Recommendations related to in vitro permeation test studies in product-specific guidances for topical drug products

Mengmeng Niu, Priyanka Ghosh, Tannaz Ramezanli, Markham Luke and Sam G. Raney

Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland, 20993

CONTACT INFORMATION: Mengmeng.Niu@FDA.HHS.GOV

Introduction

An in vitro skin permeation test (IVPT) study is used to assess the rate and extent to which a drug from a topical product becomes available at or near a site of action in the skin, and may be used to compare the rate and extent of bioavailability of a drug from a test product and reference standard. Therefore, IVPT studies have been included as part of topical product characterization-based bioequivalence (BE) approaches in certain product-specific guidances (PSGs). In the current study, we summarize the FDA's recommendations in PSGs and the rationale related to recommending IVPT studies.

Learning Objectives

Understanding the role of IVPT studies that are recommended to support a demonstration of BE for topical products applied to the skin.

Methods

The total number of PSGs that currently (as of February 2023) recommend IVPT studies to support a demonstration of BE for topical products applied to the skin were obtained from the FDA's website of PSGs.[2] The BE approaches in the PSGs were categorized based on the types of studies recommended. The consistency with which IVPT studies are recommended as a component of topical product characterization-based BE approaches, and notable exceptions, are summarized.

Conclusions

IVPT studies can be an important element of a characterization-based BE approach. The evidence from IVPT studies mitigates the risk of failure modes for BE that may arise from the complexity of the dosage form, or the site or mechanism of action of the drug product.

Results

❑ *PSGs for topical drug products*

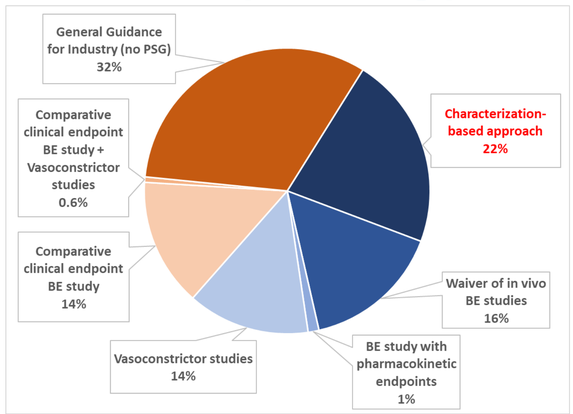

Figure 1: PSG recommendations for topical drug products (data till Feb 2023). PSGs that include multiple BE approaches were classified based on the approach that is listed first in the current PSG page (characterization-based approaches are typically listed first, when a PSG includes multiple approaches)

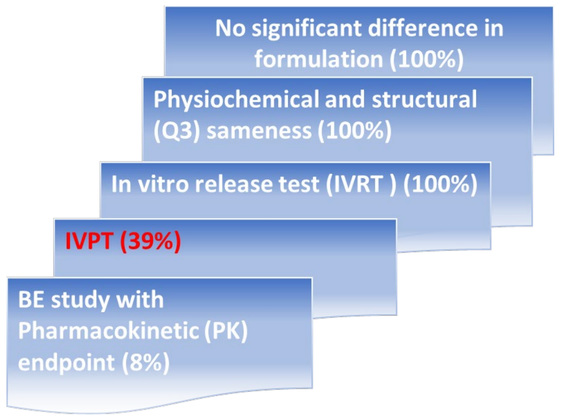

Figure 2: Studies recommended in PSGs within the scope of the characterization-based BE approach for topical drug products (data till Feb 2023)

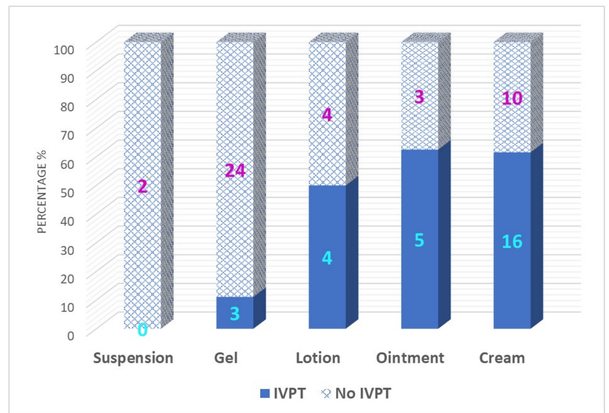

Figure 3: Percentage of PSGs that include IVPT as a component of the characterization-based BE approach for relevant topical dosage forms (data till Feb 2023). Numbers of PSGs for each dosage form are marked on the columns.

- As of February 2023, characterization-based BE approaches have been recommended within 71 of the 220 published PSGs that are available for topical drug products (Figure 1).
- Among the 71 products, 28 (39%) products included a recommendation for an IVPT study as a component of the characterization-based approach (Figure 2).
- IVPT studies are consistently recommended to address failure modes for BE that arise in most situations where the complex interactions of a multiphasic formulation (e.g., an emulsion) with the stratum corneum (SC) may influence the bioavailability of the drug. IVPT studies are typically recommended for topical emulsion-based gels, creams and lotions, and some ointments (Figure 3).

