Current methods for assessing bioequivalence of drug products applied to the skin – a US FDA perspective

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INTRODUCTION

The Office of Generic Drugs (OGD) at the U.S. Food and Drug administration (FDA) 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). A commonly recommended BE approach for topical products applied to the skin are comparative clinical endpoint bioequivalence (CCEPBE) studies, in which the efficacy of the prospective generic product and the RLD are compared, and both products are assessed to be superior compared to a placebo (Figure 3). In recent years, OGD has begun recommending efficient characterization-based approaches for generic topical drug products applied to the skin within its PSGs. 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 various BE approaches.

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 (Figure 4).

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 the approval of the generic drug product was determined through internal data sources (Figure 5).

RESULTS

How generic topical products demonstrate BE

Comparative clinical endpoint BE (CCEPBE) study

- In vivo study 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)

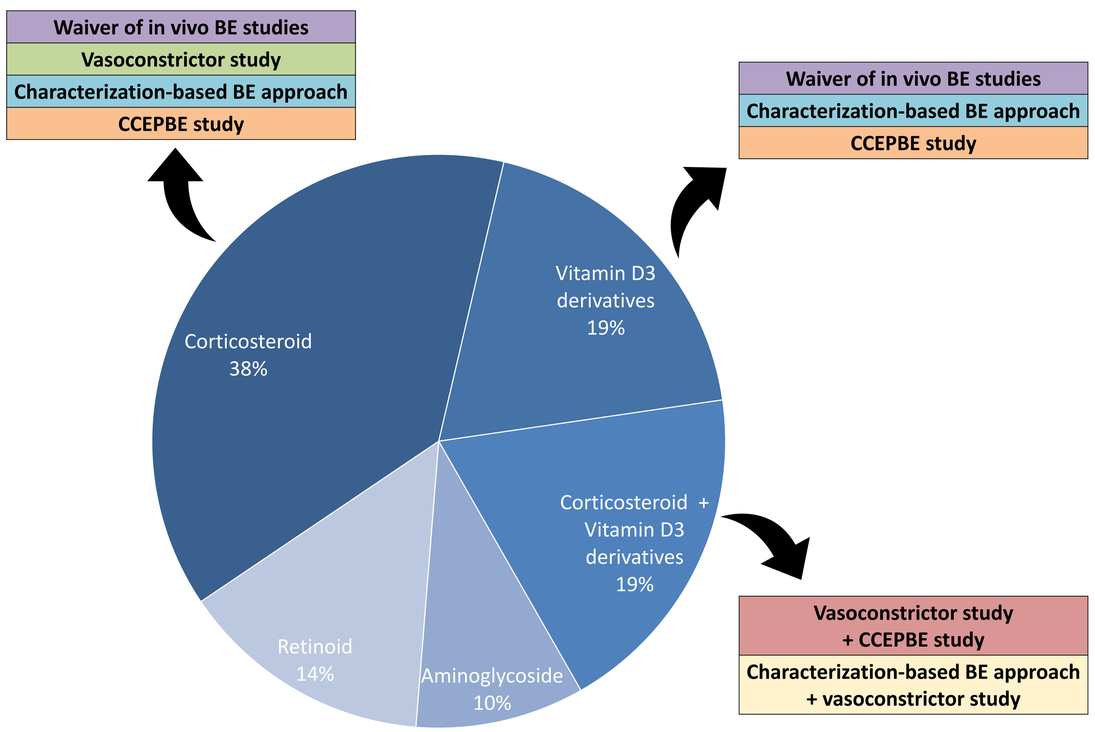

Figure 2. Assessment of the available topical treatments and recommended BE approaches for a model disease state (psoriasis). Center: Distribution of drug classes of topical products indicated for the treatment of psoriasis that have an available PSG as of May 2023 (n=21 RLD products). Left/Right: Types 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

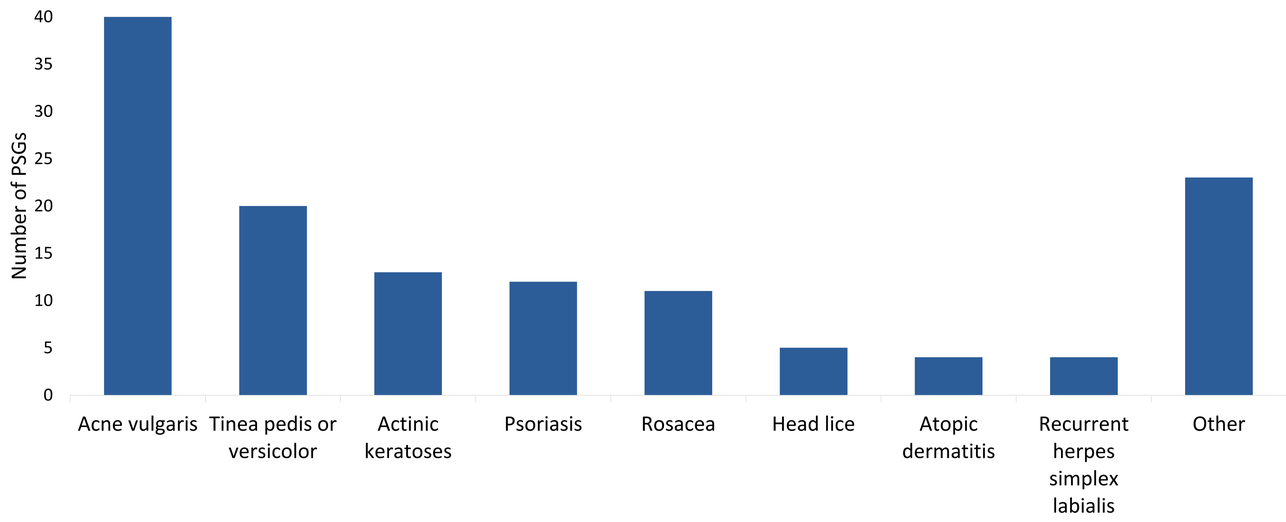

Figure 3. Number of PSGs that recommend a CCEPBE study based on the study population recommended in the PSG as of May 2023 (n=132 PSGs). The "other" group includes disease states/indications with ≤3 PSGs (e.g., impetigo, hair loss, mycosis fungoides, etc.).

