Development and Status of Product-Specific Guidances for Topical Products

FDA Workshop: Guidance Development and Regulatory Assessment of Generic Topical and Dermal Drug Products

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CDER | U.S. FDA
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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.

Agenda

- Overview of BE approaches within PSGs for topical products
- Characterization-based BE approaches
  - Development of the approach via research
  - Components of the approach
  - Current recommendations within PSGs

BE: Bioequivalence; PSG: Product-specific guidances

Establishing BE for topical products

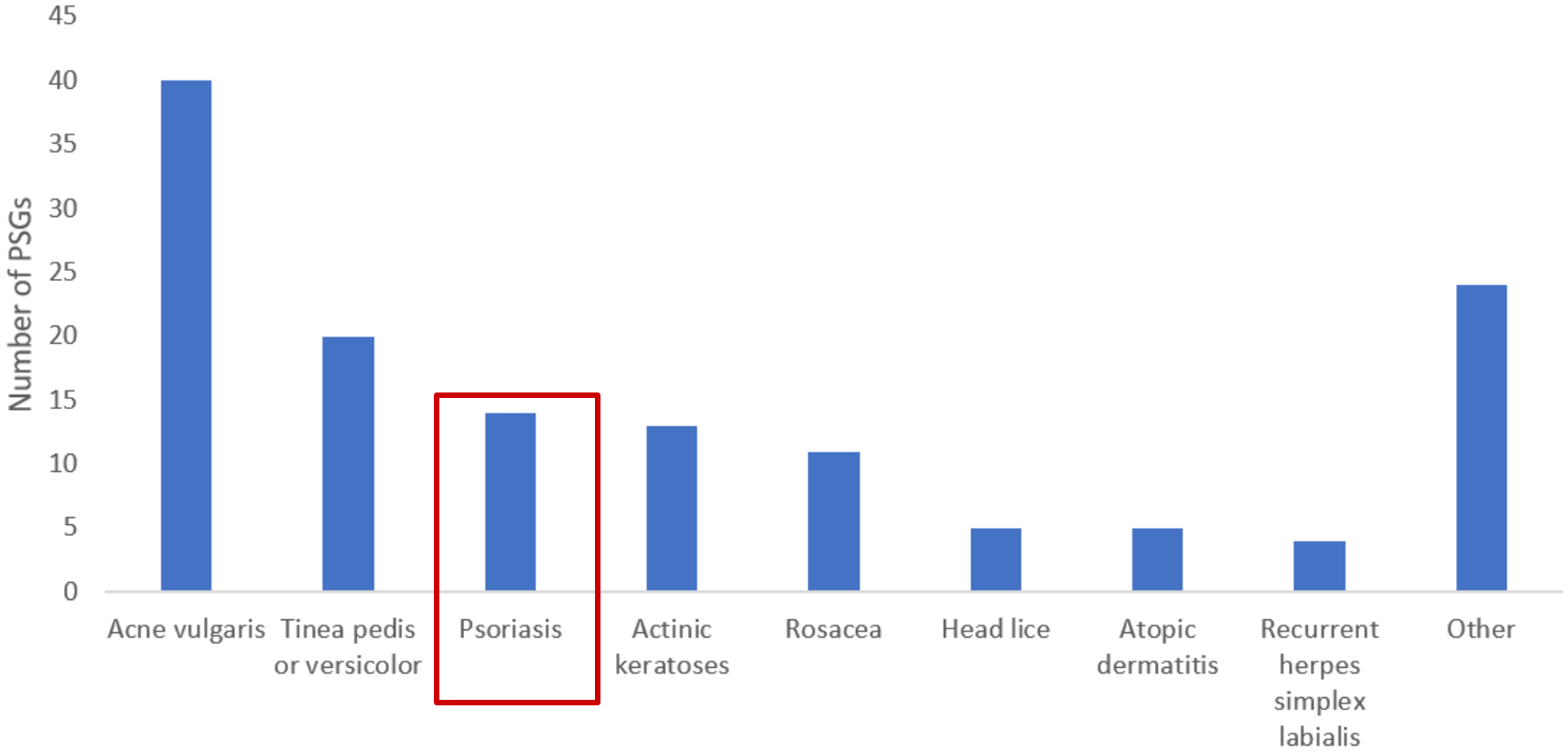
Main examples for BE approaches:

