U.S. FOOD & DRUG ADMINISTRATION

How research supports development of product-specific guidance for topical products

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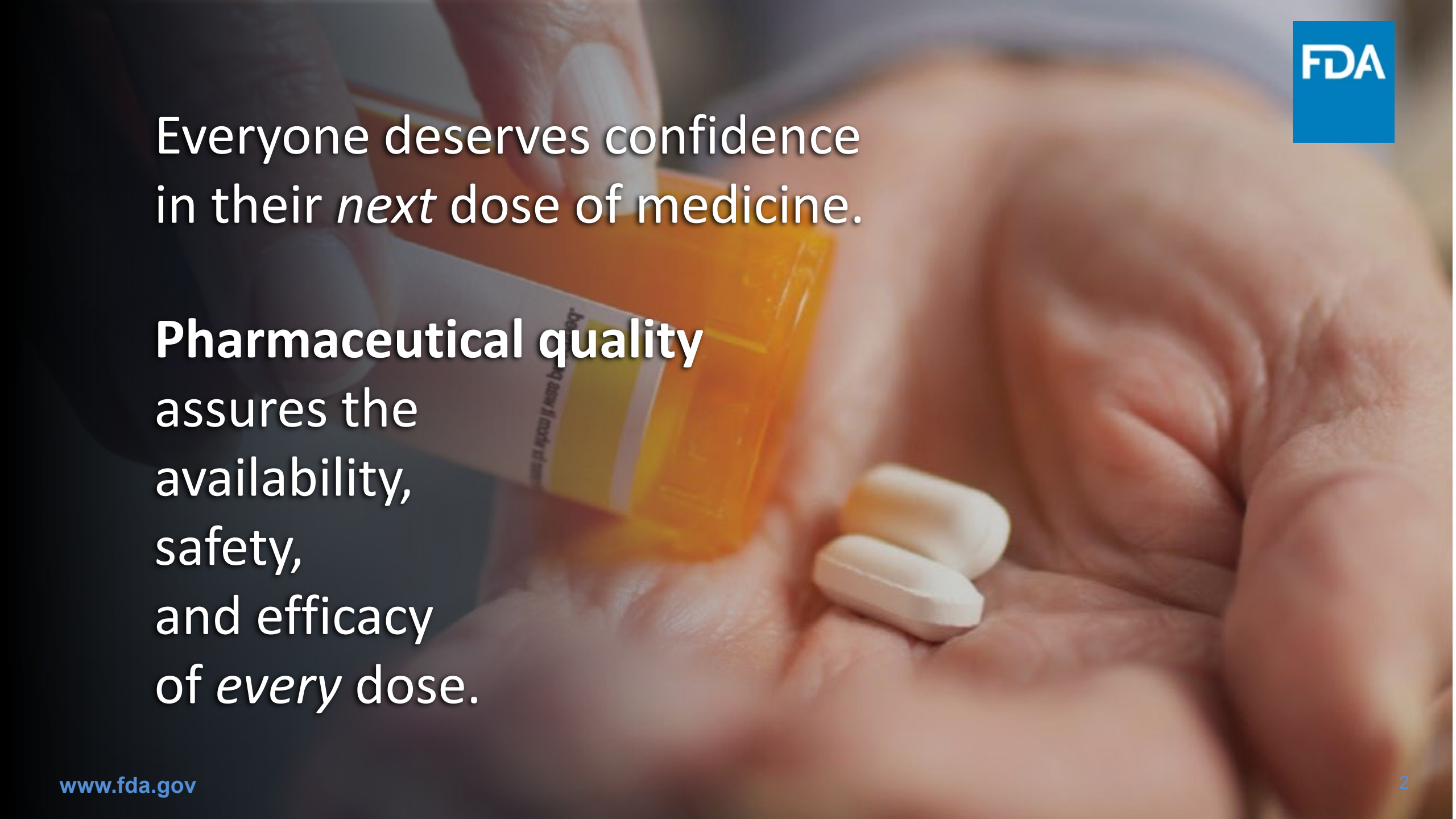
Sep 13th, 2023

Fall 2023 SBIA Workshop: Advancing Generic Drug Development: Translating Science to Approval
Session 1: Noteworthy Guidance Publications for Topical and Transdermal Products



Everyone deserves confidence
in their *next* dose of medicine.

Pharmaceutical quality
assures the
availability,
safety,
and efficacy
of *every* dose.

Role of research in guideline development for topicals

Formulation Development	Excipient selection and compatibility studies Formulation design for enhanced topical penetration
Product performance	In vitro: IVRT, IVPT, rheology, sensory attributes, etc. In vivo: PK, biodistribution, elimination, etc.
Safety and Efficacy Assessment	Toxicology studies: Safety of topical products Clinical trials: Efficacy, dosing, and patient outcomes
Data Collection and Analysis	Robust data collection and statistical analysis Compliance with regulatory requirements

Patient Access to Topical Products

Overview

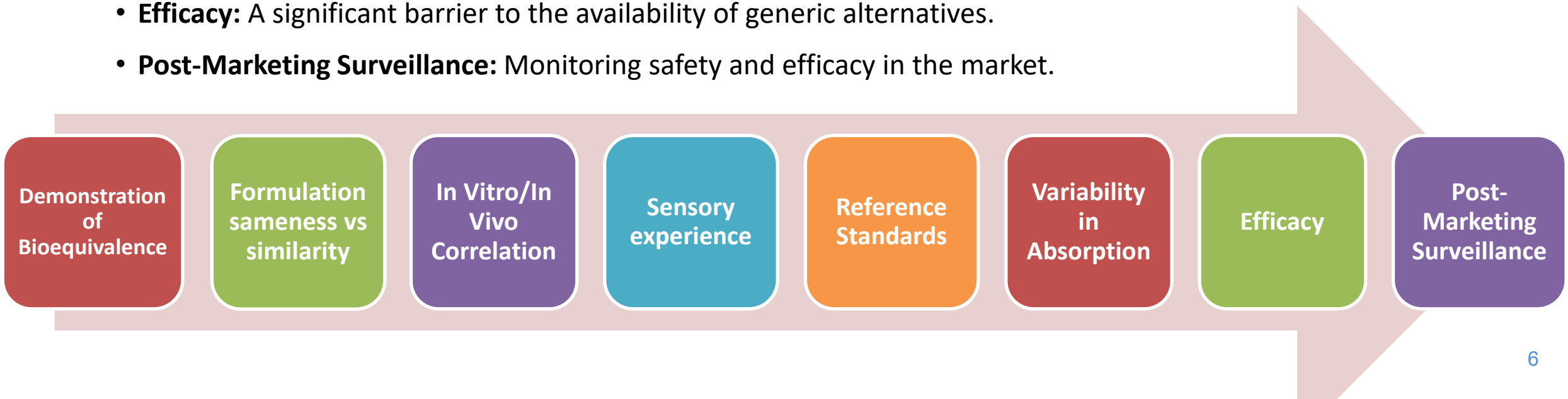
- Availability of generic topical products
- Demonstration of bioequivalence
- In vitro characterization data support PSG development
- Case studies of GDUFA research:
    - Tirbanibulin topical ointment
    - Clascoterone topical cream
- Key takeaways
- Challenge question

