U.S. FOOD & DRUG ADMINISTRATION

Generic Drugs and Dermatology: Bioequivalence and Access Equity

Noah Worcester Dermatological Society
64th Annual Meeting

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Disclaimer

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

FDA Centers

Most Relevant to Dermatology:

- **Center for Drug Evaluation and Research (CDER)**
  - Office of New Drugs (OND)
    - Division of Dermatology and Dental Drug Products
  - Office of Generic Drugs (OGD)
- **Center for Devices and Radiological Health (CDRH)**
- **Center for Biologics Evaluation and Research (CBER)**
- **Center for Food Science and Nutrition (CFSAN)**
  - Office of Cosmetics and Colors

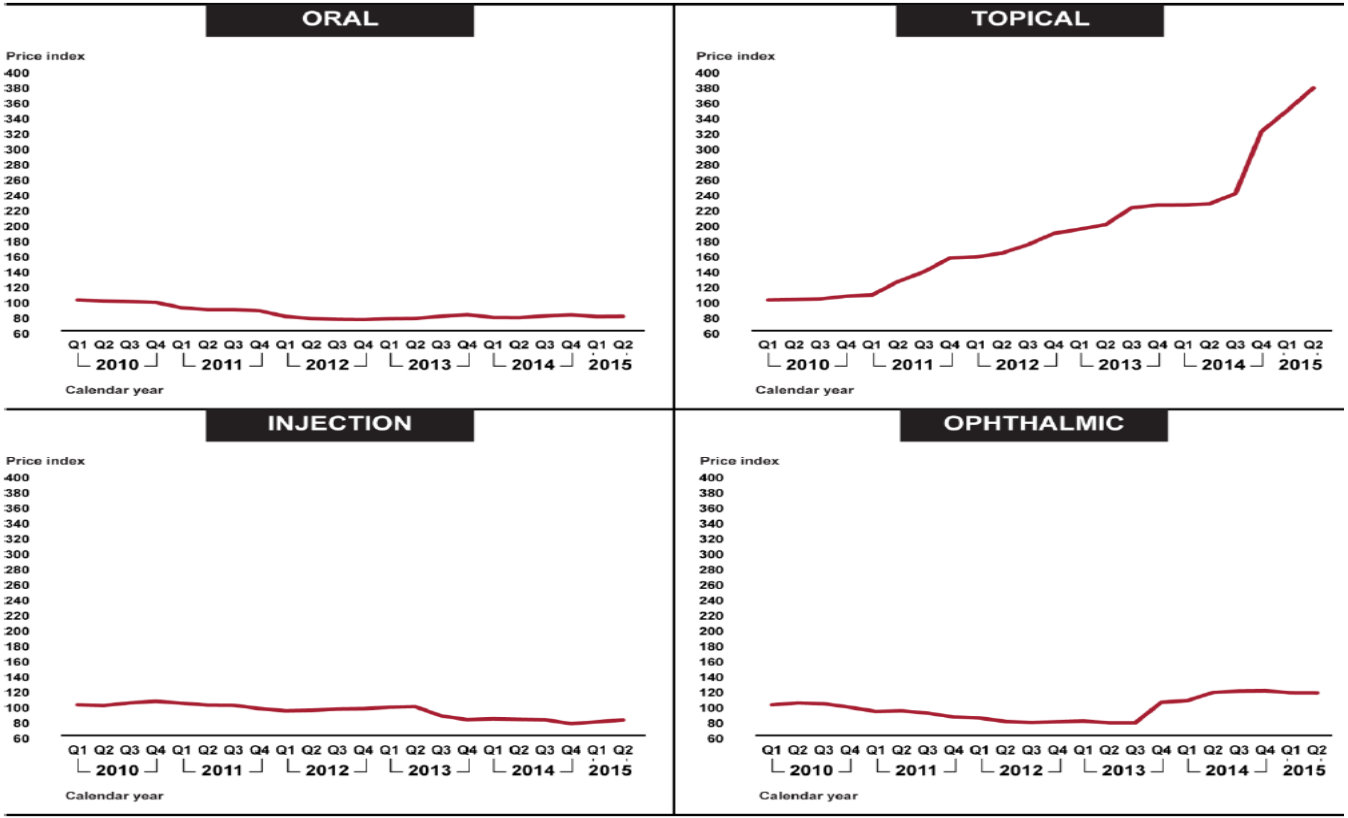
Generic Drugs

- Why should generic drugs be important to dermatology patients?
- What are specific considerations for “topical drugs” that are applied to the skin?

