



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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Senior Pharmacologist

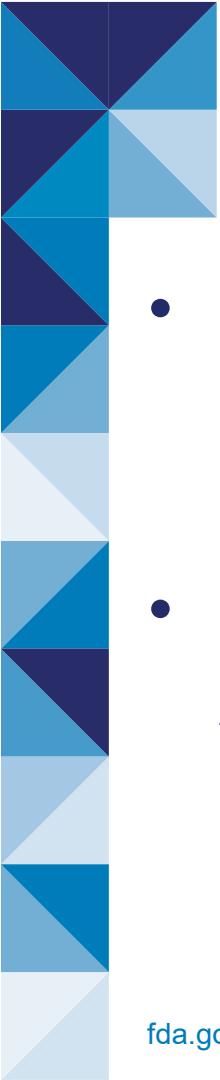
Division of Therapeutic Performance I, Office of Research and Standards,
Office of Generic Drugs
CDER | U.S. FDA

September 24, 2024

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



BE approaches for topical products



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

BE approaches in PSGs



CCEP
BE study

Highest
priority
for PSG
revision

Characterization-
based BE
approach

VC study

Waiver of in
vivo studies

Characterization-based BE approach



In PSGs for topical products...

No significant difference (NSD) in formulation

Comparative physicochemical and structural (Q3) characterization

In vitro release test (IVRT) study

In vitro permeation test (IVPT) study or other bio-relevant study

In vivo systemic pharmacokinetic (PK) study



NSD standard

FDA

- 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.

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)

