FDA Perspective on Current Challenges with the Use of Pharmacodynamic Endpoint Evaluation of Bioequivalence of Topical Dermatologic Corticosteroids

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Purpose
Topical dermatologic corticosteroids are locally-acting drug products which are not intended for systemic absorption. The FDA issued the Guidance on Topical Dermatology Corticosteroids: In Vivo Bioequivalence in 1995 for approval generic versions of topical corticosteroids. This guidance describes the vasoconstrictor assay, a surrogate marker for clinical efficacy by using skin blanching as the pharmacodynamic endpoint. A pilot dose duration-response study and pivotal bioequivalence (BE) study is recommended. Data analysis of the vasoconstrictor response is based on an Emax (maximal effect) model. The comparison of the generic and reference product in the pivotal BE study is conducted based on the ED50 (half-maximal effect) determined in the pilot study. The objective of this study is to evaluate challenges to estimate ED50 values.

Methods
The four current challenges to estimating the ED50 values investigated were as follows: 1) appropriate selection of dose-duration times for estimation ED50 value, 2) impractically short ED 50 values, 3) low Area under the Effect Curve (AUEC) for doses and truncation of dose duration-response and 4) bio-phasic dose duration-response. Based on available data to the Agency, the evaluated drug products were: 1) Fluticasone Propionate Lotion; 2) Clobetasol Propionate Lotion; 3) Desoximetasone Ointment; and 4) Clobetasone Butyrate Cream.

Results
The results indicated potency is a major factor for all challenges. First, selection of dose-duration times: For high-potency corticosteroids, inclusion of early time points is necessary. Whereas, for low-potency drug products, longer-duration times along with occlusion may be necessary to reliably estimate ED50 values. Second, shorter ED values can yield impractical dose durations to be used in the pivotal BE study. Third, low potency corticosteroids may produce variable PD response that may include background noise and generate non-meaningful AUEC and ED50 values. And fourth, the normal Emax model fit may over-estimate the early dose duration times and under-estimate the later dose duration times. An alternative fitting method and unusual data should be further investigated.

Conclusion
The overall potency, formulation and dosage form will have an impact on the outcome of the studies. The design of the pilot study, along with the evaluation of the population modeling will impact the estimation of the ED50 value.