Science-Based Advancements in Assessing Performance of Topical Generic Products

Society of Investigational Dermatology

From Laboratory Tools to Product Approval

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

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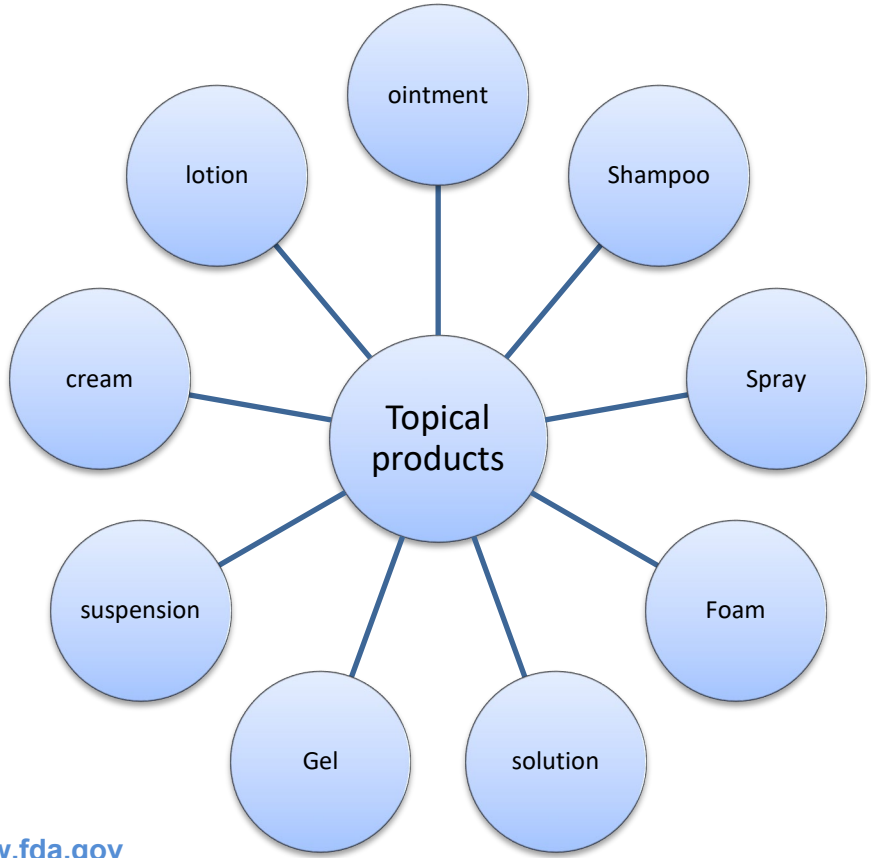
Topical Drug Products



www.fda.gov

https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm

Bioequivalence (BE) for Topical Products

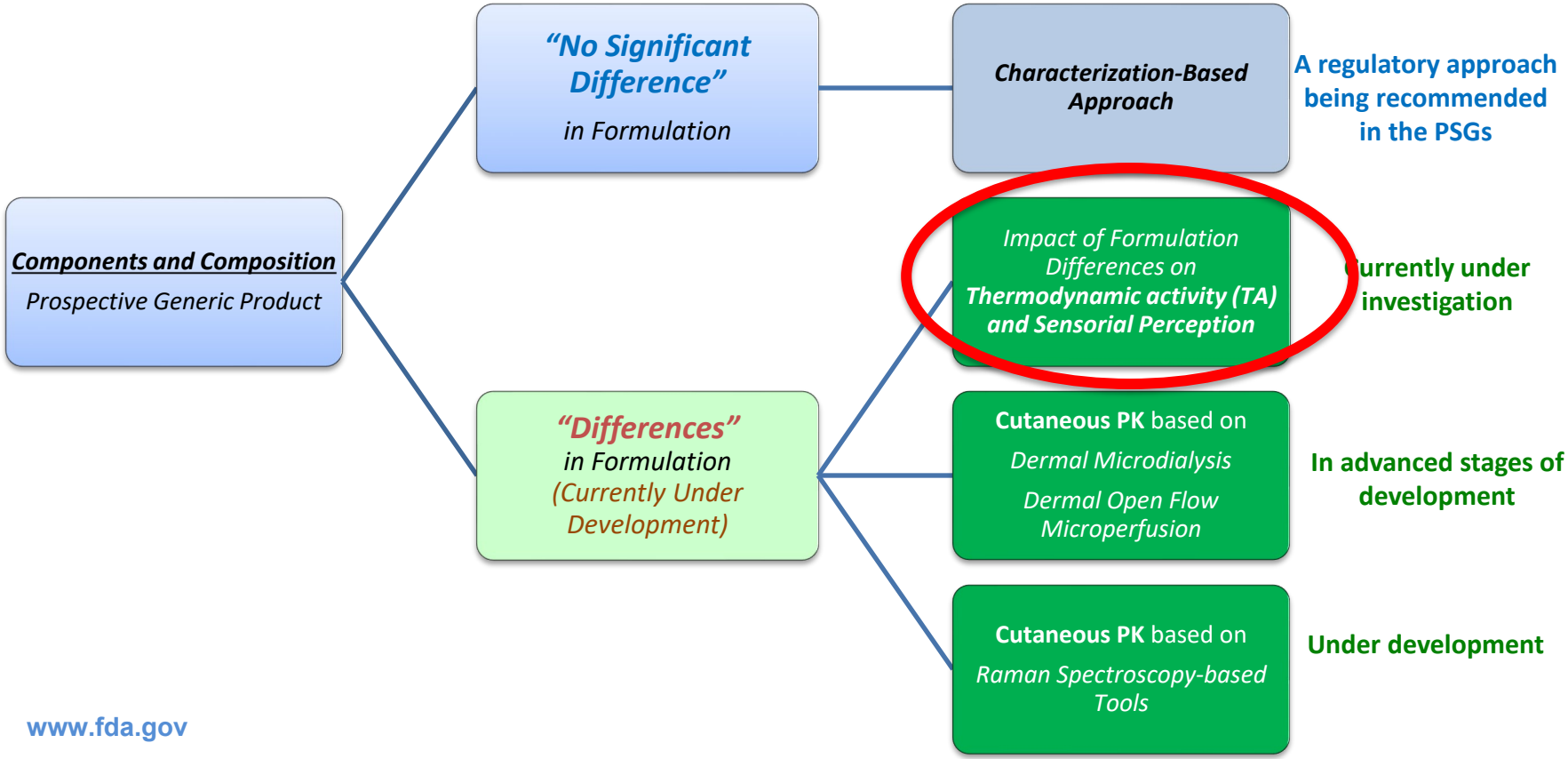
Establishing equivalent performance, conventionally via:

