Contains Nonbinding Recommendations

Draft Guidance on Nicotine

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Metered, spray; nasal

Recommended Studies: 2 options: in vitro or in vivo studies

The Agency recommends the following in vitro or in vivo studies to establish bioequivalence (BE) of the test (T) and reference (R) nasal spray containing nicotine.

In vitro option

If the T product formulation is qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the R product formulation, and the nasal spray device (e.g., the pump and actuator design) of the T product is comparable to that of the R product, BE can be established solely by in vitro performance tests. The following in vitro BE tests are recommended:

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

Additional Comments: The above in vitro BE studies should be conducted using at least three batches of each of T and R products with no fewer than 10 units of each batch. Single batch of solution can be split-filled into three equal size sub-lots of product. The sub-lots should be prepared from three different batches of the same device (pump and actuator) components. Refer to the draft product-specific recommendations for fluticasone propionate metered nasal spray[3] for recommendations on design and equivalence criteria for the aforementioned in vitro tests, and general recommendations on the conduct of in vitro bioequivalence studies and data submission.

[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.
[3] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM461051.pdf

In vivo option

If the T product is not Q1 and Q2 the same as the R product, the following study is recommended to document BE of the T product to the R product:

Type of study: Fasting
Design: Single-dose, two-way crossover in-vivo
Strength: 0.5 mg/spray (dose: 1.0 mg, administered as one spray in each nostril)
Subjects: Healthy males and females (nonpregnant), naïve to nicotine-containing products.
Additional Comments: Subjects should adhere to R product labeling for drug product administration. The analytical method should have sufficient sensitivity to adequately quantify the concentration of nicotine in plasma.

Analytes to measure (in appropriate biological fluid): Nicotine in plasma

Equivalence based on: AUC and C_{max} for nicotine. 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

The T product is recommended to deliver the same number of doses as the R product. The device should be similar in shape, size, and external operating principles to ensure substitutability with the R product without additional need to retrain patients upon use of the T product.