Current Trends in Product-Specific Guidance Development & Revisions for Topical Products

Advancing Generic Drug Development 2024:
Translating Science to Approval
Day 1, Session 2: Research to Support Guidance Development for Topical Drug Products

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Disclaimer

This presentation reflects the view of the author and should not be construed to represent FDA's views or policies.

Learning Objectives

- Describe how research contributes to the evolution of PSGs for topical products applied to the skin
- Identify scenarios where obtaining the Agency's feedback may be beneficial during product development

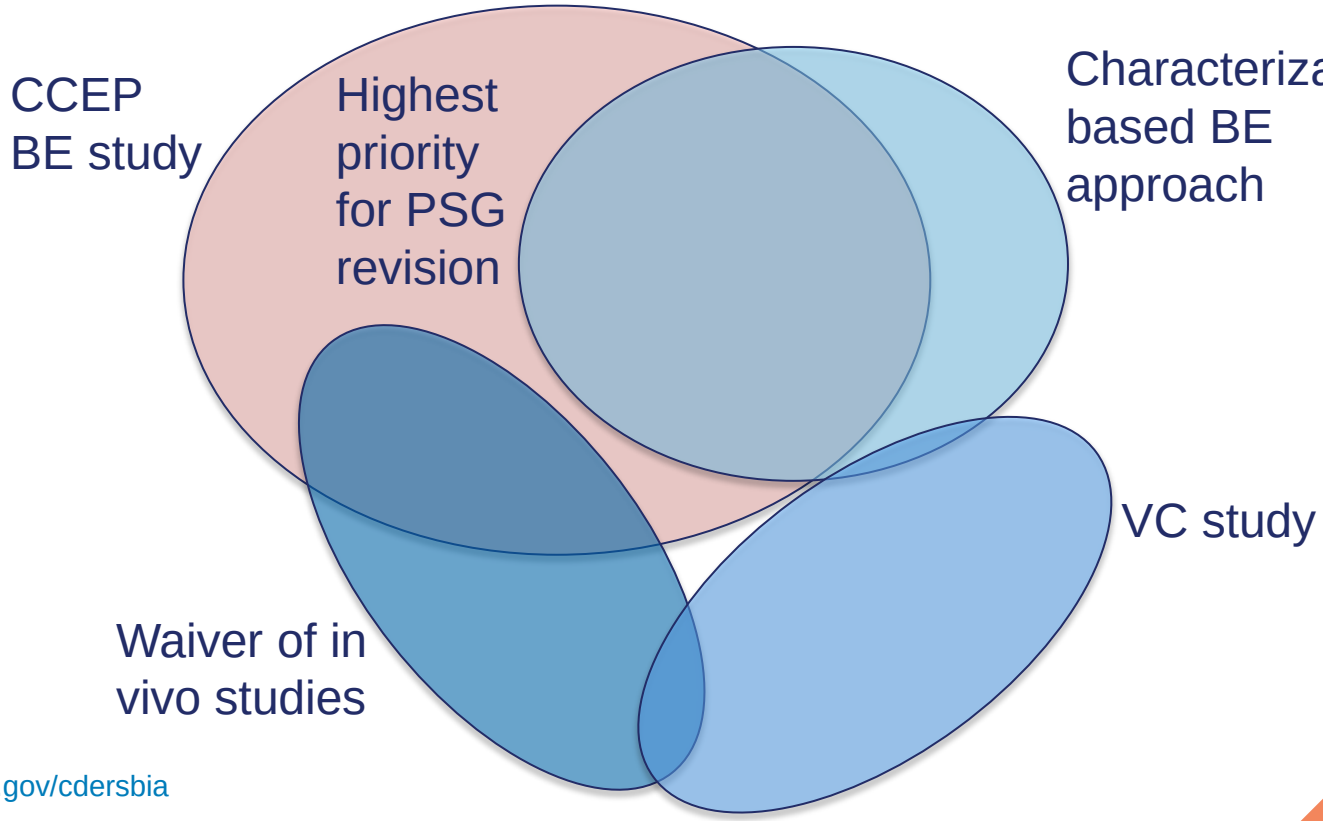
PSG: Product-specific guidance

BE approaches for topical products

- CCEP BE study
- Characterization-based BE approach
- VC study
- Waiver of in vivo studies