- Comparative in vivo BE studies
  - Clinical endpoint
  - Pharmacodynamic endpoint (e.g., vasoconstrictor (VC) studies)

Developing more efficient BE approaches:

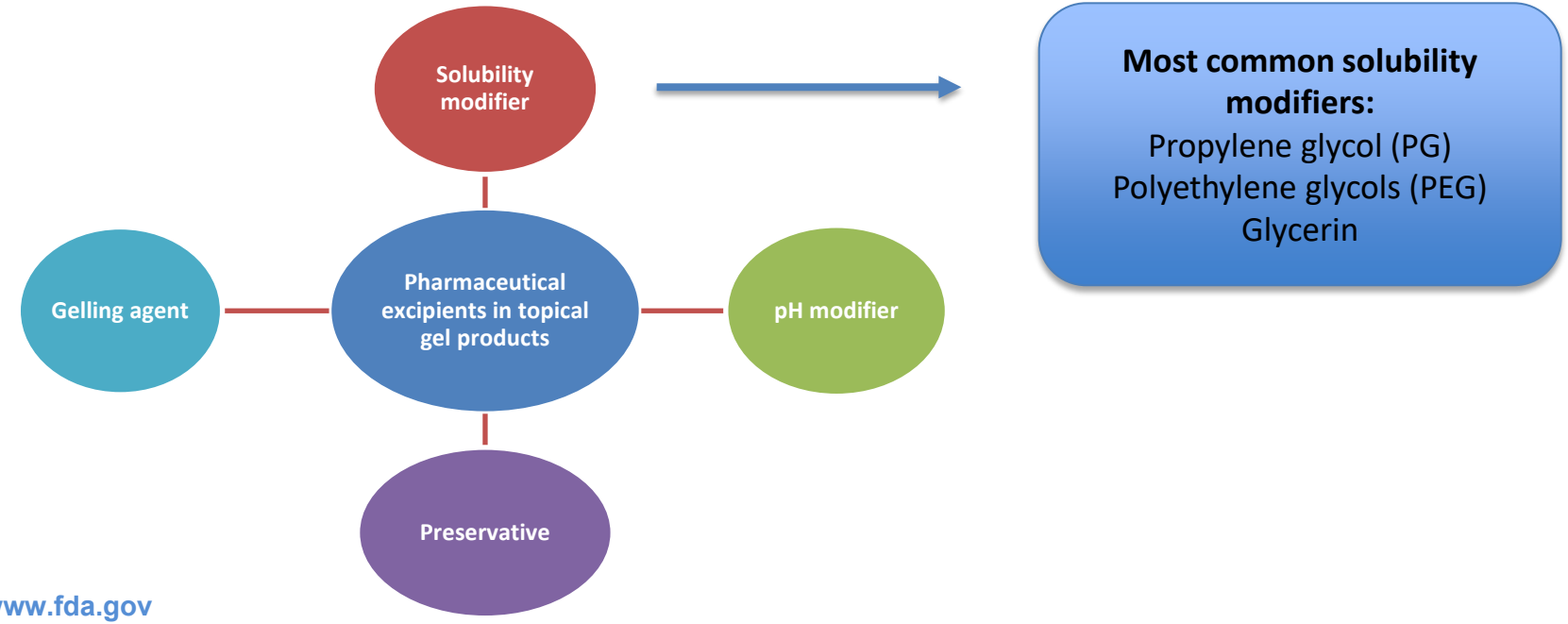
- in vitro characterization and performance tests
- cutaneous pharmacokinetic studies

