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

SBIA 2023—Advancing Generic Drug Development: Translating Science to Approval

Day 1, Session 1: Noteworthy Guidances and Generic Approvals for Topical and Transdermal Products

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Disclaimer

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

Learning Objectives

- Identify the various approaches for bioequivalence (BE) for topical products outlined in product-specific guidances (PSGs)
- Explain the rationale for inclusion of different components within the scope of characterization-based BE approaches for topical products
- Describe how to obtain the Agency's feedback on a proposed BE approach when a PSG is not available

Establishing BE for topical products

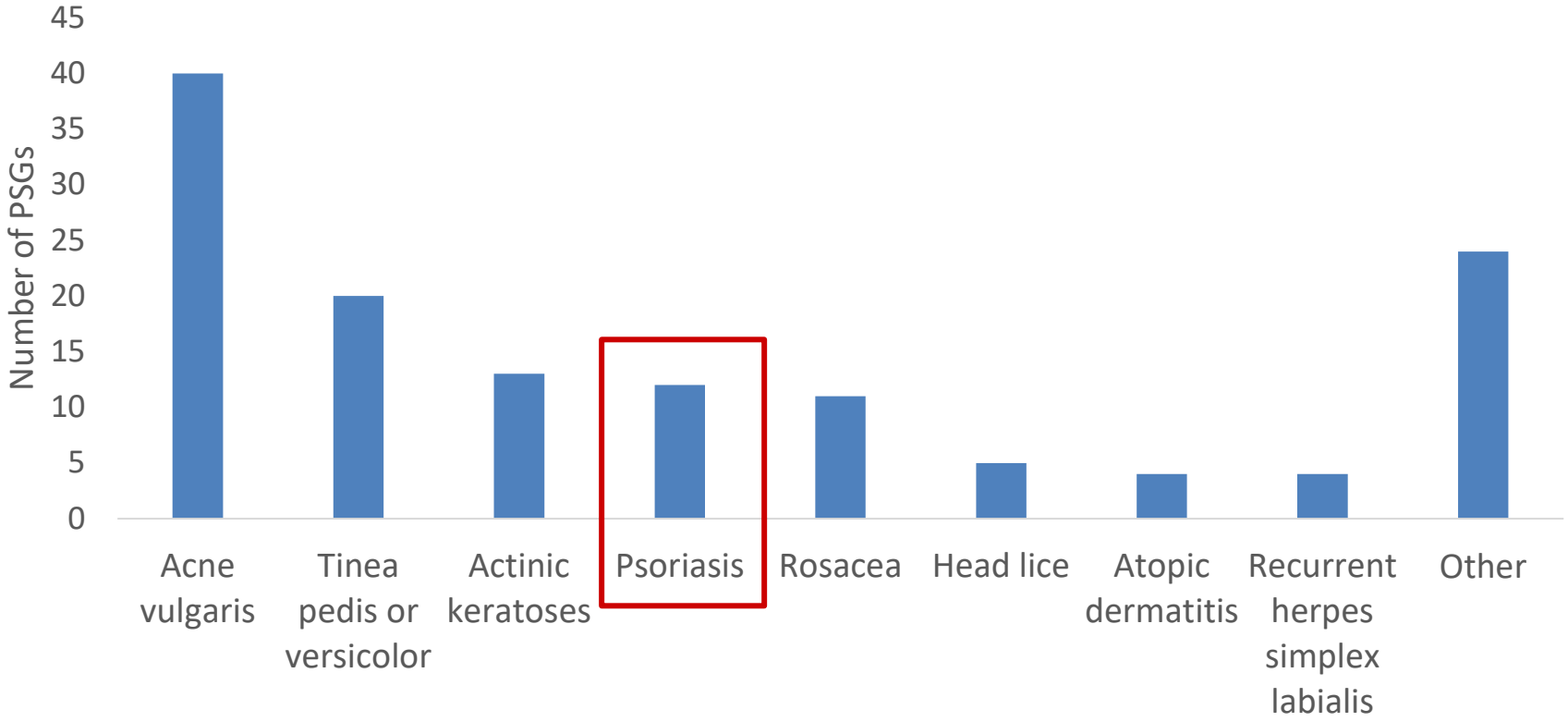
Main examples for BE approaches:

- Comparative clinical endpoint BE (CCEPBE) study
- Characterization-based BE approach
- Vasoconstrictor (VC) study
- Waiver of in vivo BE studies