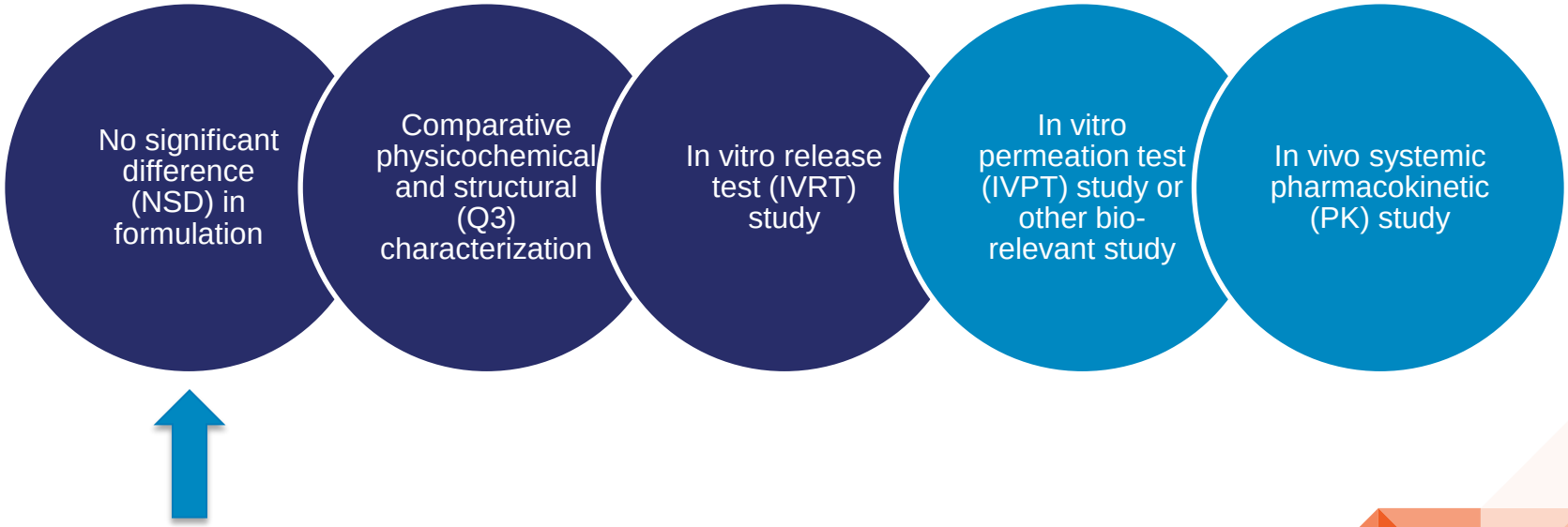
BE: Bioequivalence; CCEP: Comparative clinical endpoint; VC: Vasoconstrictor

BE approaches in PSGs



Characterization-based BE approach

In PSGs for topical products…



NSD standard

- The NSD standard is based upon the principles for assessing Q1/Q2 sameness, but also considers certain differences that have previously been determined to be acceptable based on available scientific evidence.