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

PSGs often include multiple BE approaches

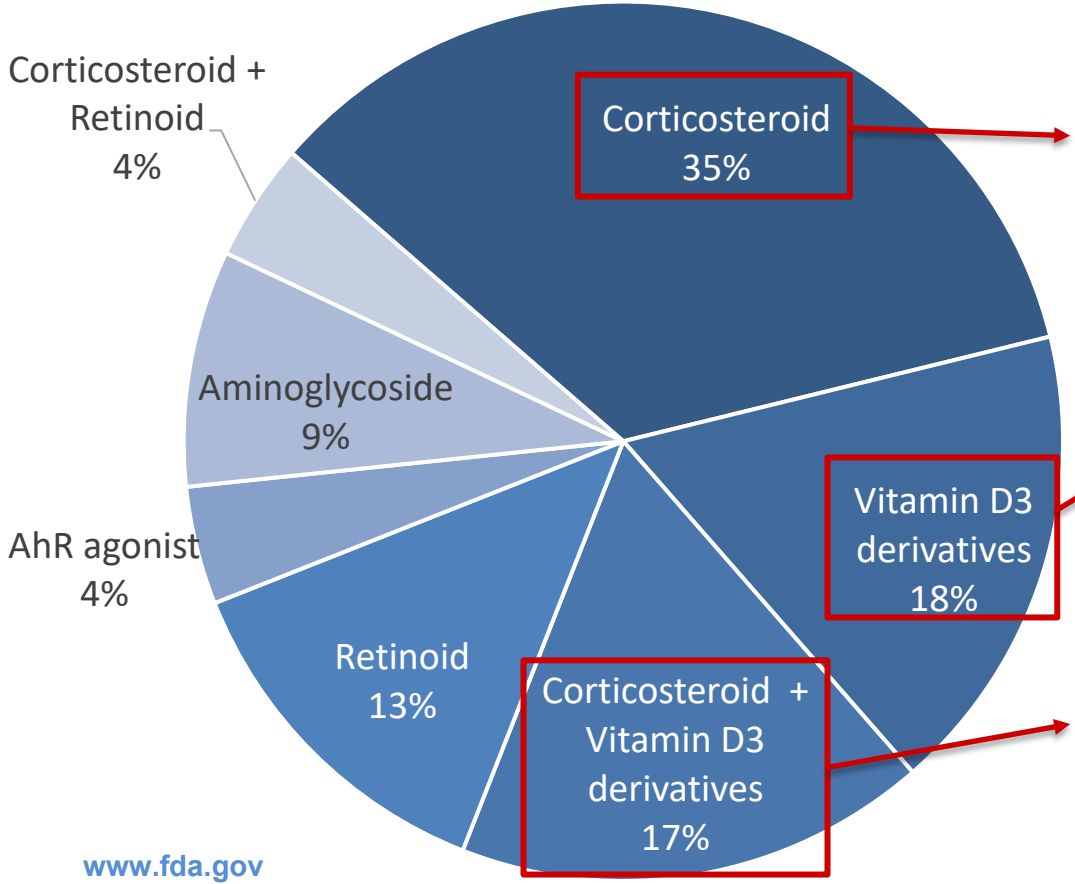
- Examples:
  - Two options: (1) Characterization-based BE approach, or (2) CCEP BE study
  - Two options: (1) Waiver of in vivo BE studies, or (2) VC study

CCEP BE studies for topical products



Data as of September 2024

BE approaches for psoriasis



- Corticosteroid 35%
  - Waiver of in vivo BE studies
  - VC study
  - Characterization-based BE approach
  - CCEPBE study
- Vitamin D3 derivatives 18%
  - Waiver of in vivo BE studies
  - Characterization-based BE approach
  - CCEPBE study
- Corticosteroid + Vitamin D3 derivatives 17%
  - VC study + CCEPBE study
  - VC study + Characterization-based BE approach