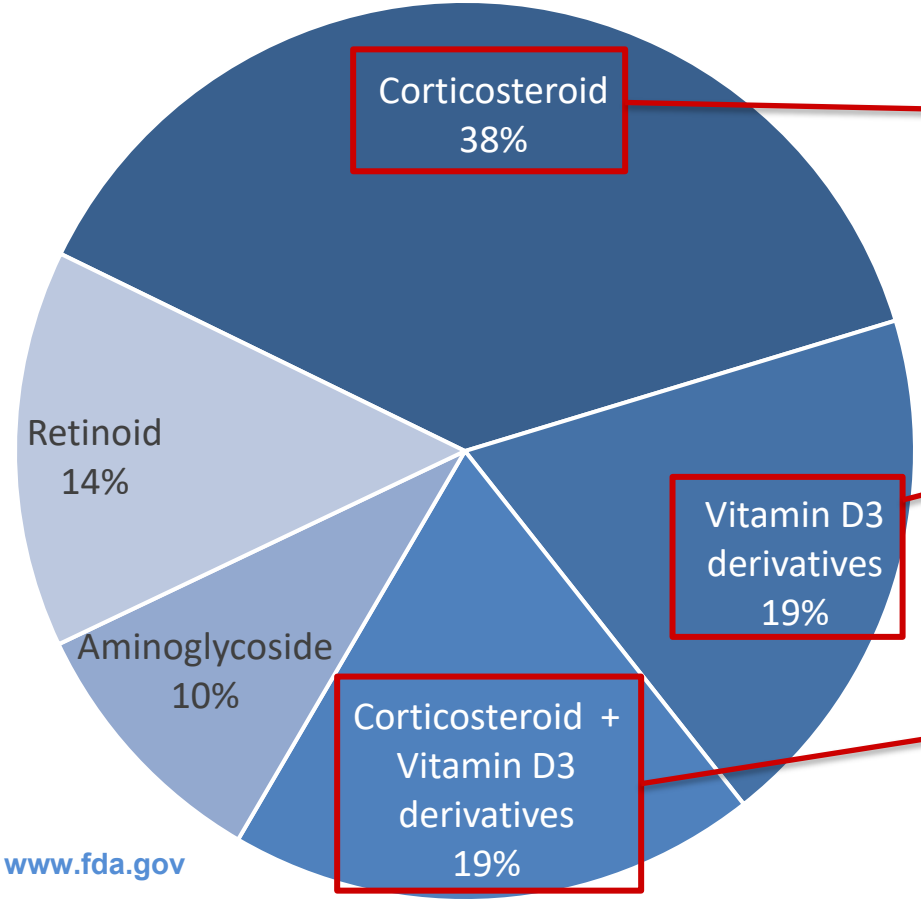
PSGs often include multiple BE approaches

- Examples:
  - Two options: (1) Characterization-based BE approach, or (2) CCEPBE study
  - Two options: (1) Waiver of in vivo BE studies, or (2) VC study