Potential Strategies for BE



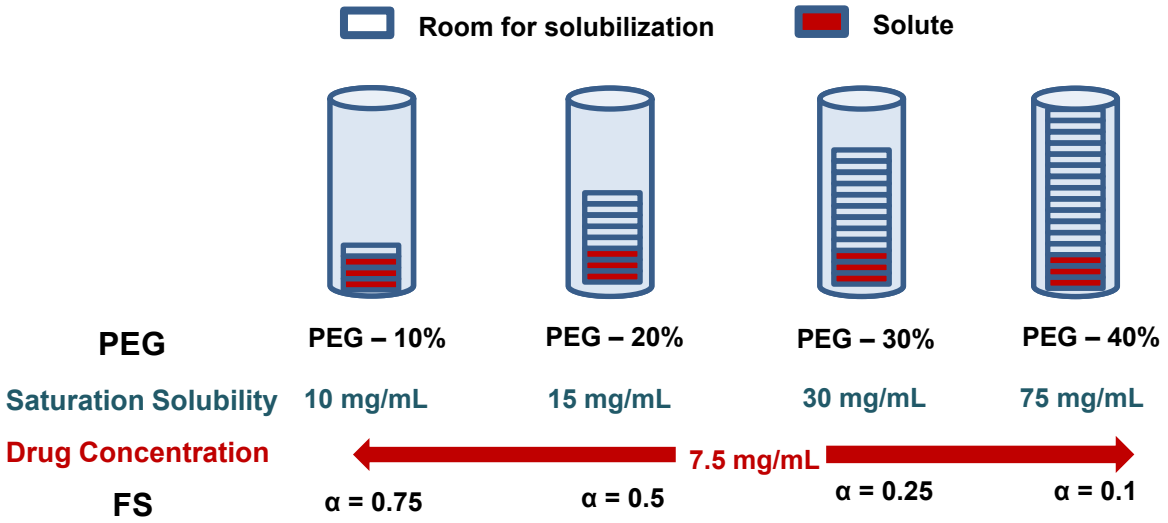
Single Phase Gels

Understanding the function of excipients and their impact on thermodynamic activity (TA) of the drug in the topical formulations.



Fractional Solubility

$$Fractional\ Solubility\ (FS)\ , \alpha = \frac{Conc.\ of\ Solute}{Saturation\ solubility\ of\ solute\ in\ the\ solvent}$$

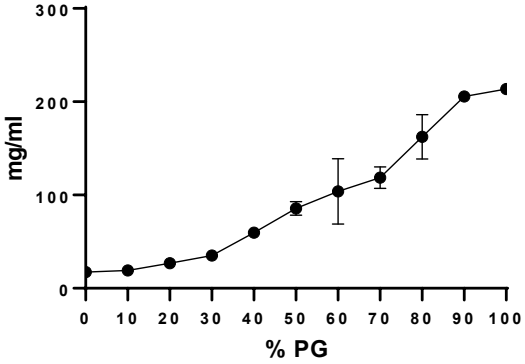


- Fractional solubility is often predictive of TA of the drug in the formulation

FS and BA

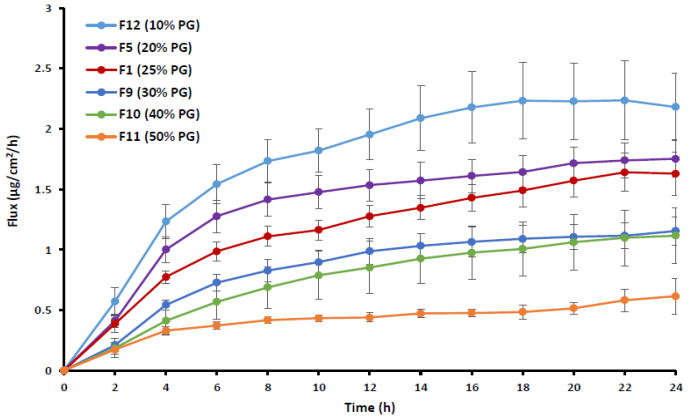
Diclofenac sodium in PG:water formulations

Drug Solubility in PG-water



Data are presented as mean±SD, n=3

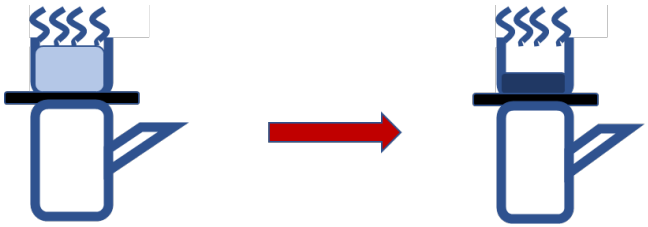
IVPT (infinite dose)



Data are presented as mean±SE, 3 donors 3 replicates

Courtesy of Dr.Mike Roberts and Dr.Yousuf Mohammad , FDA award U01FD006496

Metamorphosis and Change in FS

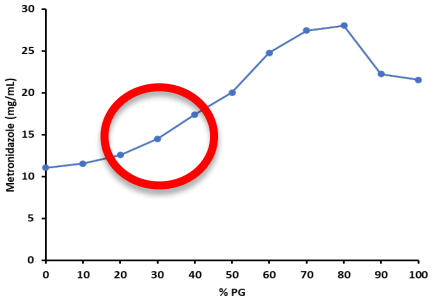
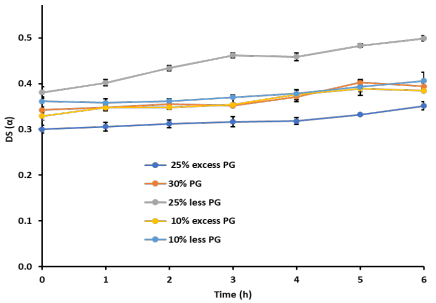
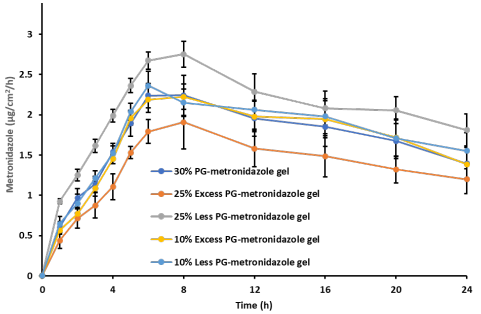
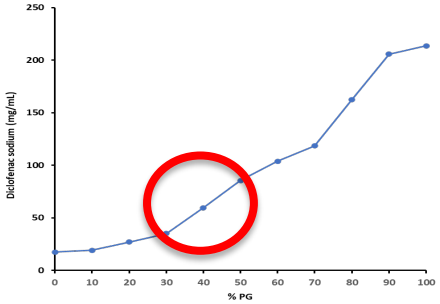
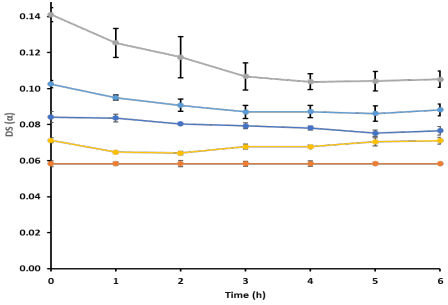
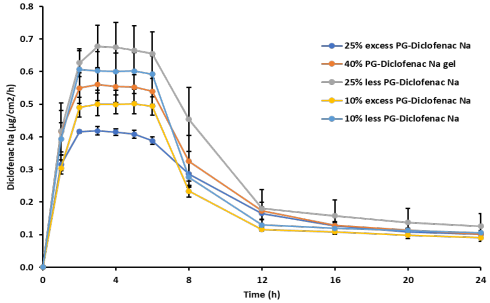


