Generic Drugs for Dermatology

Markham C. Luke, MD PhD

Office of Generic Drugs, CDER

March 3, 2019

FDA Symposium at the 2019 AAD Annual Meeting

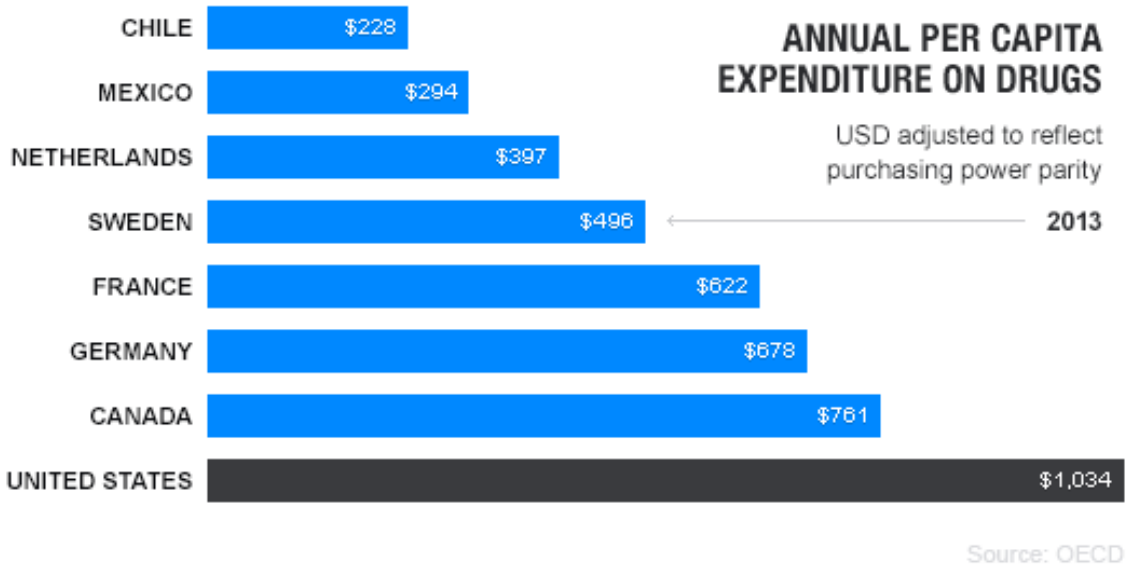
Generic Drugs:

- Are medications created to be the same as an already marketed brand-name drug in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use.

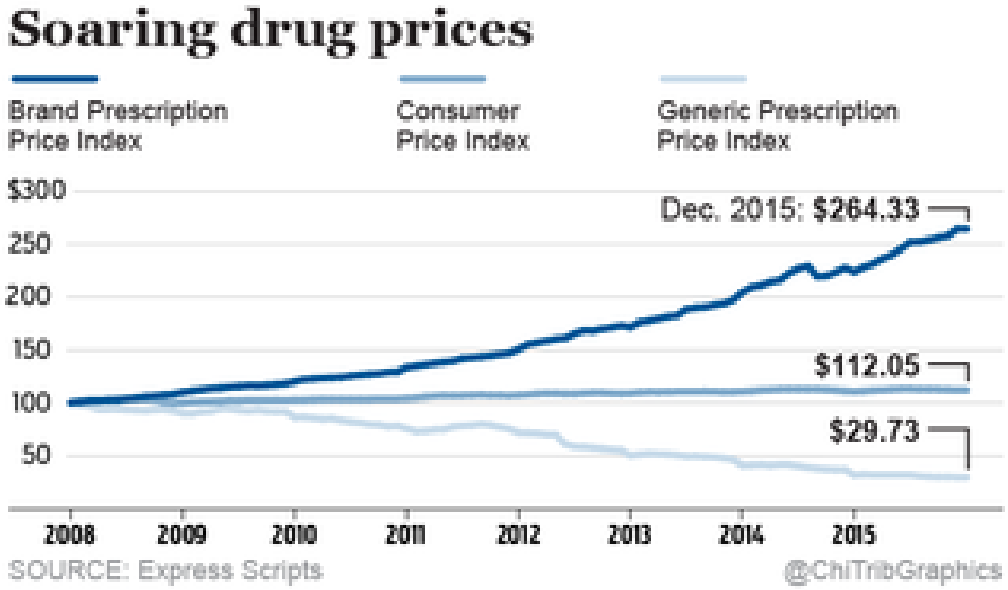
From FDA website – Understanding Generic Drugs
https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/default.htm

Generic Drugs

- Each ANDA (Abbreviated New Drug Application) relies on a reference listed drug (RLD)
- Generic drugs mostly cost less to develop because applicants do not repeat the safety and efficacy studies used to approve the RLD



