Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Budesonide

August 2021

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

This guidance, which interprets the Agency's regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA guidances means that something is suggested or recommended, but not required.

In September 2019, FDA issued a draft product-specific guidance for industry on generic budesonide. We are now issuing revised draft guidance for industry that replaces the previously issued guidance.

Active Ingredient: Budesonide

Dosage Form; Route: Capsule, delayed release; oral

Recommended Studies: Four studies

1. Type of study: Fasting
   Design: Single-dose, partially or fully replicate crossover design in vivo
   Strength: 3 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: Females of reproductive potential should use effective contraception. Alternate study design is acceptable if appropriate. Specific recommendations are provided below.

2. Type of study: Fed
Design: Single-dose, partially or fully replicate crossover design in vivo
Strength: 3 mg
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments: See comments in Study 1.

---

3. Type of study: Fasting, sprinkle-in-applesauce
Design: Single-dose, partially or fully replicate crossover design in vivo
Strength: 3 mg
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments: See comments in Study 1. Mix the drug granules with applesauce and keep the mixture for 30 minutes at room temperature before administration.

Analyte to measure: Budesonide in plasma

Bioequivalence based on (90% CI): Budesonide

Additional comments regarding the bioequivalence study with pharmacokinetic (PK) endpoints:

(1) Applicants may consider using a reference-scaled average bioequivalence approach for budesonide. If using this approach, provide evidence of high variability in the PK parameters (i.e., within-subject variability ≥30%) for the reference product. For general information on this approach, refer to the Progesterone Capsule Guidance for additional information regarding highly variable drugs.

(2) For Studies 1 and 3, submit the following PK parameters: maximum plasma concentration (C_{max}), log-transformed AUC_{0-4}, AUC_{4-t}, and $AUC_{0-\infty}$, where AUC_{0-4} is the area under the plasma concentration vs. time curve from 0 to 4 hours, and AUC_{4-t} is the AUC from 4 hours to the last measurable time point. Applicants should have extensive sampling points around time to maximum plasma concentration (T_{max}) to have accurate estimation of C_{max} and T_{max}, and at least four non-zero measurements of concentration are recommended for each partial AUC. For the fed study, submit the following PK parameters: C_{max}, log-transformed AUC_{0-t} and $AUC_{0-\infty}$. Submit AUC_{0-4} and AUC_{4-t} data as supportive evidence of comparable therapeutic outcome.

---

4. Type of study: In vitro comparative dissolution study
Strength: 3 mg
Apparatus: U.S. Pharmacopoeia (USP) Apparatus 2 (paddle), with capsule sinker
Pretreatment stage: 2 hours in 1000 mL 0.1N HCl at 75 rpm
Evaluation stage: Each of
(1) pH 4.5 acetate buffer at 75 rpm
(2) pH 6.0 phosphate buffer at 75 rpm

(3) pH 6.5 phosphate buffer at 75 rpm
(4) pH 6.8 phosphate buffer at 75 rpm
(5) pH 7.2 phosphate buffer at 75 rpm
(6) pH 7.5 phosphate buffer at 75 rpm

Volume: 1000 mL
Temperature: 37˚C
Sample times: 0.5, 1, 1.5, 2, 2.5, 3, 4, 6 and 8 hours, or as needed for profile comparison
Additional comments: The applicant should use at least 12 dosage units for each of the test and reference products per test.

Additional strengths: Not applicable

Dissolution test method and sampling times (for product specification)**:**
For modified release drug products, applicants should develop specific discriminating dissolution methods. Alternatively, applicants may use the dissolution method set forth in any related official United States Pharmacopeia (USP) drug product monograph, or in the FDA's database, http://www.accessdata.fda.gov/scripts/cder/dissolution/, provided that applicants submit adequate dissolution data supporting the discriminating ability of such a method. If a new dissolution method is developed, submit the dissolution method development and validation report with the complete information/data supporting the proposed method. Conduct comparative dissolution testing on 12 dosage units for each of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

Revision History: Recommended October 2009; Withdrawn January 2015; Revised March 2015, September 2019, August 2021

Unique Agency Identifier: PSG_021324