Impact of GDUFA Regulatory Science and Research Program on Topical Product Availability

Dermatology Innovation Webinar

The Science Behind Innovations In Topical Generic Drug Assessment Opportunities And Challenges

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Lead Pharmacologist

Office of Research and Standards

Office of Generic Drugs| CDER | U.S. FDA

September 19, 2023

Disclaimer

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

Strategy for Research

Components and Composition

Prospective Generic Product

"No Significant Difference" in Formulation
(Characterization Based Approach)

- *Characterization of the Physical and Structural Properties* ***(Q3)***
- ***IVRT*** *(In Vitro Release Test)*
- ***IVPT*** *(In Vitro Permeation Test)*
- *In vivo systemic pharmacokinetic* ***(PK)*** *studies*
- *In* ***silico****-based tools (Modeling and Simulation)*

"Differences" in Formulation
(Currently Under Development)

- *Impact of Formulation Differences on* ***Thermodynamic*** *Potential*
- ***Cutaneous PK*** *Approaches*
  - *Dermal Microdialysis*
  - *Dermal Open Flow Microperfusion*
  - *Raman Spectroscopy-based Tools*
- *Comparative Clinical Endpoint Studies*

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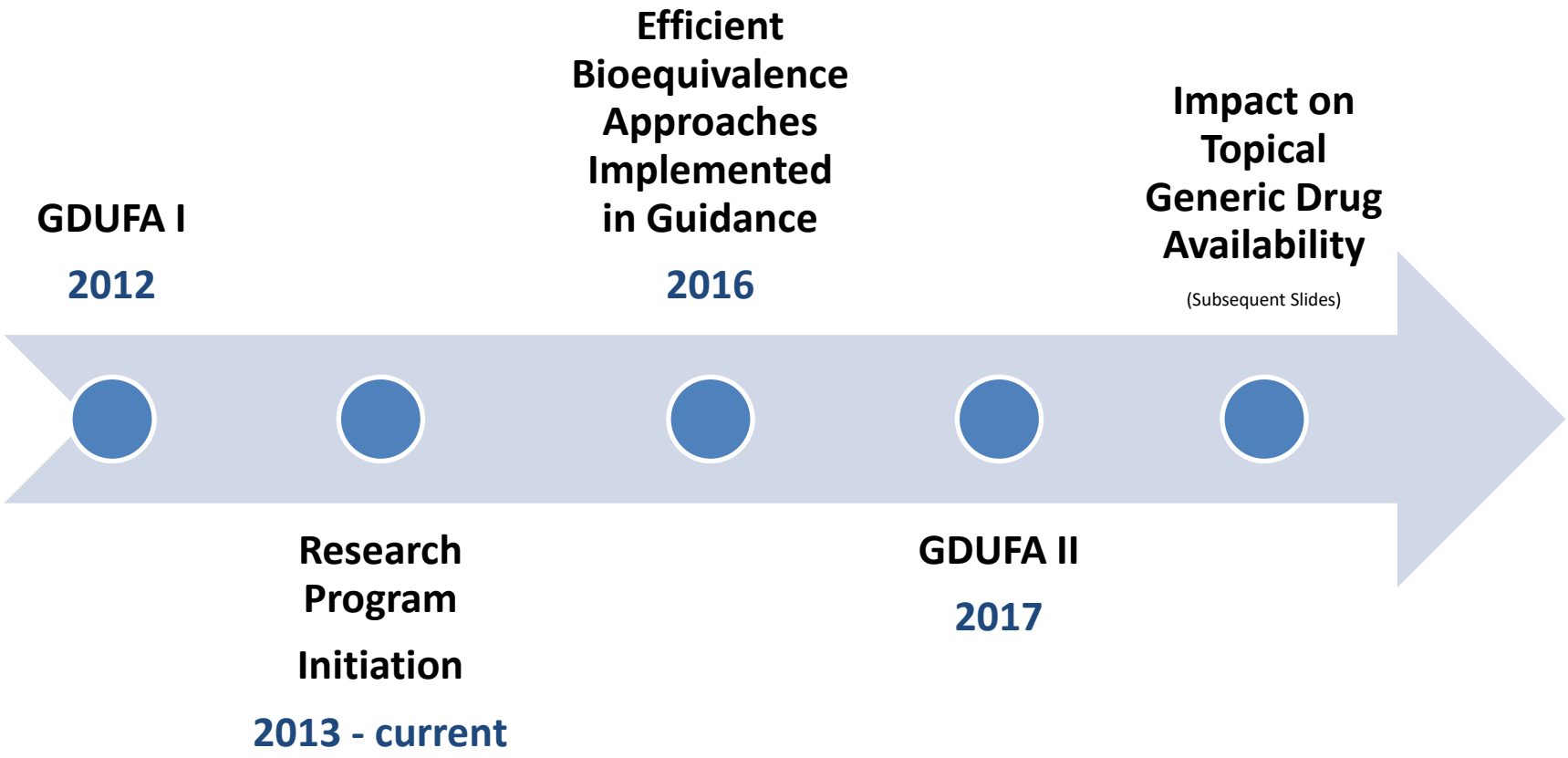
Timeline for the Program