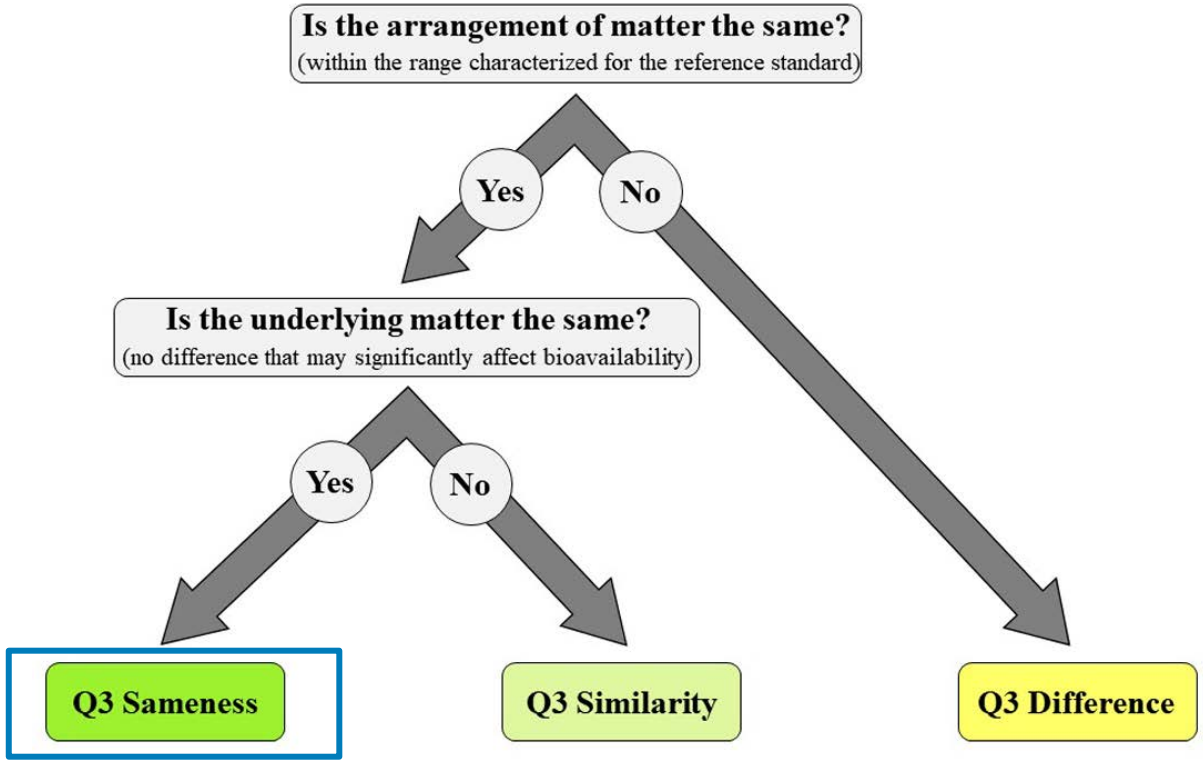
To demonstrate bioequivalence for doxepin hydrochloride topical cream, 5% using a combination of in vitro studies and an in vivo study with pharmacokinetic endpoints, the following criteria should be met:

1. The test product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference standard that may significantly affect the local or systemic availability of the active ingredient. For example, if the test product and reference standard are qualitatively (Q1) and quantitatively (Q2) the same, as defined in the most recent version of the FDA guidance for industry on *ANDA Submissions – Refuse-to-Receive Standards*[a], and the criteria below are also satisfied, the bioequivalence of the test product may be established using a characterization-based bioequivalence approach.

Q1: Qualitative sameness; Q2: Quantitative sameness

"General Considerations for the "No Significant Difference" Evaluation for a Proposed Generic Formulation"

Q3 sameness


Is the arrangement of matter the same?
(within the range characterized for the reference standard)
Yes
No
Is the underlying matter the same?
(no difference that may significantly affect bioavailability)
Yes
No
Q3 Sameness
Q3 Similarity
Q3 Difference

What are some examples of topical PSG evolution over time?

PSGs for topical aqueous gels

September 2023

Active Ingredient	NSD	Visual appearance and texture	Microscopic images	Rheology	pH	Specific gravity	PSD	GSD	Water activity	Drying rate	Oleaginous components	IVRT	IVPT	PK
ADAPALENE														
ADAPALENE														
ADAPALENE; BENZOYL PEROXIDE														
ADAPALENE; BENZOYL PEROXIDE														
BENZOYL PEROXIDE; CLINDAMYCIN PHOSPHATE														
BENZOYL PEROXIDE; CLINDAMYCIN PHOSPHATE														
BENZOYL PEROXIDE; CLINDAMYCIN PHOSPHATE														
CLINDAMYCIN PHOSPHATE; TRETINOIN														
TAZAROTENE														
TAZAROTENE														
TRETINOIN														
CLINDAMYCIN PHOSPHATE														
CLINDAMYCIN PHOSPHATE														
CLINDAMYCIN PHOSPHATE; TRETINOIN														
DICLOFENAC SODIUM														
METRONIDAZOLE														
METRONIDAZOLE														
DAPSONE														
DAPSONE														
DICLOFENAC SODIUM														

GSD: Globule size distribution

"An Overview of the Current Product-Specific Guidances for Topical Products"