AhR: Aryl hydrocarbon receptor

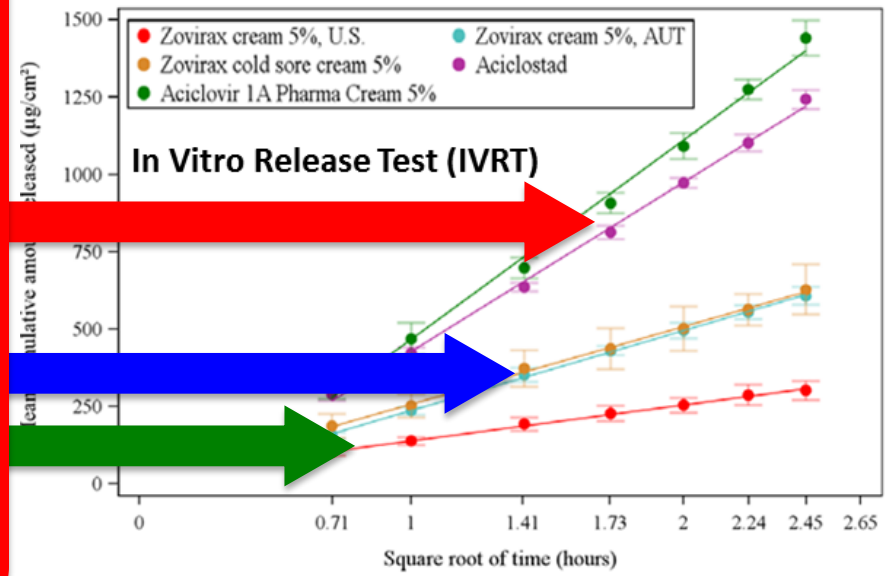
Characterization-based BE approach

- The components (Q1) and quantitative composition (Q2) of a topical product (and how it is manufactured) can modulate its physical and structural arrangement of matter (Q3)
- These Q3 characteristics influence molecular interactions that control the rate and extent of topical bioavailability
- One approach to developing generic topical products is to:
  - Characterize the complexity of the RLD
  - Match the Q1, Q2, and Q3 characteristics of the RLD

RLD: Reference listed drug

In vitro quality and performance

	Zovirax (USA)	Zovirax (UK)	Zovirax (Austria)	Aciclostad (Austria)	Aciclovir-1A (Austria)
	Water	Water	Purified water	Water	Water
	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol
	Mineral oil	Liquid Paraffin	Liquid Paraffin	Liquid Paraffin	Viscous Paraffin
	White petrolatum	White soft paraffin	White Vaseline	White Vaseline	White Vaseline
	Cetostearyl alcohol	Cetostearyl alcohol	Cetostearyl alcohol	Cetyl alcohol	Cetyl alcohol
	SLS	SLS	SLS		
	Poloxamer 407	Poloxamer 407	Poloxamer 407		
		Dimethicone 20	Dimethicone 20	Dimethicone	Dimethicone
		Arlacel 165	Glyceryl Mono Stearate	Glyceryl Mono Stearate	Glyceryl Mono Stearate
		Arlacel 165	Polyoxyethylene stearate	Macrogol stearate	Polyoxyethylene stearate
Density (g/cc)	1.02	1.02	1.02	1.02	1.01
Content Uniformity (%)	97.9 ± 0.7	99.6 ± 1.4	100 ± 2.2		
Polymorphic Form	2,3 hydrate	2,3 hydrate	2,3 hydrate		
Crystilline Habit	Rectangular	Rectangular	Rectangular	Ovoid	Ovoid
Particle size (d50) (µm)	3.8				
pH	7.74	7.96	7.54	4.58	6.05
Work of Adhesion	59	81	60	17	18
Drug in Aq (mg/g)	0.49	0.64	0.49	0.37	0.26
Drying Rate (T-30%)	>12h	~8h	~7h	<1h	<1h
Water Activity	0.75	0.73	0.74	0.95	0.95



Data provided courtesy of Prof. Narasimha Murthy (University of Mississippi) ***FDA Award U01-FD005223***

