Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Budesonide

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Aerosol, foam; rectal

Recommended Studies: A combination of in vitro studies and an in vivo study with pharmacokinetic endpoints

To demonstrate bioequivalence for budesonide rectal aerosol, foam, 2 mg/actuation using a combination of in vitro studies and an in vivo study with pharmacokinetic endpoints, the following criteria should be met:

A. The test product should contain no difference in inactive ingredients or in other aspects of the formulation (relative to the reference product) that may significantly affect the local or systemic availability of the active ingredient. For example, if the test and reference products are qualitatively (Q1) and quantitatively (Q2) the same, as defined in the guidance for industry *ANDA Submissions – Refuse-to-Receive Standards* and the criteria below are also satisfied, the bioequivalence of the test product with respect to the reference product may be established using a bioequivalence approach that is a combination of in vitro studies and an in vivo study with pharmacokinetic endpoints.

B. The test and reference products should be physically and structurally similar based upon an acceptable comparative physicochemical characterization of a minimum of three batches of the test product and three batches (as available) of the reference product. The test and reference product batches should ideally represent the product at different ages throughout its shelf life. The comparison of the test and reference products should include characterizations of the following physical and structural attributes:

    i. pH should be evaluated on the dispensed and collapsed foams.

    ii. Weight per volume should be conducted on the uncollapsed foams.

    iii. Delivery amount per dose should be conducted over the entire contents of the canister using the proposed canister and applicator following the approved reference product labeling.

    iv. Comparative canister pressures should be compared between the test and reference drug products.

v. Microscopic birefringence analysis should be conducted on the dispensed foams after complete collapse to determine whether any crystals of undissolved drug form during dispensing.

vi. Time to break analysis should be conducted at 30°C, 33°C, 35°C, and 40°C. Time to break is the time from dispensing to complete foam collapse (i.e., break).

C. The test and reference products should demonstrate bioequivalence based upon an acceptable in vivo pharmacokinetic study with one batch each of the test and reference products, selected from among those batches for which the physical and structural similarity is characterized and compared.

Type of study: Bioequivalence study with pharmacokinetic endpoints
Design: Single-dose, two-way crossover, in vivo study under fasted conditions
Strength: 2 mg/actuation
Subjects: Males and nonpregnant, nonlactating females, general population
Additional comments: None

Analyte to measure: Budesonide in plasma

Bioequivalence based on (90% CI): Budesonide

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: Not applicable

Applicants intending to propose an alternative approach by which to demonstrate bioequivalence should refer to the guidance for industry *Controlled Correspondence Related to Generic Drug Development* and the guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* for additional information describing the procedures on how to clarify regulatory expectations regarding your individual drug development program.

Additional comments regarding the device:

The Agency recommends applicants consider the following characteristics of the reference drug product in designing the test drug product:

- A metered, multi-dose device capable of delivering the same number of doses as the reference drug product
- Similar external design (size, shape, and components) as the reference drug product
- Similar external operating principles as the reference drug product

Applicants should refer to the guidance for industry *Comparative Analyses and Related Comparative Use Human Factors Studies*, 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 reference product.

Early in product development and/or prior to the submission of an abbreviated new drug application (ANDA), the Agency recommends applicants submit to the Office of Generic Drugs 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 test product when compared to the reference product, as described in the guidance referenced above.