PSGs for topical aqueous gels

Previous PSG (revised Oct 2022)

Active Ingredient: Dapsone

Dosage Form; Route: Gel; topical

Recommended Studies: Two options: (1) two in vitro bioequivalence studies, one in vivo bioequivalence study with pharmacokinetic endpoints, and other characterization tests or (2) one in vivo bioequivalence study with clinical endpoint

I. Option 1: Two in vitro bioequivalence studies, one in vivo bioequivalence study with pharmacokinetic endpoints, and other characterization tests

Revised PSG (revised Feb 2024)

Active Ingredient: Dapsone

Dosage Form: Gel

Route: Topical

Strength: 7.5%

Recommended Studies: Two options: (1) one in vitro bioequivalence study and other characterization tests or (2) one comparative clinical endpoint bioequivalence study

I. Option 1: One in vitro bioequivalence study and other characterization tests

PSGs for topical aqueous gels

September 2024

Active Ingredient	NSD	Visual appearance and texture	Microscopic images	Rheology	pH	Specific gravity	PSD	GSD	Water activity	Drying rate	Oleaginous components	IVRT	IVPT	PK
ADAPALENE														
ADAPALENE														
ADAPALENE; BENZOYL PEROXIDE														
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BENZOYL PEROXIDE; CLINDAMYCIN PHOSPHATE														
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BENZOYL PEROXIDE; ERYTHROMYCIN														
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TAZAROTENE														
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TRETINOIN														
CLINDAMYCIN PHOSPHATE														
CLINDAMYCIN PHOSPHATE														
CLINDAMYCIN PHOSPHATE; TRETINOIN														
DICLOFENAC SODIUM														
METRONIDAZOLE														
METRONIDAZOLE														
DAPSONE														
DAPSONE														
DICLOFENAC SODIUM														

PSG for clascoterone topical cream

Previous PSG (recommended Nov 2021)

Active Ingredient: Clascoterone

Dosage Form; Route: Cream; topical

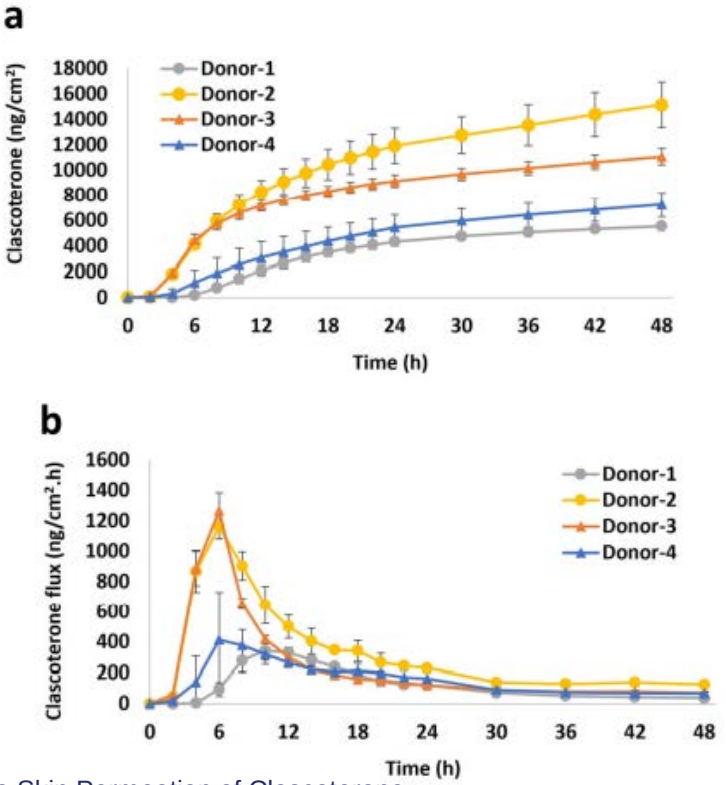
Recommended Study: One study

1. Type of study: Bioequivalence study with clinical endpoint
   Study Design: Randomized, double blind, parallel, placebo controlled, in vivo
   Strength: 1%
   Subjects: Males and non-pregnant, non-lactating females with acne vulgaris
   Additional comments: Specific recommendations are provided below

PSG for clascoterone topical cream

IVPT method parameters:

- Apparatus
- Receptor solution
- Volume of receptor solution
- Sampling method
- Volume of sample
- Study duration



Yang Y., et al. 2024. Evaluation of In Vitro Skin Permeation of Clascoterone from Clascoterone Topical Cream, 1% (w/w). AAPS PharmSciTech, 25: 186.