In vitro quality and performance

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	Water	Water	Purified water	Water	Water
	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol
	Mineral oil	Liquid Paraffin	Liquid Paraffin	Liquid Paraffin	Viscous Paraffin
	White petrolatum				
	Cetostearyl alcohol	Cetostearyl alcohol	Cetostearyl alcohol	Cetyl alcohol	Cetyl alcohol
	SLS	SLS	SLS		
	Poloxamer 407	Poloxamer 407	Poloxamer 407		
		Dimethicone 20	Dimethicone 20		
		Arlacel 165	Glyceryl Mono Stearate	Glyceryl Mono Stearate	Glyceryl Mono Stearate
		Arlacel 165	Polyoxyethylene stearate	Macrogol stearate	Polyoxyethylene stearate
Density (g/cc)	1.02	1.02	1.02	1.02	1.01
Content Uniformity (%)	97.9 ± 0.7	99.6 ± 1.4	100 ± 2.2	99.7 ± 1.7	98.3 ± 2.6
Polymorphic Form	2,3 hydrate	2,3 hydrate	2,3 hydrate	2,3 hydrate	2,3 hydrate
Crystilline Habit	Rectangular	Rectangular	Rectangular	Ovoid	Ovoid
Particle size (d50) (µm)	3.8	2.5	3.4	6.8	6
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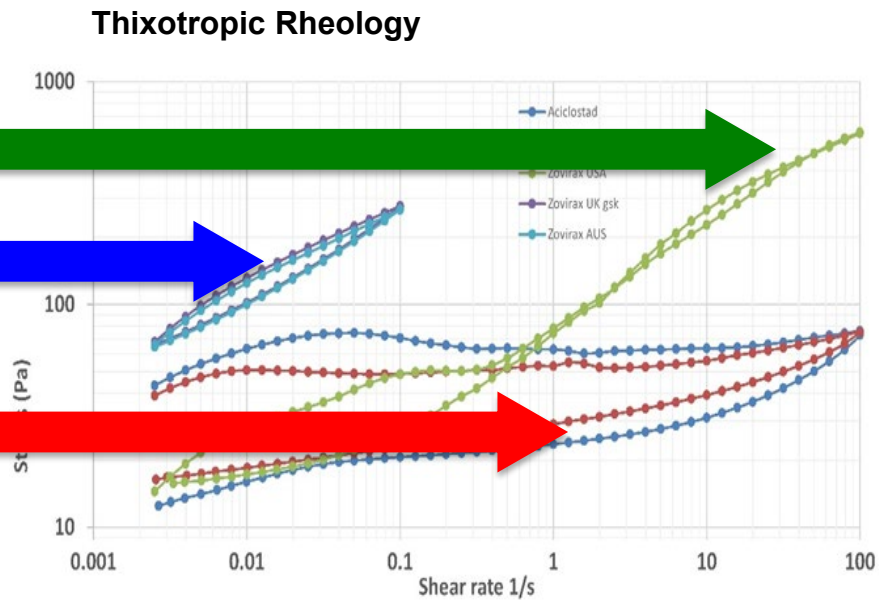

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In vitro cutaneous PK study

	Zovirax (USA)	Zovirax (UK)	Zovirax (Austria)	Aciclostad (Austria)	Aciclovir-1A (Austria)
	Water	Water	Purified water	Water	Water
	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol
	Mineral oil	Liquid Paraffin	Liquid Paraffin	Liquid Paraffin	Viscous Paraffin
	White petrolatum	White soft paraffin	White Vaseline	White Vaseline	White Vaseline
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Polymorphic Form	2,3 hydrate	2,3 hydrate	2,3 hydrate	2,3 hydrate	2,3 hydrate
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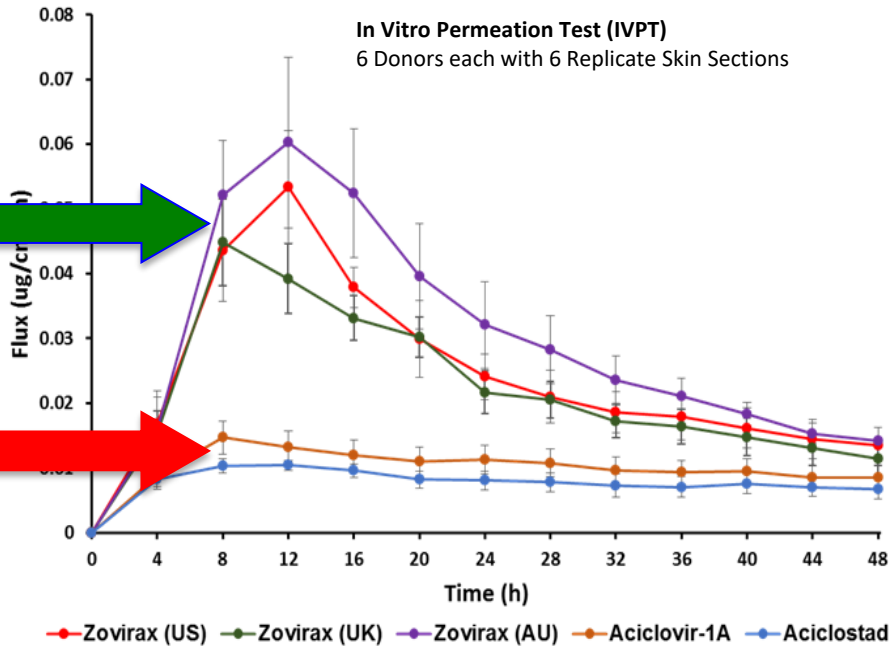


