# Current Bioequivalence Approaches Utilized in Generic Drug Applications For Topical Drug Products Applied to the Skin

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## INTRODUCTION

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, three types of bioequivalence (BE) approaches were used to support generic drug approval for topical 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 2023 and how the approaches have contributed to generic drug approval.

## METHODS

Received ANDAs, ANDA status, and BE approach used in each ANDA were obtained from the Agency's internal data sources. Received ANDAs for the topical route of administration were defined as those submitted between FY 2018 and FY 2023 (10/01/2018-9/30/2023) 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 ANDA application status in the current work were summarized for the received ANDAs (withdrawn ANDAs were excluded from the application status analysis) as of February 28, 2024. 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, VC, and waiver of in vivo BE studies. ANDAs that only conducted an in vivo 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 a 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 supporting an assessment of BE of topical generic drug products

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| **Comparative clinical endpoint BE (CCEP BE) study** | • 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<br>• Can be used for: Majority of topical products |
| **Vasoconstrictor study** | • In vivo clinical BE study comparing the pharmacodynamic effect (i.e., skin blanching) of the prospective generic product and the RS<br>• Can be used for: Corticosteroid products |
| **Waiver of in vivo BE studies** | • Comparison of the formulation and/or dosage form of the prospective generic product and the RS<br>• Can be used for: Simple topical products (e.g., solutions) |
| **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 RS<br>• 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.

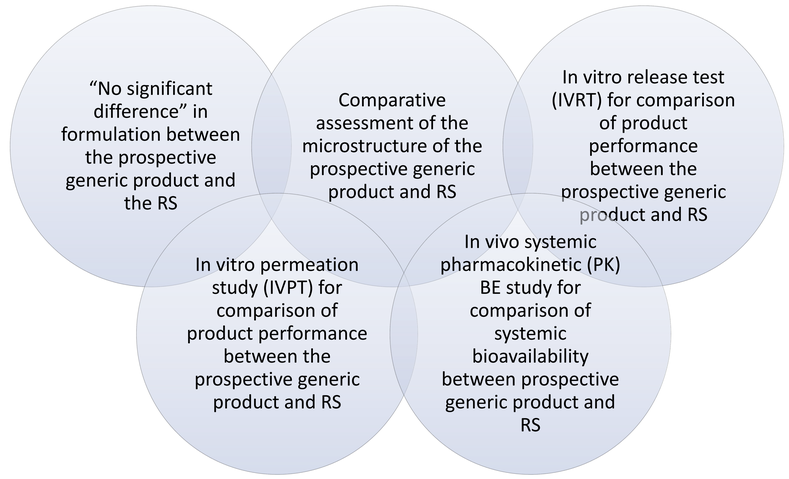


**Figure 2**. Components of a characterization-based BE approach commonly utilized for topical drug products applied to the skin. Components in the top row are recommended as part of the characterization-based BE approaches for all products; components in the bottom row are recommended for a subset of topical drug products depending on the complexity and/or site of action of the drug product.

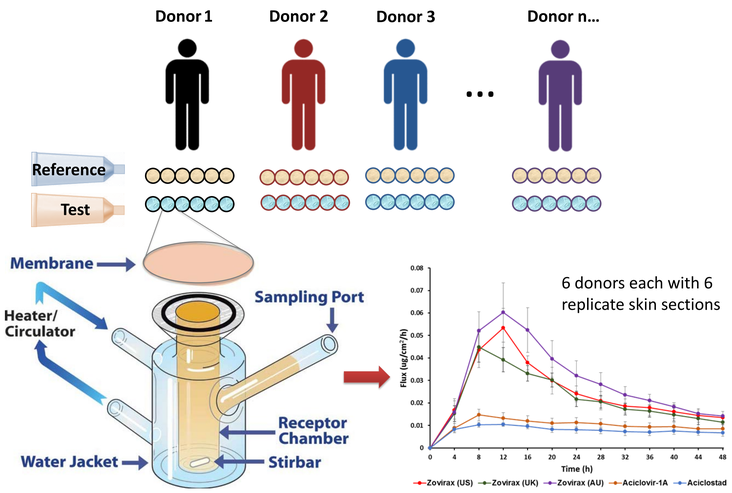


**Figure 3.** Illustration of IVPT study design to compare the in vitro product performance between a prospective generic product (test) and RS (reference). Data courtesy of Dr. Narasimha Murthy, Grant U01FD005233