Learning Objectives

- Gain a comprehensive understanding of the framework used to assess bioequivalence of generic topical products.
- Explore the multifaceted aspects of bioequivalence, including in vitro dissolution and permeation studies, among others.
- Comprehend the pivotal role of GDUFA research in shaping the PSGs for topical drug products.

Availability of Generic Topical Products

- **Demonstration of Bioequivalence**: In vivo vs in vitro approaches
- **Formulation sameness vs similarity:** Complex excipients and microstructure
- **In Vitro/In Vivo Correlation:** Scale up and post approval changes
- **Sensory experience:** Comparable perceptions of grittiness, silky-smoothness, and cooling sensation
- **Reference Standards**: Lack of appropriate reference standards can hinder demonstration of comparability.
- **Variability in Absorption:** Differences in excipients, formulation, or manufacturing processes.
- **Efficacy:** A significant barrier to the availability of generic alternatives.
- **Post-Marketing Surveillance:** Monitoring safety and efficacy in the market.



Demonstration of Bioequivalence

BE approaches

In vivo approaches

- In vivo pharmacokinetic (PK)
- In vivo pharmacodynamic (vasoconstriction)
- Clinical endpoint studies

In silico approach

- Quantitative methods, modeling and simulation

In vitro approaches

- Formulation sameness
- Structural similarity
- IVRT (in vitro release testing)
- IVPT (in vitro permeation testing)

?

Research

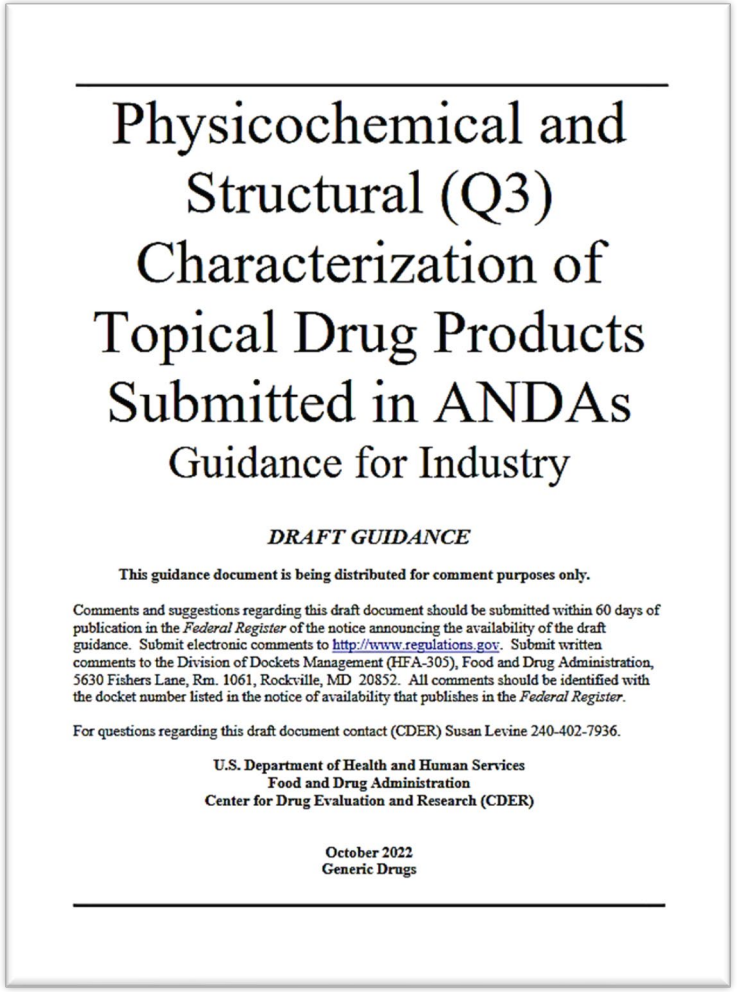
PSG

Patient access to topical generic products

Physicochemical and structural (Q3) sameness are critical to BE performance for topical products

21 CFR 314.94(a)(9)(v)

- Generally, a drug product intended for topical use,… shall contain the same inactive ingredients as the reference [product] …. However, an ANDA may include **different inactive ingredients** provided that the applicant identifies and **characterizes the differences** and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.



Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in 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 http://www.regulations.gov. Submit written comments to the Division of Dockets Management (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) Susan Levine 240-402-7936.