PSG for clascoterone topical cream

Current PSG (revised Aug 2023)

Active Ingredient:	Clascoterone
Dosage Form:	Cream
Route:	Topical
Strength:	1%
Recommended Studies:	Two options: (1) two in vitro characterization tests or (2) on bioequivalence study

4. The test product and reference standard should have equivalent rate and extent of clascoterone permeation through excised human skin based upon an acceptable in vitro permeation test (IVPT) bioequivalence study comparing a minimum of one batch each of the test product and reference standard using an appropriately validated IVPT method.

Type of study: Bioequivalence study with IVPT endpoints
Design: Single-dose, two-treatment, parallel, multiple-replicate per treatment group study design using an unoccluded finite dose, in vitro
Strength: 1%
Test system: Barrier-competent human skin from male and/or female donors of at least 18 years of age in a diffusion cell system
Analyte to measure: Clascoterone and cortexolone in receptor solution
Equivalence based on: Clascoterone (IVPT endpoints: total cumulative amount (AMT) and maximum flux (J_{max}))
Additional comments: Refer to the most recent version of the FDA guidance for industry on *In Vitro Permeation Test Studies for Topical Drug Products Submitted in ANDAs*[a] for additional information regarding the development, validation, conduct and analysis of acceptable IVPT methods/studies. The batches of test product and reference standard evaluated in the IVPT bioequivalence study should be the same as those evaluated in the IVRT bioequivalence study.

Upcoming new and revised PSGs

Planned New PSGs for Complex and Non-Complex Generic Drug Products
Updated August 22, 2024

Search: topical

Active Ingredient(s)	Route of Administration	Dosage Form	RLD or RS Application Number	Prodi Comp
Adapalene; Benzoyl Peroxide; Clindamycin Phosphate	Topical	Gel	216632	Comp
Cantharidin	Topical	Solution	212905	Non-(
Clobetasol Propionate	Topical	Cream	209483	Comp
Estrogens, Conjugated	Topical, Vaginal	Cream	020216	Comp
Lidocaine; Tetracaine	Topical	Patch	021623	Comp
Roflumilast	Topical	Cream	215985	Comp

Planned Revised PSGs for Complex and Non-Complex Generic Drug Products
Updated August 22, 2024

Search: topical

Show 10 entries

Active Ingredient(s)	Route Of Administration	Dosage Form	RLD or RS Application Number	Planned Revision Category with Description	Product Complexity	Planned Publication
Azelaic Acid	Topical	Gel	021470	Minor Revision: Add an in vitro BE option	Complex	11/2024
Fluorouracil	Topical	Cream	020985	Minor Revision: Add an in vitro BE option	Complex	Beyond 12 months
Ruxolitinib Phosphate	Topical	Cream	215309	Editorial Revision: Correct Typos Minor Revision: Add an in vitro BE option	Complex	11/2024
Tacrolimus	Topical	Ointment	050777	Minor Revision: Add an in vitro BE option	Complex	11/2024
Tazarotene	Topical	Cream	021184	Minor Revision: Add an in vitro BE option	Complex	11/2024

Key take-home point

The PSG recommendations for topical products evolve over time based on cutting-edge research, leading to streamlined recommendations across similar products.

