# Innovation and Topical Generic Drug Science: A case of targeted and planned innovation

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# Why are Recent Advances in Generic Topical Drug Science a Good Example of Innovation?

- As a vital part of the dermatologic armamentarium, topical drugs play an important role in the treatment of our patients.
- Dramatic price increases occurred for dermatologic topical drug products as compared to other drugs during the last decade. This is partially attributable to lack of generic drugs.
- FDA and others in this field have applied scientific understandings of topical product formulation attributes and the science of in vitro physico-chemical evaluations of drugs towards good regulation practices when it comes to evaluating bioequivalence of topical drugs applied to the skin. This facilitates the pathway to getting good generic drugs to market.

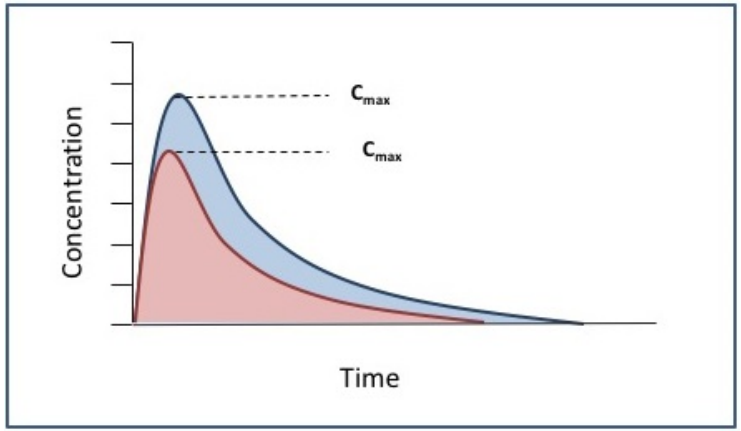
# The Promise of Generic Drugs


- Generic drug products use the same active ingredient(s) and can be expected to have the same clinical effect and safety profile when administered under conditions specified in the labeling, as the brand-name (reference) listed drug products
- Generic drug products can be substituted for the reference listed drug product
- ….And they can cost less money



https://www.fda.gov/drugs/generic-drugs/generic-drug-facts

# How are Most Generic Drugs Approved?





Bioavailability (BA) is assessed, and bioequivalence (BE) is typically established by showing that a generic drug product and the reference standard are similar in terms of their concentrations over time at the site of action (e.g., in the blood – pharmacokinetics or PK)