CCEPBE studies for topical products



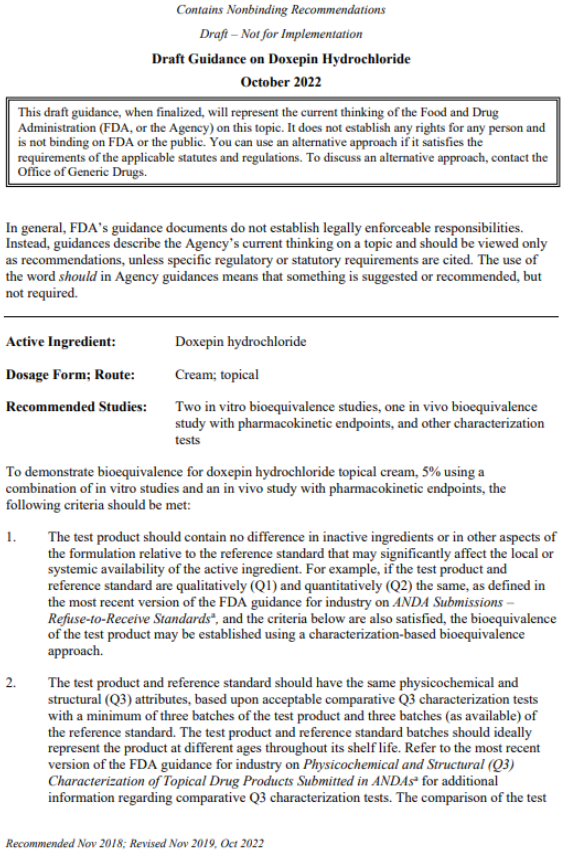
BE approaches for psoriasis



- Corticosteroid 38%
  - Waiver of in vivo BE studies
  - VC study
  - Characterization-based BE approach
  - CCEPBE study
- Vitamin D3 derivatives 19%
  - Waiver of in vivo BE studies
  - Characterization-based BE approach
  - CCEPBE study
- Corticosteroid + Vitamin D3 derivatives 19%
  - VC study + CCEPBE study
  - VC study + Characterization-based BE approach

Guidances for topical products

- October 2022
  - New draft guidances for industry:
    - *Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs*
    - *In Vitro Release Test (IVRT) Studies for Topical Drug Products Submitted in ANDAs*
    - *In Vitro Permeation Test (IVPT) Studies for Topical Drug Products Submitted in ANDAs*
  - Revised draft guidance for industry:
    - *Topical Dermatologic Corticosteroids: In Vivo Bioequivalence*
  - 80+ new or revised PSGs for topical products



Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Doxepin Hydrochloride

October 2022

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient: Doxepin hydrochloride

Dosage Form; Route: Cream; topical

Recommended Studies: Two in vitro bioequivalence studies, one in vivo bioequivalence study with pharmacokinetic endpoints, and other characterization tests

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.

2. The test product and reference standard should have the same physicochemical and structural (Q3) attributes, based upon acceptable comparative Q3 characterization tests with a minimum of three batches of the test product and three batches (as available) of the reference standard. The test product and reference standard batches should ideally represent the product at different ages throughout its shelf life. Refer to the most recent version of the FDA guidance for industry on *Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs*[a] for additional information regarding comparative Q3 characterization tests. The comparison of the test

Recommended Nov 2018; Revised Nov 2019, Oct 2022

NSD standard

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- The "no significant difference" (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.
- A NSD standard expands the eligibility for a characterization-based BE approach for topical products.

Q1: Qualitative sameness; Q2: Quantitative sameness

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

NSD standard

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Example of the NSD standard

A topical test product may be considered to have NSD if it contains minor differences in ingredient grade.

RS Formulation		Test Formulation	
Carbopol 934P	2.00%	Carbomer homopolymer type B, NF (Carbopol 974P)	2.00%
Petrolatum, USP	5.00%	White Petrolatum, USP	5.00%

Comparative Q3 characterization

2. The test product and reference standard should have the same physicochemical and structural (Q3) attributes, based upon acceptable comparative Q3 characterization tests with a minimum of three batches of the test product and three batches (as available) of the reference standard. The test product and reference standard batches should ideally represent the product at different ages throughout its shelf life. Refer to the most recent version of the FDA guidance for industry on *Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs*[a] for additional information regarding comparative Q3 characterization tests. The comparison of the test product and reference standard should include characterizations of the following Q3 attributes:
    a. Characterization of visual appearance and texture
    b. Characterization of phase states and structural organization of matter
        - Microscopic examination with representative high-resolution microscopic images at multiple magnifications
        - Analysis of globule size distribution
    c. Characterization of rheological behavior which may be characterized using a rheometer that is appropriate for monitoring the non-Newtonian flow behavior of semi-solid dosage forms. The following evaluations are recommended:
        - A characterization of shear stress vs. shear rate and viscosity vs. shear rate. At minimum, this should consist of numerical viscosity data at three shear rates (low, medium, and high).
        - A complete flow curve across the range of attainable shear rates, until low or high shear plateaus are identified.
        - Yield stress values should be reported if the material tested exhibits plastic flow behavior.
        - The linear viscoelastic response (storage and loss modulus vs. frequency) should be measured and reported. Any non-linear viscosity behavior over a range of shear rates should also be investigated, measured and reported.
    d. Characterization of pH
    e. Characterization of specific gravity
    f. Characterization of any other potentially relevant Q3 attributes

Guidance for industry *Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs*

IVRT study

3. The test product and reference standard should have an equivalent rate of doxepin hydrochloride release based upon an acceptable in vitro release test (IVRT) bioequivalence study comparing a minimum of one batch each of the test product and reference standard using an appropriately validated IVRT method.