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

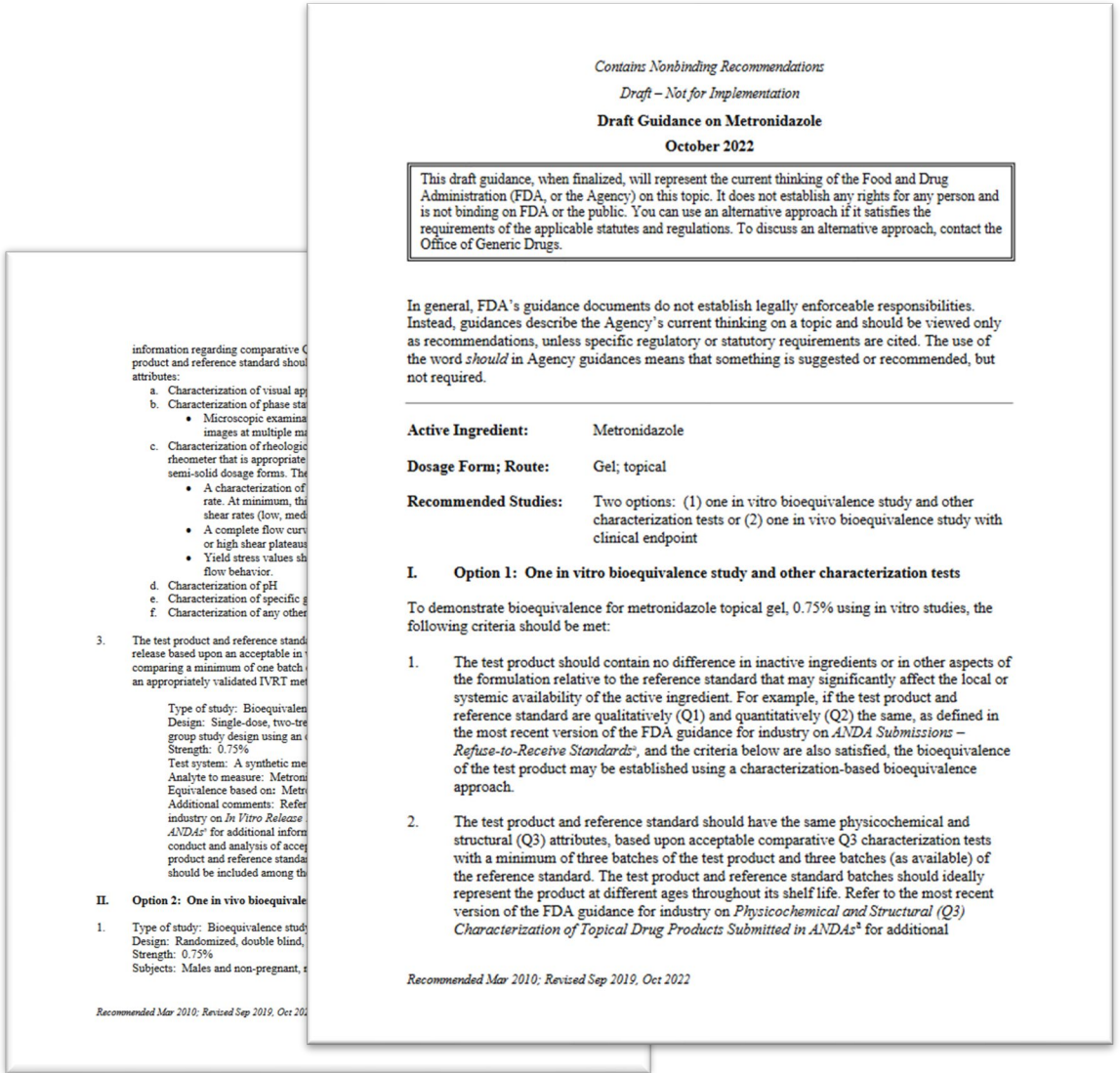
October 2022
Generic Drugs

Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs - Guidance for Industry https://www.fda.gov/media/162471/download
PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-314

Physicochemical and structural (Q3) sameness are critical to BE performance for topical products

Example: PSG of metronidazole cream - draft Oct 2022

- **Recommended studies:**
  - In vivo BE study with clinical endpoint, or
  - In vitro BE study and other characterizations
    - Formulation sameness
    - Physicochemical characterization
      - Visual appearance and texture
      - Phase states and structural organization of matter
      - Rheological behavior
      - pH
      - Specific gravity
      - Any other potentially relevant Q3 attributes
    - IVRT



Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Metronidazole

October 2022

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Active Ingredient: Metronidazole

Dosage Form; Route: Gel; topical

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

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

To demonstrate bioequivalence for metronidazole topical gel, 0.75% using in vitro studies, 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*, 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* for additional

Recommended Mar 2010; Revised Sep 2019, Oct 2022

https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_019737.pdf

In vitro characterization data support PSG development

In vitro physicochemical characterization data and innovative research

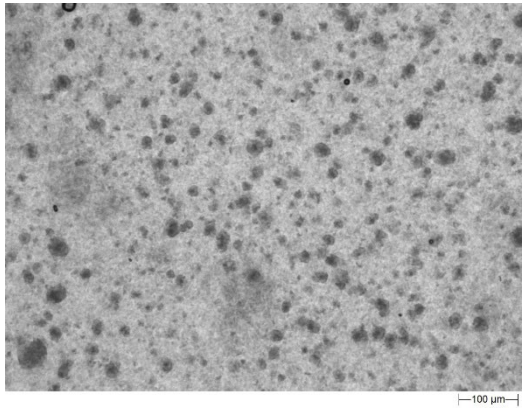
- Inclusion in bioequivalence guidance
- Introduction and validation of novel analytical techniques
- Addressing challenges of multi-phasic formulations
- Real-world data and evidence integration into the bioequivalence evaluation process
- Continuous improvement to refine and update existing PSGs
- International harmonization efforts

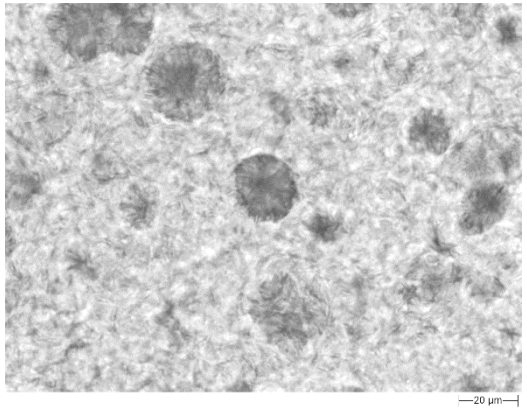
Case studies of GDUFA research supporting PSG development for topical products

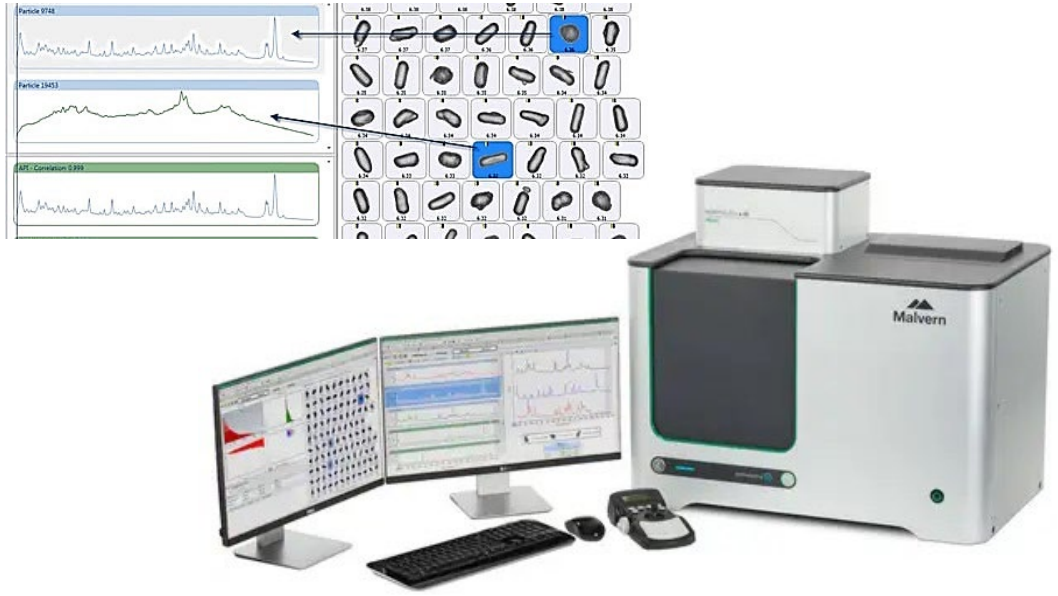
https://www.fda.gov/media/150142/download