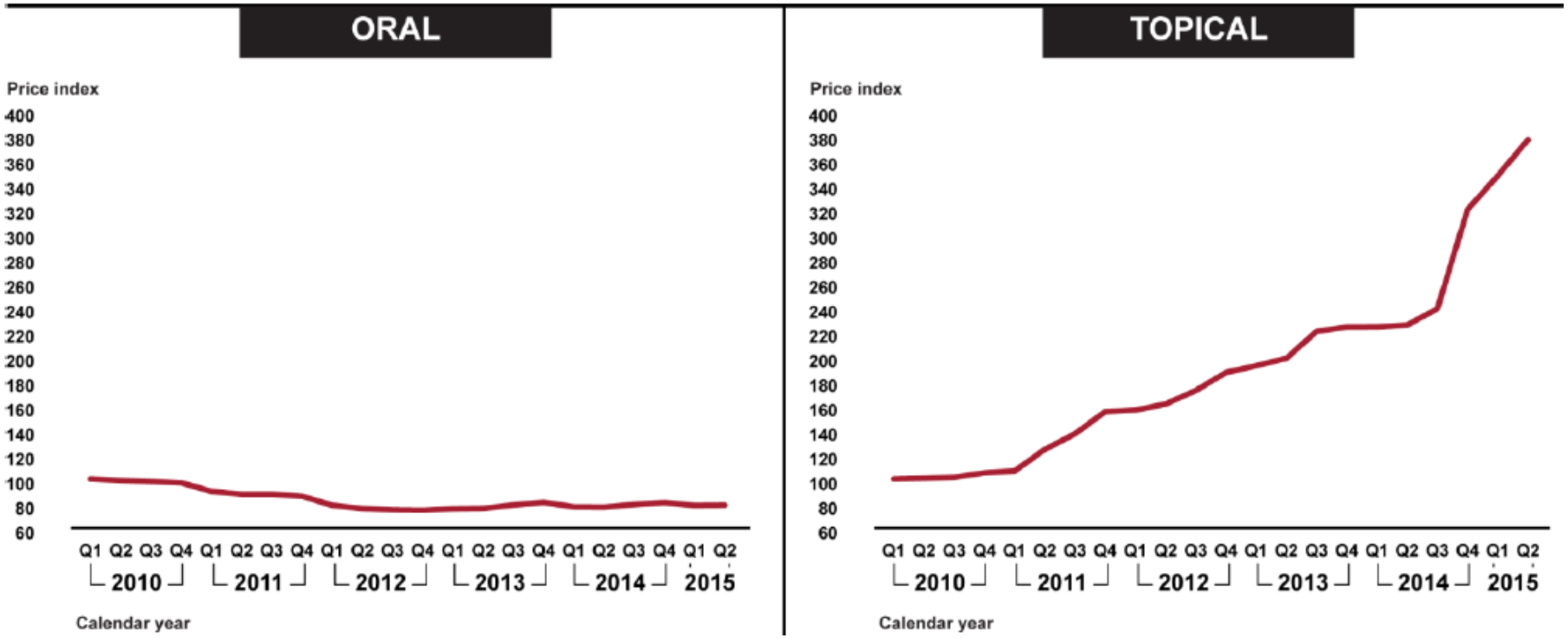
Fortune, 2015



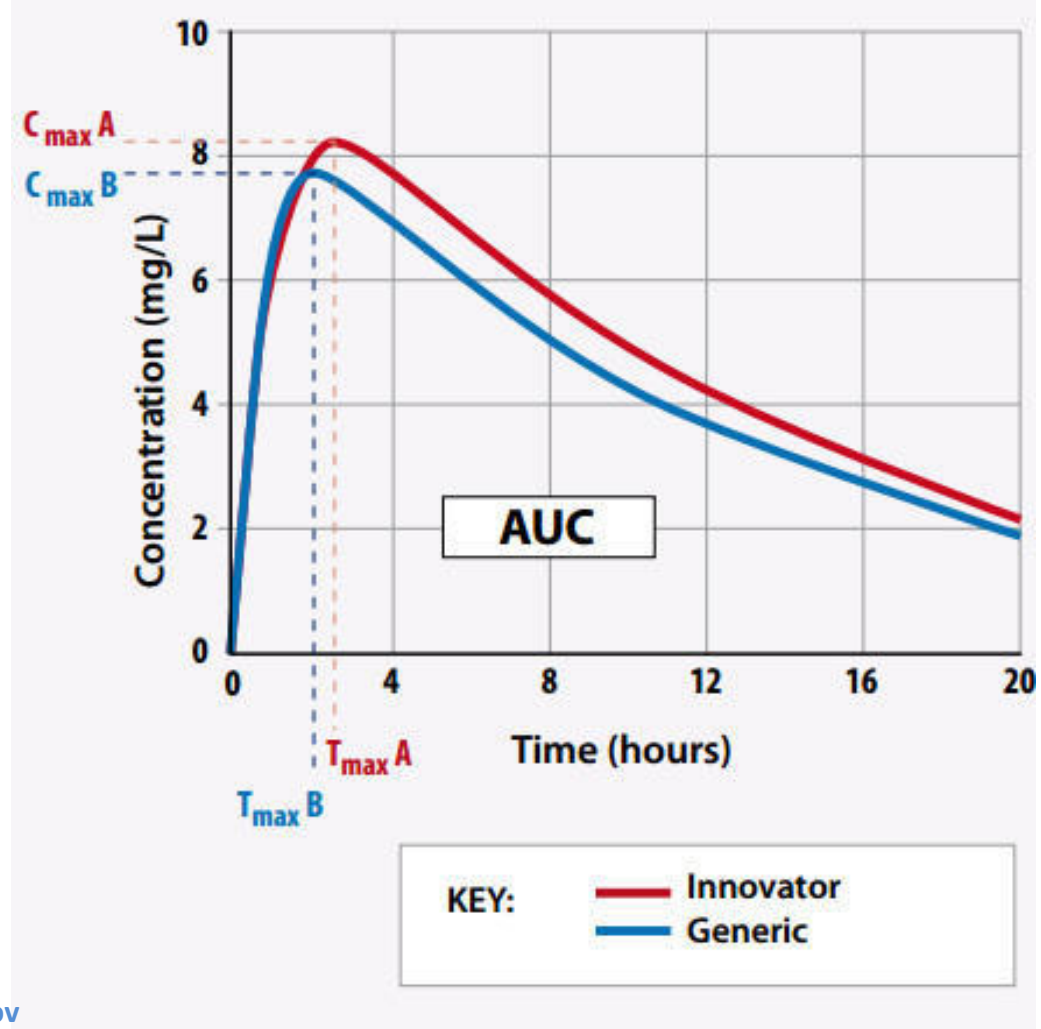
Chicago Tribune, 2016

Pricing effect - Topical drug generic dearth

- **Public Health Issue**
  - Many old and new topical products with no generics developed
  - Average price of topical products increased 276% in 2010-2015
  - Patient access to medicines impacted



Bioequivalence Determinations



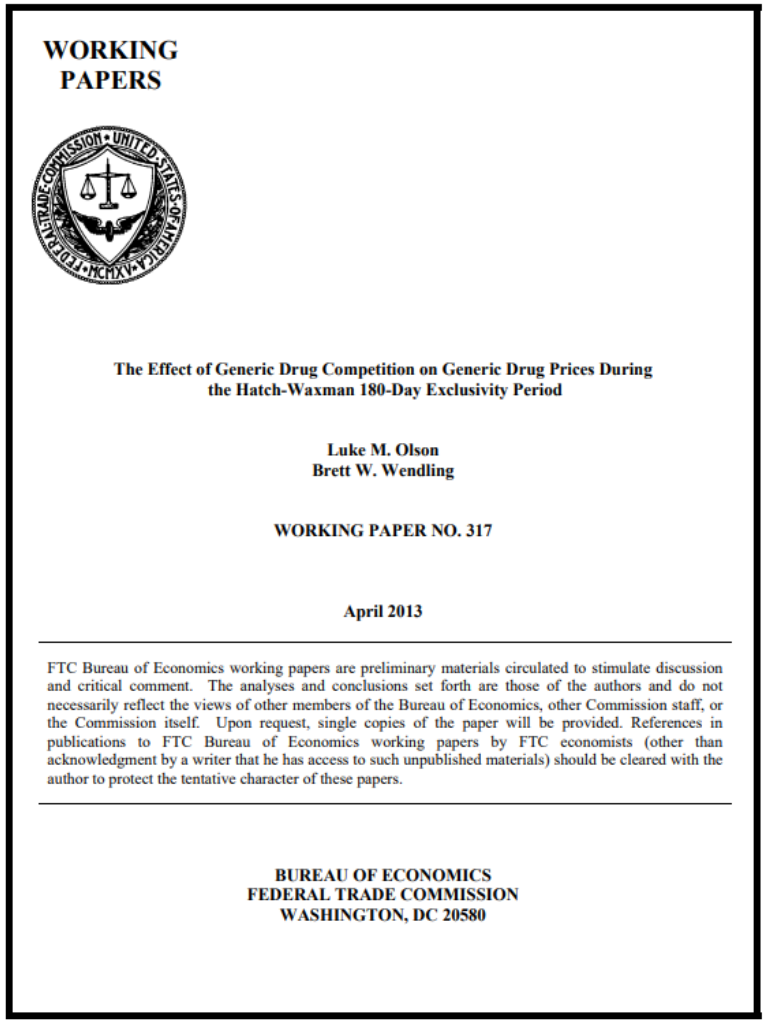
- For products with systemic site of action, BE via systemic PK endpoints (e.g. C_{max} and AUC) helps infer comparable safety and efficacy
- For products that are locally acting, it is more difficult to assess local exposure
- The site of action may not be directly correlated with systemic PK

FDA Drug Competition Action Plan

- List of off-patent, off-exclusivity branded drugs without approved generics is published
- New policy to expedite review of generic drug applications where competition is limited
- Use of good review management practices
- Reduce application cycles – improved pre-ANDA interaction

Impact of Generic Drug Availability on Price

- The first generic has a muted effect on lowering drug price in the marketplace.
- Subsequent generics help reduce the price more, especially the third and fourth generic.
- FDA Drug Competition Action Plan – expedite review of generic drug applications until there are three approved generics for a given drug product.



WORKING PAPERS

The Effect of Generic Drug Competition on Generic Drug Prices During the Hatch-Waxman 180-Day Exclusivity Period