- Solvent evaporation during metamorphosis of the formulation can lead to
  - Change in drug solubility at the application site (can be monitored by measuring drug concentration in the donor compartment)
  - Change in microstructure/Q3 properties

  May lead to change in drug permeation and BA

Q2 Differences and BA- PG

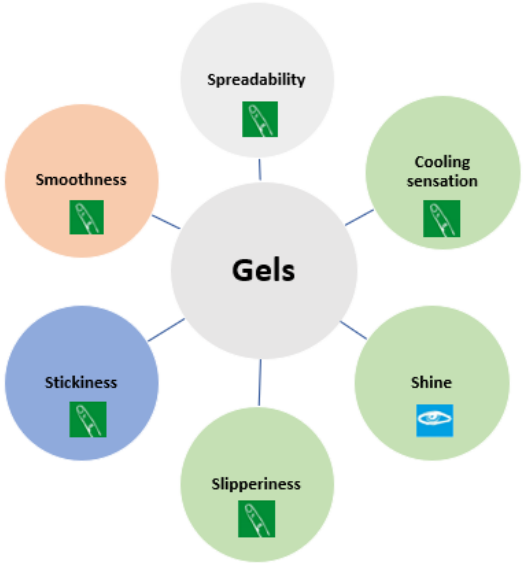
Composition	(Reference)				
% change in PG	+25	+10	0	-10	-25

Drug	Solubility Data	FS	IVPT Data
Metronidazole			
Diclofenac sodium			

Courtesy of Dr. Narasimha Murthy, FDA Award U01FD006507

Sensory Attributes and TE

Potential sensory attributes of gels that may impact TE



Sensory attributes	Instrumental technique	Formulation variables	Q3 attributes
Cooling sensation	Gravimetric measurement of drying rate/ corneometer	Amount of solvent/cosolvent (e.g., water, alcohol, etc.)	Evaporation of volatile components
Firmness/ stickiness	Texture analyzer	Amount of gelling agent(s)	Zero sheer viscosity, yield stress, adhesiveness
Spreadability	Rheometer	Amount of gelling agent(s)	Zero sheer viscosity, yield stress, adhesiveness

Courtesy of Dr. Yousuf Mohammad FDA Award U01FD006700

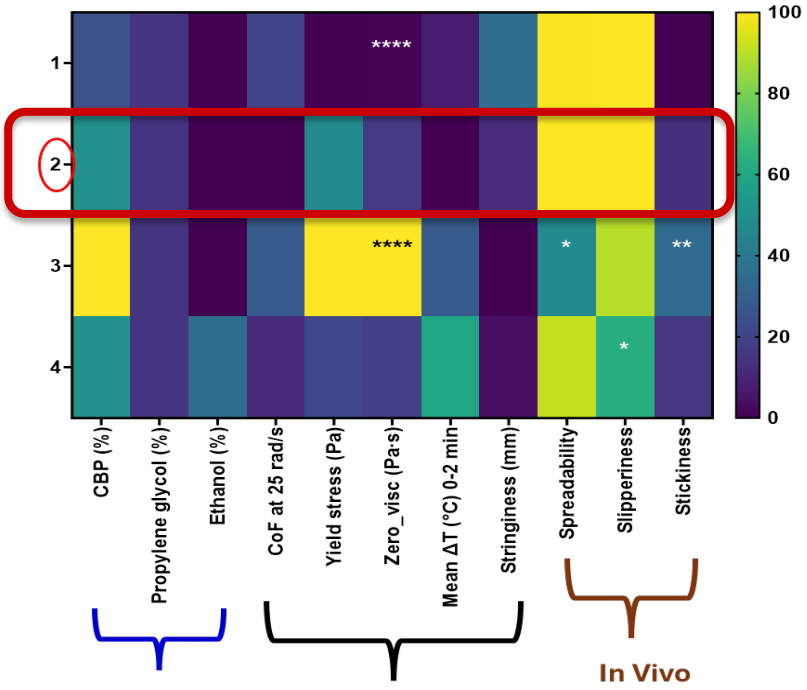
Differences Beyond BA

- Would differences in Q1/Q2/Q3 of topical products result in differences in the feel of the topical drug product and subsequently in therapeutic equivalence (TE)?
  - Establish a correlation between Q2, Q3 and sensory perception
- Can characterization of the arrangement of matter, (e.g., rheological characterizations) correlate with and/or be predictive of sensorial differences perceived by human subjects?
  - Develop objective instrumental tests measuring some Q3 attributes that can provide prediction of sensory perception of topical products

