Advanced Techniques for Characterizing the Form & Function of Topical Dermatological Drug Products

Society for Investigative Dermatology Annual Meeting, 2022

FDA Session: Advances in Topical Dosage Form Characterization and Measuring Drug Concentrations in the Skin

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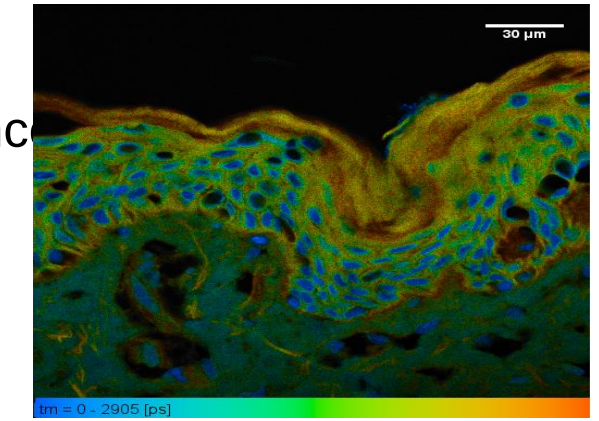
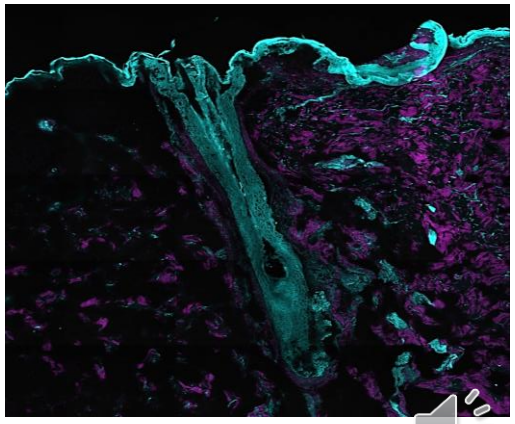
Scope of presentation

- Topical Products on US market today
- Evaluation of their topical bioequivalence
  - Reference listed drug products (RLD)
  - Generics
    - Integrating of critical quality attributes for a product with its performanc
    - *In vitro* methods
    - *In silico* approaches
    - Combinatorial strategies to demonstrate bioequivalence
    - Extension to body sites and disease states
    - Sensorial
  - And, along the way, I will raise a range of advanced and novel concepts in characterizing topical dermatological drug products
    - Components, Composition, Physical, Structural
    - Metamorphic and thermodynamic properties;
    - Concepts of Q1, Q2, and Q3 sameness and similarity; and
    - Potential failure modes for therapeutic performance