Luke M. Olson
Brett W. Wendling

WORKING PAPER NO. 317

April 2013

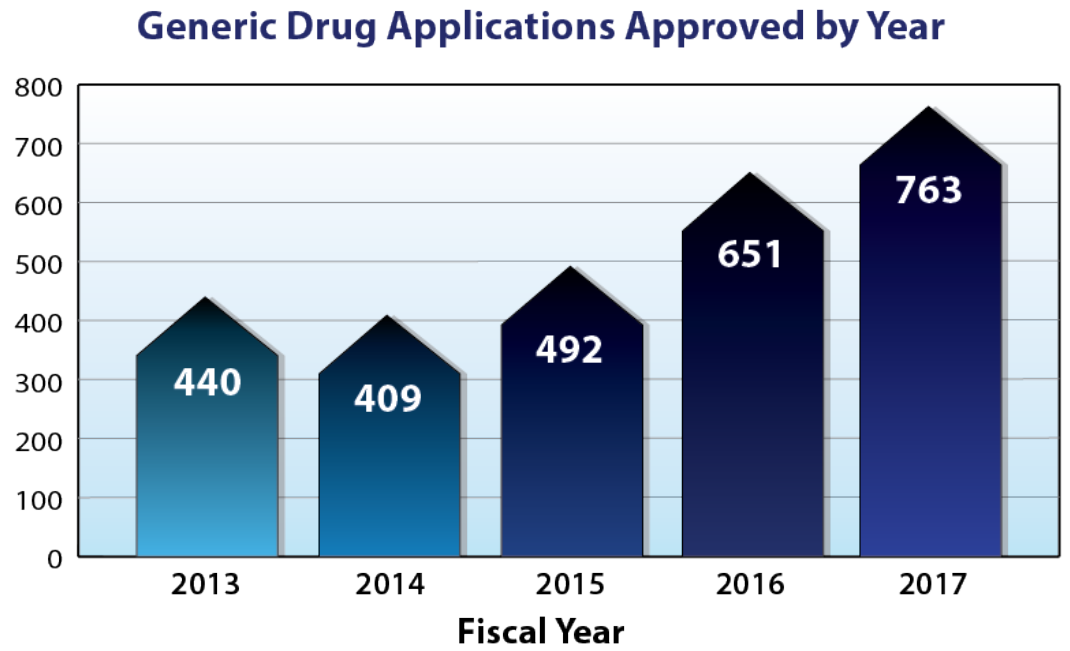
FTC Bureau of Economics working papers are preliminary materials circulated to stimulate discussion and critical comment. The analyses and conclusions set forth are those of the authors and do not necessarily reflect the views of other members of the Bureau of Economics, other Commission staff, or the Commission itself. Upon request, single copies of the paper will be provided. References in publications to FTC Bureau of Economics working papers by FTC economists (other than acknowledgment by a writer that he has access to such unpublished materials) should be cleared with the author to protect the tentative character of these papers.

BUREAU OF ECONOMICS
FEDERAL TRADE COMMISSION
WASHINGTON, DC 20580

GDUFA Regulatory Science

- FDA has been playing a more active role in performing and funding research to advance drug science
- This provides new tools for FDA and industry to evaluate generic drug equivalence, to enable more efficient development of generic drugs and thus improve access
- ~$30 million per year for stakeholder-driven generic drug regulatory science
  - Goal: Access to generics in all product categories
  - 90+ on-going projects
  - Recent focus on complex drug products

Generic Drug Science & Research Website:
https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/ucm567695.htm



Complex Generic Products in GDUFA II

- Complex active ingredients
  - Complex mixtures of APIs, polymeric compounds, peptides
- Complex formulations
  - Liposomes, suspensions, emulsions, gels
- Complex routes of delivery
  - Locally acting such as dermatological and inhalational drugs
- Complex dosage forms
  - Long acting injectables, implantable drugs
- Complex drug-device combination products
  - Transdermals, metered dose inhalers (MDIs)
- Other products where complexity or uncertainty concerning the approval pathway or other alternative approach would benefit from early scientific engagement

https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf

Topical Dermatological Products

Examples:

- Solutions
- Powders
- Gels
- Ointments
- Lotions
- Creams
- Aerosols/Foams

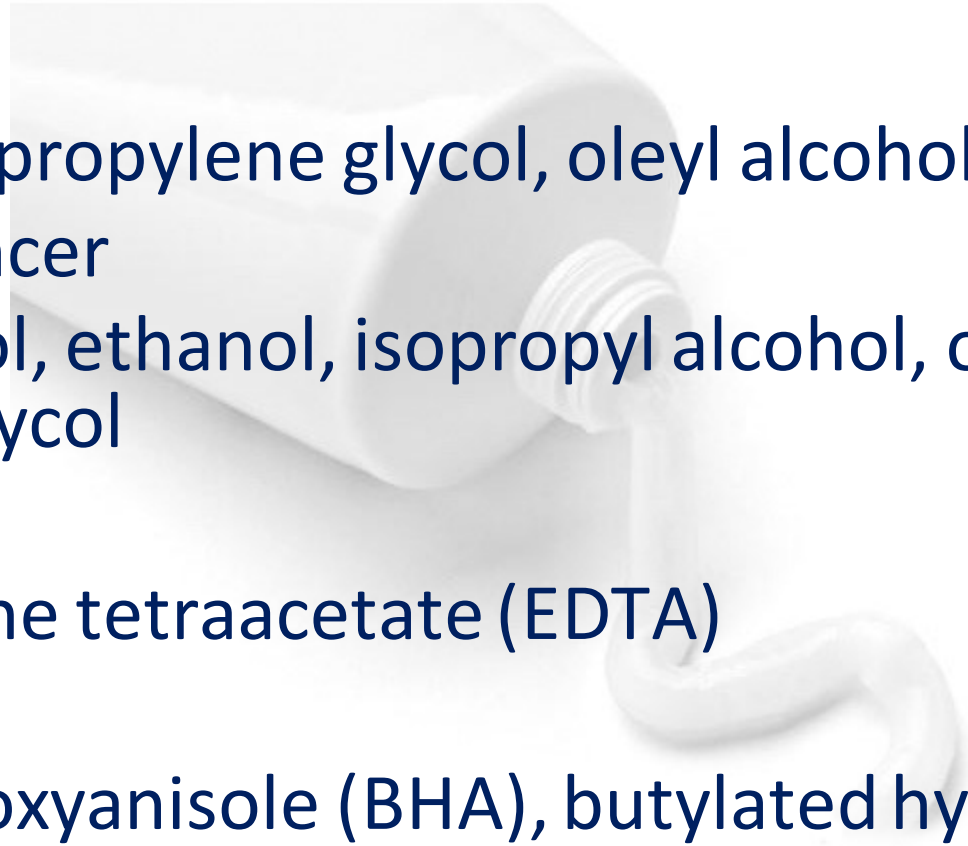
Main Components of a Topical Drug

- Active Product Ingredient (API) – Source is important with attention to impurities, residual solvents, and physical characteristics such as particle size, morphic form, solubility properties, sensitivity to degradation.
- Excipients – Compendial vs. non-compendial – understand the role for each excipient – attention to impurities, etc.
- Container closure system – important for product integrity and should be as close to RLD as possible.

Common Topical Formulation Components

- Emollient/stiffening agent/ointment base
  - Carnauba wax, cetyl alcohol, lanolin, paraffin, petrolatum, polyethylene glycol, stearic acid
- Emulsifying agent/solubilizing agent
  - Polysorbate 20, poloxamer, sodium lauryl sulfate, diethylene glycol monoethyl ether, docusate sodium
- Humectent – water retention
  - Glycerin, propylene glycol, sorbitol solution, polyethylene glycol
- Thickening/gelling agent
  - Carbomer, methyl cellulose, carrageenan, sodium alginate, gelatin
- Preservative – prevents microbial growth
  - Benzoic acid, propyl or methyl parabens, imidurea, potassium sorbate, benzalkonium chloride, phenoxyethanol