Sensorial Studies of the Gels

Gels made using Carpool 980 (CBP) with different compositions of the gelling agent and alcohol

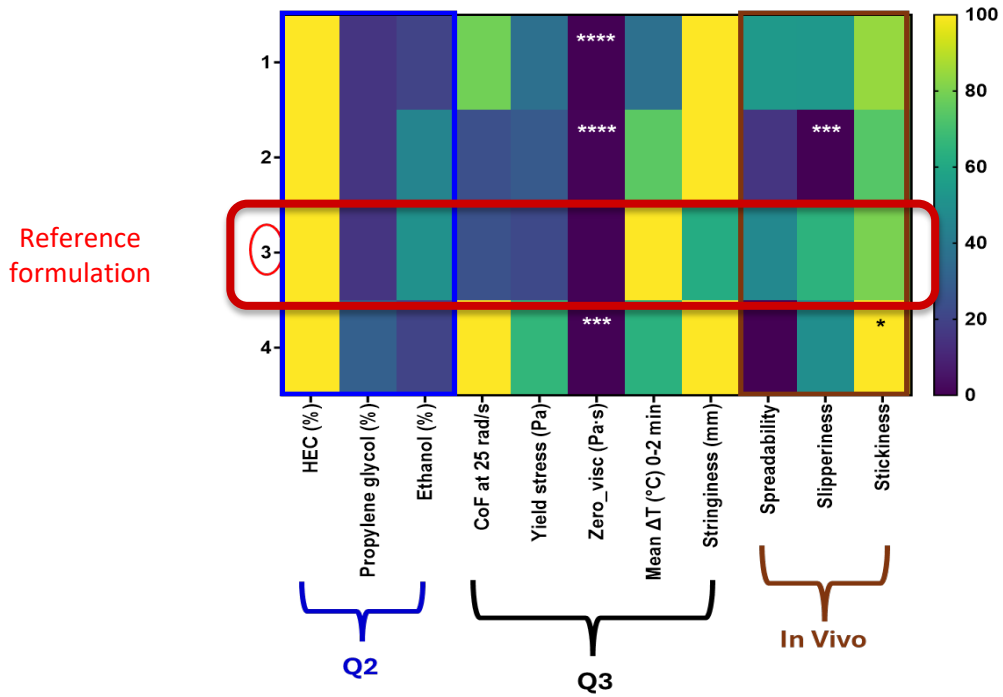
Reference formulation



Phan et al. CRS poster 2024, FDA Award U01FD006700

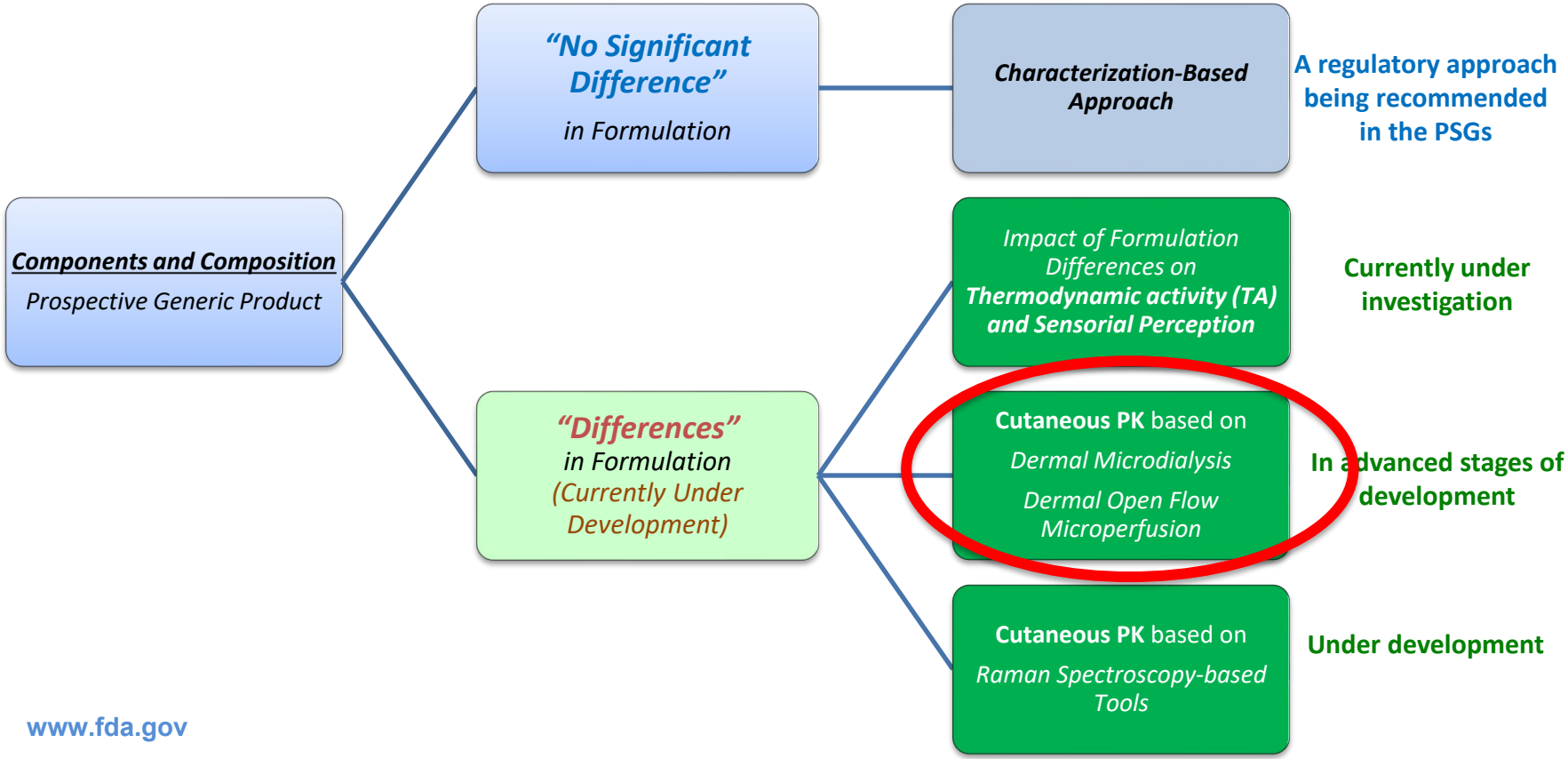
Sensorial Studies of the Gels

Gels made using hydroxyethyl cellulose (HEC) with different compositions and PG and alcohol.