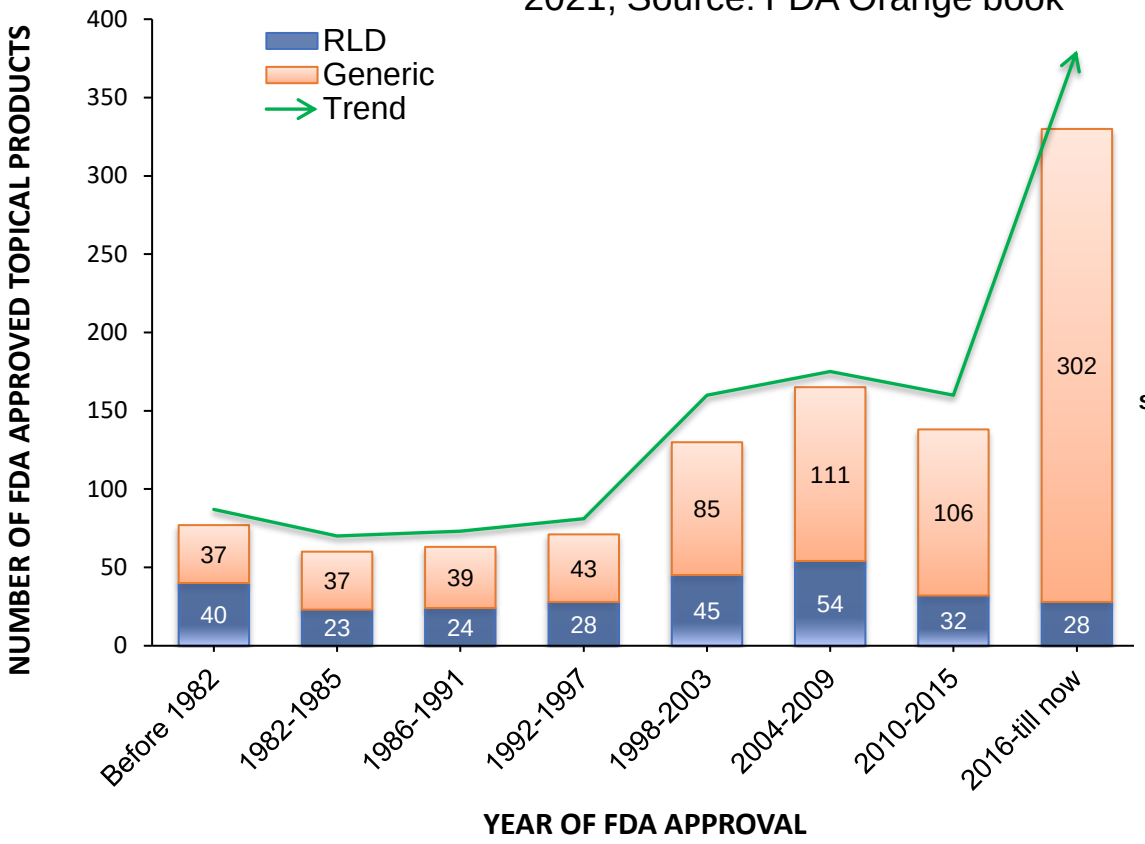


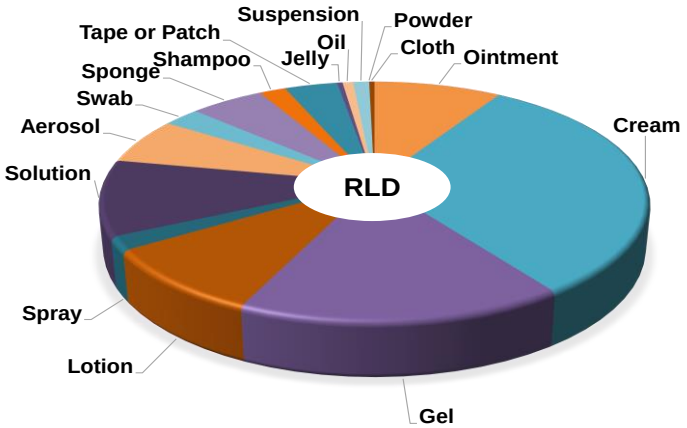


My key message: This an exciting area where one can make a real difference

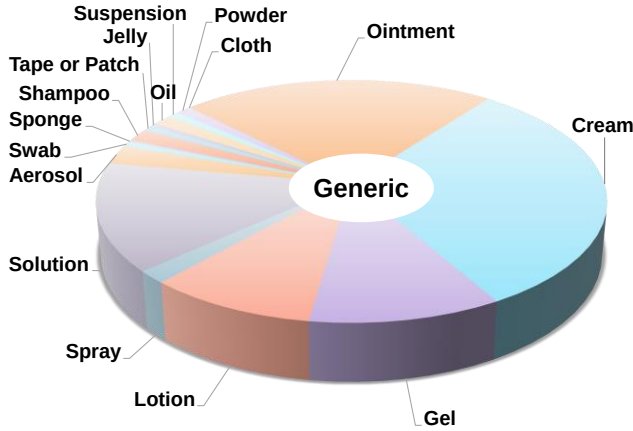
Our focus - topical products on US

FDA-approved reference listed drug (RLD) and generic topical products from before 1982 to June 2021; Source: FDA Orange book