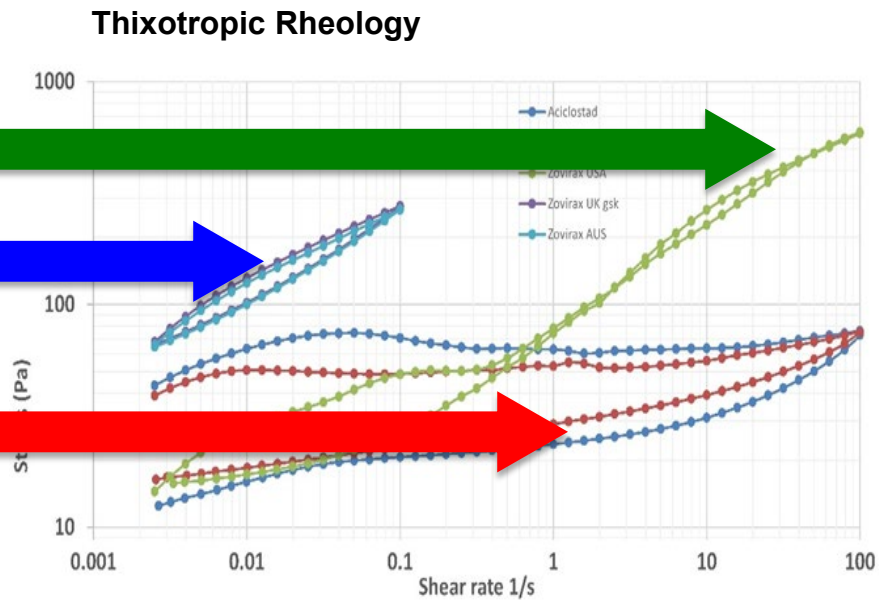
Research Portfolio

*Supporting the Development of the **Characterization Based Approaches***

- *1U01FD004947 Bioequivalence of Topical Drug Products: In Vitro-In Vivo Correlations with Audra Stinchcomb at University of Maryland*
- *1U01FD005233 Topical Products and Critical Quality Attributes with Sathyanarayana Murthy at University of Mississippi*
- *1U01FD005226 Characterization of Critical Quality Attributes for Semisolid Topical Drug Products with Michael Roberts at University of South Australia*
- *HHSF223201610125C Assessment of the In Vitro Percutaneous Absorption, In Vitro Rate of Release, and Physicochemical Properties of Selected Commercially Available AT Rated Ointment Formulations with Shanna Geigle at QPS, LLC*
- *1U01FD006521 Characterization of Key System Parameters of Mechanistic Dermal PBPK Models in Various Skin Diseases and Performance Verification of the Model Using Observed Local and Systemic Concentrations with Sebastian Polak at Simcyp, Ltd.*
- *1U01FD006522 Formulation Drug Product Quality Attributes in Dermal Physiologically-Based Pharmacokinetic Models for Topical Dermatological Drug Products and Transdermal Delivery Systems with Michael Roberts at University of Queensland*
- *1U01FD006526 Assessment of Transdermal Drug Product Quality and Performance Attributes via Enhanced Virtual Bioequivalence Simulations with Jessica Spires at Simulations Plus, Inc*

Correlation Between Q3 & Bioavailability

	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				
	Cetostearyl alcohol	Cetostearyl alcohol	Cetostearyl alcohol	Cetyl alcohol	Cetyl alcohol
	SLS	SLS	SLS		
	Poloxamer 407	Poloxamer 407	Poloxamer 407		
		Dimethicone 20	Dimethicone 20		
		Glyceryl Mono Stearate	Glyceryl Mono Stearate	Glyceryl Mono Stearate	Glyceryl Mono Stearate
		Polyoxyethylene stearate	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
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 Dr. Narasimha Murthy associated with FDA funding for award U01FD005233

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	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
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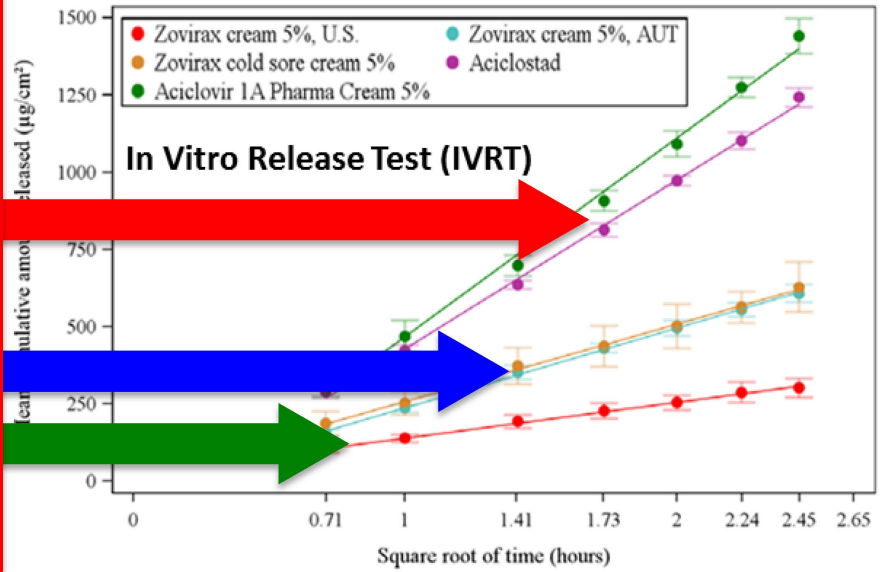

