Draft Guidance on Budesonide

Active Ingredient: Budesonide

Dosage Form; Route: Extended release capsule; oral

Recommended Studies: Three studies

1. Type of study: Fasting
   Design: Single-dose, partially or fully replicate crossover design, in vivo
   Strength: 9 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: Alternate study design is acceptable if appropriate. Specific recommendations are provided below. Female subjects of child-bearing potential should practice abstinence or contraception.

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2. Type of study: Fed
   Design: Single-dose, partially or fully replicate crossover design, in vivo
   Strength: 9 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: See comments above.

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

Bioequivalence based on (90% CI): Budesonide

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

1) Applicants may consider using a reference-scaled average BE approach for PK metrics that exhibit a high variability (i.e., within-subject variability $\geq$ 30%) of the reference product. For general information on this approach, refer to the Progesterone Capsule Guidance for additional information regarding highly variable drugs.

2) For the fasting study, the following PK parameters will be evaluated: Log-transformed area under the plasma concentration time curve from 0 to 4 hours (AUC_{0-4}), AUC from 4 to the last measurable time point (AUC_{4-t}), AUC from 0 hours to the last measurable time point (AUC_{0-t}), AUC from 0 hours extrapolated to infinite time,

and maximum plasma concentration (C_{max}). Applicants should have extensive sampling points around T_{max} (time of maximum plasma concentration observed) to have accurate estimation of C_{max}, and at least four non-zero measurements of concentration are recommended for each partial AUC.

3) For the fed study, the following PK parameters will be evaluated: Log-transformed AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}. Submit AUC_{0-4} and AUC_{4-t} data as supportive evidence of comparable therapeutic outcome.

3.	Type of study:	In vitro comparative dissolution study
	Strength:	6 mg and 9 mg
	Apparatus:	United States Pharmacopeia (USP) Apparatus 2 (paddle), with capsule sinker
	Pretreatment Stage:	2 hours in 1000 mL 0.1 N 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:	37ºC
	Sampling times:	15 mins, 20 mins, 30 mins, 45 mins, 1 hour, 2 hours, 4 hours, 6 hours, and 8 hours or as needed for profile comparison

Additional comments: Use at least 12 dosage units per test. The f2 metric should be used to compare dissolution profiles.

Additional strength: Bioequivalence of 6 mg strength to the corresponding reference product strength may be demonstrated based on principles laid out in the FDA guidance on "Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA."

Dissolution test method and sampling times:
For product specification: for modified release drug products, FDA recommends that applicants develop specific discriminating dissolution methods. Applicants may also use the dissolution method set forth in any related official USP drug product monograph, or in the FDA's database (available at 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 for the modified release drug product, FDA recommends that the submission includes the dissolution method development and validation report with the complete information/data supporting the proposed method. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

Due to a concern of dose dumping of drug from this drug product when taken with alcohol, the Agency currently requests that additional dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: Volume: 1000 mL 0.1 N HCl, USP apparatus 2 (paddle) at 75 rpm, with and without alcohol;

Test 1: Twelve units tested according to the proposed method, with data collected every 15 minutes for a total of 2 hours.

Test 2: Twelve units analyzed by substituting 5% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours.

Test 3: Twelve units analyzed by substituting 20% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours.

Test 4: Twelve units analyzed by substituting 40% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours.

Both test and RLD products should be tested accordingly and data should be provided on individual unit, means, range and %CV on all strengths.