Case 1: BE for Tirbanibulin topical ointment, 1% using in vitro studies

- Tirbanibulin ointment 1% contains mono- and di-glycerides and propylene glycol.
- **Question**: What is the composition of the immiscible droplets? Are the formulation's phase characteristics and API states critical for product performance?
- **Research:** Microscopic examination → Staining test → Chemical identification using Raman spectroscopy.
- **Tool:** Morphologically-directed Raman spectroscopy (MDRS)



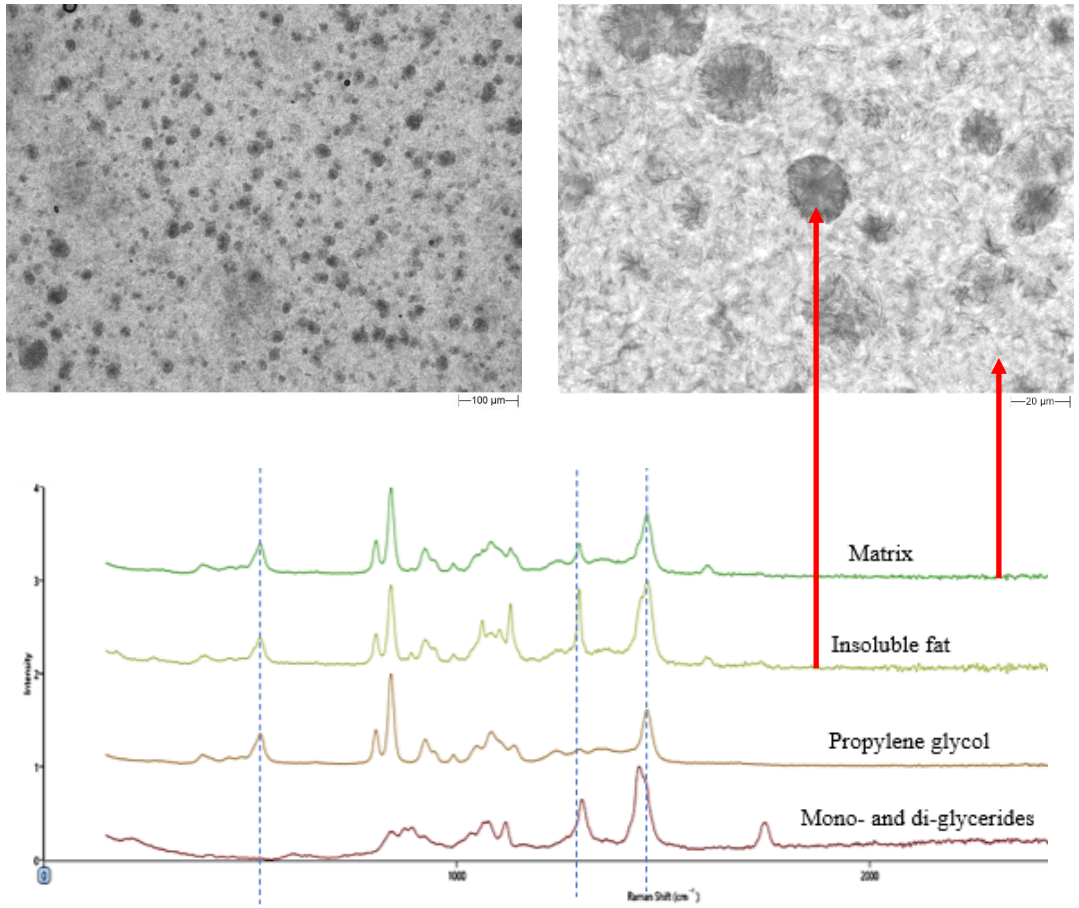


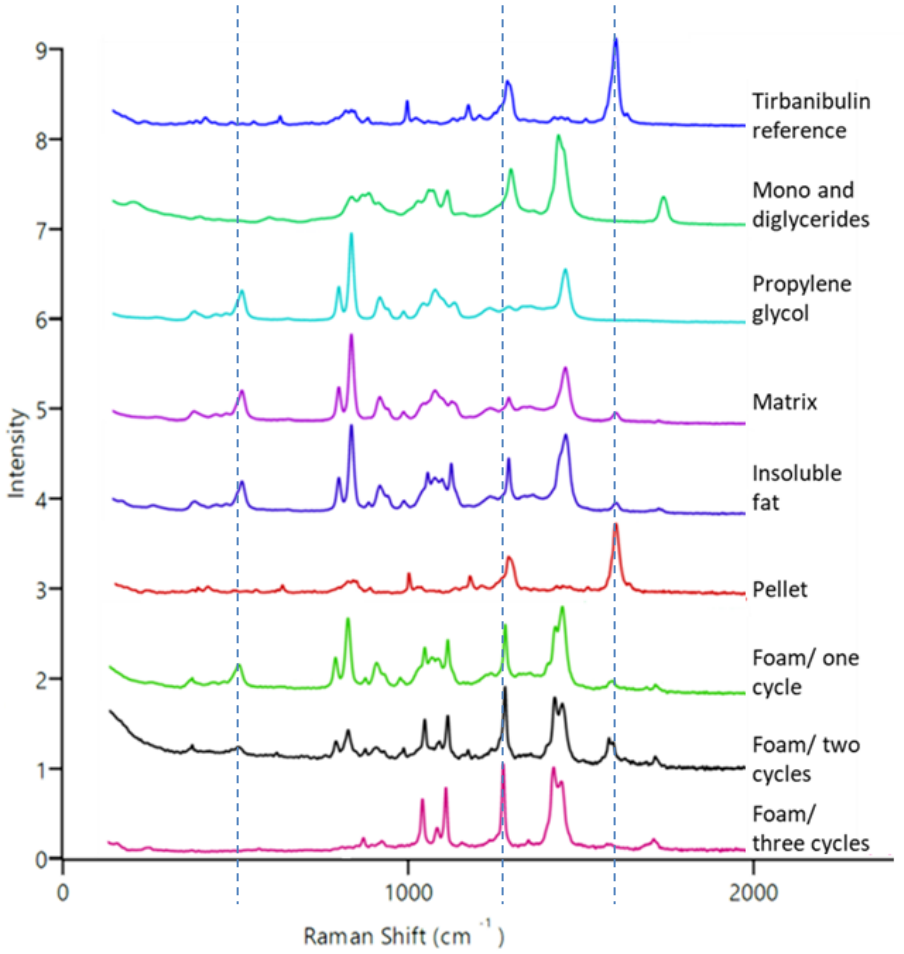


(https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213189s000lbl.pdf)

The AAPS Journal volume 21, Article number: 14 (2019)

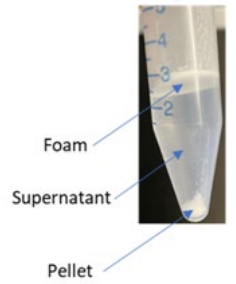
Case 1: BE for Tirbanibulin topical ointment, 1% using in vitro studies





Phase separation

Centrifugation cycles

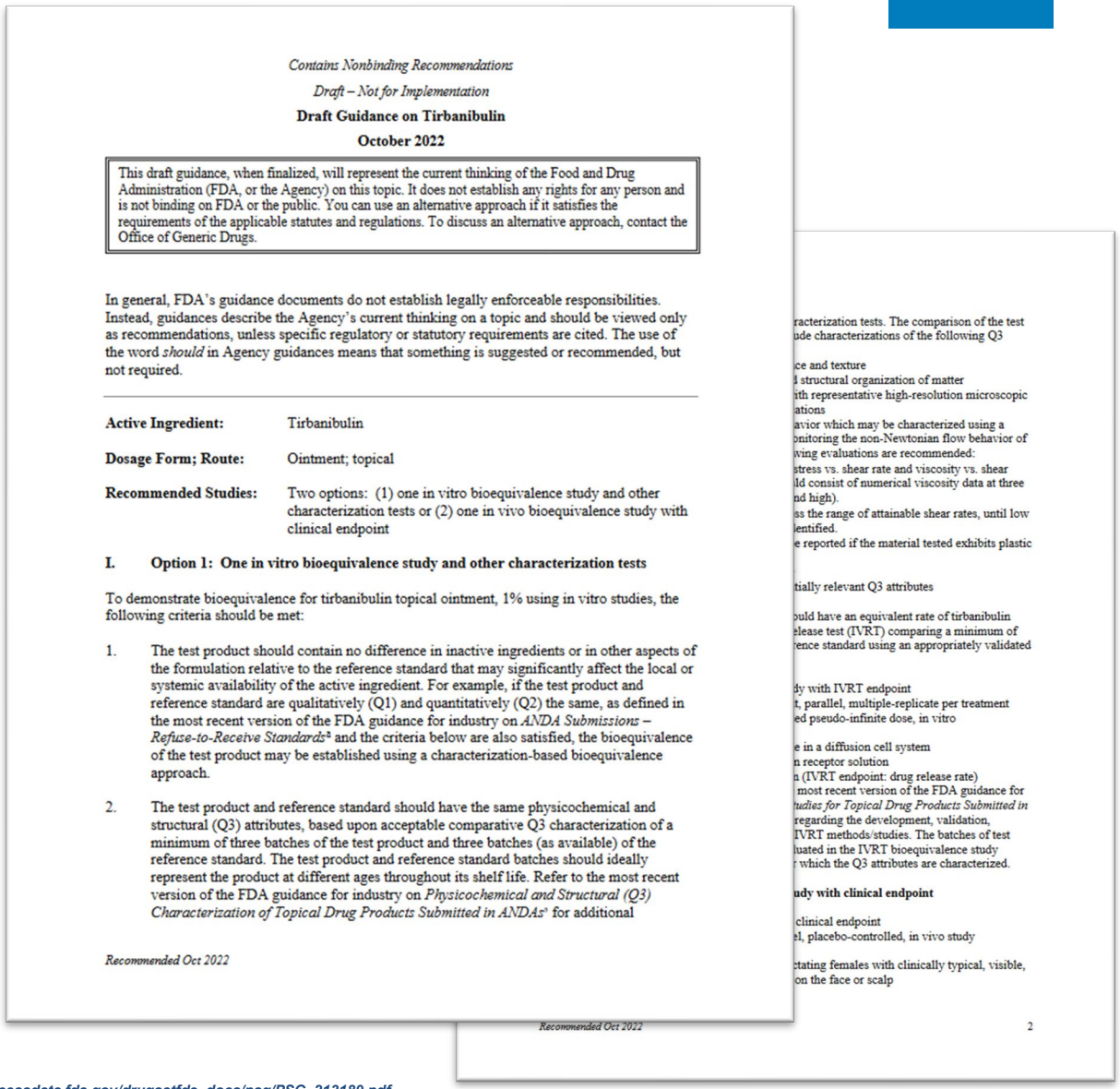


- The developed method of Raman spectroscopy efficiently detected the individual components of tirbanibulin ointment.
- Raman spectra of matrix and the insoluble fat showed unique peaks of all ingredients of the ointment

Case 1: BE for Tirbanibulin topical ointment, 1% using in vitro studies

PSG recommendations (among others) Oct 2022:

- **IVPT was not recommended.**
- Characterization of visual appearance and texture
- Characterization of phase states and structural organization of matter
  - ➢ Microscopic examination with representative high-resolution microscopic images at multiple magnifications



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Draft – Not for Implementation

Draft Guidance on Tirbanibulin

October 2022

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Active Ingredient: Tirbanibulin

Dosage Form; Route: Ointment; topical

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

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

To demonstrate bioequivalence for tirbanibulin topical ointment, 1% using in vitro studies, 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*[3] 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 of 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*[5] for additional

