Contains Nonbinding Recommendations

Draft Guidance on Prednisolone Acetate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Suspension/drops; ophthalmic

Strength: 1%

Recommended Studies: Two options: in vitro or in vivo study

I. In vitro option

To qualify for the in vitro option for this drug product all of the following criteria should be met:

i. The test and reference listed drug (RLD) formulations are qualitatively[1] and quantitatively[2] the same (Q1/Q2).[3]

ii. Acceptable comparative physicochemical characterization of the test and Reference Standard (RS) products. The comparative study should be performed on at least three batches of both the test and RS products and should include:[4]
- Comparable appearance, pH, specific gravity, osmolality, surface tension, buffer capacity, and viscosity
- Comparable soluble fraction of prednisolone acetate in the final drug product
- Comparable drug particle size distribution. The particle size distribution should be compared using PBE (95% upper confidence bound) based on D_{50} and SPAN [i.e. $(D_{90}-D_{10})/D_{50}$)]. The applicant should provide no fewer than ten data sets from three different batches of both the test and reference products for PBE analysis. Full profiles of the particle size distributions should also be submitted for all samples tested.

[1] Q1 (qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference product.
[2] Q2 (quantitative sameness) means that the concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the reference listed drug product.
[3] For ophthalmic drug products, FDA has determined that, as a scientific matter, any qualitative or quantitative deviations from the RLD, even in inactive ingredients listed in 21 CFR 314.94(a)(9)(iv), should be accompanied by an appropriate in vivo BE study or studies. Guidance for industry *ANDA Submissions–Refuse-to-Receive Standards*.
[4] The manufacturing process used for the exhibit batches should be reflective of the process to be utilized for commercial batches.

iii. Acceptable comparative in vitro drug release of prednisolone acetate from the test and RS formulations. The methodology used for in vitro drug release testing should be able to discriminate the effect of process variability in the production of the test formulation.

II. In vivo option

1. Type of study: Bioequivalence study with pharmacokinetic (PK) endpoints
Design: Single-dose, crossover or parallel design, in vivo in aqueous humor
Strength: 1%
Subjects: Patients undergoing indicated cataract surgery and scheduled to receive ophthalmic corticosteroids just prior to their eye surgery
Additional comments: Specific recommendations are provided below.

Analytes to measure (in appropriate biological fluid): Prednisolone acetate in aqueous humor

Bioequivalence based on (90% CI): Prednisolone acetate

Additional comments regarding the in vivo pharmacokinetic study in aqueous humor:

1. The study is conducted in patients undergoing indicated cataract surgery and scheduled to receive ophthalmic corticosteroids just prior to their eye surgery. A single dose of the test or reference product is instilled into the inferior cul de sac of the eye prior to cataract extraction. Only one single sample of aqueous humor is collected from one eye of each patient, at one assigned sampling time point.

   Applicant may consider a parallel design for the bioequivalence study. If using a parallel study design, please note that each patient should receive only one treatment, test or reference, but not both. Alternatively, a crossover study design may be used in patients undergoing indicated cataract surgery for both eyes. When a crossover study design is used, each patient should receive both test and reference treatments. The wash-out period for the crossover study should not exceed 35 days.

2. To demonstrate bioequivalence, an adequate estimation of the rate (Cmax) and extent (AUC) of prednisolone acetate absorption is needed. The following statistical model is recommended:

   The mean AUCt for each product and time point t of measurement is calculated by using the mean concentrations ($\overline{C_t}$) at each time point t to derive the mean profile for each product. The trapezoid rule, mean AUCt is computed as the weighted linear combination of these mean concentrations at each time point through time t. The AUCt is the area under the concentration - time curve from zero to the time t. Generally, we have j concentration measurements at times t1 < t2 < t3 .., < tj (t1 > 0).

AUC_{t_j} is calculated for time from 0 to tj as:

$$AUC_{t_j} = t_1 \times \overline{C_{t_1}} / 2 + \sum_{i=1}^{j-1} \left(\overline{C_{t_i}} + \overline{C_{t_{i+1}}} \right) \times \left(t_{i+1} - t_i \right) / 2$$

The ratio (R_t) of AUC_t from the test product to AUC_t from the reference product is used to assess bioequivalence for each time t of interest. Estimation of the standard deviation(s) of R_t may be done via the bootstrapping technique or a parametric method.

Bioequivalence is supported if the 90% confidence interval for R_t ($R_t \pm 1.645\ s_t$) lies within (0.8, 1.25). The bootstrapping technique or a parametric method can be used to determine Cmax and Tmax and assess bioequivalence for Cmax.

3. The study design and statistical analysis plan should be specified a priori in the protocol. If bootstrapping is used for estimation, all details of the computations, including computation code should be submitted in the application.

4. Generally, a drug product intended for ophthalmic use contains the same inactive ingredients and in the same concentration as the RLD. For an ophthalmic drug product that differs from the RLD in preservative, buffer, substance to adjust tonicity, or thickening agent [as permitted by the chemistry, manufacturing, and controls (CMC) regulation for abbreviated new drug applications (ANDAs), 21 CFR 314.94(a)(9)(iv)], the regulation specifies that the applicant must identify and characterize the differences and provide information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.