### ❖ Received and approved ANDAs for the topical route of administration

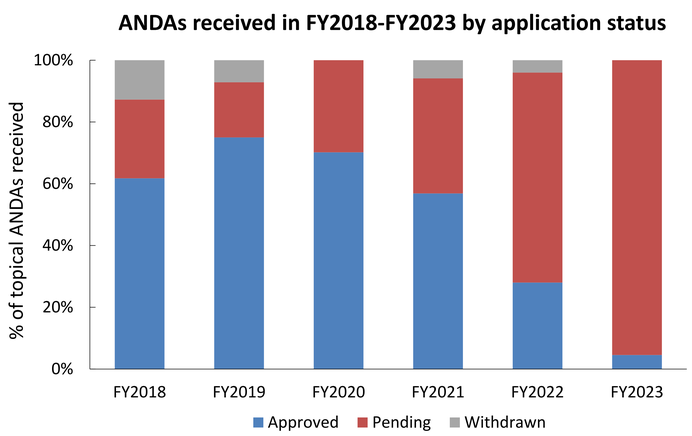


**Figure 4**. Topical ANDAs received between FY 2018-FY 2023 by application status (as of 02/28/2024). Bars represent ANDAs received with a given application status normalized by the number of topical ANDAs received in a given FY. ANDAs with an approved or tentative approval status were categorized as approved ANDAs. ANDAs with a pending or complete response status were categorized as pending ANDAs.

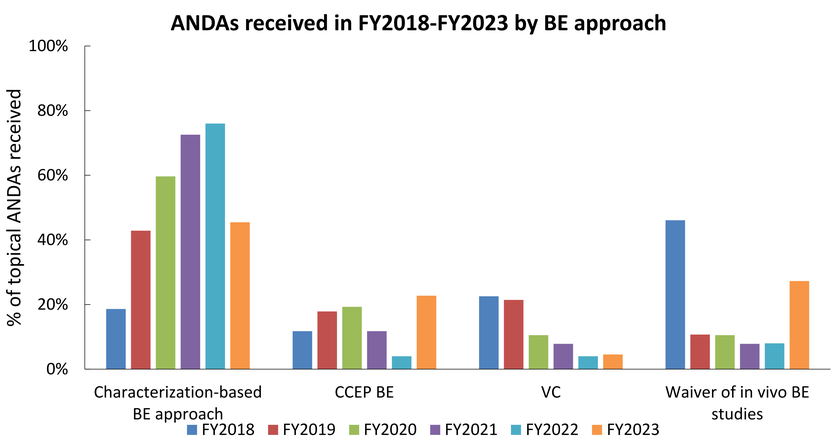


**Figure 5.** Topical ANDAs received between FY 2018-FY 2023 by the four most common BE approaches for topical products. Bars represent ANDAs received using a given BE approach normalized by the number of topical ANDAs received in a given FY.

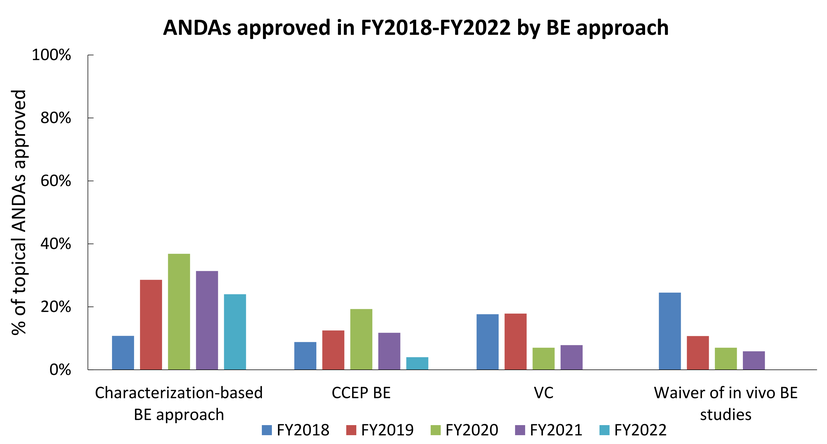


**Figure 6**. Approved topical ANDAs received between FY 2018-FY 2022 by the four most common BE approaches for topical products (as of 02/28/2024). Bars represent approved ANDAs using a given BE approach normalized by the total number of ANDAs received in a given FY.

## CONCLUSIONS

The number of received ANDAs using efficient characterization-based BE approaches has generally increased since FY 2018. Among the approved ANDAs received between FY 2018 and FY 2022, the characterization-based BE approach was primarily used among the four most common BE approaches, and the percent of approved ANDAs that used this approach has increased since FY 2018. CCEP BE 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.

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