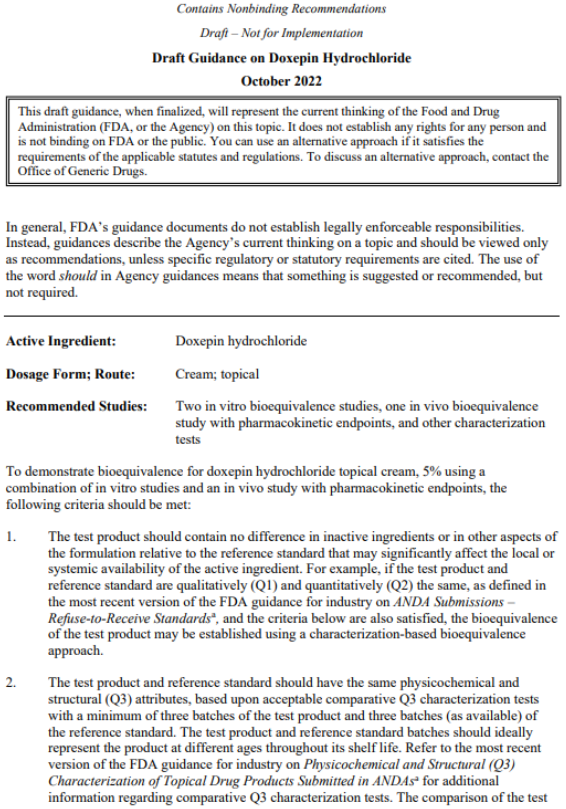
PK: Pharmacokinetics

Data provided courtesy of Prof. Narasimha Murthy (University of Mississippi) ***FDA Award U01-FD005223***

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*



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

ANDA: Abbreviated new drug application

NSD standard

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

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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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Dosage Form; Route: Cream; topical

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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%

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

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.

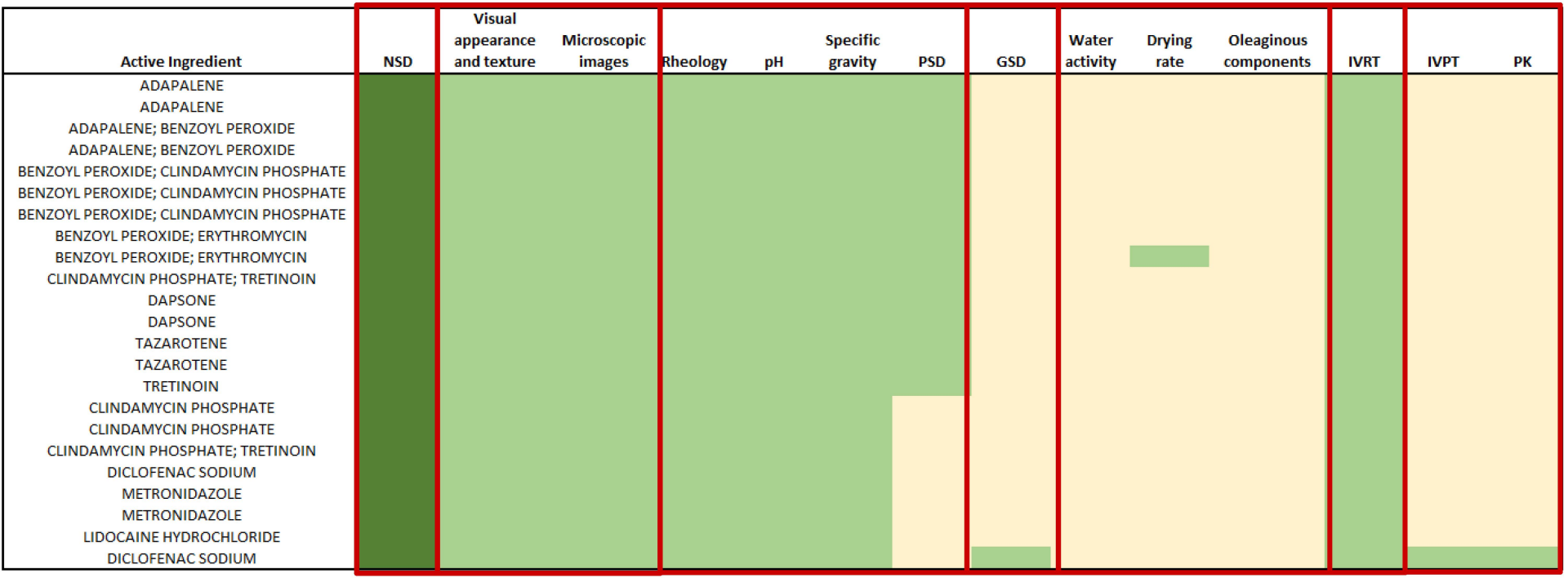
In vivo systemic PK study

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.