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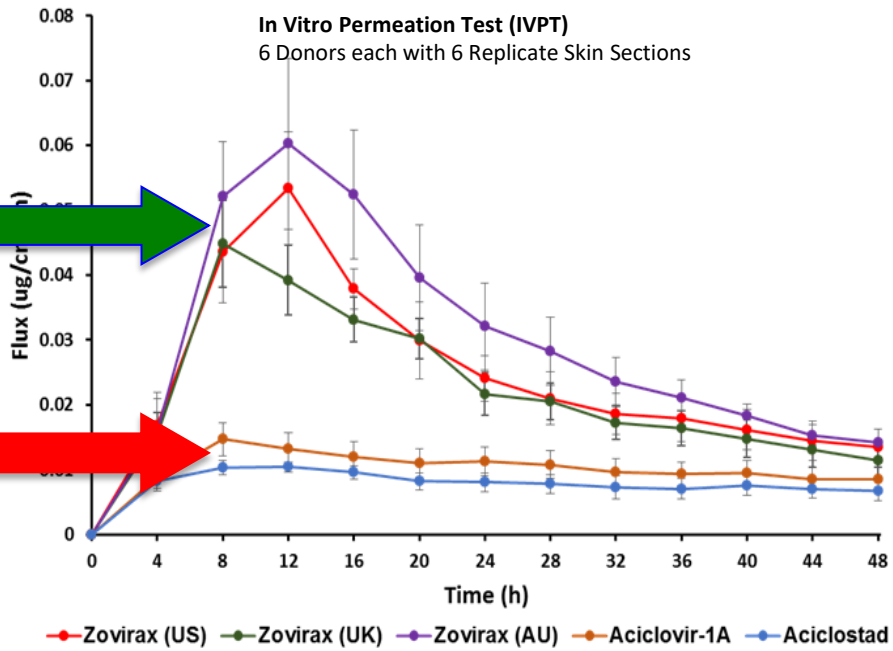

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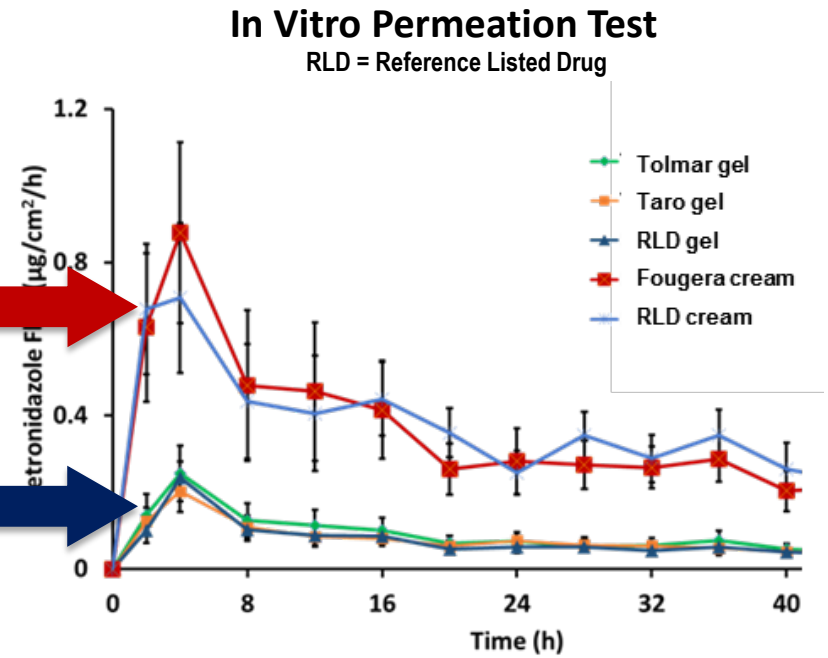
Correlation Between Q3 & Bioavailability

Quality Attribute	MetroCream® (RLD Cream)	Generic Crear (Fougera)	Metrogel® (RLD Gel)	Generic Gel (Tolmar)	Generic Gel (Taro)
pH	4.8	5.1	5.2	5.0	5.4
Density (g/cc)	1.02	1.02	1.01	1.02	1.02
WOA (g.sec)	57.6	63.9	39.4	43.9	42.0
Particle size (µm)	Active ingre				
Drug in Aq (mg/g)	4.20	2.92	---	---	---
Drug in Oil (mg/g)	2.58	3.94	---	---	---
Solvent Activity	0.977	0.974	0.992	0.994	1.002
Globule size, d_{50} (µm)	2.8	2.2	---	---	---
Drying, T_{30} (min)	17	11.4	5.5	4.7	6.5



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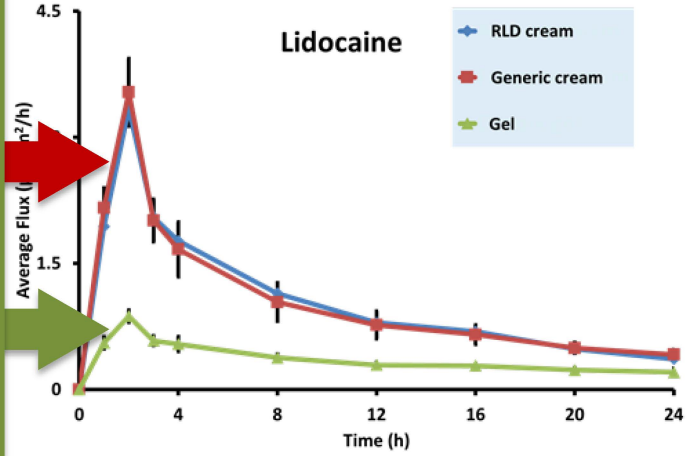
Correlation Between Q3 & Bioavailability