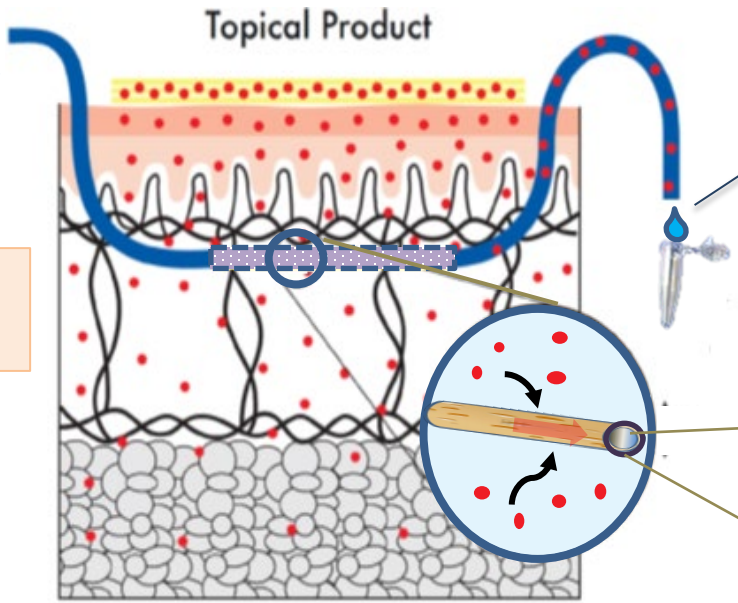
Phan et al. CRS poster 2024, FDA Award U01FD006700

Potential Strategies for BE



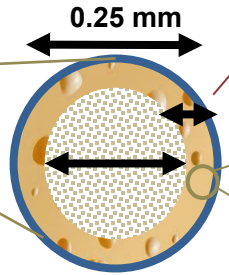
dMD

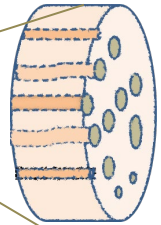
Isotonic fluid



Collected sample concentration is proportional to the interstitial fluid concentration

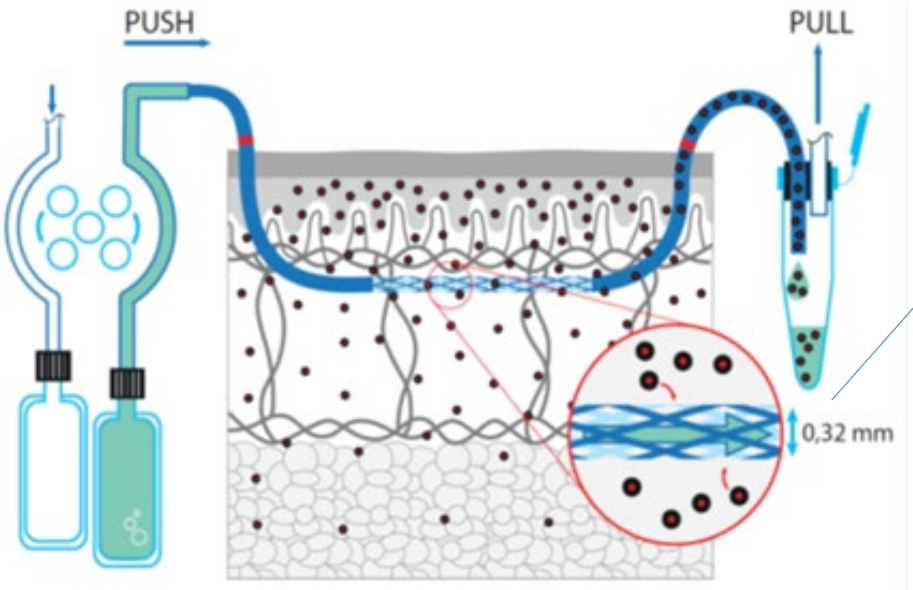
Tubular hollow dialysis fiber from an artificial kidney



