches of the drug substance and three different batches of device components (e.g., device, nosepiece, capsule). The T product should consist of the final device constituent part and final drug constituent formulation intended to be marketed.

1. Type of study: Single Actuation Content (SAC)
   Design: The SAC test should be performed at the beginning (B), middle (M), and end (E) lifestages of the product,[1] using a compressed air flow rate of 15 L/min, 30 L/min and 45 L/min. The U.S. Pharmacopoeia (USP) <601> Apparatus B or another appropriate apparatus with a compressed air source may be used to determine the SAC using a validated assay. The number of nosepieces used per determination should be one. The number of actuations per determination should be one. The volume of air drawn through the delivery system should be 2 L.

   Equivalence based on: Population bioequivalence (PBE) analysis of SAC. Refer to the product-specific guidance for *Budesonide Inhalation Suspension* for relevant principles regarding PBE analysis procedures.

[1] Based on the labeled number of actuations, the terms, B lifestage, M lifestage, and E lifestage represent the first actuation(s), the actuation(s) corresponding to 50 percent of the labeled number of actuations, and the actuation(s) corresponding to the labeled number of actuations, respectively.

2. Type of study: Particle Size Distribution by Laser Diffraction
Design: Particle size distribution should be determined using laser diffraction or an appropriately validated alternative methodology. Particle size distribution should be measured for fully developed phase only at B and E lifestages using flow rates of 30 L/min and 45 L/min. It is recommended that the studies be performed at one distance within a range of 2 to 7 cm from the nosepiece tip.[2]

Additional comments: Single particle size distribution (D_{10}, D_{50}, D_{90}) and span should be reported based on the volume (mass). Mean D_{10}, D_{50}, and D_{90} values for a given unit can be computed from the mean of up to three consecutive nosepieces from that unit at each lifestage. Span can be computed as $[(D_{90} - D_{10})/D_{50}]$. To assess precision, the data of each nosepiece should also be reported.

Equivalence based on: PBE analysis of D_{50} and span at the one selected distance.

BE data submission recommendations for Particle Size Distribution by Laser Diffraction

- In addition to submission of all raw data, the following supporting documentation for Particle Size Distribution by Laser Diffraction should be provided:
  - Documentation includes instrument output reports and photographic or graphic material as applicable. Documents should be clearly labeled to indicate the product (e.g., T or R), batch number, and testing conditions (e.g., distance, lifestage, delay time), as appropriate.
  - Profiles of particle size and obscuration or percent transmission over the complete life of the single actuation should be submitted.
  - Supporting documentation should include representative copies, preferably electronic, of > 20 percent of the total observations.

Pharmacokinetic (PK) BE Study

3. Type of study: Fasting
Design: Single-dose, two-way crossover
Strength: EQ 11 mg Base
Dose: EQ 22 mg Base of sumatriptan (two nosepieces, one nosepiece per each nostril)
Subjects: Adult males and non-pregnant, non-lactating females, general population

Additional comments: (1) Subjects should adhere to the R product labeling for administration. (2) The analytical method should have sufficient sensitivity to adequately quantify the concentration of sumatriptan in plasma.

[2] The distance between the nosepiece tip and the laser beam should be the same for both T and R products.

Analyte to measure (in appropriate biological fluid): sumatriptan in plasma

Equivalence based on: AUC and C_{max} for sumatriptan. The 90% confidence intervals for the geometric mean T/R ratios of AUC and C_{max} should fall within the limits of 80.00 - 125.00%.

Additional Information

Formulation:

FDA recommends that the T formulation contains identical amount of the identical active drug ingredient[3] in a dry powder form with no excipients as the R formulation.

Device:

Prospective applicants should refer to the FDA guidance for industry entitled, *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*, which, when finalized, will provide the Agency's current thinking on the identification and assessment of any differences in the design of the user interface for a proposed generic drug-device combination product when compared to its RLD.

FDA recommends that prospective applicants consider the following characteristics of the R product in designing the T product:

- Pre-metered single-unit dose capsule-based format
- External operating principles and external critical design attributes of the R product
- Size and shape of the R product
- Number of doses in the R product
- Device resistance of the R product

[3] Refer to 21 CFR 314.3(b) for the definition of pharmaceutical equivalents.