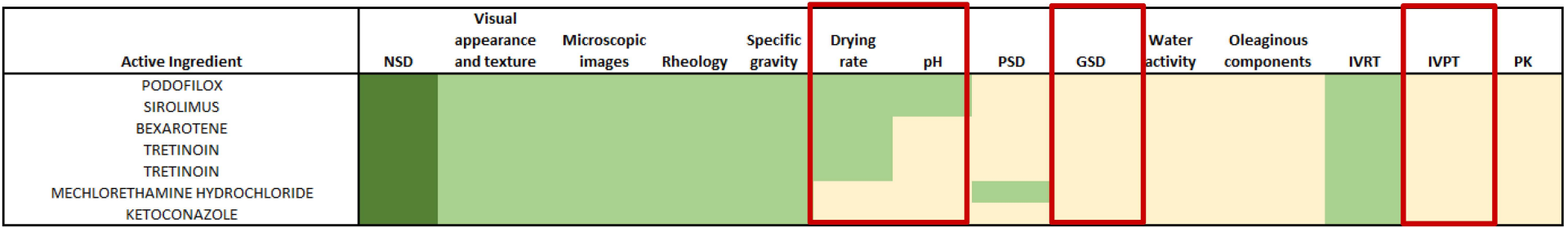
Guidance for industry *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*