Total products=274



Total products=770

Roberts MS et al. Topical drug delivery: History, percutaneous absorption, and product development. Adv Drug Del Rev. 177 (2021) 113929

Reference listed drug (RLD) topical products

Development & Evaluation

- **Create a product to meet a consumer need**
  - ❖ Define opportunity by characterising topical drug product market and unmet need
    - Driven by therapeutic focus, patients, drivers for use, able to compete, economics
  - ❖ Create a vision of the product that can produced to meet that need
    - Driven by perception and brand, value, price, return on investment, cost of goods, licensing/royalties
  - ❖ Characterise **Quality Target Product Profile (QTPP)**
    - Indications, Population, Dosing & Administration (duration, route, dose form, regimen), Efficacy & Safety (Clinical Pharmacology, Clinical studies, Contraindications, Warnings & Precautions, Adverse reactions), Description, Storage & handling
- **Test by preclinical and clinical trials**

Outcomes: good returns if successful but risk of failure, long time & costs in $m

Tebbey & Rink doi: 10.1057/jmm.2009.34;
https://www.fda.gov/patients/drug-development-process/step-3-clinical-research
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080593.pdf.

Preclinical – *in vitro*, *in silico*, animal; Skin - *in vitro* release test (IVRT), *in vitro* permeation test (IVPT)

↓

Phase 1 Volunteer humans, N=20-100; Safety and dosage (several months); **topical bioequivalence**

↓ **70%**

Phase 2 humans with condition, N=up to 100s; Explore efficacy & side effects in target (diseased) population (few months – 2 years)

FDA Guidance on Phase 3 design ↓ **33%**

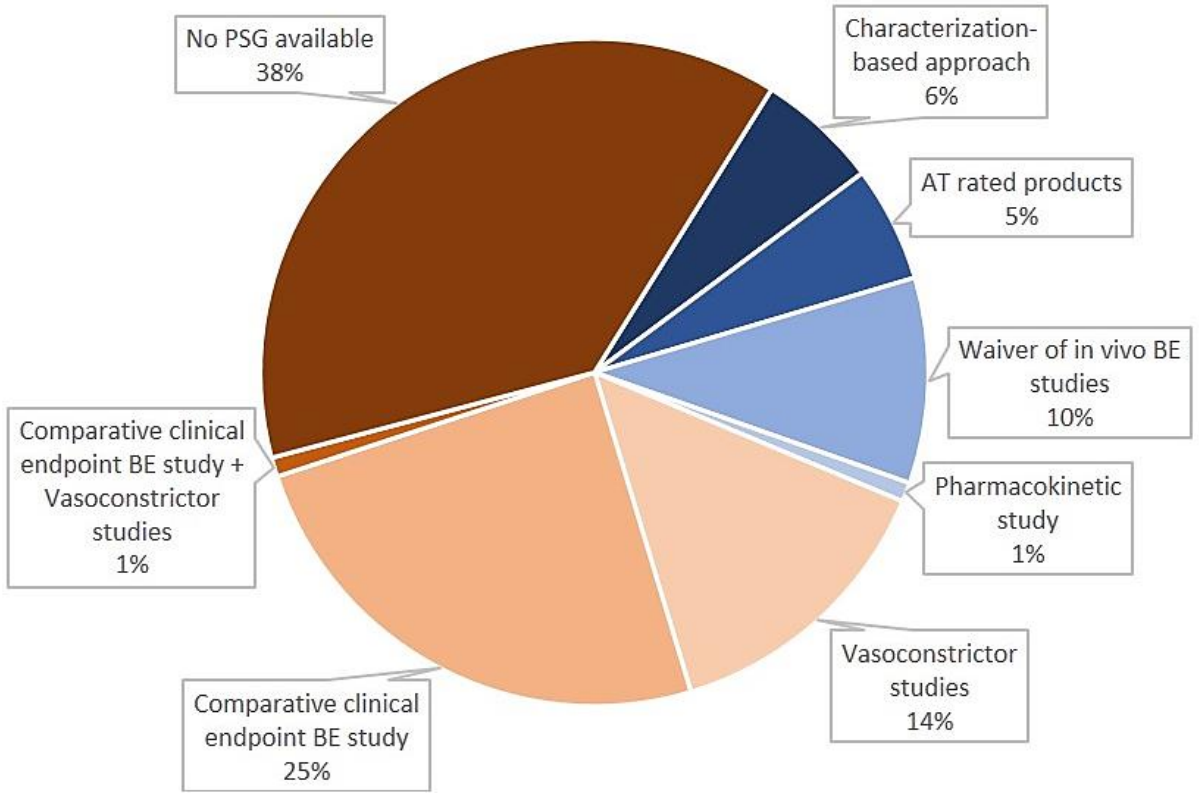
Phase 3 humans with condition, N=300 to 3000; Pivotal - provide treatment benefit; confirm efficacy & monitor adverse reactions