Type of study: Bioequivalence study with IVRT endpoint
Design: Single-dose, two-treatment, parallel, multiple-replicate per treatment group study design using an occluded pseudo-infinite dose, in vitro
Strength: 5%
Test system: A synthetic membrane in a diffusion cell system
Analytes to measure: Doxepin in receptor solution
Equivalence based on: Doxepin (IVRT endpoint: drug release rate)
Additional comments: Refer to the most recent version of the FDA guidance for industry on *In Vitro Release Test Studies for Topical Drug Products Submitted in ANDAs*[a] for additional information regarding the development, validation, conduct and analysis of acceptable IVRT methods/studies. The batches of test product and reference standard evaluated in the IVRT bioequivalence study should be included among those for which the Q3 attributes are characterized.

Guidance for industry *In Vitro Release Test (IVRT) Studies for Topical Drug Products Submitted in ANDAs*

IVPT study

4. The test product and reference standard should have an equivalent rate and extent of doxepin 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: 5%
Test system: Barrier-competent human skin from male and/or female donors of at least 18 years of age in a diffusion cell system
Analytes to measure: Doxepin in receptor solution
Equivalence based on: Doxepin (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.

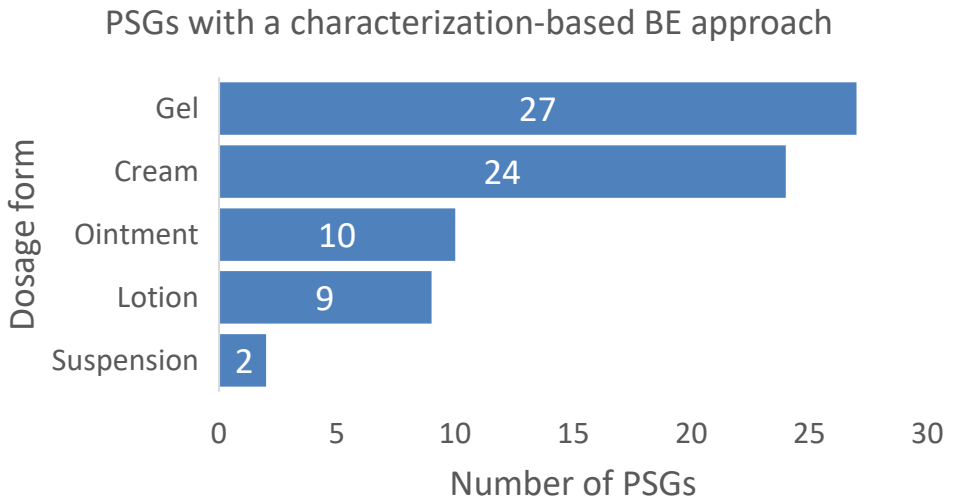
In vivo systemic PK study

5. The test product and reference standard should demonstrate bioequivalence based upon an acceptable in vivo pharmacokinetic study with one batch each of the test product and reference standard.

Type of study: In vivo pharmacokinetic study
Design: Single-application, two-way crossover study design
Strength: 5%
Subjects: Males and non-pregnant, non-lactating females, general population
Analytes to measure: Doxepin and its active metabolite nordoxepin in plasma
Equivalence based on: Doxepin
Additional comments: The study conditions such as the dose of the test product and reference standard, the site of dose application, etc. should be consistent across the study and the bioanalytical method should be sufficiently sensitive to be able to adequately characterize the pharmacokinetic profiles of the test product and reference drug products. Refer to the most recent version of the FDA guidance for industry on *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*[a] for additional information regarding the analysis of the pharmacokinetic bioequivalence study. The batches of test product and reference standard evaluated in the in vivo pharmacokinetic study should be the same as those evaluated in the IVRT and IVPT studies.