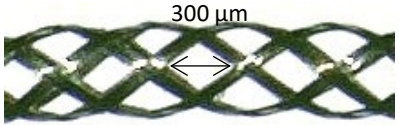


Adapted from: Bodenlenz, Manfred, et al. Clinical pharmacokinetics 56.1 (2017): 91-98 and courtesy of Dr Ben Kuzma

dOFM



Metal mesh design



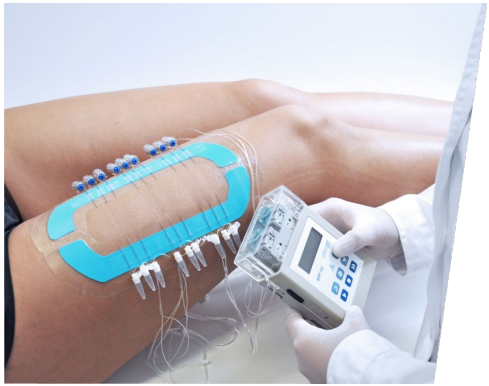
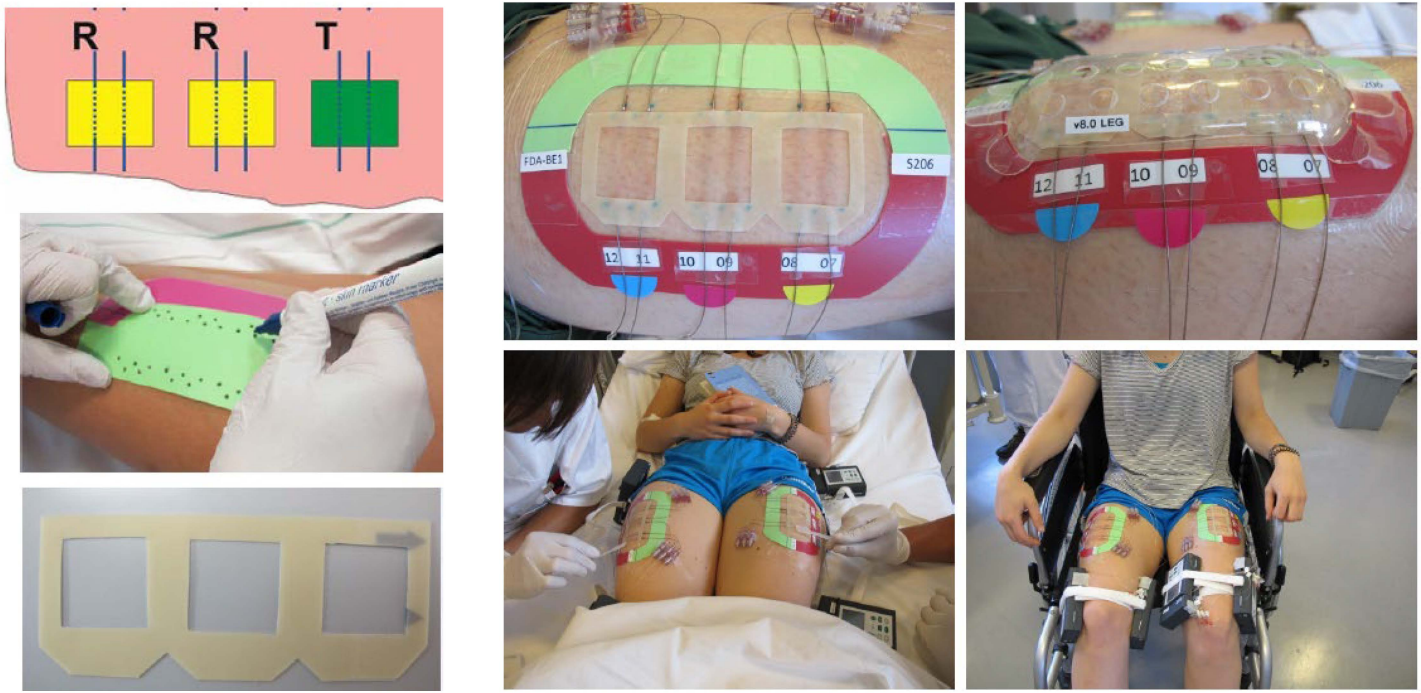


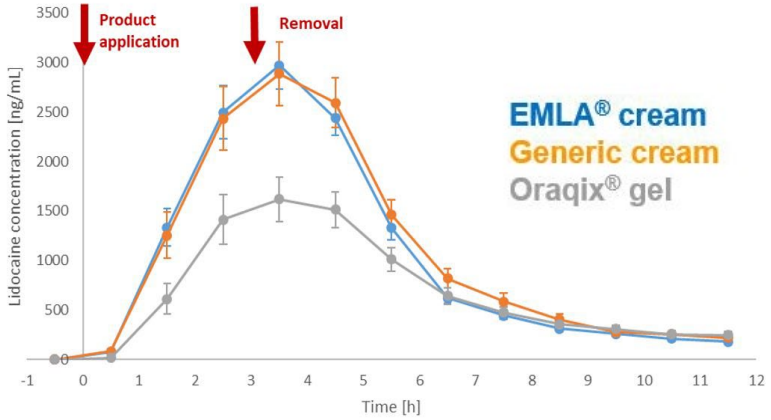
Image provided courtesy of Dr. Frank Sinner, Joanneum Research