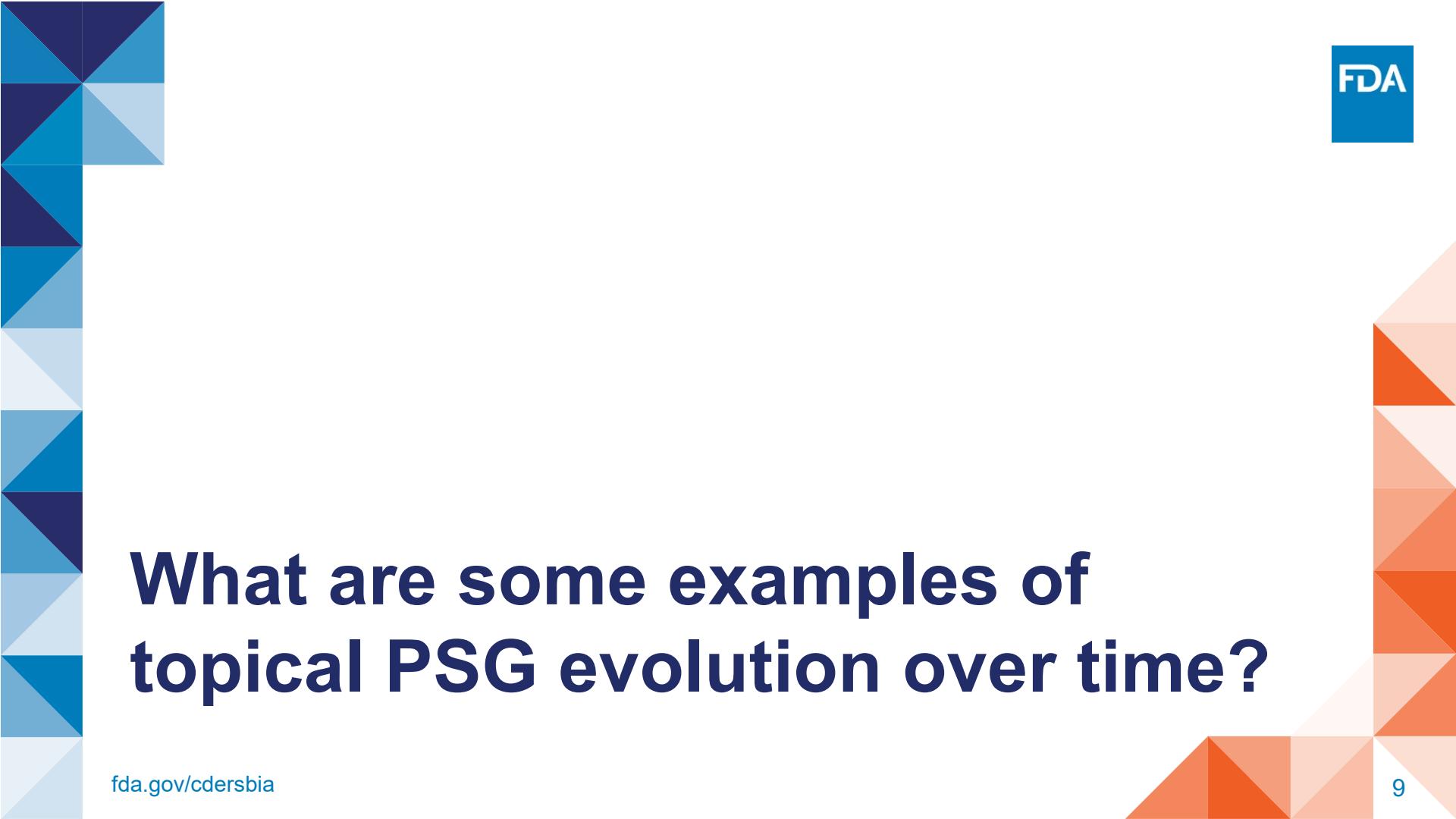
Yes

No

Q3 Sameness

Q3 Similarity

Q3 Difference

The slide features decorative geometric patterns in the corners. The left side has a vertical column of triangles in shades of blue and dark blue. The right side has a vertical column of triangles in shades of orange and light orange. The bottom right corner contains a larger, more complex triangular pattern in the same color scheme.