The 2016 GAO Report

- The U.S. Government Accountability Office (GAO) Report (GAO-16-706; August 2016) had analyzed a period spanning Quarter 1 of 2010 through Quarter 2 of 2015
- **57%** of the topical drug products experienced an extraordinary price increase in that period
- The average price of topical generic drugs was **276% higher** by the end of the period analyzed
- Manufacturers and other stakeholders reported that market **competition**, influenced by various factors, drives generic drug prices

The GAO Report (GAO-16-706)



Source: GAO analysis of Medicare Part D prescription drug event data. | GAO-16-706

Retail Prices for Topical Products

Drug	Type	Price, US $ 2009	2011	2014	2015	Absolute Change, 2009-2015	% Change, 2009-2015
Altabax, 15 g	I	92.50	106.18	168.75	196.86	104.36	112.82
Benzaclin, 50 g	A	166.79	205.80	451.29	503.85	337.06	202.08
Carac cream, 30 g	N	159.40	227.16	2939.68	2864.70	2705.30	1697.18
Clobex spray, 4 oz	S	389.57	500.29	827.11	958.01	568.44	145.91
Cloderm cream, 30 g	S	96.47	132.92	220.75	360.02	263.55	273.19
Cutivate lotion 120 mL	S	305.00	493.92	918.63	1067.25	762.25	249.91
Derma-Smoothe FS oil, 4 oz	S	45.70	47.23	247.84	322.67	276.97	606.06
Finacea, 50 g	A	124.42	185.42	288.92	284.30	159.88	128.51
Olux-E foam, 100 g	S	307.58	382.79	750.79	841.76	534.18	173.67
Oracea, 40 mg (30 tablets)	A	439.01	416.09	632.80	702.46	263.45	60.01
Oxistat cream, 30 g	I	76.50	119.25	399.00	544.66	468.16	611.97
Oxsoralen-Ultra, 10 mg (50 capsules)	P	1227.32	2150.49	4568.54	5204.31	3976.99	324.04
Retin-A Micro, 0.1%, 50 g	A	178.05	335.73	791.47	914.52	736.47	413.64
Solaraze gel, 100 g	N	442.89	618.56	1738.91	1883.98	1441.09	325.38
Soriatane, 25 mg (30 capsules)	P	757.75	958.50	1452.50	1595.27	837.52	110.53
Taclonex, 60 g	P	465.99	522.58	848.21	962.90	496.91	106.64
Targretin gel, one 60-g tube	N	1686.78	1787.97	15 708.40	30 320.12	28 633.34	1697.51
Tazorac cream, 0.1%, 60 g	A	266.18	464.96	656.20	722.27	456.09	171.34
Xolegel, 30 g	I	212.50	278.00	389.25	641.96	429.46	202.10

Abbreviations: A, acne and rosacea; I, antiinfective; N, antineoplastic; P, psoriasis; S, corticosteroid.

Source: Miranda E. Rosenberg, BA and Steven P. Rosenberg, MD (2016) *Changes in Retail Prices of Prescription Dermatologic Drugs From 2009 to 2015*. JAMA Dermatology. 152(2):158-163. doi:10.1001/jamadermatol.2015.3897

Generic Drug Access

- The Association for Accessible Medicines (AAM) 2022[1] Generic Drug Access & Savings Reports have documented the ***overall*** success of generic drugs
- **91%** of the of prescriptions filled in the United States during 2021 were dispensed as generics, up from 90% in 2019. These accounted for about 18% of all Rx drug expenses, and about 3% of total health care expenditures.
- **93%** of generic prescriptions were filled at ≤ $20, up from 90% in 2016; the average generic copay in 2021 was **$6.16**
- ***Overall***, this represented **exceptional patient access** to high quality, safe, effective, affordable medicines

[1] AAM Report: 2022 Generic Drug & Biosimilars Access & Savings in the U.S. (https://accessiblemeds.org)