Q3 Attribute	Lidocaine2.5%, Prilocaine2.5% RLD Cream		Lidocaine-2.5%, Prilocaine-2.5% Generic Cream		Lidocaine-2.5%, Prilocaine-2.5% Gel
pH	9.22 ± 0.08		8.92 ± 0.03		7.76 ± 0.05
Density (g/cc)	1.0142 ± 0.0002		1.0148 ± 0.0002		1.0374 ± 0.0001
WOA (g.sec)	59.427 ± 0.338		65.893 ± 0.614		3.186 ± 0.207
Particle Size of API (µm)	Lidocaine and Prilocaine completely dissolved				the formulation
Globule Size, d50 (µm)	3.30		3.00		---
Drug in Aqueous Phase (µg/g)	Lidocaine	1.64 ± 0.06	Lidocaine	1.74 ± 0.12	---
	Prilocaine	1.99 ± 0.06	Prilocaine	2.11 ± 0.15	
Drug in Oil Phase (µg/g)	Lidocaine	23.45 ± 0.36	Lidocaine	23.21 ± 0.18	---
	Prilocaine	23.47 ± 0.18	Prilocaine	23.12 ± 0.2	
Water Activity	1.003 ± 0.002		1.004 ± 0.007		1.002 ± 0.005
Drying,T50 (min)	3.37 ± 0.15		3.82 ± 0.73		7.9 ± 0.46
Rheology Yield Stress(Pa)	36.7 ± 1.2		35.7 ± 0.6		15.7 ± 2.3



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Implementation in Guidances

Contains Nonbinding Recommendations

Draft Guidance on Acyclovir

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.

Active Ingredient: Acyclovir

Dosage Form; Route: Cream; topical

Recommended Studies: Two options: in vitro or in vivo study

I. In vitro option:

To qualify for the in vitro option for this drug product the following criteria should be met:

A. The test and Reference Listed Drug (RLD) products are qualitatively (Q1) and quantitatively (Q2) the same as defined in the Guidance for Industry *ANDA Submissions – Refuse-to-Receive Standards,* Revision 1 (May 2015).[1]

B. The test and RLD products are physically and structurally similar based upon an acceptable comparative physicochemical characterization of a minimum of three lots of the test and three lots (as available) of the RLD product.

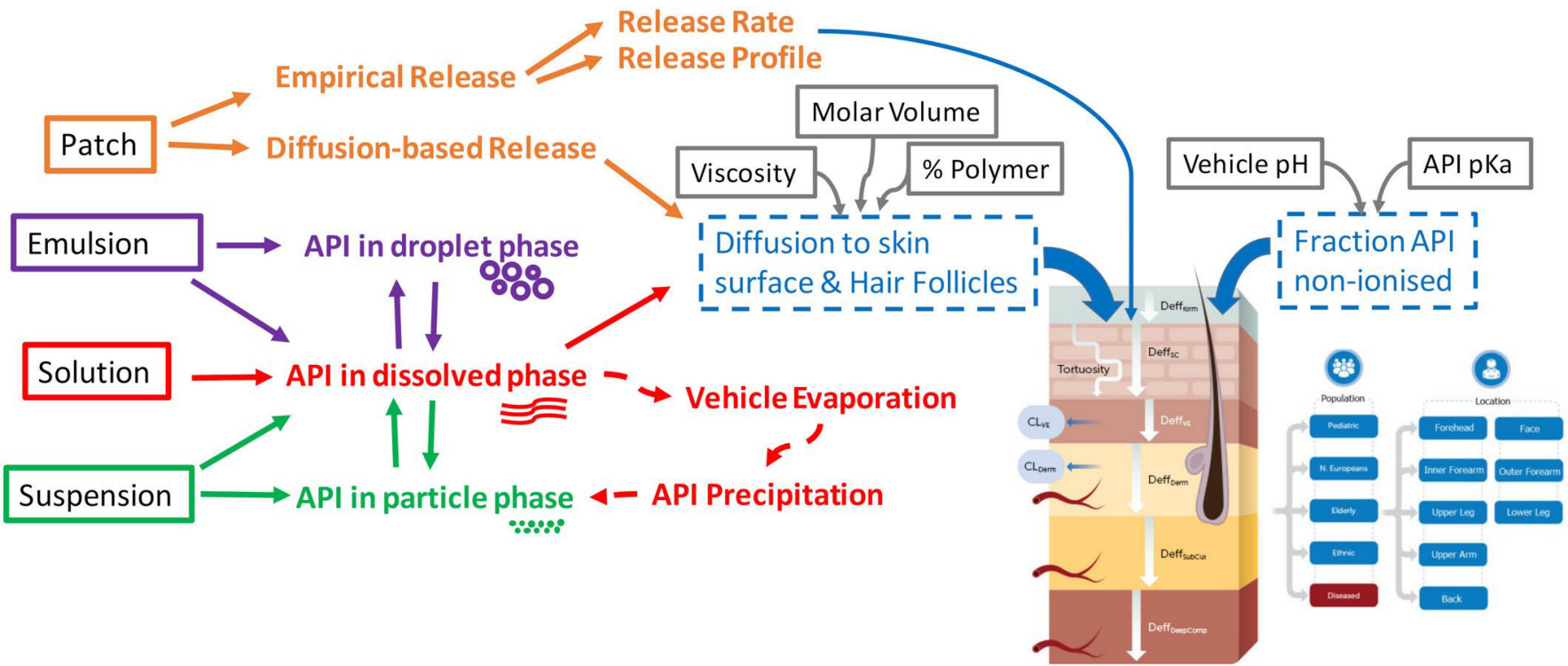
C. The test and RLD products have an equivalent rate of acyclovir release based upon an acceptable in vitro release test (IVRT) comparing a minimum of one lot each of the test and RLD products using an appropriately validated IVRT method.