PSGs for topical aqueous gels

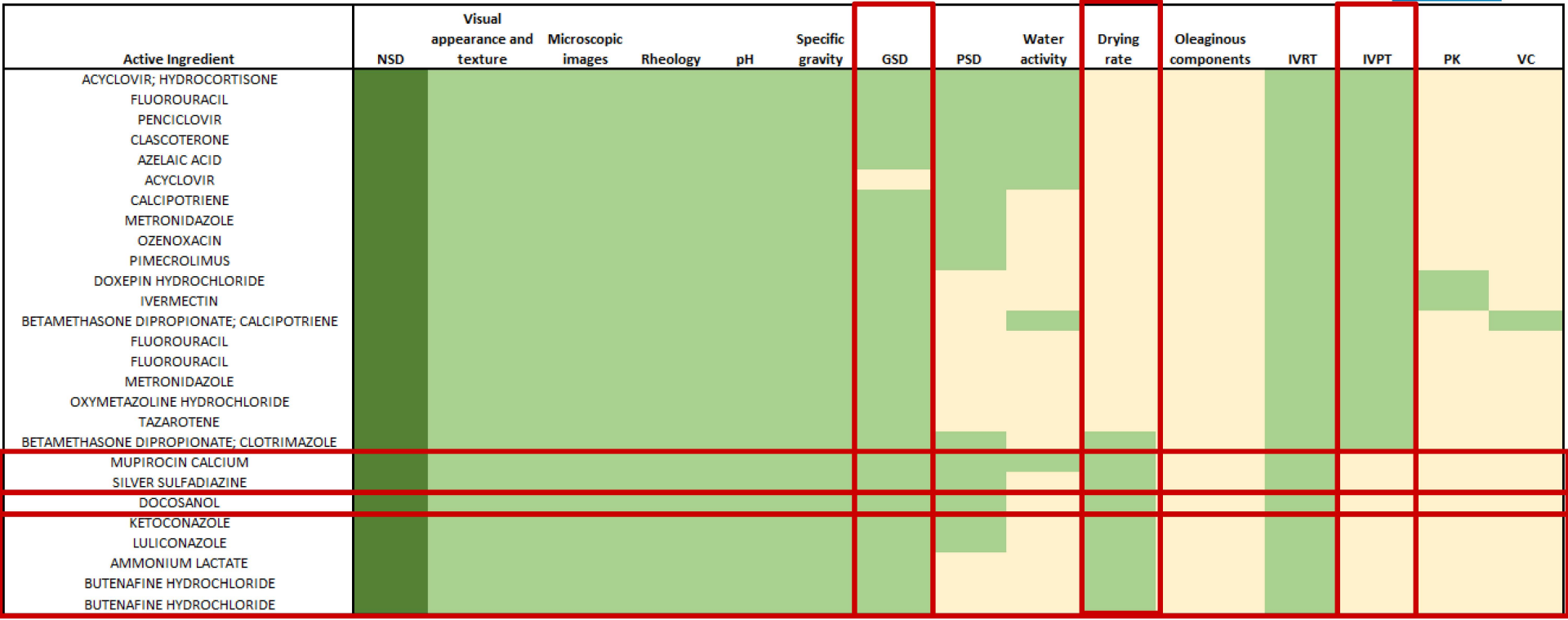


PSD: Particle size distribution; GSD: Globule size distribution

PSGs for topical non-aqueous gels



PSGs for topical creams

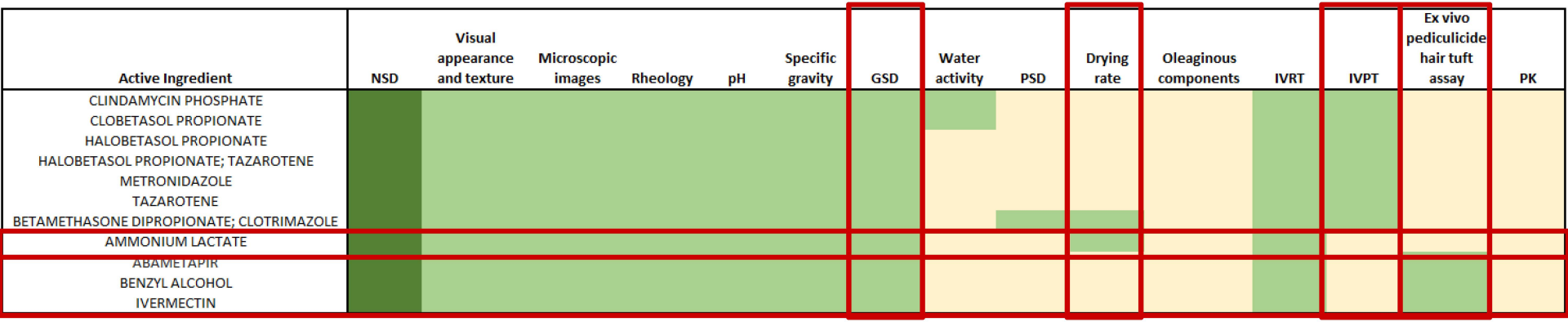


Applied to skin with no stratum corneum

Unique physicochemical properties/dosage form

Site of action is in the superficial stratum corneum

PSGs for topical lotions

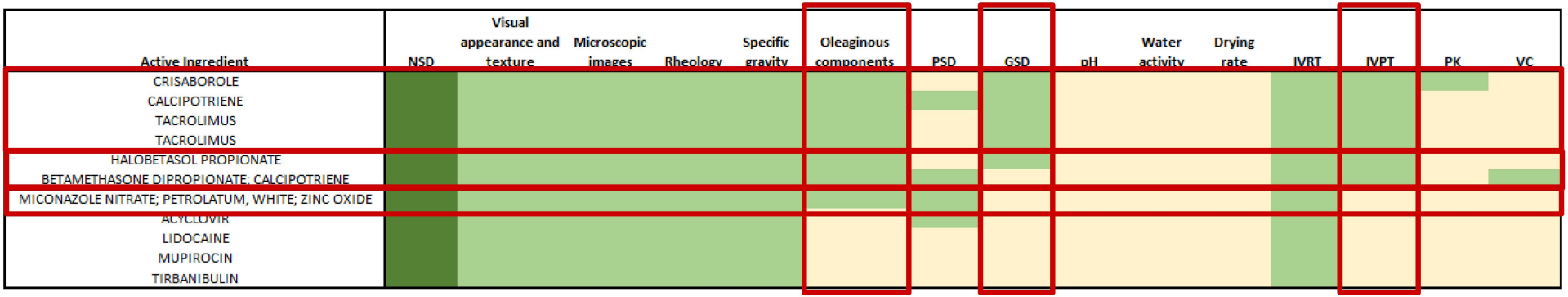


Active Ingredient	NSD	Visual appearance and texture	Microscopic images	Rheology	pH	Specific gravity	GSD	Water activity	PSD	Drying rate	Oleaginous components	IVRT	IVPT	Ex vivo pediculicide hair tuft assay	PK
CLINDAMYCIN PHOSPHATE															
CLOBETASOL PROPIONATE															
HALOBETASOL PROPIONATE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

