How comparative clinical endpoint bioequivalence studies facilitate the development of generic topical drug products

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INTRODUCTION

The Office of Generic Drugs (OGD) ensures high-quality, affordable generic drugs are available to the American public. Generic drugs account for approximately 90% of prescriptions filled in the United States.[1] Increasing the availability of generic drugs, including those for dermatological diseases, helps make treatments more affordable, allowing increased access to medications for patients. To support generic drug development, OGD publishes product-specific guidances (PSGs) describing the Agency's current thinking on the appropriate methodologies to demonstrate bioequivalence (BE) of prospective generic drugs to their respective brand name drugs (reference listed drugs (RLDs)).

For topical products applied to the skin, there are four common BE approaches (Figure 1). While certain BE approaches may be applicable to a specific subset of prospective generic drugs, such as those with a specific formulation, product class, or dosage form, comparative clinical endpoint BE (CCEPBE) studies can be used to support a demonstration of BE for all types of topical products. The purpose of the current work is to summarize OGD's consistent recommendations for developing high-quality generic topical products applied to the skin using CCEPBE.

METHODS

The total number of RLD products for which a PSG could be developed was obtained from the FDA's Orange Book[2] (through May 2023) by filtering the list of approved drug products by route of administration (topical only) and RLD status.

The number of PSGs for topical products (through May 2023) that are currently available on the FDA's PSG for Generic Drug Development website[3] were classified based on the recommended BE approaches. A PSG that covers multiple strengths of the same brand name product were included only once in the analysis.

The number of generic topical drug products applied to the skin that were approved in Fiscal Year (FY) 2022 (October 1, 2021 to September 30, 2022) were obtained from the FDA's Orange Book. The BE approach used to support to support the approval of the generic drug product was determined through internal data sources.

CONCLUSIONS

The recommendations within PSGs for topical drug products applied to the skin comprehensively and consistently summarizes OGD's current thinking for design and conduct of the CCEPBE studies (that are product specific), thus increasing the efficiency of drug development programs. CCEPBE study, along with other BE approaches, serve an essential role to support the approval of generic topical drug products, leading to increased availability of high-quality generic drugs for patients.

REFERENCES [1] U.S. Food and Drug Administration, Office of Generic Drugs website, https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/office-generic-drugs [2] Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations website, https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book [3] Product-Specific Guidances for Generic Drug Development website, https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm

RESULTS

How generic topical products demonstrate BE

Comparative clinical endpoint BE (CCEPBE) study

- In vivo BE study with clinical endpoints comparing the efficacy of a prospective generic product and the RLD, and both products are assessed to be superior compared to a placebo
- Can be used for: Majority of topical products
- 60% of all PSGs for topical products applied to the skin include a CCEPBE study as a BE approach

Characterization-based BE approach

- Combination of in vitro and, in some cases, in vivo BE studies comparing formulation, microstructure, and performance of the prospective generic product and the RLD
- Can be used for: Semisolid (e.g., gels, creams, etc.) topical products with certain formulations
- 33% of all PSGs for topical products applied to the skin include a characterization-based BE approach

Vasoconstrictor study

- In vivo clinical BE study comparing the pharmacodynamic effect (i.e., skin blanching) of the prospective generic product and the RLD
- Can be used for: Corticosteroid products
- 26% of all PSGs for topical products applied to the skin include a vasoconstrictor study

Waiver of in vivo BE studies

- Comparison of the formulation and/or dosage form of the prospective generic product and the RLD
- Can be used for: Simple topical products (e.g., solutions)
- 24% of all PSGs for topical products applied to the skin include a waiver of in vivo BE studies or basic physicochemical and structural characterization studies

Figure 1. Common BE approaches for topical products applied to the skin. OGD has published 221 PSGs for topical products as of May 2023.[3]

❖ Available BE approaches for a model disease state (psoriasis)