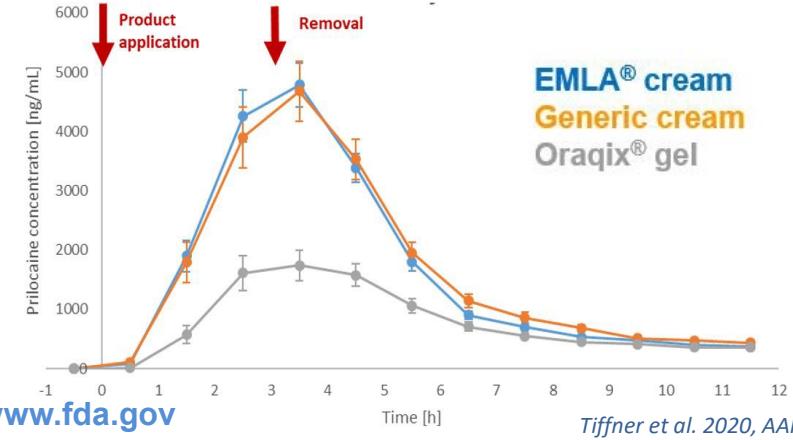
dOFM Study Set UP



Images provided courtesy of Dr. Frank Sinner (Joanneum Research) FDA Award U01FD004946

BE Study for Lidocaine Prilocaine Cream



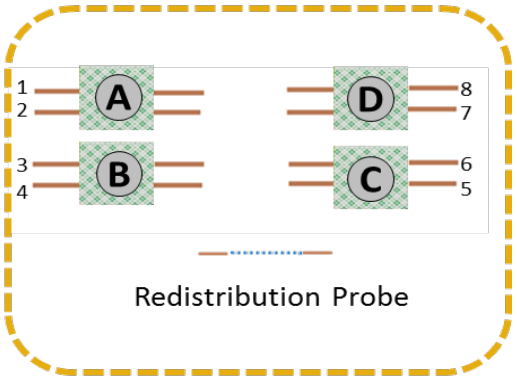


R: EMLA® (lidocaine; prilocaine) topical cream, 2.5%; 2.5 %
$T_{generic}$: generic lidocaine; prilocaine cream, 2.5%; 2.5%
$T_{non\text{-}equ}$: Oraqix®(lidocaine; prilocaine) dental gel, 2.5%; 2.5%

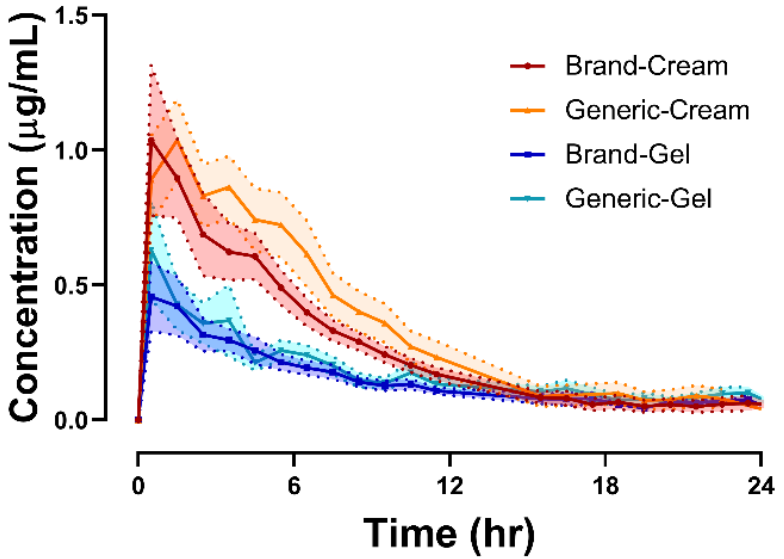
	PK endpoint	Drug	95% upper confidence bound	BE - criterion satisfied	Result
T_{gen} vs. R_1	$AUC_{0\text{-}12}$	lidocaine	-0.053	Yes	The generic cream is **bioequivalent** to the reference cream.
	C_{MAX}		-0.055	Yes	
	$AUC_{0\text{-}12}$	prilocaine	-0.051	Yes	
	C_{MAX}		-0.043	Yes	
$T_{non\text{-}equ}$ vs. R_2	$AUC_{0\text{-}12}$	lidocaine	0.330	No	The gel is **not bioequivalent** to the reference cream.
	C_{MAX}		0.623	No	
	$AUC_{0\text{-}12}$	prilocaine	0.703	No	
	C_{MAX}		1.174	No	

Tiffner et al. 2020, AAPS poster, FDA Award U01FD005861

Cutaneous PK of Metronidazole Products



- MetroGel® topical gel, 0.75% “Brand Gel”
- Metronidazole topical gel, 0.75% “Generic Gel”
- MetroCream® topical cream, 0.75% “Brand Cream”
- Metronidazole topical cream, 0.75% “Generic Cream”



*Average dermal concentration profiles using **dMD**, (mean ± SEM, n=7), in rabbits*

Senemar et al. 2019 AAPS poster, FDA Award U01FD005862

Summary and Conclusions

- FDA is investigating alternative, scientifically valid methods, including in vitro approaches, to support the assessment of BE for topical drug products that have compositional differences compared to the reference standard.
- The current research data suggests that when there are differences in FS-time profiles and TA, such differences may result in differences in BA of the topical drug as evaluated using IVPT.
- The Q3 properties assessed instrumently, in vitro, may be valuable in understanding most of the sensorial differences among topical gels assessed in vivo.
- Cutaneous PK-based approaches using dOFM and dMD have the potential to support a demonstration of BE when the proposed method is optimized and controlled to be adequately discriminating and reproducible.
- Goal of the Generic Drug User Fee Amendments (GDUFA)-funded research program is to develop efficient BE approaches for complex generic drug products including topical products applied to the skin.

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- Robert Lionberger, PhD

Research Collaborators

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GDUFA Award U01FD006930, Long Island University

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GDUFA Award UU01FD006507, Topical Products Testing LLC

- **Dr. S. Narasimha Murthy**

GDUFA Award U01FD006496, University of Queensland

- **Dr. Yousuf Mohammad**

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