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Bioequivalence approaches utilized in generic drug applications for topical drug products applied to the skin

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PURPOSE

The Office of Generic Drugs (OGD) at the U.S. Food and Drug Administration ensures high-quality, affordable generic drugs are available to the American public. Historically, there have been three types of bioequivalence (BE) approaches used to support generic drug approval for topical drug products applied to the skin: comparative clinical endpoint (CCEP) BE studies, vasoconstrictor (VC) studies, or a waiver of in vivo BE studies. Currently, OGD recommends characterization-based BE approaches as an alternative, efficient method to support a demonstration of BE for topical products. The purpose of this work is to summarize the distribution of BE approaches utilized in abbreviated new drug applications (ANDAs) for topical products received during fiscal years (FYs) 2018 to June 2024 and how the approaches have contributed to generic drug approval.

METHODS

In this work, received ANDAs, ANDA status, and the BE approach used in each ANDA were obtained from the Agency's internal databases. Received ANDAs for the topical route of administration were defined as those submitted to the Agency between FY 2018 and partial FY 2024 (October 1, 2018-June 30, 2024) that did not have a refuse-to-receive or unacceptable submission status determination. ANDA application status in the current work were summarized for the received ANDAs (withdrawn ANDAs were excluded from the application status analysis) as of June 30, 2024. Within the scope of this work, ANDAs with an approved or tentative approval status were categorized as approved ANDAs. ANDAs with a pending or complete response status were categorized as pending ANDAs. The application status (e.g., approved, pending, etc.) analysis is based on the FY that the ANDA was received.

The BE approach used in the received ANDAs were categorized into the four most common BE approaches: characterization-based BE approach, CCEP BE study, VC study, and waiver of in vivo BE studies. ANDAs that only conducted an in vivo pharmacokinetic (PK) BE study were not categorized into these four BE approaches and are outside the scope of the current analysis. ANDAs using a combination of in vivo BE approaches were categorized into the least efficient in vivo BE approach (e.g., ANDAs that conducted both CCEP BE and VC studies were categorized into the CCEP BE group). ANDAs that included physiochemical and structural (Q3) characterization in addition to a CCEP BE or VC study were categorized into the characterization-based BE approach group.

RESULTS

Approaches to support an assessment of BE of topical generic drug products

Comparative clinical endpoint (CCEP) BE study	Vasoconstrictor (VC) study	Waiver of in vivo BE studies	Characterization-based BE approach
• In vivo BE study comparing the efficacy of a prospective generic product and the reference standard (RS), and both products are assessed to be superior compared to a placebo • Can be used for: Majority of topical products	• In vivo clinical BE study comparing the pharmacodynamic effect (i.e., skin blanching) of the prospective generic product and the RS • Can be used for: Corticosteroid products	• Comparison of the formulation and/or dosage form of the prospective generic product and the RS • Can be used for: Simple topical products (e.g., solutions)	• Combination of in vitro and, in some cases, in vivo BE studies comparing formulation, microstructure, and performance of the prospective generic product and the RS • Can be used for: Semisolid (e.g., gels, creams, etc.) topical products with certain formulations

Figure 1. Common BE approaches for topical products applied to the skin.

Components of a characterization-based BE approach commonly utilized for topical drug products

- "No significant difference" in formulation between the prospective generic product and RS
- Comparative assessment of the microstructure of the prospective generic product and RS
- In vitro release test (IVRT) for comparison of product performance between the prospective generic product and RS
- In vitro permeation study (IVPT) for comparison of product performance between the prospective generic product and RS
- In vivo systemic PK BE study for comparison of systemic bioavailability between prospective generic product and RS

Figure 2. Components of a characterization-based BE approach commonly utilized for topical drug products applied to the skin. IVPT and PK BE studies are typically recommended for a subset of topical drug products depending on the complexity and/or site of action of the drug product.