FDA Regulatory approval ↓ **25 -30%**

Phase 4 humans with condition, N= thousands; Post market surveillance of safety & efficacy

Generic drug topical product evaluation

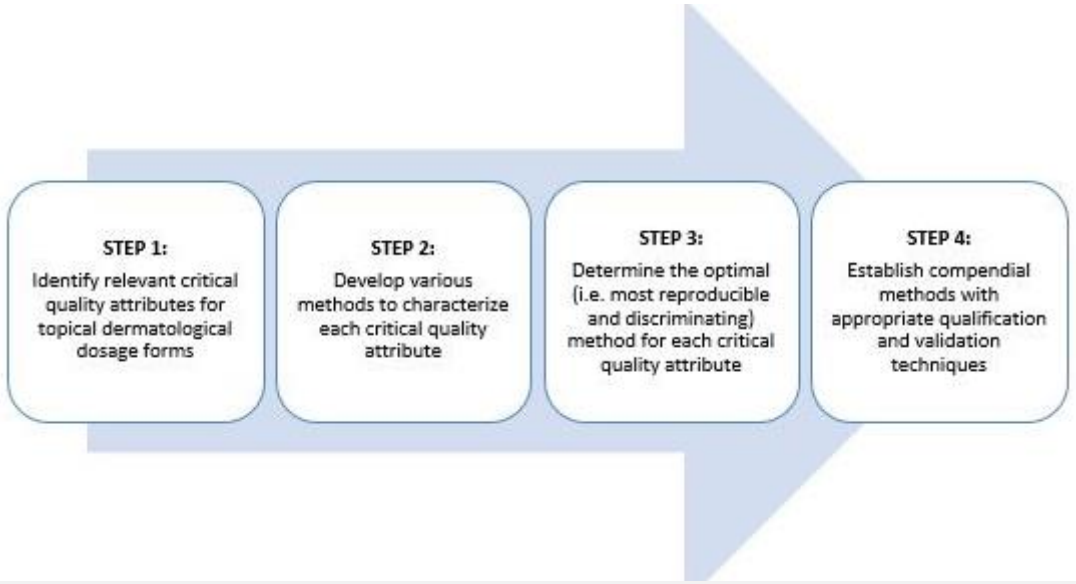
- Classical approach is clinical endpoint (Phase 1) BE studies
- FDA has fostered an efficient characterization-based (BE) approach defined by product-specific guidances (PSGs)
- By 2019, 200 PSGs (~ 62% of all products) published with in vivo studies (e.g., comparative clinical endpoint BE studies and vasoconstrictor studies) mainly recommended.
- Characterization-based BE approaches available for less than 10% of all products
- Here, we explore some of the contributions we have been making to this unmet need.



Integrating of critical quality attributes for a product with its performance

What are the key quality attributes?