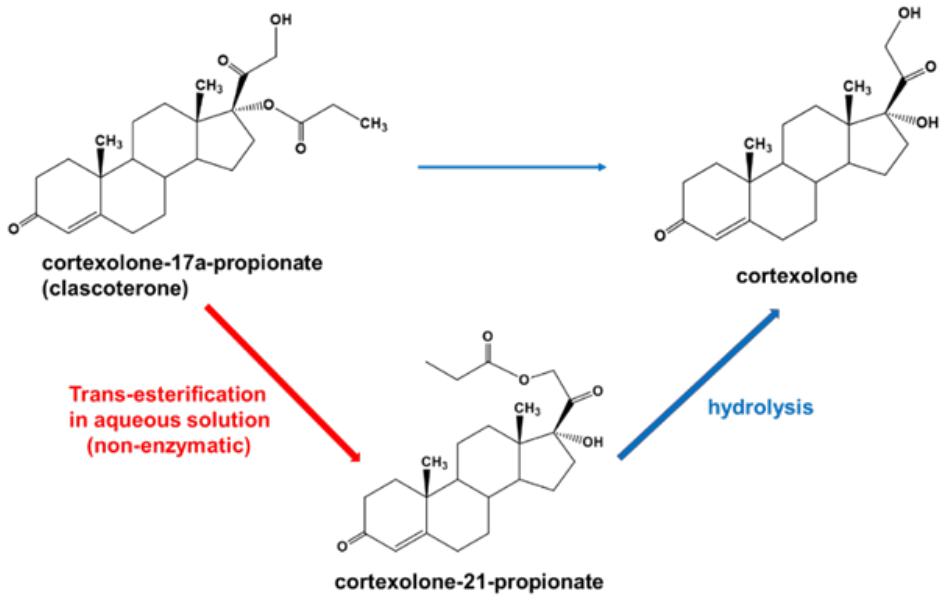
Recommended Oct 2022

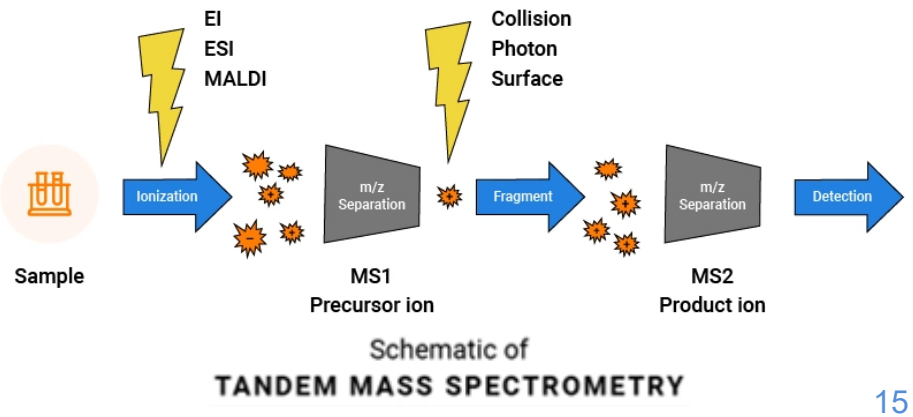
Recommended Oct 2022 2

https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_213189.pdf

Case 2: BE for clascoterone topical cream , 1% using in vitro studies

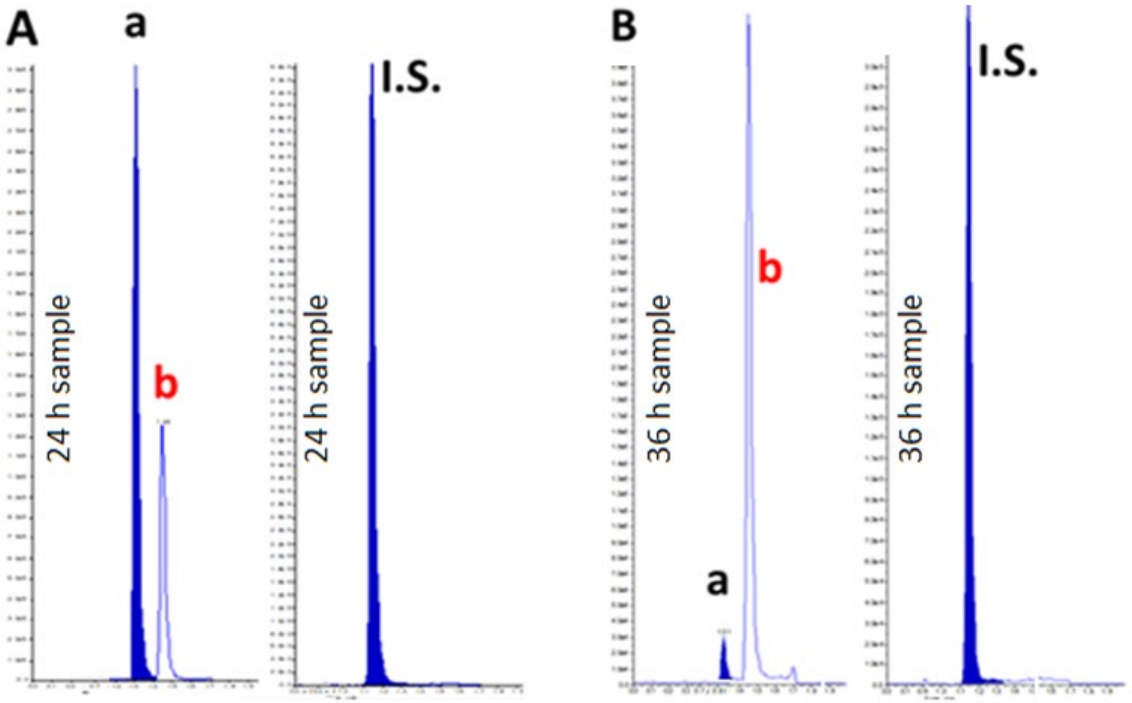
- Clascoterone in topical cream (1%) is not stable in physiological solutions and can be hydrolyzed to cortexolone via cortexolone 21-propionate at body temperature.
- **Question**: What is potential analyte(s) to be used for quantification in IVPT samples?
- **Research:** Develop an analytical method for the evaluation of clascoterone, cortexolone, and cortexolone 21-propionate following permeation testing.
- **Tool:** IVPT → Mass-balance → LC-MS/MS.