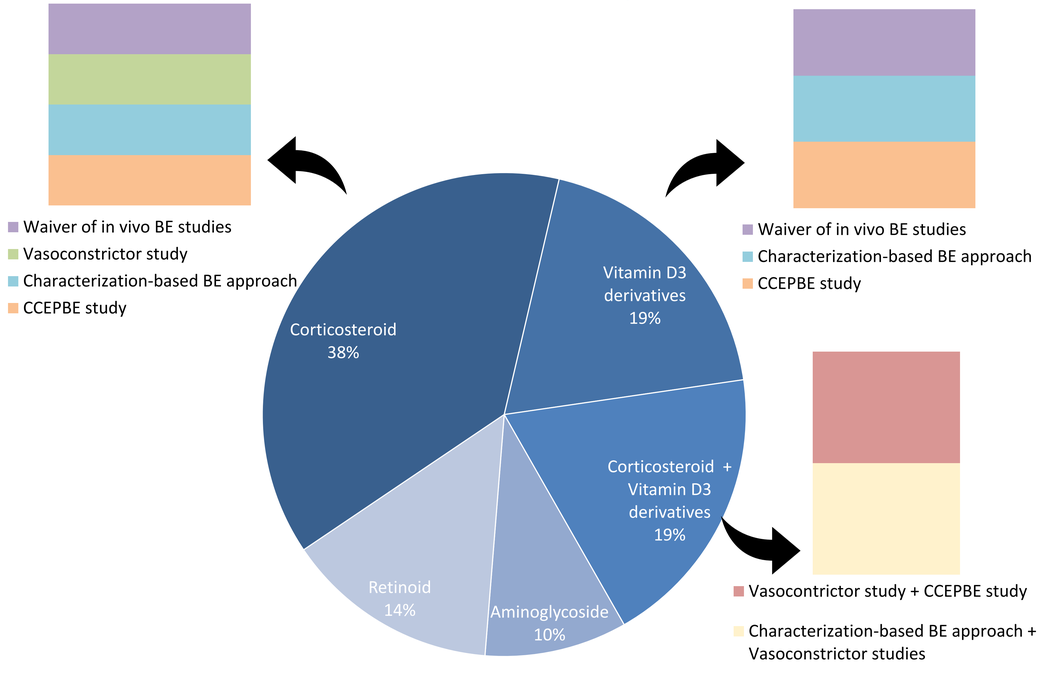

Figure 3. Assessment of the available topical treatments and recommended BE approaches for a model disease state (psoriasis). Center: Distribution of drug classes of topical products indicated for the treatment of psoriasis that have an available PSG (n=21 RLD products). Left/Right: Types of BE approaches recommended in PSGs for topical products indicated for the treatment of psoriasis by drug class.

❖ Comparative clinical endpoint BE (CCEPBE) study recommendations

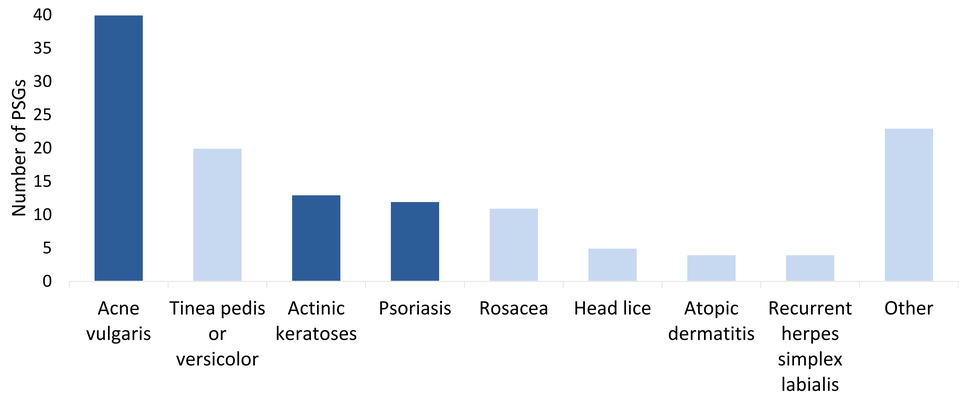

Figure 2. Number of PSGs that recommend a CCEPBE study based on the study population recommended in the PSG (n=132 PSGs). Disease states that are aligned with the International Dermatology Outcome Measures (IDEOM)'s focus work groups are shown in dark blue. The "other" group includes disease states/indications with ≤3 PSGs (e.g., impetigo, hair loss, mycosis fungoides, etc.).

Table 1. Primary endpoint(s) recommended as part of CCEPBE study for disease states that are aligned with IDEOM's focus groups

Disease state	Primary endpoint(s) generally recommended for a CCEPBE study
Acne	• Mean percent change from baseline to end of the study in the inflammatory (papules and pustules) lesion count • Mean percent change from baseline to end of the study in the non-inflammatory (open and closed comedones) lesion count
Actinic keratoses	Proportion of subjects with treatment success (100% clearance of all lesions within the treatment area) at a specified time after completion of the study (e.g., 30 days after completion of treatment)
Psoriasis	• Proportion of subjects with treatment success (defined as absent or very mild disease, a score of 0 or 1, within the treatment area) on the Physician's Global Assessment (PGA) at the end of the study • Proportion of subjects with clinical success (defined as absent or mild, a score of 0 or 1, at the target lesion site) on the Psoriasis Area Severity Index (PASI) at the end of the study

❖ BE approaches utilized in approved ANDAs (FY 22)

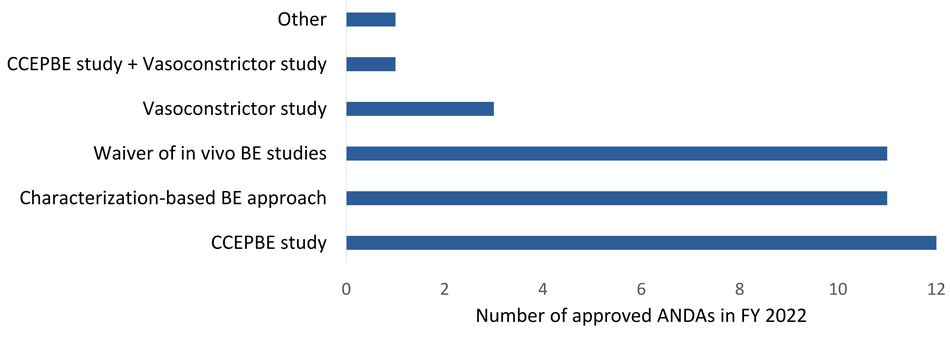

Figure 4. BE approaches utilized to support the approval of generic topical drug products in FY 2022 (n=39 approved generics).