Patient Access to Generic Drugs

- Generic drugs must demonstrate bioequivalence (BE)
  - Per 21 CFR 314.3: *BE is the absence of a significant difference in the **rate and extent to which the active ingredient** or active moiety in pharmaceutical equivalents or pharmaceutical alternatives **becomes available at the site of drug action** when administered at the same molar dose under similar conditions in an appropriately designed study.*
- For systemically acting drug products, it is **efficient** to demonstrate BE by pharmacokinetics (PK) based studies
- For locally acting (e.g., topical dermatological) drug products, it has been **challenging** to directly assess the rate and extent to which active ingredient becomes available at the site of action

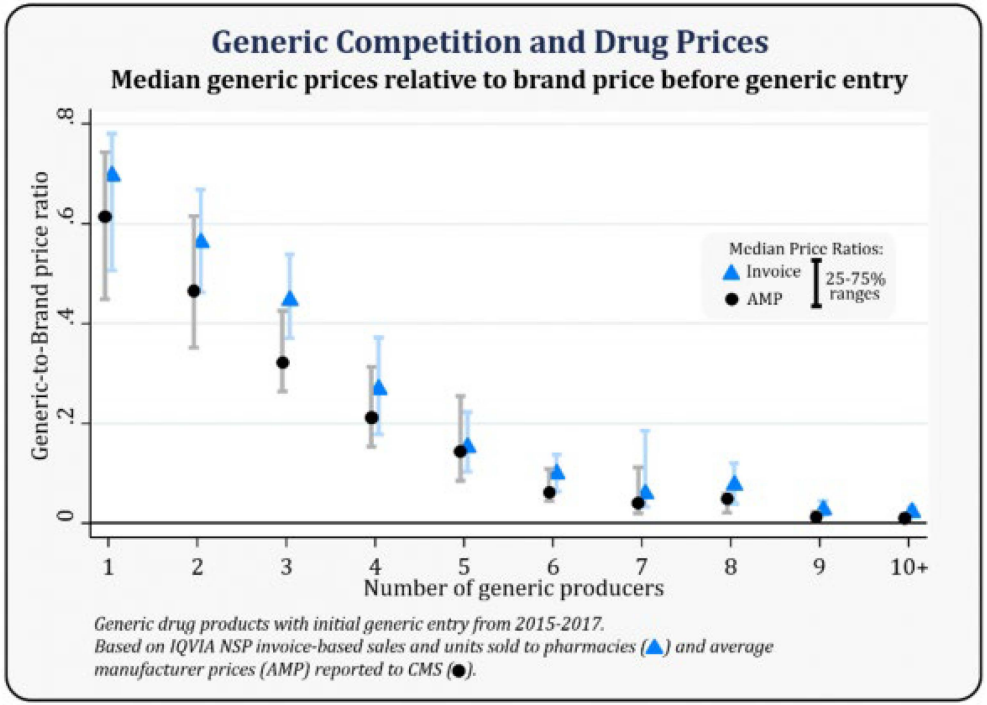
Economics of Generic Drugs

- Pharmaceuticals are generally inelastic with regard to demand (i.e., patients generally will pay what is needed to get certain drugs).
- Generic drugs help improve access to drugs by lowering overall cost of drugs for patients and payors.
- Prices may be complicated by third-party payers and payment arrangements such as through pharmacy benefit managers.

Understanding Drug-Price Competition

2013 FTC Paper
L Olsen and
B Wendling

Impact of number of Manufacturers



Patient Access to Topical Products

- Most topical dermatological drug products had fewer than three generic competitors; for many products, no generics were available at all
- This may have been attributable to the historical challenges impacting the development of topical dermatological generic drug products, possibly including
  - Absence of efficient PK-based approaches by which to demonstrate BE
  - Inefficiency of high risk, costly, comparative clinical endpoint BE studies
  - The complex nature of topical formulations
- FDA had begun research to develop more efficient ways to demonstrate BE for complex generics, including topicals