**What are some examples of
topical PSG evolution over time?**

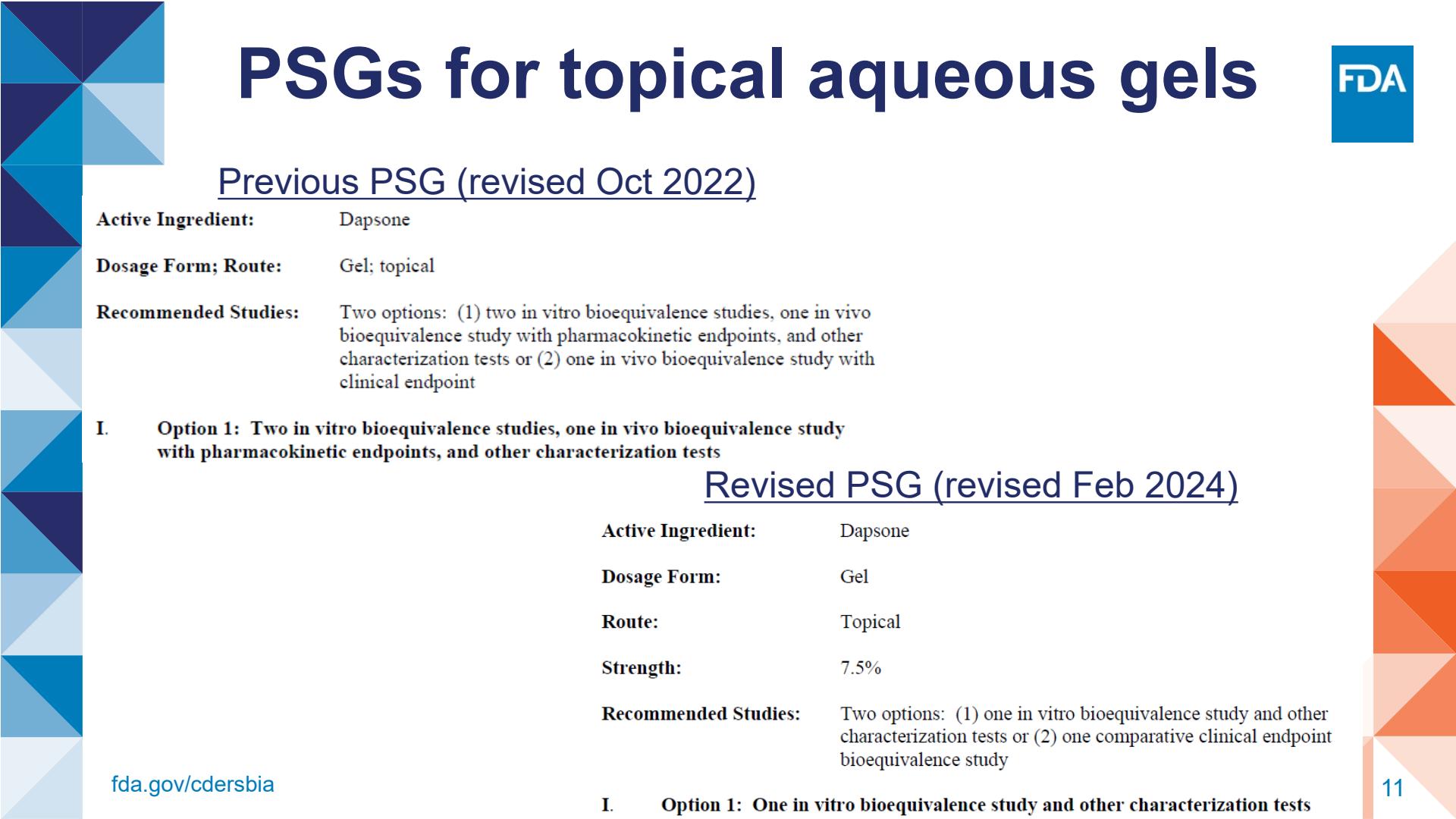


PSGs for topical aqueous gels



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														



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

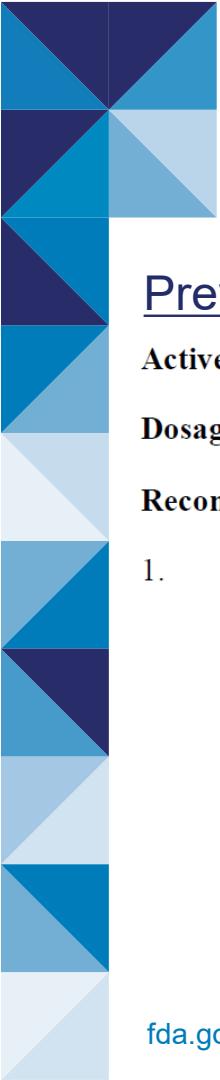


PSGs for topical aqueous gels



September 2024

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DICLOFENAC SODIUM														