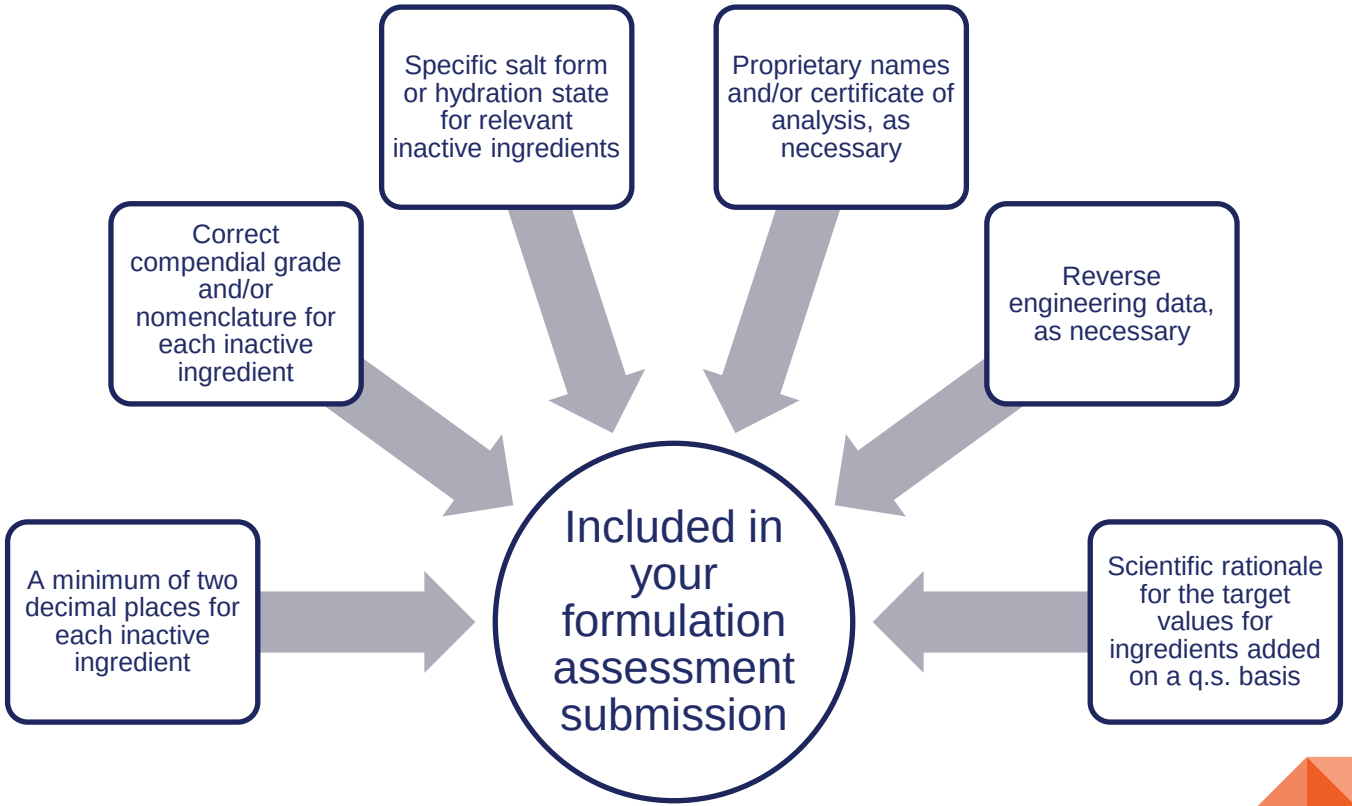
When should I seek feedback from the Agency?

Feedback on formulation: Inactive ingredient assessment

- The IID can be used to help justify levels of inactive ingredients in a proposed test formulation.
- Consider context of use when selecting concentrations of inactive ingredients
  - Route of administration — Listed in the IID
  - Duration of use — Not included in the IID
  - Patient population — Not included in the IID
- Discuss your proposed concentrations or proposed formulation with the Agency early in product development, regardless of BE approach

IID: Inactive Ingredient Database
FDA's Inactive Ingredient Database website

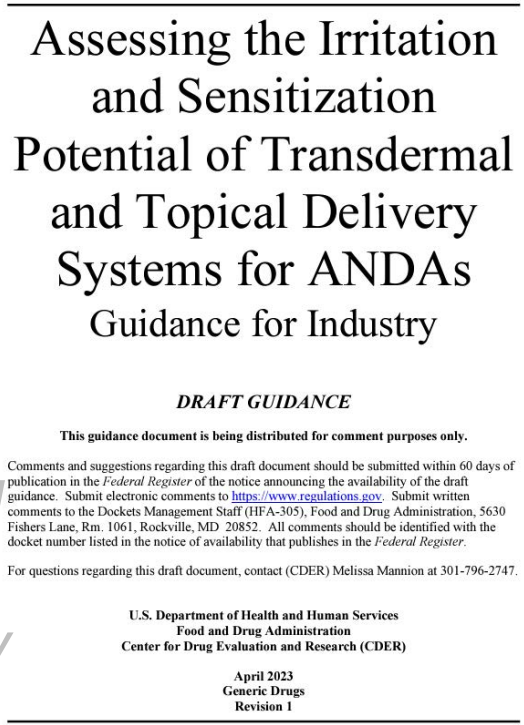
Feedback on formulation: NSD assessment



"General Considerations for the "No Significant Difference" Evaluation for a Proposed Generic Formulation"

