Strategic analysis of the roadmap for implementing characterization-based bioequivalence approaches in product-specific guidances for generic topical dermatological drug products

Megan N. Kelchen, Priyanka Ghosh, Tannaz Ramezanli, Sam G. Raney

Division of Therapeutic Performance, Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD

Purpose

Characterization-based bioequivalence (BE) approaches provide more efficient methods to establish the BE of generic topical dermatological drug products compared to comparative clinical endpoint BE studies. Research initiatives by the Office of Generic Drugs (OGD) has led to advances in analytical tools and in vitro characterization methods, supporting efficient BE approaches recommended in product-specific guidances (PSGs).[1] The first PSG in which such a BE approach was comprehensively described was in 2016 (for acyclovir topical cream, 5%). By 2018, OGD's research suggested that characterization-based BE approaches could be generally applicable for all classes of topical dermatological dosage forms.

As part of the Generic Drug User Fee Amendments (GDUFA) regulatory science priorities for fiscal year (FY) 2018, OGD intends to "expand characterization-based BE methods across all topical dermatological products." The implementation of this priority initiative will be complex due to technical challenges, scientific unknowns, and limited resources. Therefore, it is essential to perform a gap analysis and to develop a strategic plan (i.e., a roadmap) with the essential steps for establishing characterization-based methods as a generalizable approach for developing and assessing generic topical dermatological drug products.

To successfully transition the standards for establishing the BE of topical dermatological drug products to characterization-based methods, four critical steps were tentatively anticipated (Figure 1). Through GDUFA-funded research[2], relevant critical quality attributes for common topical dermatological dosage forms have been identified (Step 1). This has facilitated the development of characterization-based BE approaches for specific drug products of different classes, which have been incorporated into their respective PSGs. The purpose of this study was to assess the progress of this transition by surveying the current recommendations for establishing BE within PSGs for topical dermatological drug products.

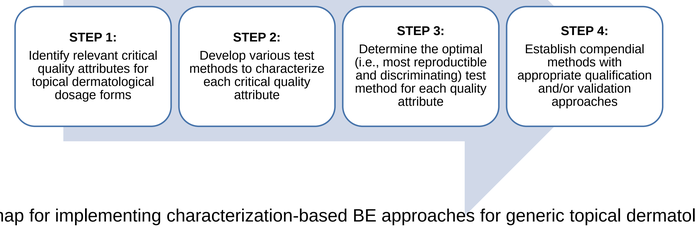

Figure 1. Roadmap for implementing characterization-based BE approaches for generic topical dermatological drug products

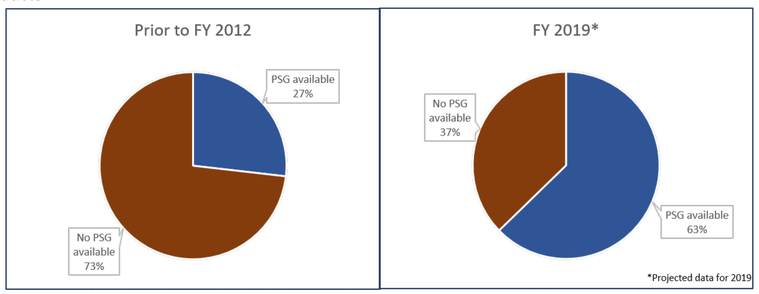

Figure 2. Percent of topical dermatological drug products with an available PSG prior to GDUFA I (FY 2012) and in FY 2019. *FY 2019 includes PSGs that are scheduled for publication within the fiscal year and is therefore a projection.

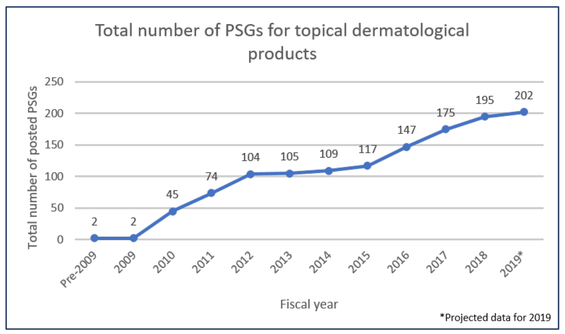

Figure 3. Total (accumulative) number of published PSGs for topical dermatological drug products from FY 2009 to present. *FY 2019 includes PSGs that are scheduled for publication within the fiscal year and is therefore a projection.

Methods

Through GDUFA-funded research, a conceptual framework for identifying the failure modes for BE was established for topical dermatological products. The general critical quality attributes of topical semisolid dosage forms were identified and various methods for evaluating these quality attributes were developed. Common trends among the dosage forms were identified and used to develop characterization-based BE approaches within PSGs for various generic topical dermatological drug products. PSGs for topical dermatological drug products published prior to July 2019 were reviewed and classified by the recommended approaches. PSGs that include options with more than one BE approach (e.g. PSGs that recommend a characterization-based BE approach or a comparative clinical endpoint BE study) were classified based on the approach that is listed first in the current PSG page. The recommendations were then categorized based on four common semisolid dosage forms (creams, gels, ointments, and lotions). The total number of topical dermatological drug products was obtained from the current Orange Book (current through July 2019) by filtering the list of approved drug products by the route of administration (topical), market status (prescription (Rx) or over-the-counter (OTC)), and reference standard (RS) drug products.