Guidance for industry *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*

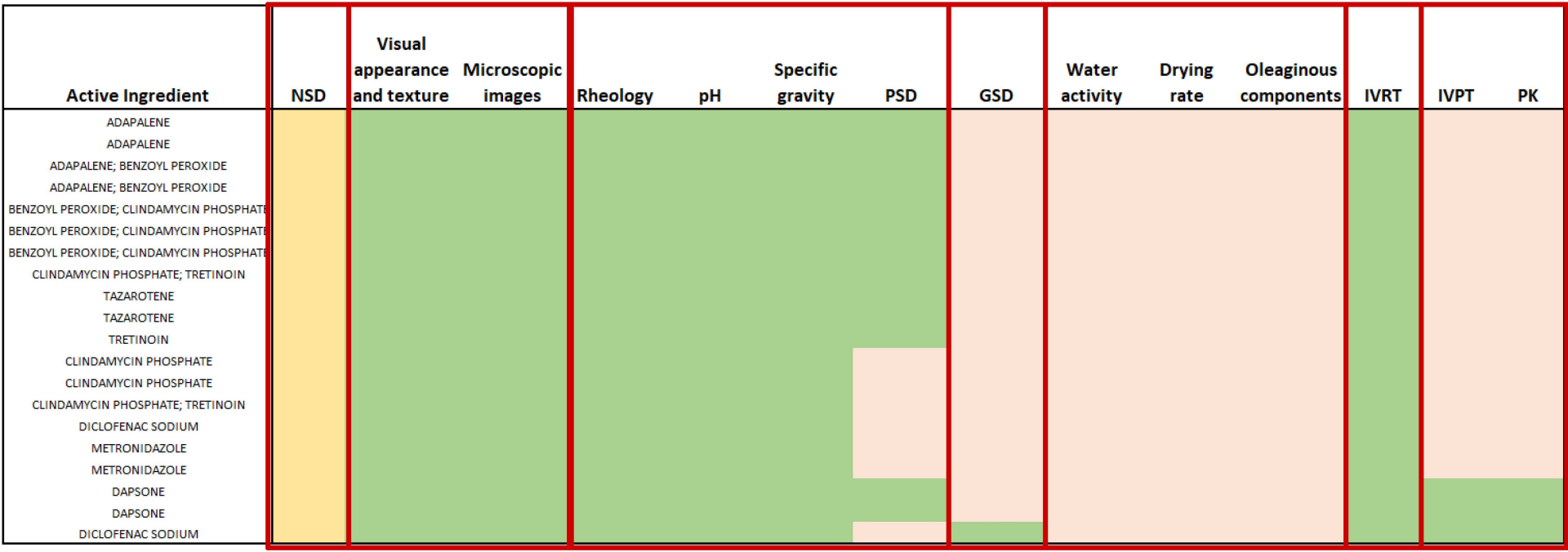
Characterization-based BE approaches



Applicants intending to propose an alternative approach by which to demonstrate bioequivalence should refer to the most recent version of the FDA guidance for industry on *Controlled Correspondence Related to Generic Drug Development*[a] and the most recent version of the FDA guidance for industry on *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*[a] for additional information describing the procedures on how to clarify regulatory expectations regarding your individual drug development program.