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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

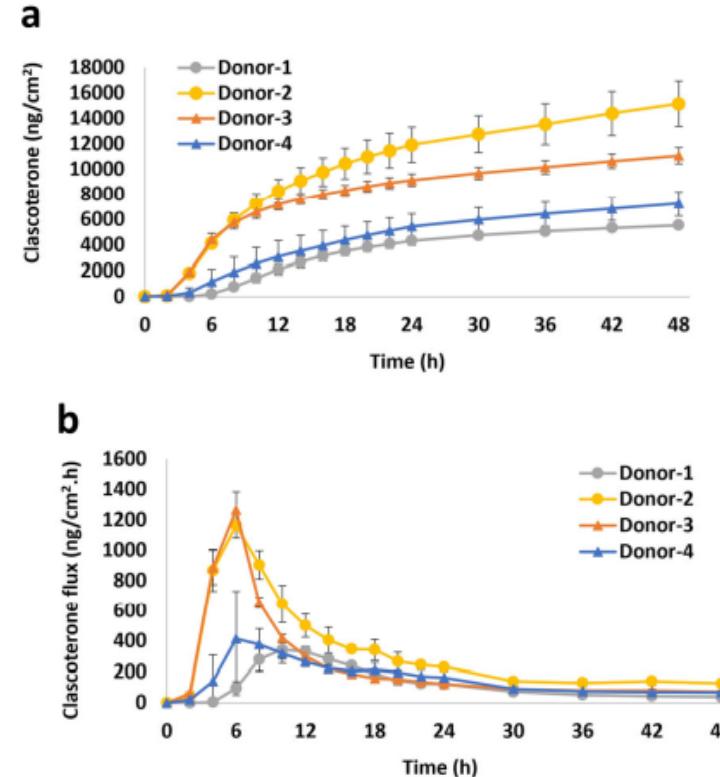
1. Type of study: Bioequivalence study with clinical endpoint
Study Design: Randomized, double blind, parallel, placebo controlled, in vivo
Strength: 1%
Subjects: Males and non-pregnant, non-lactating females with acne vulgaris
Additional comments: Specific recommendations are provided below