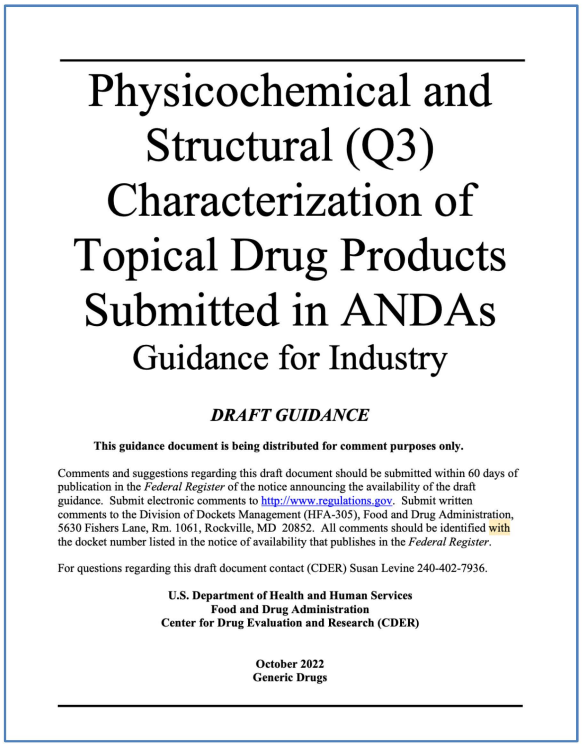
Concept of BE for Topical Products

- **In Vitro** Methods to Support a Demonstration of BE
  - **Qualitative (Q1) and Quantitative (Q2)** Sameness or '*No Difference*'
  - **Physicochemical and Structural (Q3)** Sameness/Similarity
  - **IVRT** (In Vitro Release Test)
  - **IVPT** (In Vitro Permeation Test)
- **In Vivo/In Silico** Methods to Support a Demonstration of BE
  - **In Vivo Pharmacokinetic (PK)** Studies
  - **In Vivo Pharmacodynamic** (Vasoconstrictor) Studies
  - **In Vivo Comparative Clinical Endpoint BE** Studies
  - **In Silico** Quantitative Methods, Modeling and Simulation

Topical Dermatological Formulations

- 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 Reference Listed Drug (RLD) or Reference Standard (RS), as appropriate
  - Match the Q1, Q2, and Q3 characteristics

2022 FDA Draft General Guidances



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
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October 2022
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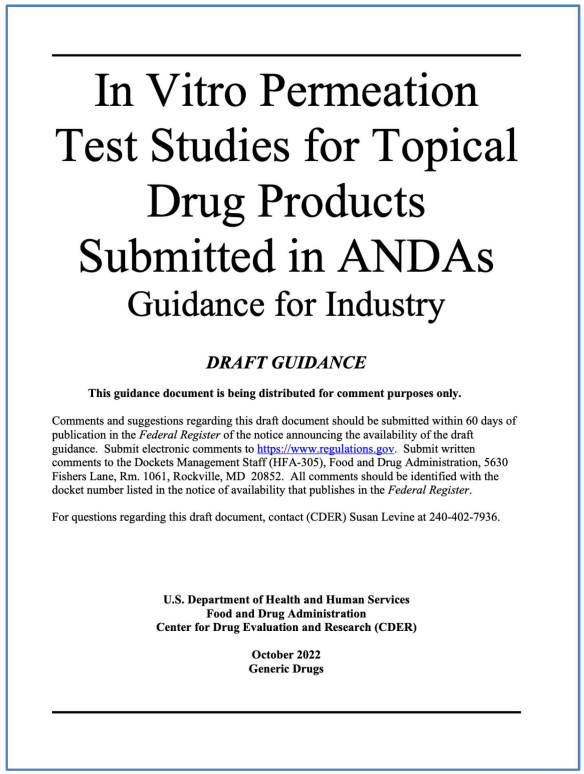

In Vitro Permeation Test Studies for Topical Drug Products Submitted in ANDAs

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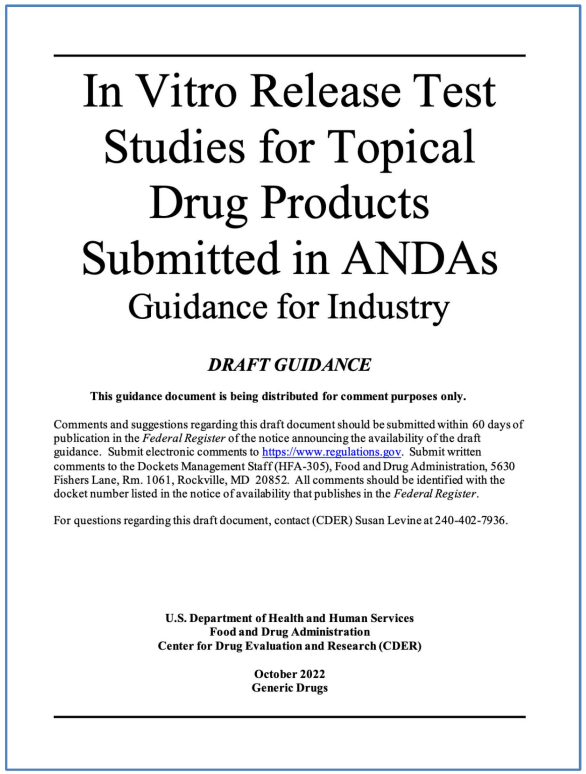