*As of July 2023

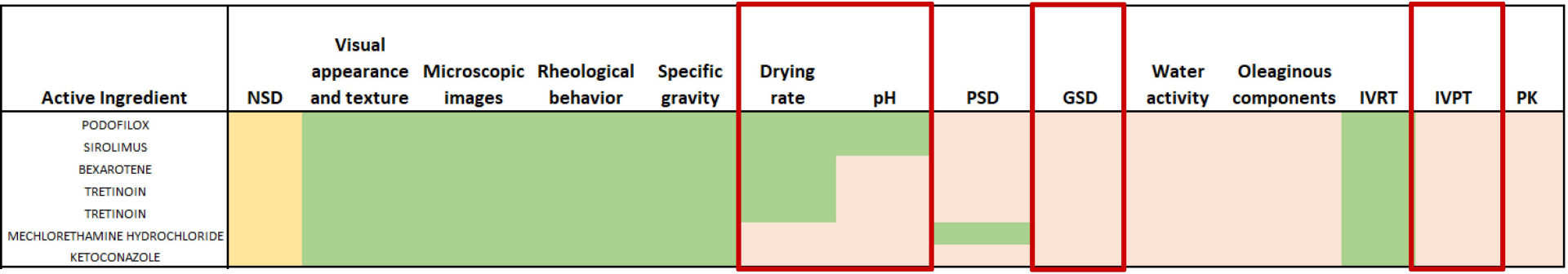
PSGs for topical aqueous gels



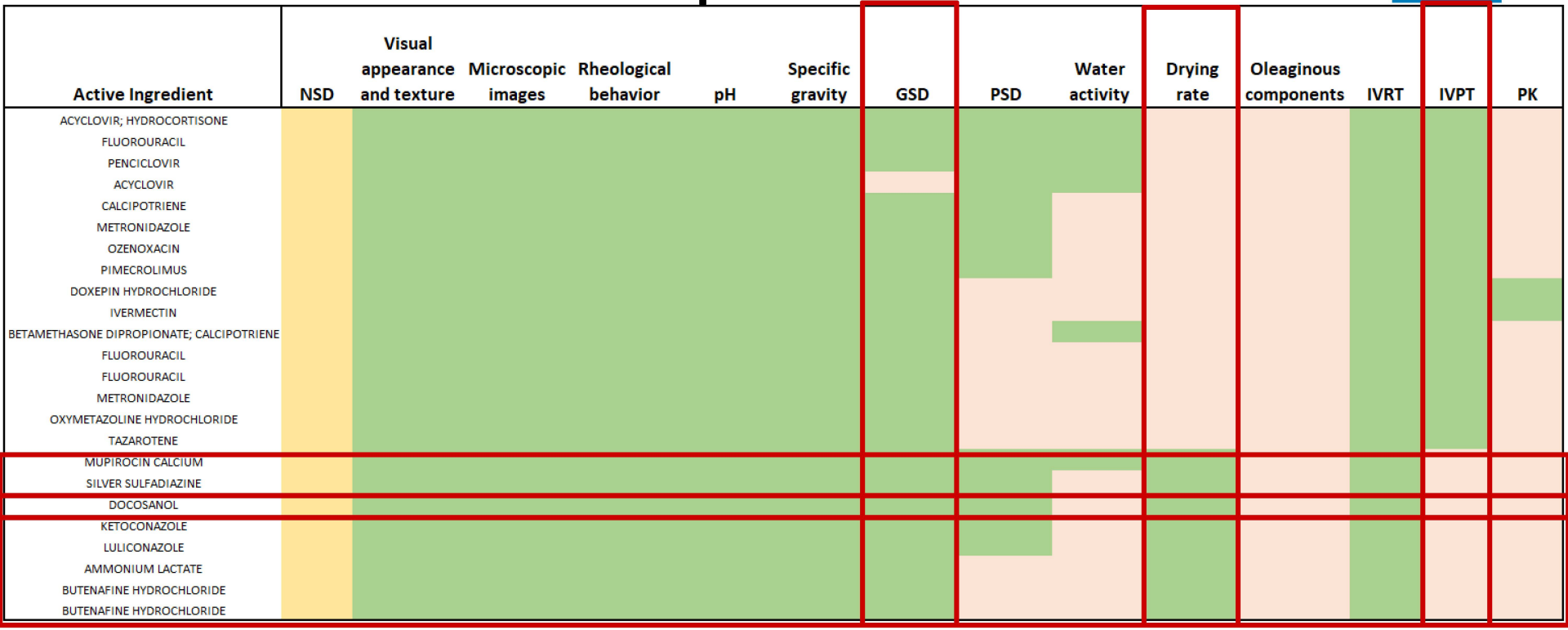
Active Ingredient	NSD	Visual appearance and texture	Microscopic images	Rheology	pH	Specific gravity	PSD	GSD	Water activity	Drying rate	Oleaginous components	IVRT	IVPT	PK
ADAPALENE														
ADAPALENE														
ADAPALENE; BENZOYL PEROXIDE														
ADAPALENE; BENZOYL PEROXIDE														
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														

PSD: Particle size distribution; GSD: Globule size distribution

PSGs for topical non-aqueous gels



PSGs for topical creams



Applied to skin with no stratum corneum

Unique physicochemical properties/dosage form

Site of action is in the superficial stratum corneum

PSGs for topical lotions

Active Ingredient	NSD	Visual appearance and texture	Microscopic images	Rheological behavior	pH	Specific gravity	GSD	Water activity	Drying rate	PSD	Oleaginous components	IVRT	IVPT	Ex vivo pediculicide hair tuft assay	PK
CLINDAMYCIN PHOSPHATE															
CLOBETASOL PROPIONATE															
HALOBETASOL PROPIONATE															
METRONIDAZOLE															
TAZAROTENE															
AMMONIUM LACTATE															
ABAMETAPIR															
BENZYL ALCOHOL															
IVERMECTIN															