PSG for clascoterone topical cream



Optimization of IVPT method parameters such as:

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



PSG for clascoterone topical cream

FDA

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) one 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	Product Complexity
Adapalene; Benzoyl Peroxide; Clindamycin Phosphate	Topical	Gel	216632	Complex
Cantharidin	Topical	Solution	212905	Non-Complex
Clobetasol Propionate	Topical	Cream	209483	Complex
Estrogens, Conjugated	Topical, Vaginal	Cream	020216	Complex
Lidocaine; Tetracaine	Topical	Patch	021623	Complex
Roflumilast	Topical	Cream	215985	Complex

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

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	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.

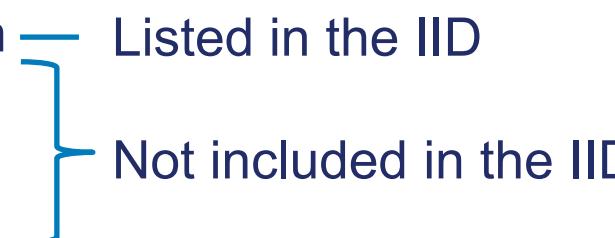


When should I seek feedback from the Agency?

Feedback on formulation: IID assessment

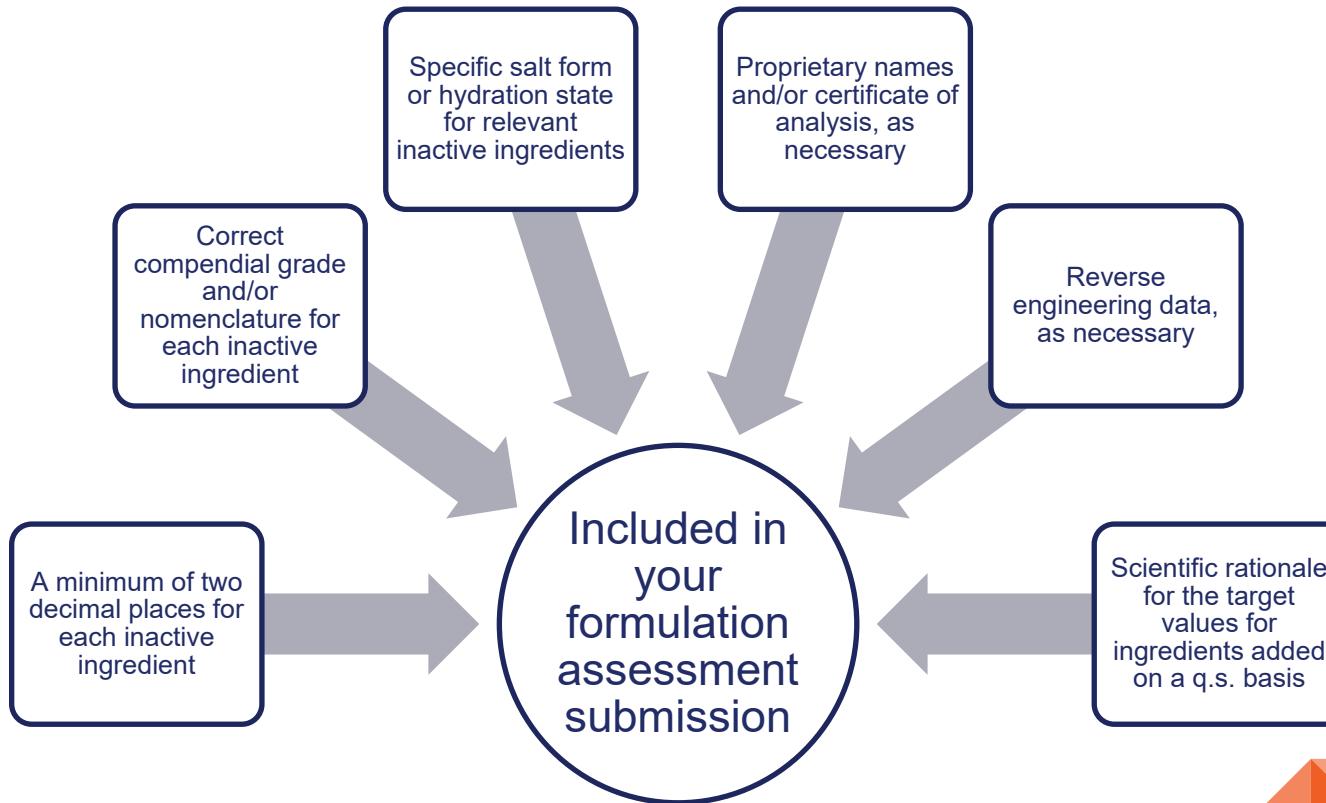


- The IID can be used to help justify levels of inactive ingredients in a proposed test formulation.
- Consider context of use when selecting concentrations of inactive ingredients
 - Route of administration
 - Duration of use
 - Patient population
- Discuss your proposed concentrations or proposed formulation with the Agency early in product development, regardless of BE approach



The diagram consists of a large blue bracket on the right side of the slide. It spans from the 'Route of administration' bullet point to the 'Not included in the IID' bullet point. The bracket is divided into two sections by a vertical line: the top section is labeled 'Listed in the IID' and the bottom section is labeled 'Not included in the IID'.

Feedback on formulation: NSD assessment



Feedback on formulation: TDS products



Active Ingredient:

Asenapine

Dosage Form; Route:

System; transdermal

Recommended Studies:

One in vivo bioequivalence study with pharmacokinetic endpoints, one in vivo adhesion study, and one in vivo skin irritation and sensitization study