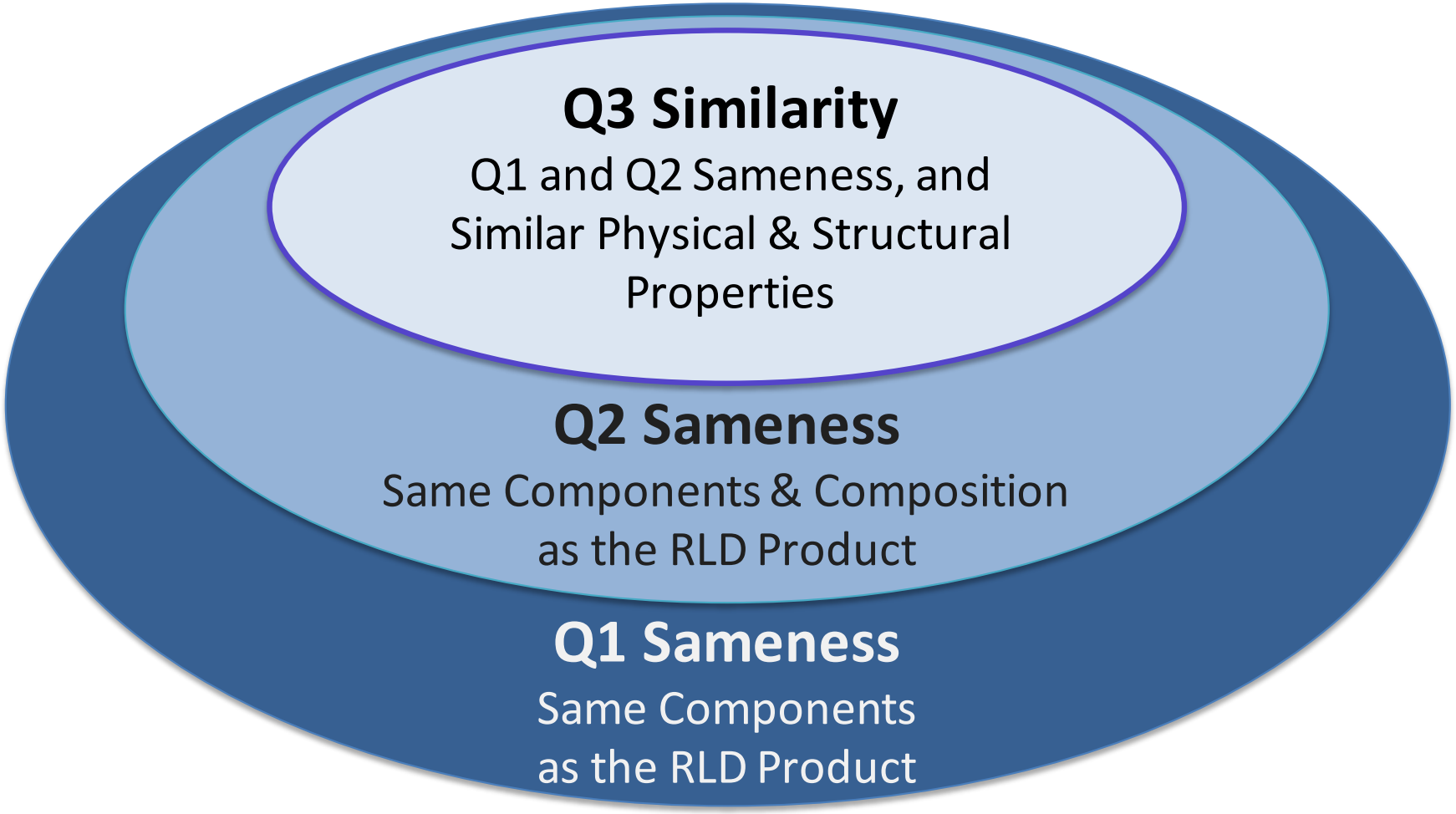
Common Topical Formulation Components



- Vehicle/solvent
  - Purified water, propylene glycol, oleyl alcohol, mineral oil
- Permeation Enhancer
  - Propylene glycol, ethanol, isopropyl alcohol, oleic acid, polyethylene glycol
- Chelating Agent
  - Ethylene diamine tetraacetate (EDTA)
- Antioxidant
  - Butylated hydroxyanisole (BHA), butylated hydroxytolutene (BHT)
- pH Adjuster
  - Citric acid, phosphoric acid, sodium hydroxide

Topical Formulation Quality Concepts

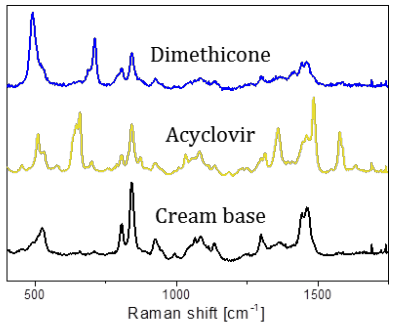
- What are Q1, Q2, and Q3?



Influence of Dispensing Stress on Q3

- Influence of Dose Dispensing on Product Quality

  Prof. Michael Roberts FDA Award U01-FD005226



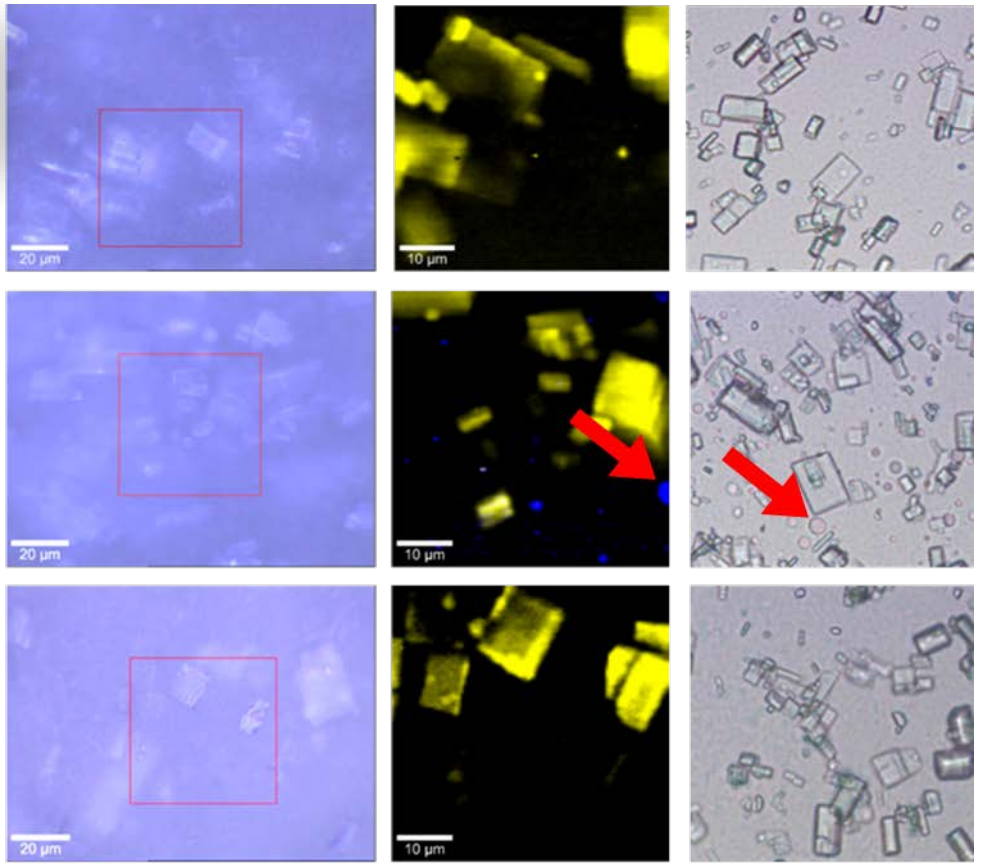
Zovirax® UK
Tube

University of South Australia

Zovirax® UK
Pump

UNIVERSITÄT DES SAARLANDES

Zovirax® UK
Pump
(from inside container)