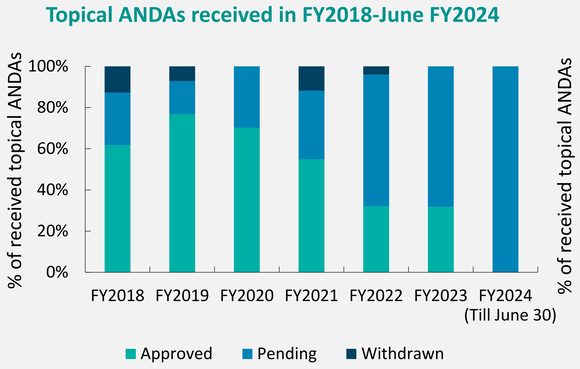

Figure 3[a]. Topical ANDAs received between FY 2018 - FY 2024 by application status (as of June 30, 2024). Bars represent ANDAs received with a given application status normalized by the number of topical ANDAs received in a given FY. ANDAs with an approved or tentative approval status were categorized as approved ANDAs. ANDAs with a pending or complete response status were categorized as pending ANDAs.

[a] Partial FY 24 data (October 1, 2024-June 30, 2024) is shown in the figure.

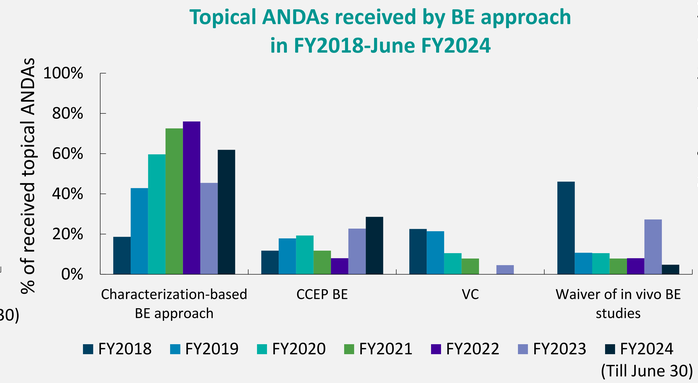

Figure 4[a]. Topical ANDAs received between FY 2018 - FY 2024 (as of June 30, 2024) by the four most common BE approaches for topical products. Bars represent ANDAs received using a given BE approach normalized by the number of topical ANDAs received in a given FY.

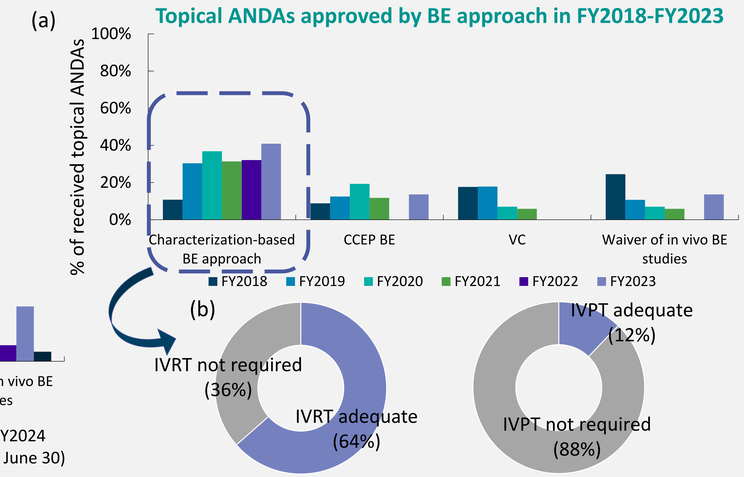

Figure 5. (a) Approved topical ANDAs received between FY 2018-FY 2023 by the four most common BE approaches for topical products. Bars represent approved ANDAs using a given BE approach normalized by the total number of ANDAs received in a given FY. (b) Use of an IVRT study (left) or IVPT study (right) as part of a characterization-based BE approach in approved ANDAs.

CONCLUSION

These data suggest the generic drug industry has generally adopted characterization-based BE approaches in topical ANDAs, and OGD has begun approving topical ANDAs that have utilized this approach. 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.

ACKNOWLEDGEMENTS AND DISCLAIMER

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