Feedback on formulation: TDS products

"In some circumstances, an in vivo sensitization evaluation of a TDS product may be unnecessary if adequate justification is provided or FDA has determined that conducting a sensitization assessment is unnecessary or unethical (e.g., where the active ingredient is known to be a skin sensitizer or based on information/data related to the components and composition of TDS product) to show that the T product is not likely to be more sensitizing than the R product."



Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Melissa Mannion at 301-796-2747.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

April 2023
Generic Drugs
Revision 1

Feedback on BE approaches and study design

Q3 sameness

- No PSG available
- Characterization-based BE approach not yet available in a PSG
- Specific questions about the design and/or conduct of specific studies (e.g., IVRT/IVPT studies)

Q3 similarity

- Questions about studies to support an alternative BE approach after receiving feedback on a proposed test formulation

In vivo CCEP BE study

- No PSG available
- Specific questions about the design and/or conduct of the study

Feedback on DDCP

Device:
The reference listed drug (RLD) has two presentations that are drug-device combination products:

- Bottle with co-packaged foaming dispensing pump with actuator
- Bottle with integrated foaming dispensing pump with actuator

The foaming dispensing pump with actuator are the device constituent parts, because it changes the drug from a solution to a foam as it delivers the drug to the user.

FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD devices when designing the test devices.

User interface assessment:
An ANDA for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.[a]

DDCP: Drug-device combination product

Feedback on DDCP

Container closure system

No comparison needed for test vs. RLD

DDCP

Requires comparative analyses of test vs. RLD

Key take-home point

The pre-ANDA program can be utilized to get feedback from the Agency during both early and late-stage development.

Challenge Question #1

Which of the following are considered to be an inefficient BE approach for topical products and is therefore prioritized for PSG revision?

A. CCEP BE study

B. Characterization-based BE approach

C. VC study

D. Waiver of in vivo BE studies

Challenge Question #2

Which scenario would benefit from a pre-ANDA interaction with the Agency?

A. The PSG recommends a CCEP BE study, but you would like to use a characterization-based BE approach instead.

B. It is not clear from the PSG if the product is a drug-device combination product.

C. You would like feedback on the proposed levels of inactive ingredients prior to conducting a CCEP BE study.

D. All of the above.

Summary

- The PSG recommendations for topical products evolve over time based on cutting-edge research, leading to streamlined recommendations across similar products.
- Engaging with the Agency through the pre-ANDA program to gain feedback throughout product development can be beneficial.

Acknowledgements

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- Hiren Patel, PhD
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- Office of Generic Drug Policy

Resources

Presentations:

- "An Overview of the Current Product-Specific Guidances for Topical Products" (presented on 09/13/2023)
- "General Considerations for the "No Significant Difference" Evaluation for a Proposed Generic Formulation" (presented on 12/06/2022)
- "Redesigned Pre-Submission Meetings in GDUFA III: Benefits for ANDA Submission and Approval" (presented on 05/09/2024)

Guidances:

- Draft guidance for industry: *Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs* (October 2022)
- Draft guidance for industry: *In Vitro Release Test (IVRT) Studies for Topical Drug Products Submitted in ANDAs* (October 2022)
- Draft guidance for industry: *In Vitro Permeation Test (IVPT) Studies for Topical Drug Products Submitted in ANDAs* (October 2022)
- Draft guidance for industry: *Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs* (April 2024)
- Final guidance for industry: *Controlled Correspondence Related to Generic Drug Development* (December 2020)
- Final guidance for industry: *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (October 2022)

Websites:

- Product-Specific Guidances for Generic Drug Development website
- Upcoming Product-Specific Guidances for Generic Drug Product Development website
- FDA's Inactive Ingredient Database website