D. The test and RLD products are bioequivalent based upon an acceptable in vitro permeation test (IVPT) comparing the rate and extent of acyclovir permeation through excised human skin from a minimum of one lot each of the test and RLD products using an appropriately validated IVPT method.

Additional comments: Specific recommendations are provided below.

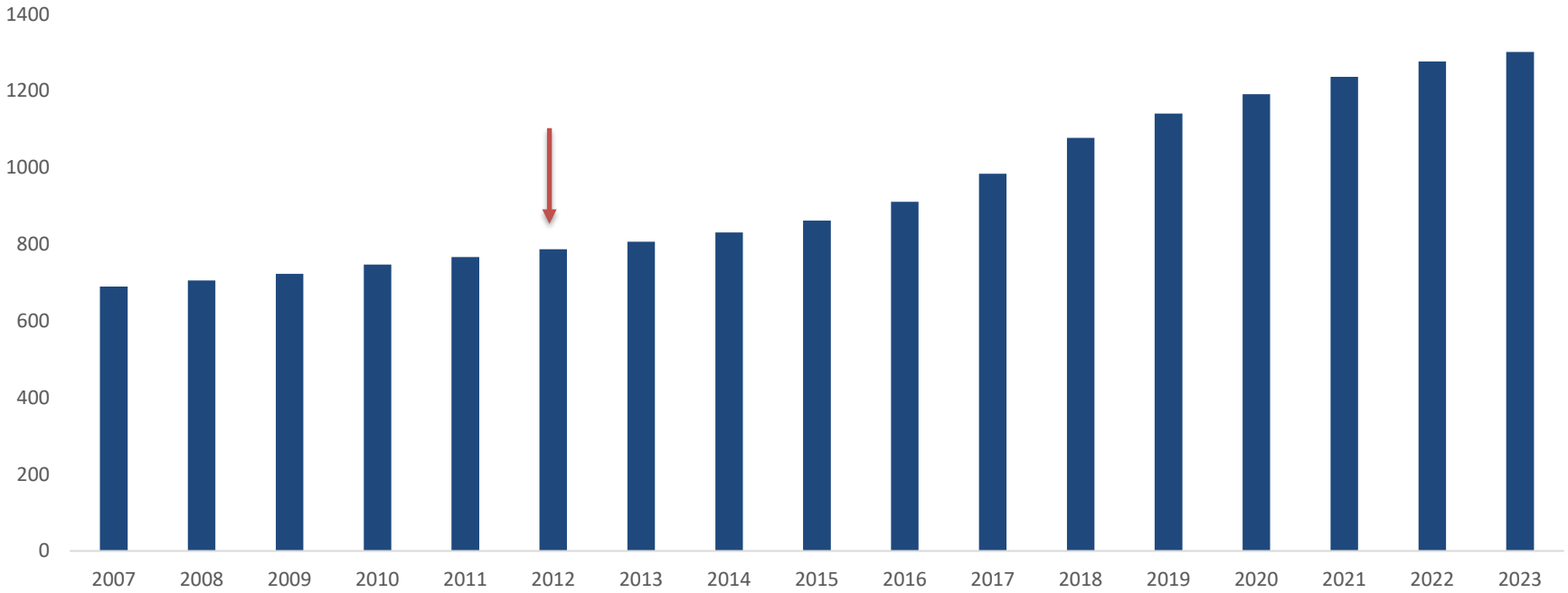
This is not the most current version of this guidance document