"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

Feedback on DDCP



Container closure system

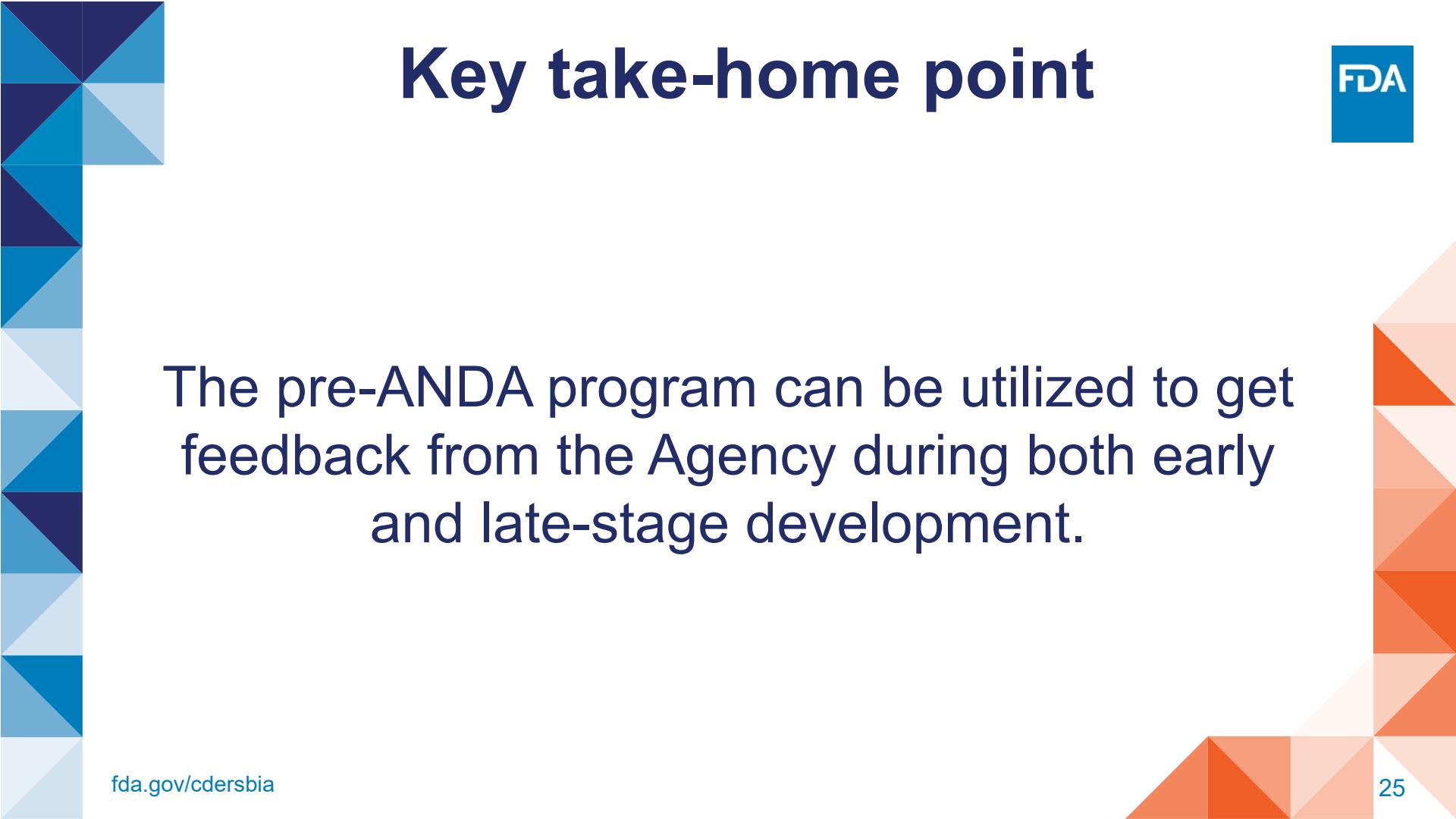


No comparison needed for test vs. RLD

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.

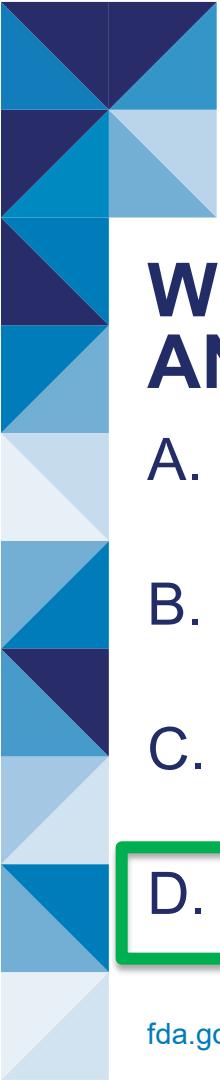


Challenge Question #1



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



U.S. Food & Drug Administration

- Priyanka Ghosh, PhD
- Tannaz Ramezanli, PharmD, PhD
- Mengmeng Niu, PhD
- Ying Jiang, PhD
- Jackson Russo, PhD
- Lingxiao Xie, PhD
- Eleftheria Tsakalozou, PhD
- Sam Raney, PhD
- Markham Luke, MD, PhD
- Robert Lionberger, PhD
- Pahala Simamora, PhD
- Bing Cai, PhD
- Ahmed Zidan, PhD
- Hiren Patel, PhD
- Office of Research and Standards PSG Team
- 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](#)



Questions?

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