❖ Characterization-based BE approaches recommendations

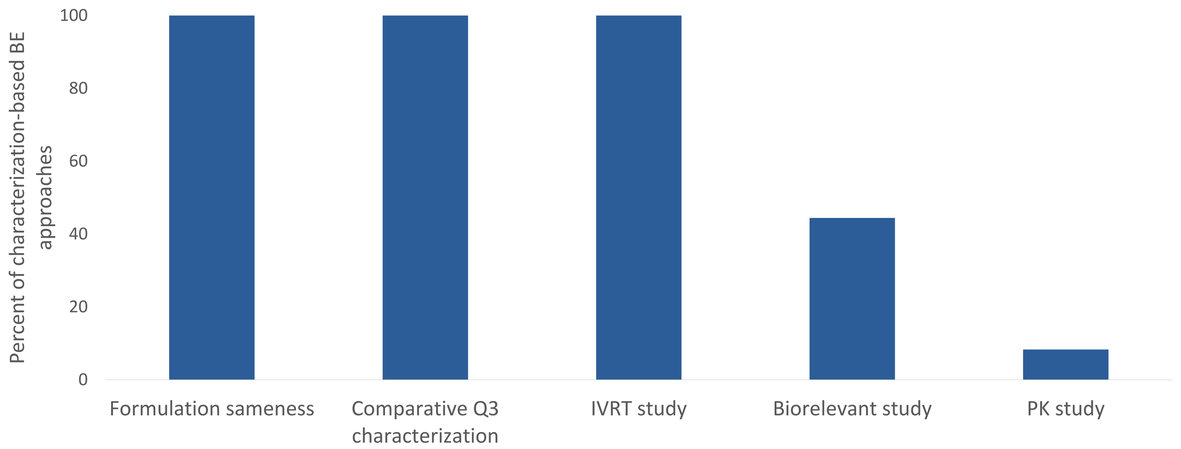

Figure 4. Percent of PSGs that include various components of a characterization-based BE approach as of May 2023 (n=72 PSGs with characterization-based BE approaches). The combination of components that are recommended as part of a characterization-based approach often depend on the complexity of the product (e.g., dosage form) and the site/mechanism of action of the drug product. "Biorelevant study" include in vitro permeation test (IVPT) studies and ex vivo pediculicide hair tuft assays. Q3: Physicochemical and structural attribute; IVRT: In vitro release test

❖ BE approaches utilized in approved ANDAs (FY 22)

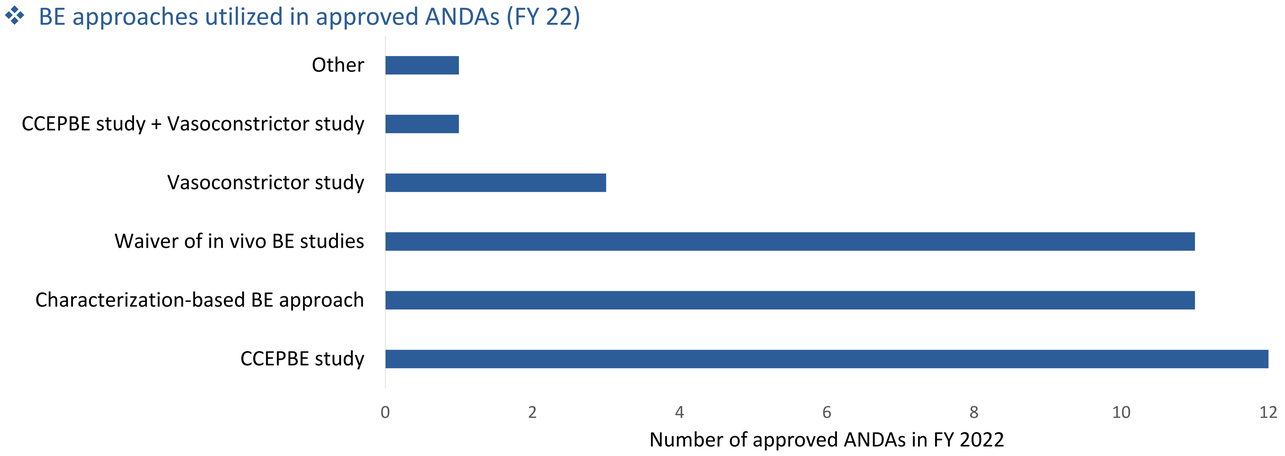

Figure 5. BE approaches utilized to support the approval of generic topical drug products in FY 2022 (n=39 approved generics).

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 BE studies (that are product specific), thus increasing the efficiency of drug development programs. CCEPBE studies and characterization-based BE approaches, along with other BE approaches, serve an essential role to support the development and 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

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