Modeling and Simulation Toolkit

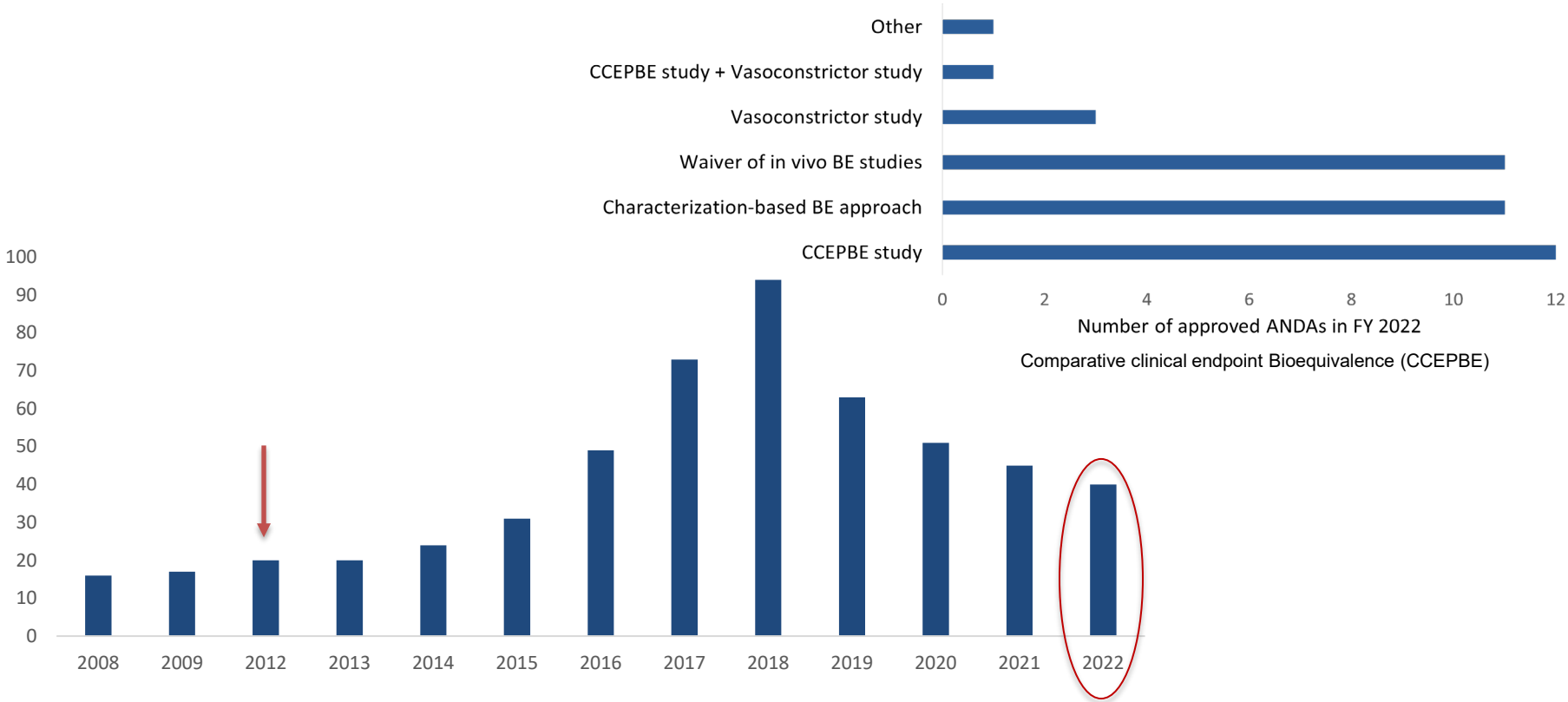


Arora et al. Mol Pharm. 2022;19(9):3139-3152. doi:10.1021/acs.molpharmaceut.2c00229
Tsakalozou et al. CPT Pharmacometrics Syst Pharmacol. 2021;10(5):399-411. doi:10.1002/psp4.12600