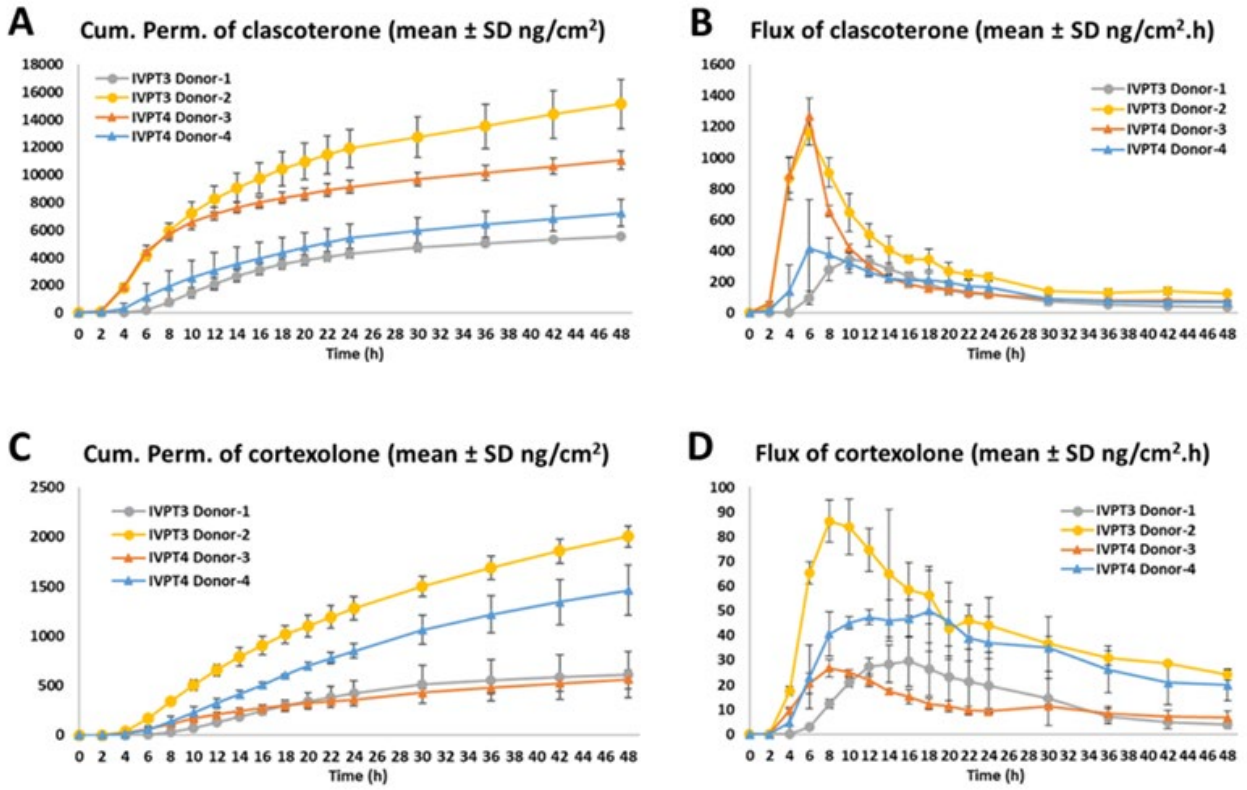
https://www.nebiolab.com/complete-guide-on-liquid-chromatography-mass-spectrometry-lc-ms/

Case 2: BE for clascoterone topical cream , 1% using in vitro studies



Moving from 24 h to 36 h:

- A significant decrease of the clascoterone peaks.
- A significant increase of the cortexolone-21-propionate peaks.
- The internal standard peak intensity was stable over the observed period.



IVPT profiles of clascoterone and cortexolone obtained using the in-line flow-through system.

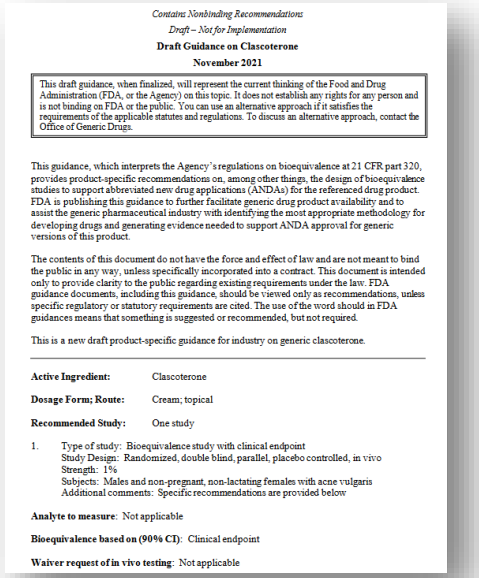
Yang Yang et al., Method development for the evaluation of in vitro skin permeation of clascoterone from clascoterone topical cream, 1%. 2023 American Chemical Society, Poster 3823563.

Case 2: BE for clascoterone topical cream , 1% using in vitro studies

PSG recommendations (among others):

- (Adequate) IVPT is feasible to characterize effect of globule size distribution of clascoterone topical cream.
  - Clascoterone and cortexolone may be used as analytes for analysis of permeation samples.
  - Timely sample processing in the permeation samples.

Nov 2021



Contains Nonbinding Recommendations
Draft – Not for Implementation
Draft Guidance on Clascoterone
November 2021

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This guidance, which interprets the Agency's regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA guidances means that something is suggested or recommended, but not required.

This is a new draft product-specific guidance for industry on generic clascoterone.