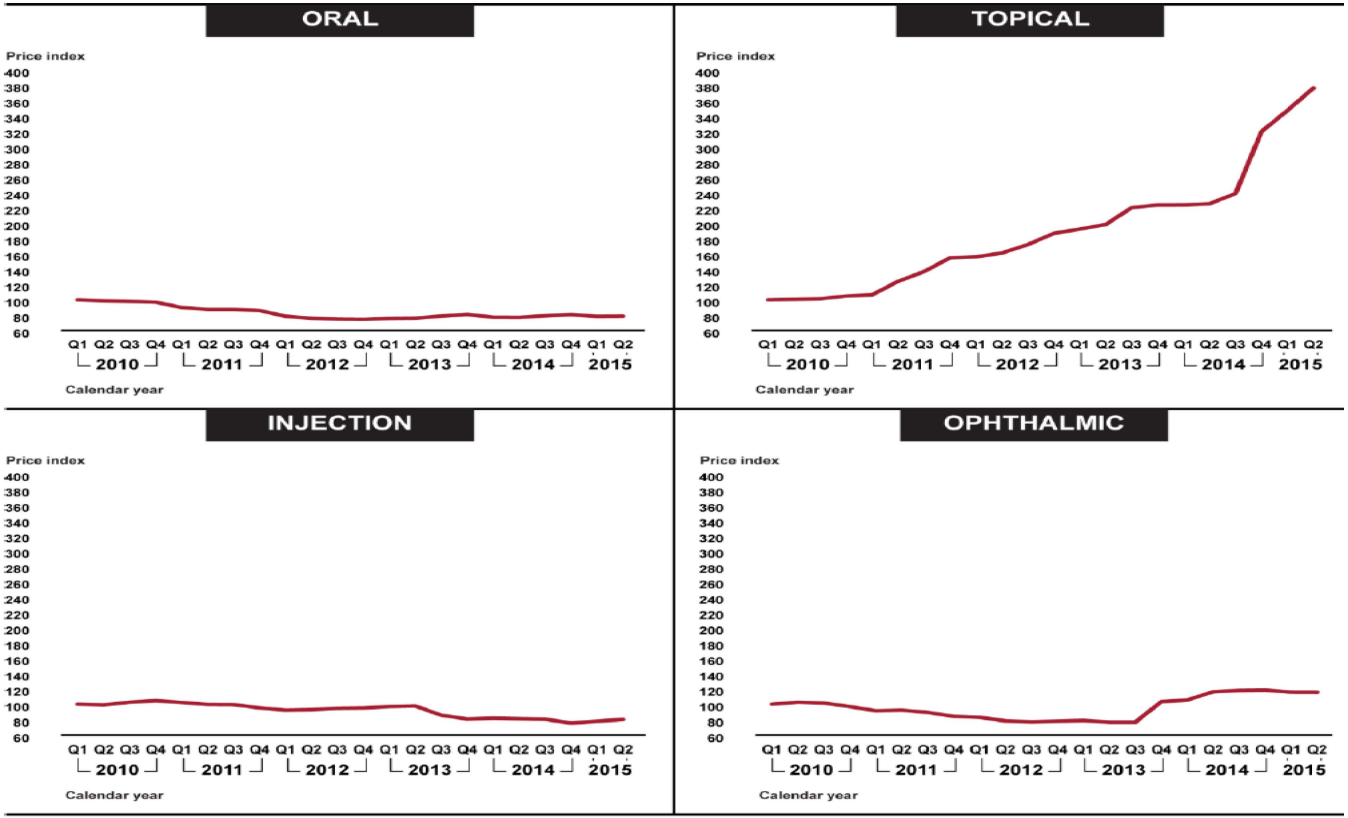


https://www.fda.gov/drugs/regulatory-science-action/impact-story-developing-new-ways-evaluate-bioequivalence-topical-drugs

# 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

# 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

PK - pharmacokinetic

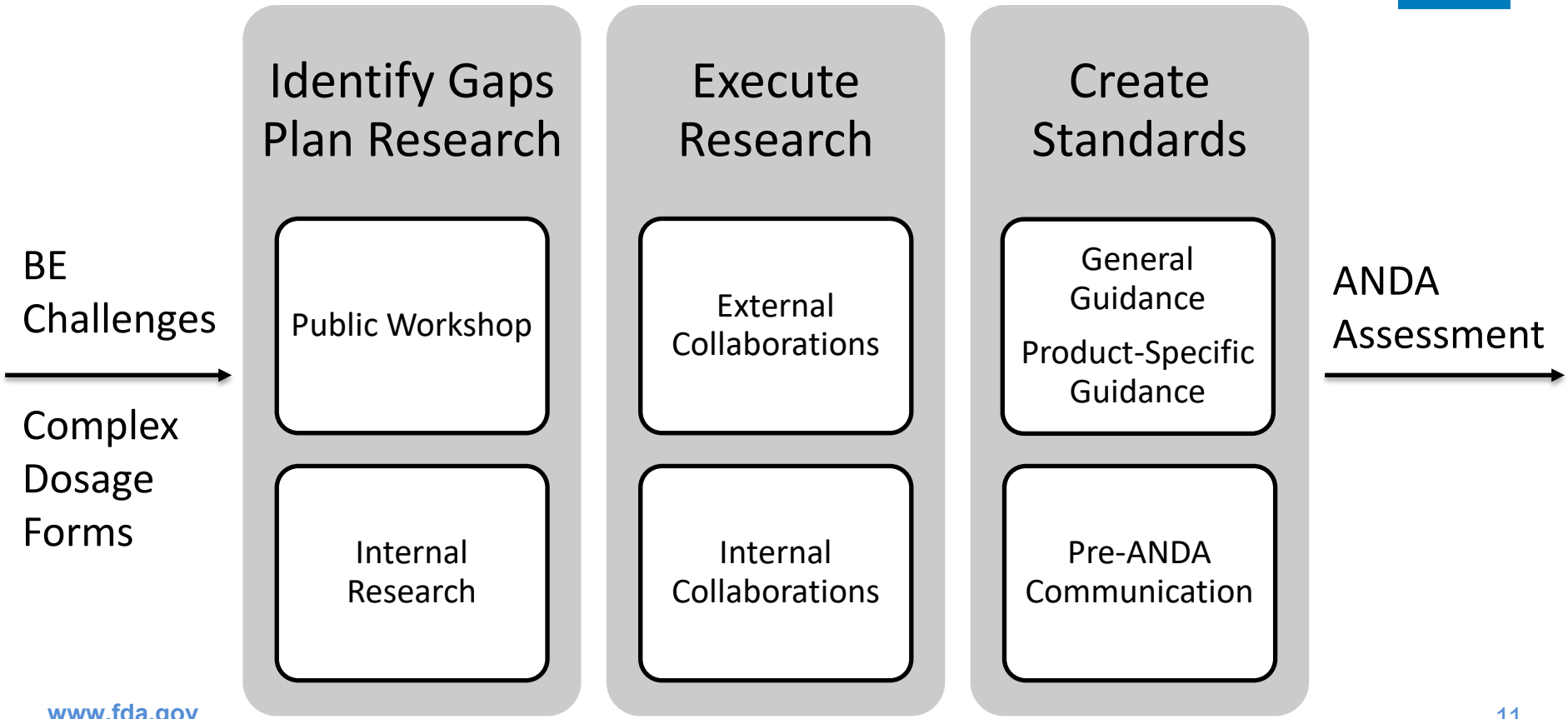
# GDUFA

- The Generic Drug User Fee Amendments (GDUFA) was signed into law in July 2012, as part of the Food and Drug Administration Safety and Innovation Act (FDASIA)
- One out of numerous User Fee Programs that help the FDA to fulfill its mission of protecting the public health and accelerating innovation in the industry
- GDUFA is designed to speed the delivery of safe and effective generic drugs to the public and improve upon the predictability of the review process
- One unique feature of GDUFA is the Regulatory Science and Research Program ~ $20 million annually
- GDUFA must be reauthorized every 5 years (currently in GDUFA III)

