Contains Nonbinding Recommendations

Draft Guidance on Cyanocobalamin

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Spray; nasal

Recommended Studies: 2 options: in vitro or 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 sprays containing cyanocobalamin.

In Vitro Option

If the test (T) formulation is qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the reference (R) 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 of the T cyanocobalamin metered nasal spray product to the R cyanocobalamin metered nasal spray product can be established solely through in vitro performance tests in lieu of a pharmacokinetic (PK) BE study. FDA recommends that 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 batches should be prepared from three different batches of the same device (pump and actuator) components. 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

Additional Comments: Refer to the product-specific recommendations for Fluticasone Propionate Nasal Spray Metered[3] 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.

[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/Q2 the same as the R product, the following study is recommended to establish BE between the T and R product:

Type of Study: Fasting
Design: Single-dose, two-way crossover in vivo
Strength: 0.5 mg / spray
Subjects: Males and females (nonpregnant), general population

Additional Comments: Subjects should adhere to the R drug product labeling for administration. Please note that cyanocobalamin is an endogenous compound with a long half-life that is obtained through the diet. ANDA applicants should consider the study design, parameters, and data evaluation (e.g., washout and confinement period, dietary restrictions, and baseline correction) and ensure they are appropriate.

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

Equivalence based on: Baseline-corrected C_{max} and AUC for cyanocobalamin. The 90% confidence interval for the geometric mean T/R ratios of baseline-corrected C_{max} and AUC should fall within the limits of 80.00 – 125.00%.

Additional Information

Device:
Sponsors should refer to FDA's guidance entitled, *Comparative Analyses and Related Comparative Use Human Factors Studies* (January 2017), which provides 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.[4]

Early in product development and/or prior to the submission of an ANDA, FDA recommends applicants submit to OGD via controlled correspondence and/or pre-ANDA meeting request, the results of the comparative analyses (e.g., comparative labeling analysis, comparative task analyses, comparison in the design of the delivery device constituent), including 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.

[4] https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536959.