❑ *Examples where IVPT may NOT be necessary*

❖ *Site of action and mechanism of action*

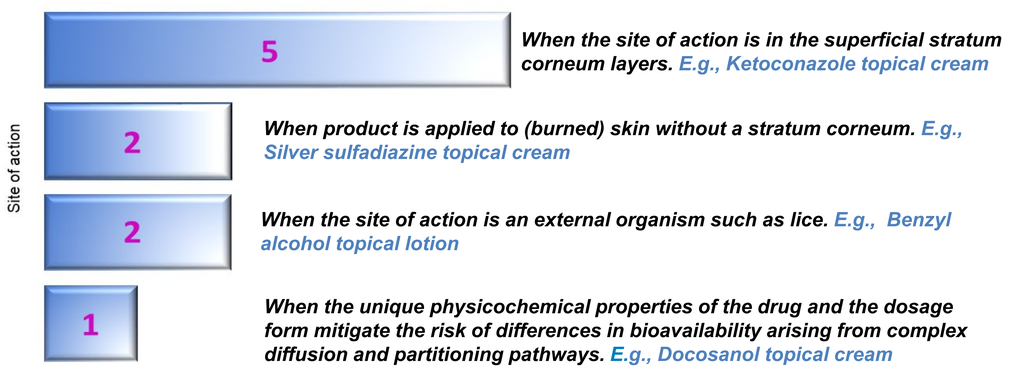

Figure 4: IVPT studies are not recommended when it is not necessary to mitigate the risk that potential differences in permeation through the stratum corneum may represent a failure mode for BE. The number of PSGs in each group is noted in each column.

❖ *Products with multiple strengths*

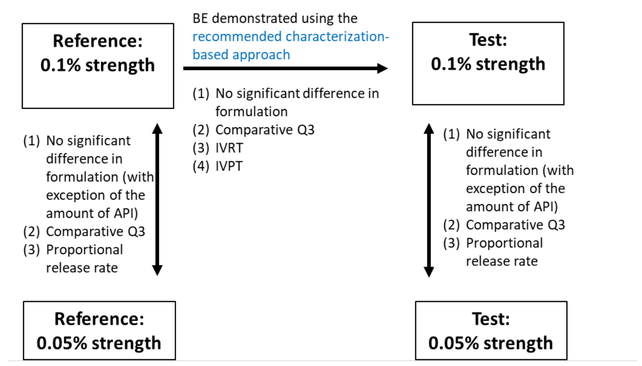

Figure 5: BE for Tazarotene topical cream, 0.1% may be established via a characterization-based approach that includes no significant difference in formulation, comparative Q3, IVRT and **IVPT**, compared to the reference standard. **An IVPT study** was **not** recommended for Tazarotene topical cream, 0.05% (Recommended Jun 2011; Revised Feb 2019, Oct 2022) when the lower strength test product (0.05%) contains no significant difference in formulation, possesses comparable Q3 properties, and has proportional rates of tazarotene release compared to the higher strength test product (0.1%).

❑ *Examples where IVPT may be necessary*

❖ *Petrolatum-based ointment*

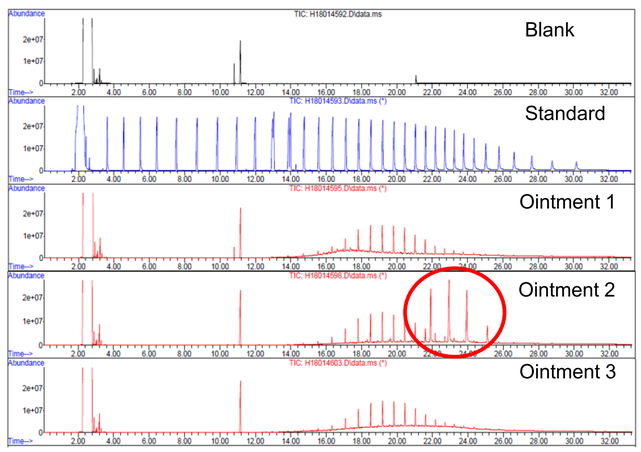

Figure 6: Gas Chromatography Mass Spectrometry (GC/MS) characterization of petrolatum based topical ointments.[1] Ointment 2 has different hydrocarbon heterogeneity compared to Ointment 1 and 3, as reflected on the GC/MS spectrum (red circle). Due to the unique complexities associated with hydrocarbon heterogeneity for petrolatum-based ointments, IVPT may be recommended to mitigate the risk of potential failure modes for BE relevant to such products.

Acknowledgement and Disclaimers

[1]These data are from work presented at the 2019 Complex Generic Drug Product Development Workshop by Sam Raney, PhD and the research was supported by the Food and Drug Administration (FDA) as part of a Contract (HHSF223201610125C) funded by FDA. This poster reflects the views of the authors and should not be construed to represent the views or policies of the Food and Drug Administration.

[2]FDA's website of PSGs: https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development

U.S. FOOD & DRUG ADMINISTRATION

www.fda.gov