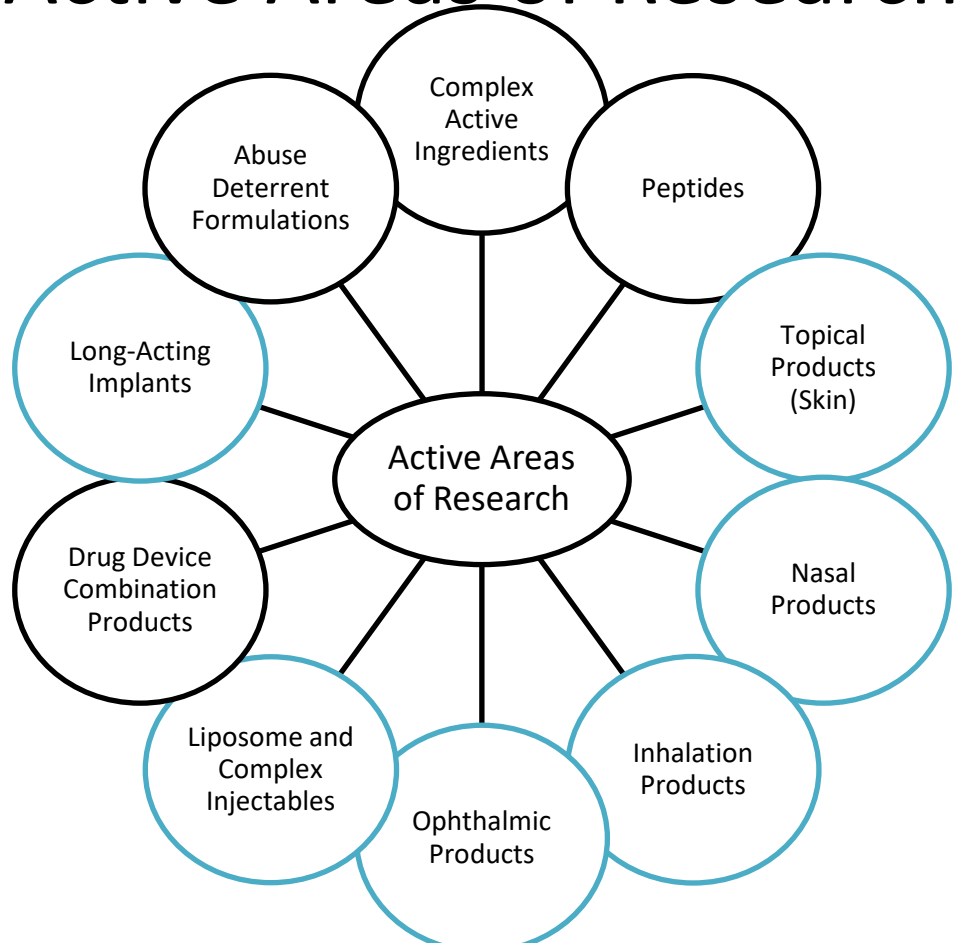


https://www.fda.gov/industry/fda-user-fee-programs
https://www.fda.gov/industry/fda-user-fee-programs/generic-drug-user-fee-amendments

# GDUFA Science and Research Program



# Active Areas of Research



# FDA Dermatopharmacology

- A large share of our research budget goes to understanding how topical drugs work and what is needed to determine bioequivalence for these products.
- One of four teams in the Division of Therapeutic Performance that works on Complex Drug Products is dedicated to dermal and trans-dermal drugs, together with a corresponding resource and personnel allocation.

# Some Lessons Learned from Studying Generic Drug Dermatopharmacology

- Evaluation of bioequivalence requires careful interpretation of difference detecting ability for various assays.
- Excipients play an important role in bioavailability of the “active ingredient”, but exact sameness is not required for two products to behave similarly.
- Understand that the skin is not a flat featureless entity. There are surface features and anatomy to reckon with. These play a role in skin penetration and skin deposition of drug.
- The targeted disease for treatment may play a role in determining what physicochemical features and sameness assays of a drug are most relevant.

# Assertions on Innovation

- Generic topical drug science is a good way to provide sound foundational understanding about drug formulation and manufacturing from an operational standpoint for a new dermatology drug startup.
- There continue to be advances in the science of topical drugs that can be gleaned from some of the projects being worked on by the FDA generic drug research team and our collaborators.
- The dynamics of this research space have led to fascinating and fruitful collaborations and advancements.

# Acknowledgements

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# Thank You

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