Topical Product Availability

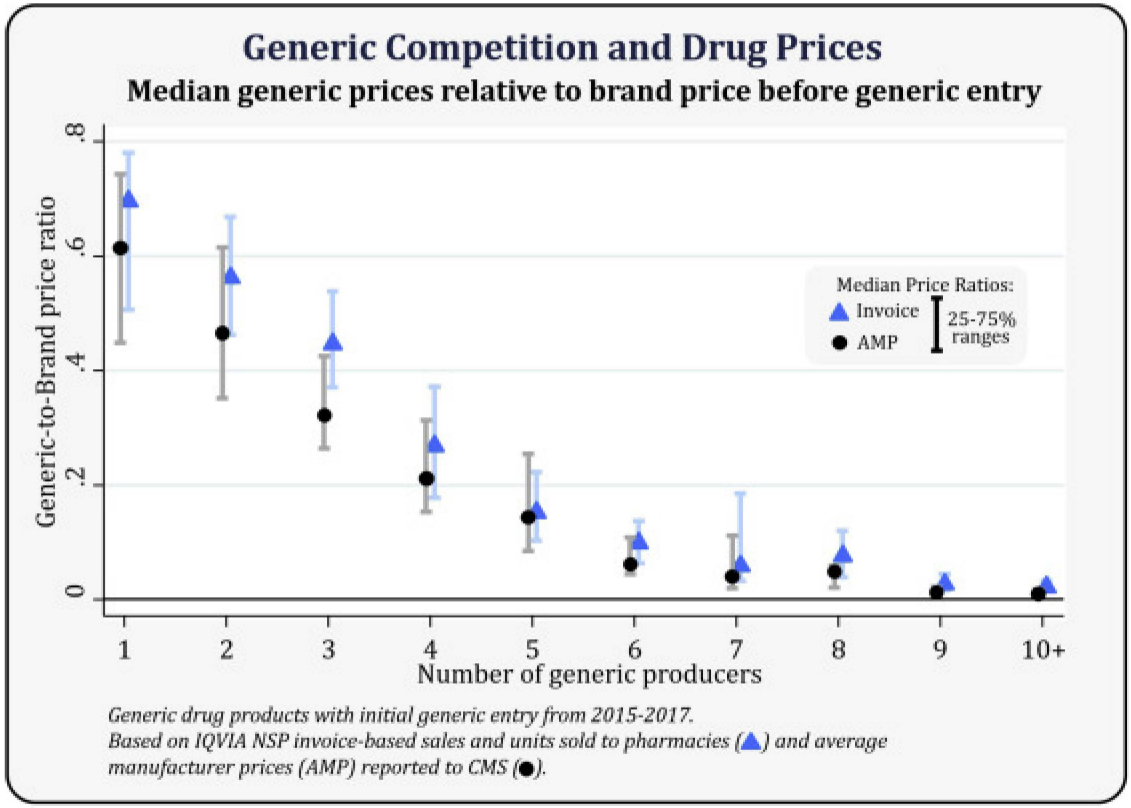


Approval of Topical Generic Products



Approved Drug Products with Therapeutic Equivalence Evaluations

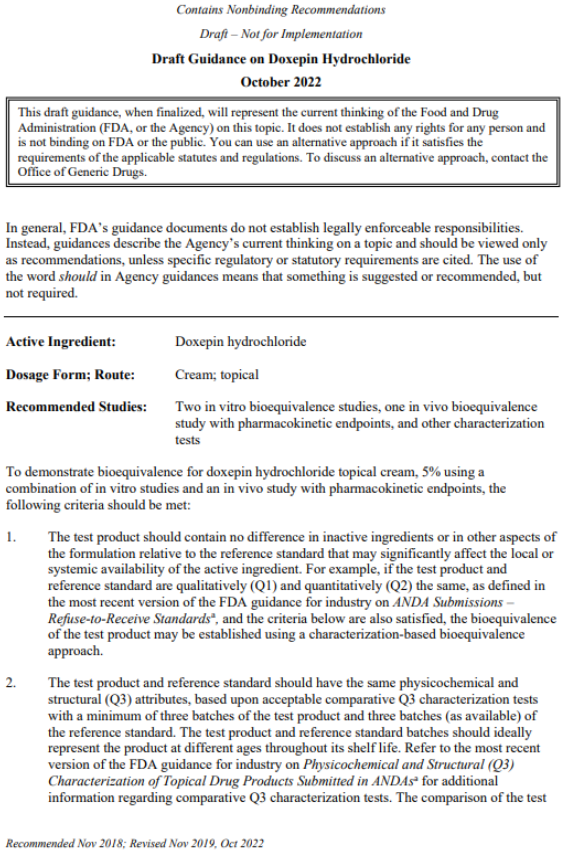
Impact of Generic Product Availability



Raney et al., J Am Acad Dermatol. 2020;82(6):1570-1571. doi:10.1016/j.jaad.2020.01.062

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



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Draft – Not for Implementation

Draft Guidance on Doxepin Hydrochloride

October 2022

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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

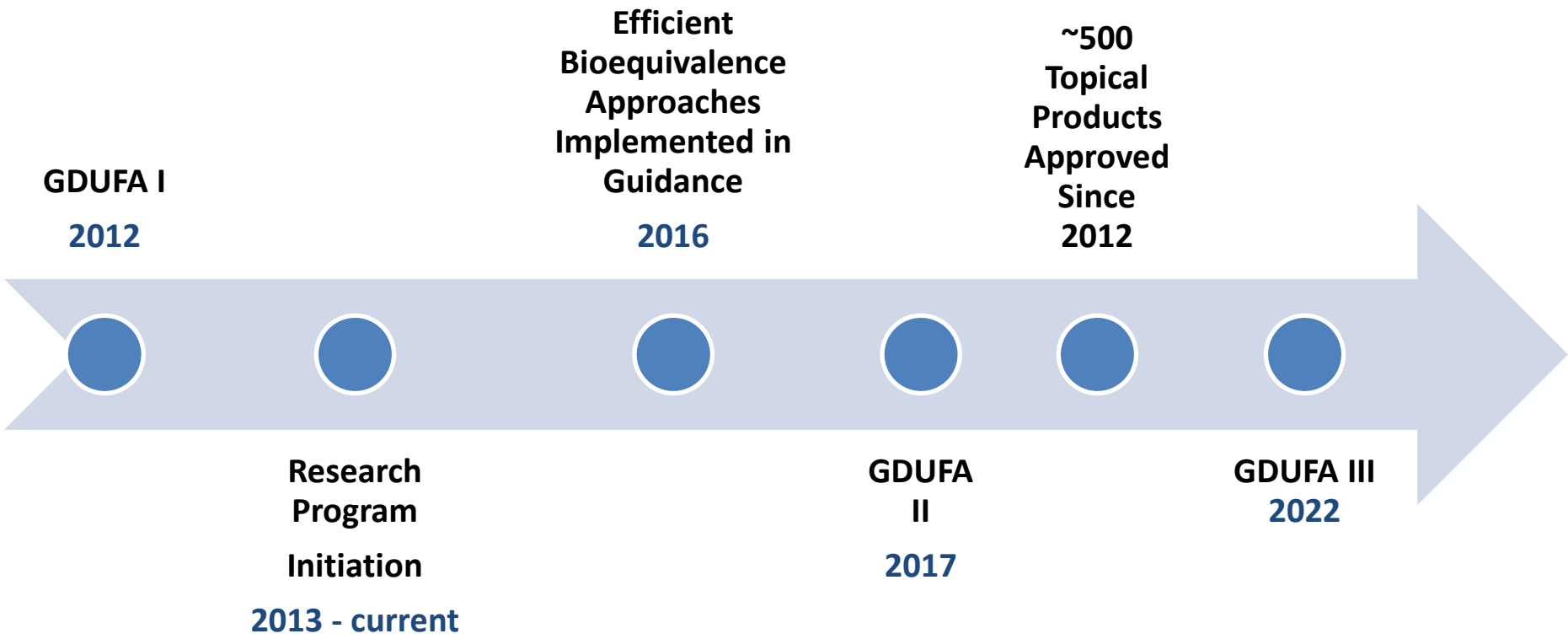
To demonstrate bioequivalence for doxepin hydrochloride topical cream, 5% using a combination of in vitro studies and an in vivo study with pharmacokinetic endpoints, the following criteria should be met:

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

Timeline for the Program



Next Steps

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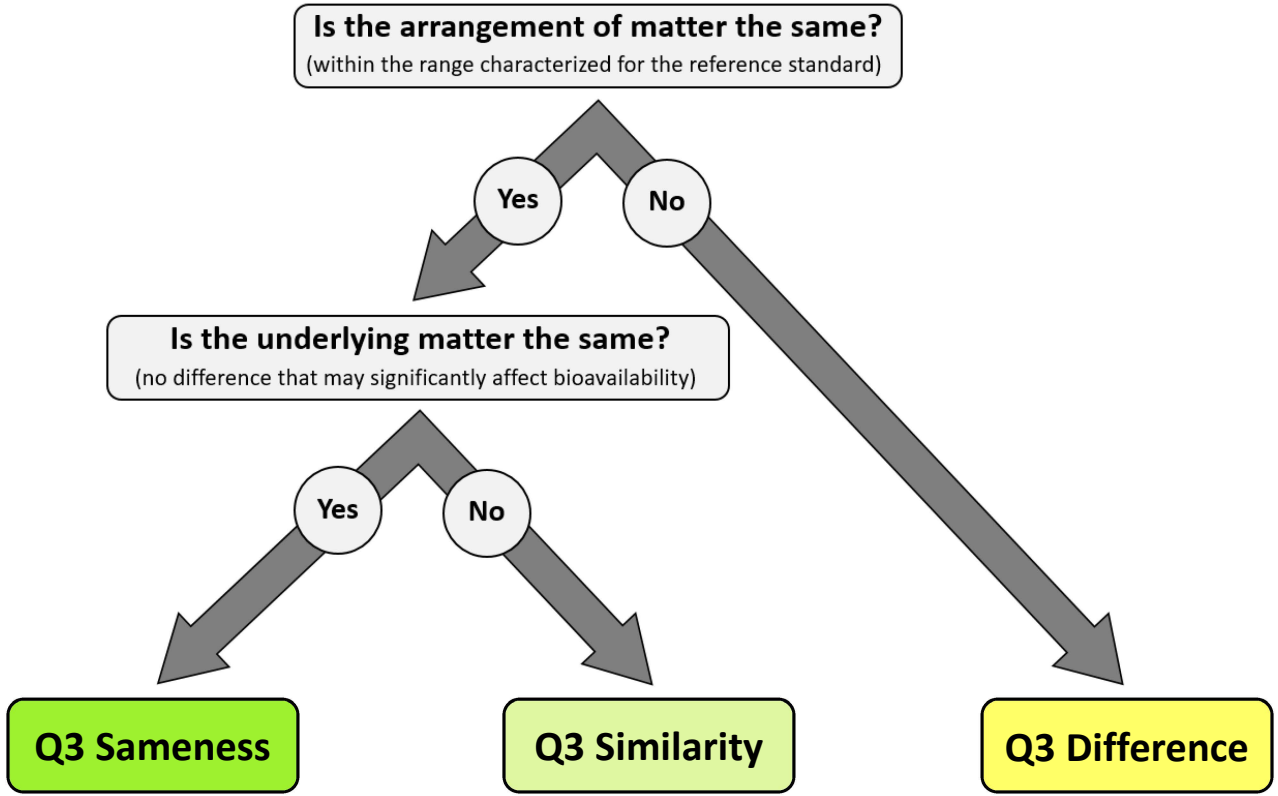
Understanding Q3 Similarity



https://www.fda.gov/media/162471/download

Summary

- Topical drug products are generally complex dosage forms
- An elaborate understanding of the correlation between Q3 and bioavailability has led to the development of efficient characterization-based approaches for topical gels, creams, lotions, etc., supported by data generated within the GDUFA regulatory science and research program
- Availability of efficient approaches have contributed to the availability of more generic products on the market, and a corresponding decrease in prices have been observed
- The goal of the GDUFA regulatory science and research program is to continue to facilitate research to enhance our understanding of how the formulation and microstructure of the product influences bioavailability

Acknowledgements

U.S. Food & Drug Administration

- Sam Raney, PhD
- Tannaz Ramezanli, PharmD, PhD
- Megan Kelchen, PhD
- Jackson Russo, PhD
- Ahmed Zidan, PhD
- Eleftheria Tsakalozou, PhD
- Andrew Babiskin, PhD
- Darby Kozak, PhD
- Lei Zhang, PhD
- Markham Luke, MD PhD
- Robert Lionberger, PhD

Research Collaborators

Collaborations within FDA

All of our collaborators within the GDUFA Regulatory Science and Research Program

U.S. FOOD & DRUG ADMINISTRATION

Thank You

Priyanka Ghosh, Ph.D.
Lead Pharmacologist
Office of Research and Standards (ORS), Office of Generic Drugs (OGD)
CDER | U.S. FDA