Evaluation of Quality of Submission of Vasoconstrictor Assay Bioequivalence Studies for Topical Dermatologic Corticosteroid Products in Abbreviated New Drug Applications (ANDAs)

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Purpose
The US Food and Drug Administration (USFDA) recommends the vasoconstrictor assay by using skin blanching as the pharmacodynamic endpoint for evaluating bioequivalence (BE) of topical corticosteroid drug products. Per the current guidance for industry entitled Guidance Topical Dermatologic Corticosteroids: In Vivo Bioequivalence (issued in 1995), for approval of generic versions of most topical corticosteroids, a pilot dose duration-response study and pivotal BE study are recommended. Data analysis of the vasoconstrictor response is based on an Emax (maximal effect) model. Over the years, the Agency has received a number of inquiries related to the submission format, study design, method for estimating ED50 (half-maximal effect) value in the pilot dose-response study and non-compliance responder criteria in the pivotal BE study. The aim of this project is to summarize the most common deficiencies in vasoconstrictor assay BE studies submitted for topical corticosteroid products in ANDAs.

Methods
The survey was conducted on 88 ANDAs with vasoconstrictor BE studies submitted from January 1992 to April 2015 for different topical corticosteroid products. The evaluated drug products were: 1) Fluticasone Propionate Lotion; 2) Clobetasol Propionate Lotion; 3) Desoximetasone Ointment; 4) Clobetasone Butyrate Cream; and 5) Clocortolone Pivalate Cream. The selected drug products ranged from low to high potency, and varied based on dosage form. We analyzed the quality of the BE studies in five critical aspects: 1) appropriate study design for the pilot and pivotal BE studies; 2) correct method for estimating ED50 in the pilot dose-duration response study; 3) correct selection of responders in the pivotal BE study; 4) complete pre-study vasoconstrictor assay method validation and 5) organization of the content of the BE study information within each ANDA submission.

Results
We determined that potency is one of the most critical factors influencing the design of the BE studies for topical corticosteroids. Among the eighty-eight (88) ANDAs, seventy-eight (78) applications used the appropriate study design for both the pilot dose-duration response study and pivotal BE study, with respect to occlusion and dose-duration times. For six (6) applications of low potency drug products, a modified study design with occlusion of the application sites was employed. We determined that the occlusion of the sites for the studies in these six applications was acceptable based on the potency of the drug product. The sponsors also provided evidence to demonstrate the great difficulty in obtaining measurable vasoconstrictor response, and lack of consistency and reproducibility in response data, under non-occluded conditions. In order to accurately estimate the ED50 values in the pilot dose-duration response study, inclusion of early dose-duration times is necessary for a high potency drug product. It was observed that for over 85% of the applications (representing 75 of the identified ANDAs), the ED50 values were correctly calculated. Of note were two special cases with unusual model fitting, namely, bi-phasic dose response and linear dose response curves, reported in the ANDA submissions. The possible alternative fitting method and unusual data are being evaluated. In most cases, the sponsors correctly selected the appropriate responders in the pivotal BE study. Only 10 of the identified applications (represents 11%) initially failed to be compliant with the responder criteria recommended in the current BE guidance.

Although the overall conduct of the BE studies were acceptable, there were two (2) common areas in the submission that prompted the FDA to request additional information from the sponsors. These were pre-study dermal assessment data for method validation, and the overall quality of the submission. For 25% of the applications, the submission of the pre-study dermal assessment was not present or incomplete in the original submissions. Usually lacking were the data for between-subject precision, between- and within-site precision, between- and within-operators precision, or between- and within- instrument precision. Lastly, the overall quality of the ANDA submission was greatly impacted by failure to follow the current Agency guidance and/or failure to provide missing information.

Conclusion
The potency, formulation and dosage form were important factors in determining appropriate study designs. While the applicants were able to conduct appropriately designed studies, the quality of vasoconstrictor assay BE study submissions is still an issue. We have developed e-CTD formatted summary tables for improvement of the study submission quality and review efficiency. These summary table templates are published at the USFDA public website http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM379421.pdf. Pre-ANDA communication from sponsors regarding alternative data modeling methods or study designs may be necessary to facilitate the review process and reduce review and submission cycles.