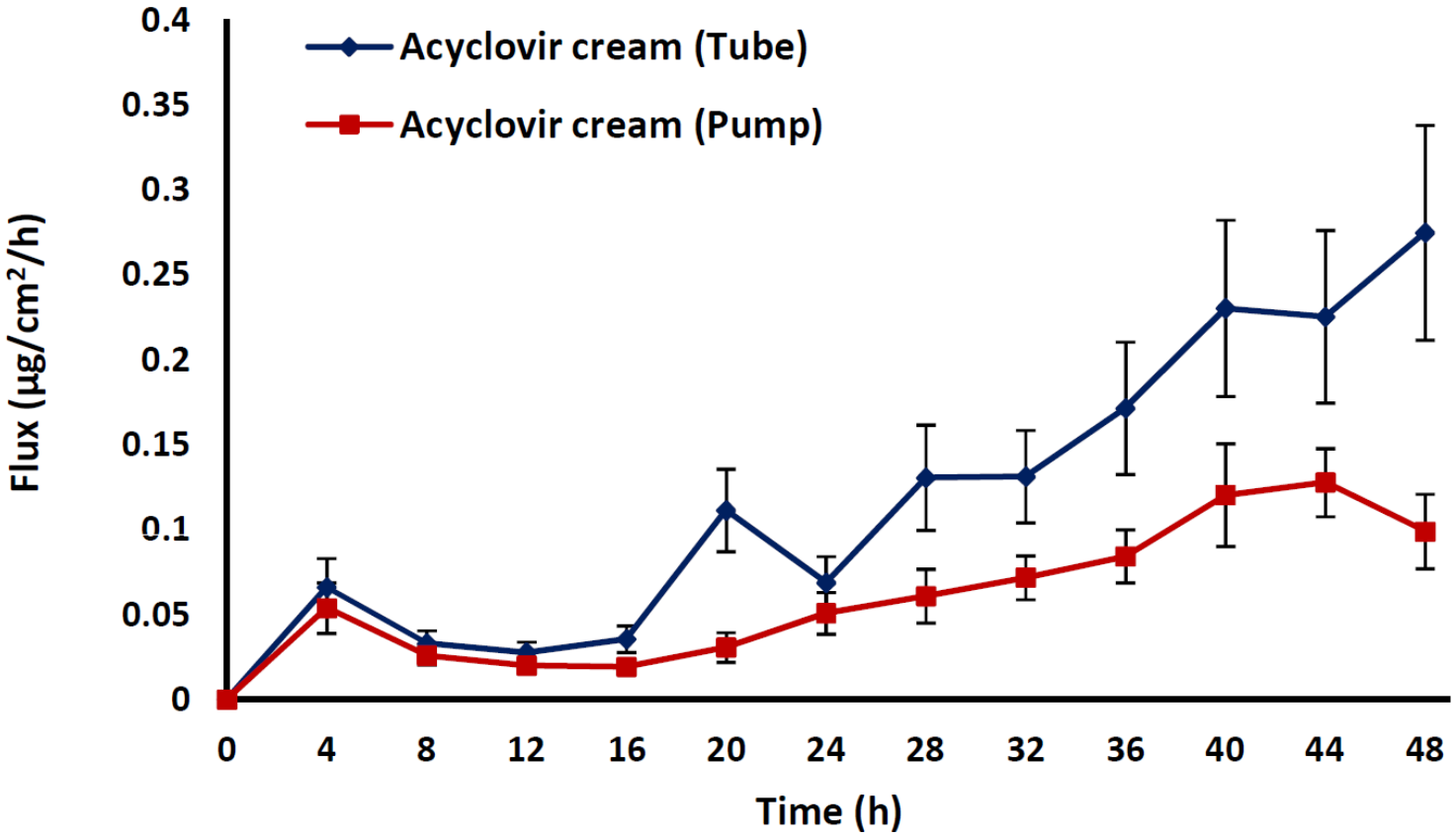
Data provided courtesy of Prof. Michael Roberts & Prof. Maike Windbergs

Influence of Dispensing Stress on Q3

- Influence of Dose Dispensing on Product Quality

  Prof. Michael Roberts FDA Award U01-FD005226

University of South Australia



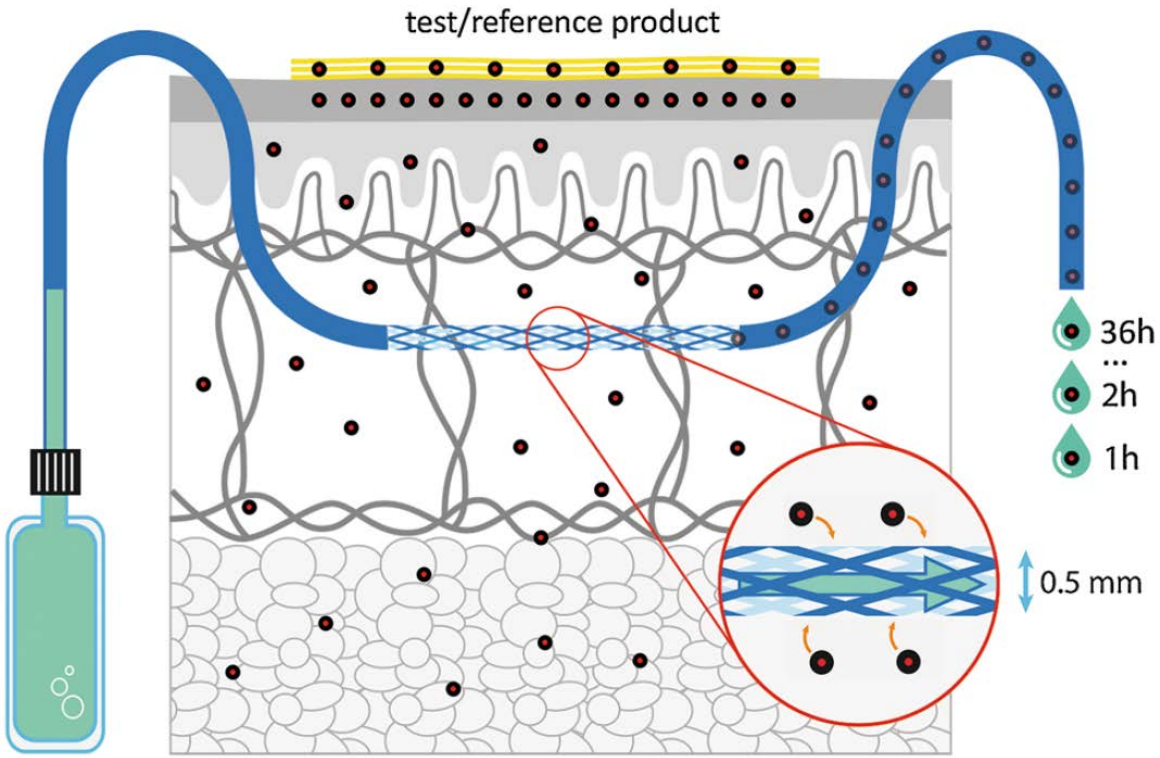
Data provided courtesy of Prof. Michael Roberts