In Vitro Release Test Studies for Topical Drug Products Submitted in ANDAs

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Formulation of the Test Product

- **Test Product = Candidate Generic Drug**
- Steps to identifying an appropriate formulation
  - Deformulation (reverse engineering) of the drug to be compared with – usually the Reference Listed Drug (RLD)
  - Understanding limitations of information in the RLD labeling and FDA's inactive ingredient database (IID)
  - Developing a thorough understanding of the product by characterizing multiple (fresh and aged) batches of the reference product
  - Formulating the test product to match the reference product, determining critical quality attributes (CQAs), and failure modes for BE

Current Research

- Physical chemical characterization of topical formulations
  - Thermodynamics of topical drugs – rheology, solvent evaporation, and water uptake
  - Characterization of the impact of certain excipients in topical formulations
- Measuring drug concentrations in the skin
  - dermal Open Flow Microperfusion (dOFM)
  - Confocal Microscopic Raman Spectroscopy

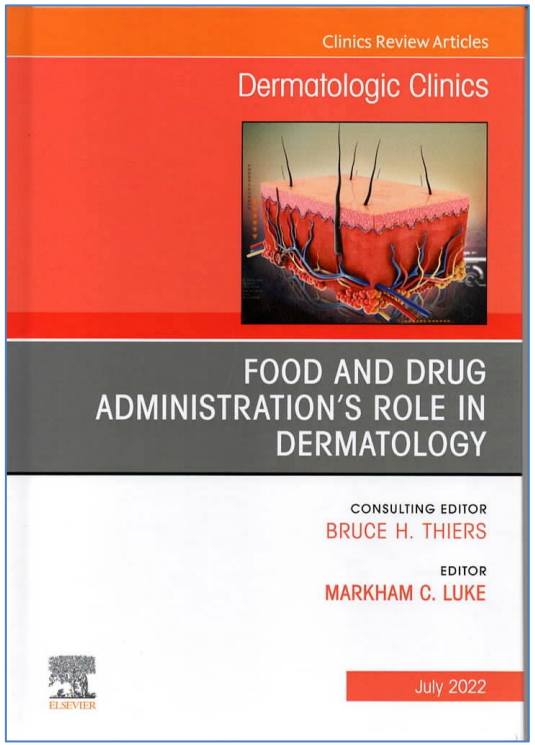
Update: 2022 First-time Approved Generics Most Dermatologically Relevant

ANDA #	Generic Name	ANDA Applicant	Brand Name	ANDA Approval Date	ANDA Indication
212710	Penciclovir Cream 1%	Teva Pharma	Denavir	11/9/2022	Recurrent herpes labialis
215433	Tazarotene Gel 0.05%	Cosette Pharma	Tazorac	9/13/2022	Plaque psoriasis
208768	Posaconazole Injection	Par Sterile	Noxafil	5/25/2022	Prophylaxis of invasive Aspergillus and Candida
215398	Bexarotene Gel	Amneal Pharma	Targretin	4/27/2022	Cutaneous lesions of CTCL
214596 212424	Phytonadione Injectable Emulsion	Cipla	AquaMEP HYTON	4/22/2022	Coagulation disorders caused by Vitamin K deficiency

Concluding Summary

- FDA serves the U.S. dermatology patient community by –
  - Bringing new products to treat dermatologic disease (weighing balance between safety and efficacy)
  - Provide access to quality generic drug products
- These efforts involve applying knowledge gained from research and a practical approach to regulation

July 2022 Dermatologic Clinics



Insightful articles on:

- The History of Dermatology at FDA
- FDA and Dermatologic Drug Development
- Postmarket Assessment for Dermatology Drugs and Cutaneous Adverse Reactions
- How does FDA Approve Generic Drugs
- Dermatology Drugs for Children
- Regulation of Medical Devices for Dermatology
- Regulation of Cosmetics in the United States
- Cutaneous Pharmacokinetic Approaches
- Measuring What Matters to Patients in Dermatology Drugs

Acknowledgements

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