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

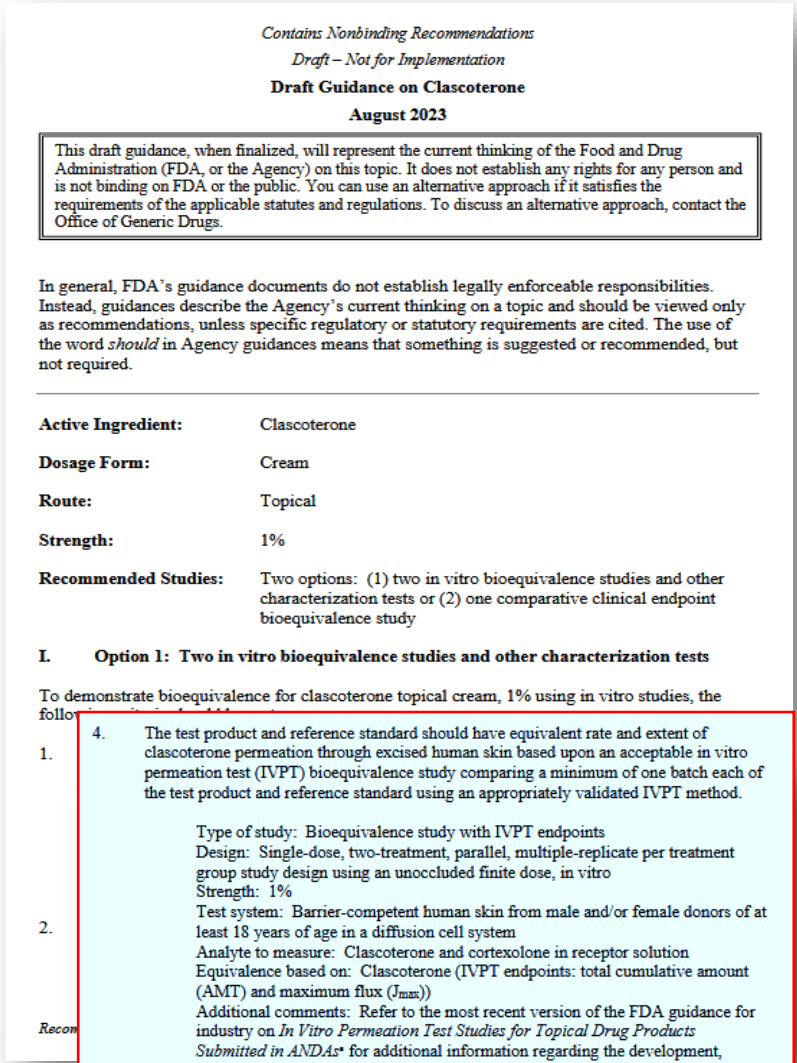
Analyte to measure: Not applicable

Bioequivalence based on (90% CI): Clinical endpoint

Waiver request of in vivo testing: Not applicable

Guidance revision and update

Aug 2023



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Draft Guidance on Clascoterone
August 2023

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Active Ingredient: Clascoterone

Dosage Form: Cream

Route: Topical

Strength: 1%

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

I. Option 1: Two in vitro bioequivalence studies and other characterization tests

To demonstrate bioequivalence for clascoterone topical cream, 1% using in vitro studies, the follo

1.

2.

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*• 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.

Recom

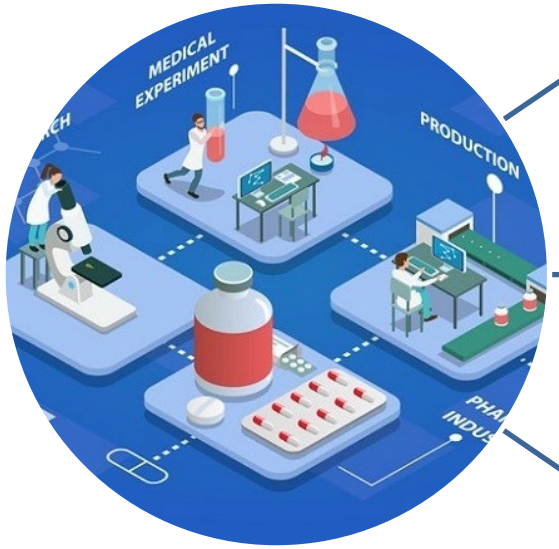
Yang Yang et al., Method development for the evaluation of in vitro skin permeation of clascoterone from clascoterone topical cream, 1%. 2023 American Chemical Society, Poster 3823563.

https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_213433.pdf
https://www.fda.gov/drugs/guidances-drugs/upcoming-product-specific-guidances-generic-drug-product-development

Key takeaways….

PSG

- Development of PSG
- Assessing BE.



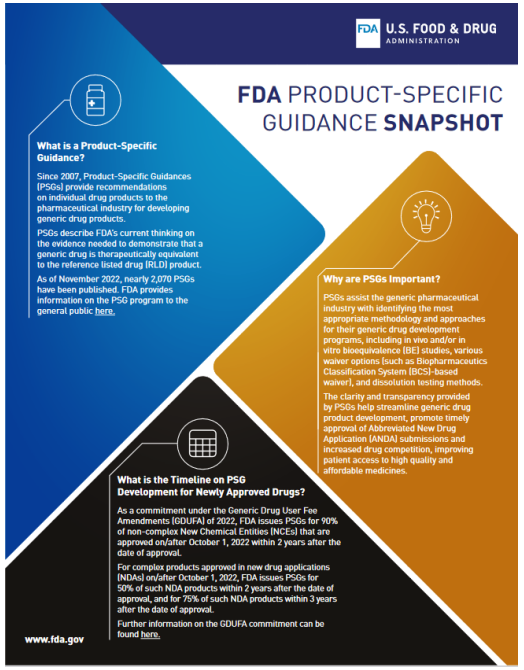
GDUFA research

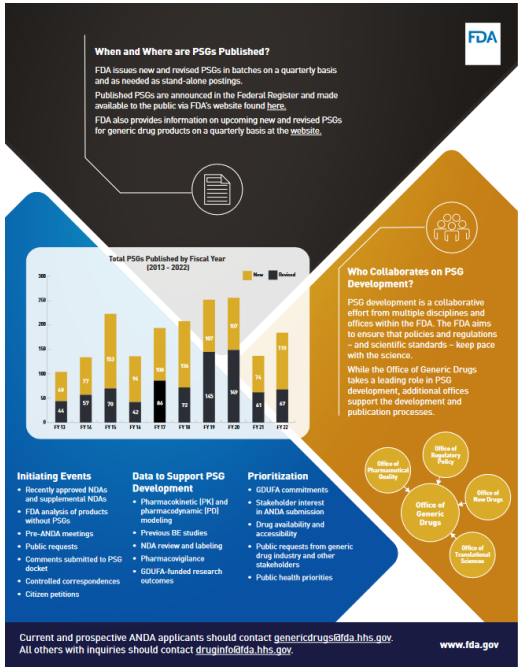
Evidence

- Safety
- Efficacy
- Therapeutic interchangeability

Approvals

- Safe
- Effective generics
- Affordable and reliable topical products





Challenge question

Which technique may be used for providing morphological information and identifying molecular components through chemical mapping of topical formulations?

A) Scanning Electron Microscopy (SEM)

B) Differential Scanning Calorimetry (DSC)

C) Fourier Transform Infrared Spectroscopy (FTIR)

D) Morphologically-directed Raman Spectroscopy (MDRS)

Acknowledgement

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Thank you