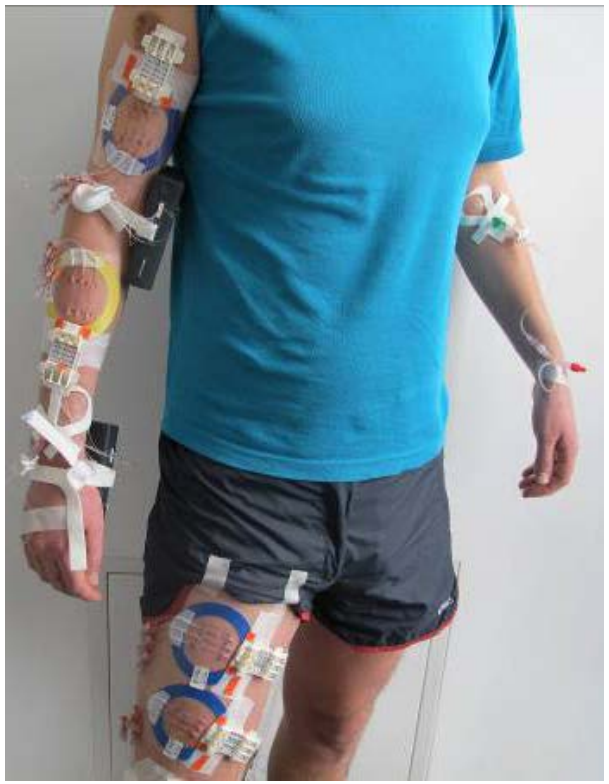
Tests for Physical & Structural Similarity

- Microscopic Analyses of Microstructure
- Dissolved vs. Undissolved Amounts of the Drug
- Concentration of Drug in the Continuous Phase
- Size Distribution of Globules/Particles
- Drug Polymorphic State (Raman, X-ray diffraction, etc.)
- Solvent/Water Activity (Drying Rate)
- Specific Gravity
- pH
- Etc.

In Vivo Cutaneous Pharmacokinetics

- Dermal Open Flow Microperfusion (dOFM)





Images courtesy of Joanneum Research

Recent Topical Drug Science-based Actions

- **2017-2018 Outcomes Based on Novel BE Approaches**
  - **Notable PSGs based upon novel BE approaches:**
    - Bimatoprost Topical Solution, 0.03% (02/2018)
    - Crisaborole Topical Ointment, 2% (02/2018)
    - Dapsone Topical Gel, 7.5% (10/2017)
    - Ivermectin Topical Cream, 1% (10/2017)
  - **Notable ANDA approvals based on novel BE approaches:**
    - 4 more generics approved for Acyclovir Topical Ointment, 5% (**8 Total**)
  - **Notable first generics approved (all with PSGs)**
    - Estradiol Vaginal Cream, 0.01% (12/2017)
    - Butenafine Hydrochloride Cream, 1% (11/2017)
    - Hydrocortisone Butyrate Lotion, 0.1% (11/2017)
    - Dapsone Gel, 5% (10/2017)

Future Directions

- Non-invasive methods to determine within skin drug concentrations
  - Con-focal spectroscopy
- Impact of formulation physicochemical attributes on
  - drug pharmacokinetics at the site of action
  - product use and other patient-centric issues
- Economics of niche drug products in the context of competition, pricing, and accessibility

Why are Generic Topical Drugs Important

- **Public Health Issue**
  - Many old and new topical products with no generics developed
  - Average price of topical products increased 276% in 2010-2015
  - Patient access to medicines was impacted
- **Scientific Research**
  - Determined key factors controlling BE for various product types
  - Identified failure modes for BE relevant to product complexity
  - Developed novel, sensitive, efficient approaches to assess BE
- **Regulatory Impact**
  - Greatly reduced barriers to entry for generic topical products
  - Product Specific Guidances (PSGs) for many classes of products
  - New generic topical products finally developed and approved

Acknowledgements

- Sam Raney, PhD
- Priyanka Ghosh, PhD
- Robert Lionberger, PhD
- Our outside-of-FDA collaborators
  - Michael Roberts, PhD
  - Frank Sinner, PhD


FDA
U.S. FOOD & DRUG
ADMINISTRATION