Results

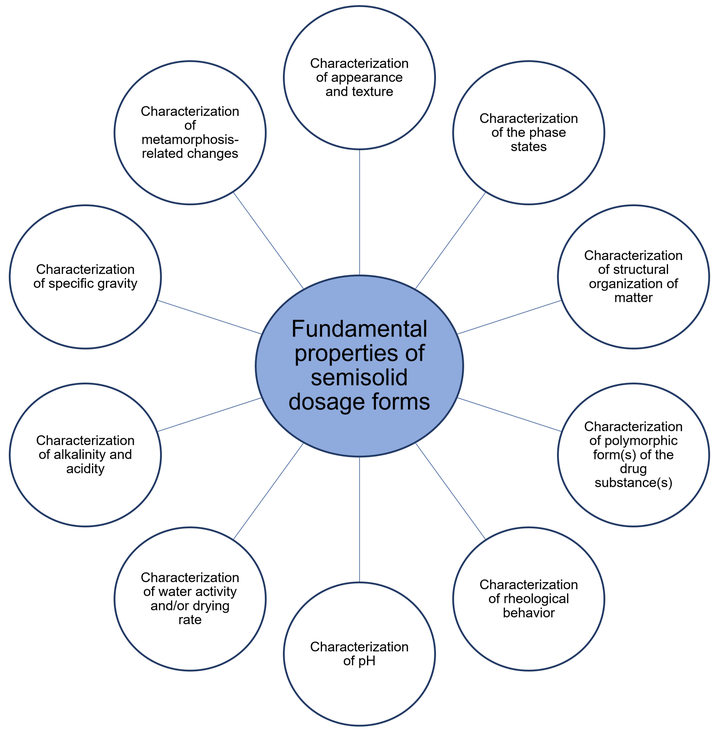

Figure 4. Ten fundamental properties of semisolid dosage forms that have been identified as part of Step 1 of the roadmap

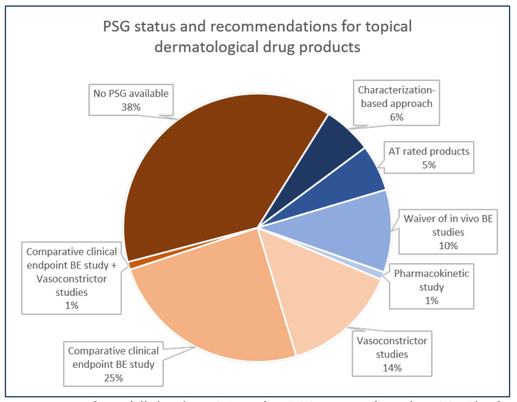

Figure 5. Current status of published PSGs (n=200 as of July 2019) for all topical dermatological reference products (n=322). Blue sections represent efficient approaches for establishing BE; brown/orange sections represent approaches that are less efficient. AT rated products refer to those for which no in vivo BE issue is known or suspected.

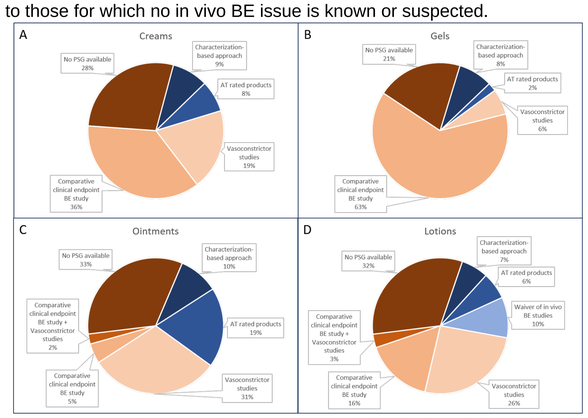

Figure 6. Current recommended approaches within posted PSGs (as of July 2019) for topical dermatological creams, gels, ointments, and lotions. PSGs are available for 68% of cream reference products (67/99), 80% of gel reference products (39/49), 67% of ointment reference products (28/42), and 68% of lotion reference products (21/31). Blue sections represent efficient approaches for establishing BE; orange sections represent approaches that are less efficient.

Conclusions

Over the last decade, characterization-based (in vitro) BE approaches have been recommended as an alternative to in vivo BE studies for many topical dosage forms based on the knowledge obtained in Step 1 of the roadmap. **The incorporation of sensitive, efficient, characterization-based BE approaches in all PSGs for generic topical dermatological drug products continues to be a priority for OGD, including those products for which less efficient approaches are currently recommend for establishing BE in an existing PSG.** Research has been underway, and is ongoing, to develop suitable test methods for characterizing each critical quality attribute (Step 2). As part of this, modeling and simulation methods, including physiologically based pharmacokinetic (PBPK) modeling, are being advanced as a method to evaluate the impact of product qualities on the performance of topical dermatological drug products, and may be able to predict the impact of differences in the formulation of a prospective generic product (compared to the reference product) on the local or systemic availability of the active ingredients. Overall, it is evident from this analysis that it is imperative to determine the optimal method for each critical quality attribute (Step 3) and to ultimately develop compendial standards for these methods (Step 4) in order to establish the comprehensive product development infrastructure that is necessary to standardize the use of efficient, characterization-based BE approaches for all topical dermatological drug products, which would be expected to enhance patient access to high quality generics.

References: [1] https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development. [2] https://www.fda.gov/drugs/generic-drugs/science-research.

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