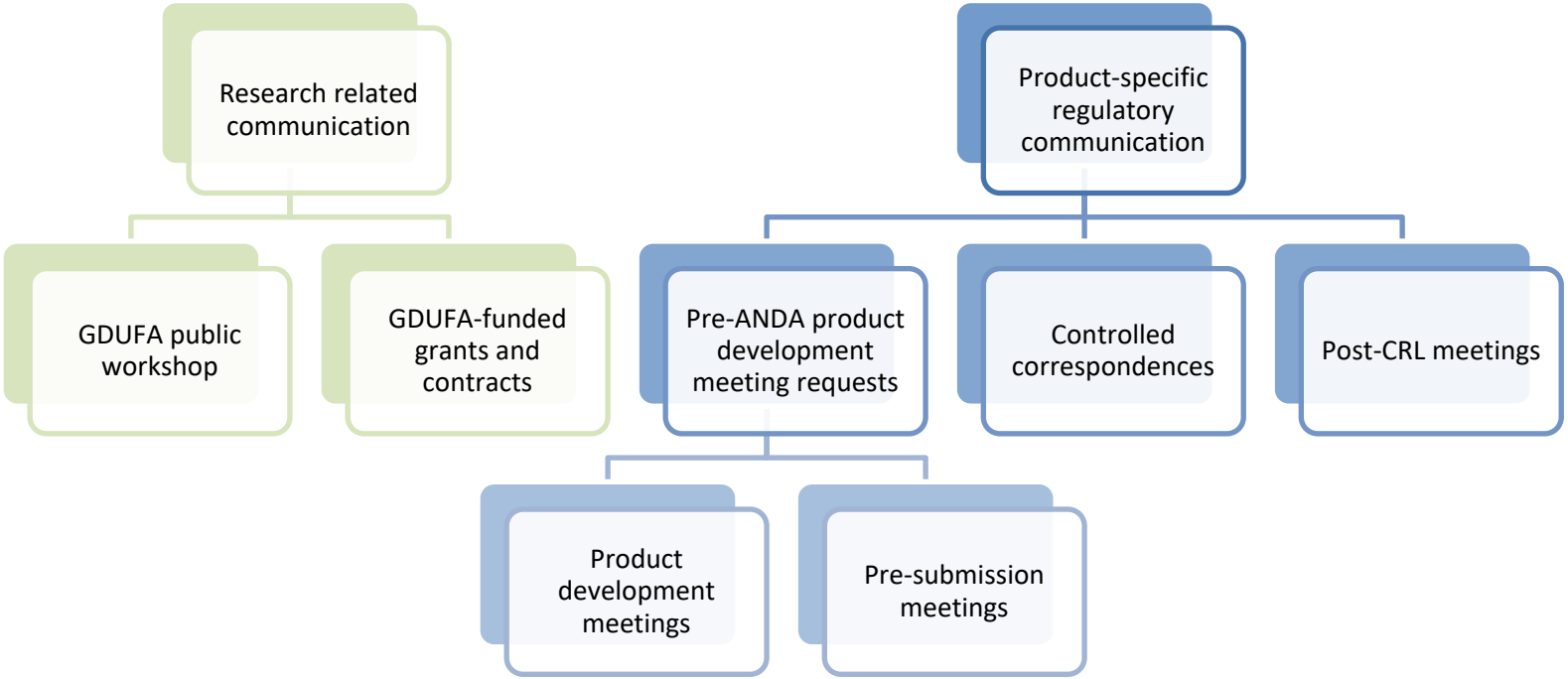
Site of action is in the superficial stratum corneum

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

PSGs for topical ointments



Communication with the Agency



GDUFA: Generic Drug User Fee Amendments; CRL: Complete response letter

Office of Generic Drugs Science & Research Program

Guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*

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.

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- Office of Generic Drug Policy

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  - Narasimha Murthy, PhD, University of Mississippi

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)
- Final Guidance for industry: *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (October 2022)
- Upcoming Product-Specific Guidances for Generic Drug Product Development website
- Office of Generic Drugs Science & Research Program

U.S. FOOD & DRUG ADMINISTRATION

Questions?

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