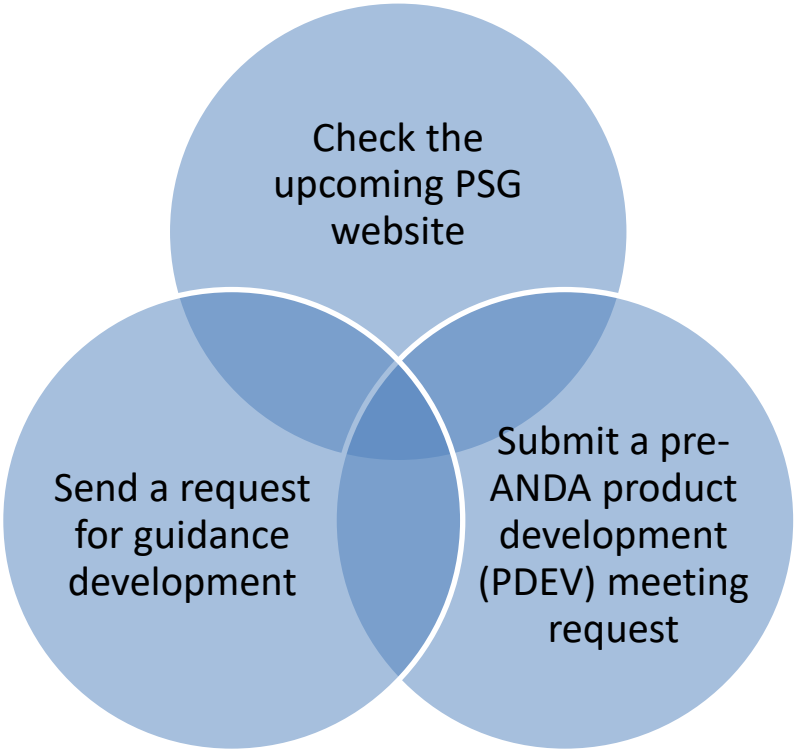
Site of action is in the superficial stratum corneum

Site of action is an external organism (e.g., lice)

PSGs for topical ointments

Active Ingredient	NSD	Visual appearance and texture	Microscopic images	Rheological behavior	Specific gravity	Oleaginous components	PSD	GSD	Drying rate	pH	Water activity	IVRT	IVPT	PK
CRISABOROLE														
CALCIPOTRIENE														
TACROLIMUS														
TACROLIMUS														
BETAMETHASONE DIPROPIONATE; CALCIPOTRIENE														
MICONAZOLE NITRATE; PETROLATUM, WHITE; ZINC OXIDE														
ACYCLOVIR														
LIDOCAINE														
MUPIROCIN														
TIRBANIBULIN														

When a PSG is unavailable



Information to submit in a PDEV meeting request:

- Clear, specific, and comprehensive outline of your exact BE approach
- Specific question(s) related to your proposed BE approach or product development program
- Formulation table with up to three proposed test formulations
- Empirical data to support the proposed BE approach

Upcoming Product-Specific Guidances for Generic Drug Product Development website

Challenge Question #1

Which of the following is false?

A. When a PSG contains a characterization-based BE approach, a NSD standard is always recommended.

B. When a PSG contains a characterization-based BE approach, comparative Q3 characterization is always recommended.

C. When a PSG contains a characterization-based BE approach, an IVRT study is always recommended.

D. When a PSG contains a characterization-based BE approach, a systemic PK study is always recommended.

Challenge Question #2

<u>In general</u>, when is an IVPT study recommended as part of a characterization-based BE approach for a topical product:

A. When the drug product is multiphasic

B. When the drug product is a petrolatum-based ointment

C. Always

D. A and B

Summary

- PSGs for topical products contain harmonized recommendations in alignment with the relevant general guidances.
- The recommendations within a characterization-based BE approach for topical products are product-specific and are based on an understanding of the microstructure and performance of the drug product.
- When a PSG is unavailable, applicants are encouraged to submit pre-ANDA PDEV meeting requests to get the Agency's feedback on a proposed BE approach.

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- Bing Cai, PhD
- Ahmed Zidan, PhD
- Hiren Patel, PhD
- Office of Research and Standards PSG Team
- Office of Generic Drug Policy

Resources

- Product-Specific Guidances for Generic Drug Development website
- "General Considerations for the "No Significant Difference" Evaluation for a Proposed Generic Formulation" (presented on 12/06/2022)
- 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: *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (August 2021)
- Final Guidance for industry: *Controlled Correspondence Related to Generic Drug Development* (December 2020)
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Questions?

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