- Q1, Same components as the reference-listed drug (e.g. provided or by LCMSMS reverse engineering);
- Q2, Same components in same concentration as the reference listed drug (e.g. by LCMSMS);
- Q3, Same arrangement of matter (microstructure) *(often assumed, but not always, with same components in same concentration)*

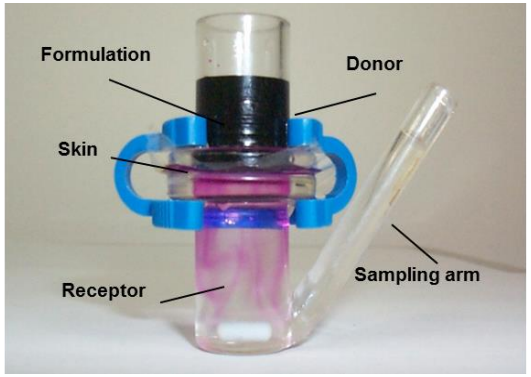


AAPS ePoster Library. Kelchen M. 11/04/19; 282949; M1130-03-20

How do we define their quality?

- By design & testing
- With Q3, measure critical quality attributes
- *In vitro* permeation test (IVPT)
- *In vivo* methods = dermal open flow perfusion, and imaging

In vitro skin permeation test - *IVPT*



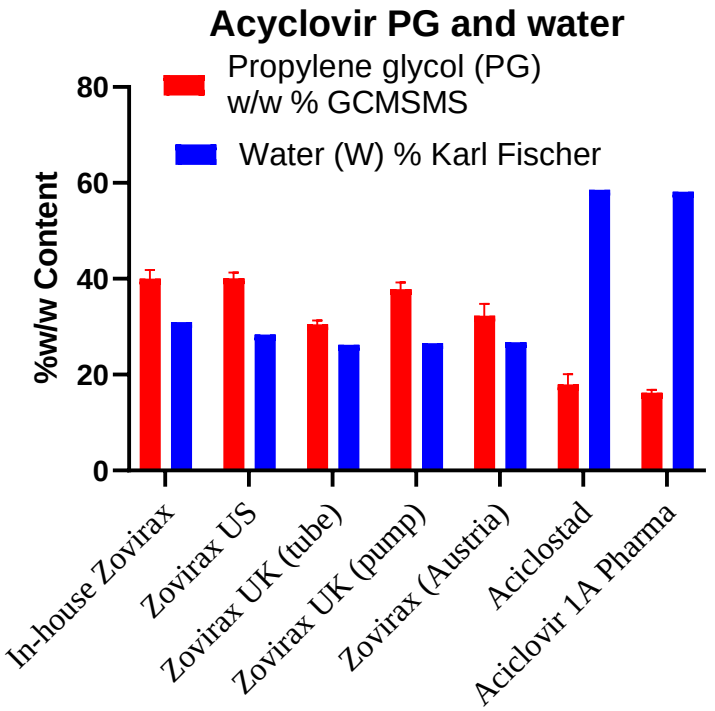
A **pharmacokinetic (PK) approach** may enable *in vitro* findings to be related to drug concentrations at the site of action (layers within the epidermis/ dermis) in other sites of the body and in diseased states

Q1, Q2 and Q3 for topical acyclovir dose forms & performance (IVPT)

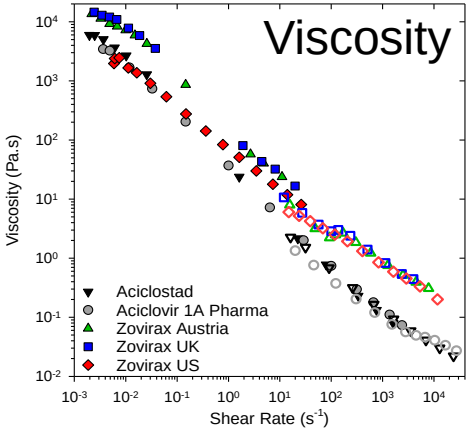
Q1 Composition

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	White soft paraffin	White Vaseline	White Vaseline	White Vaseline
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
	Arlacel 165	Polyoxyethylene stearate	Macrogol stearate	Polyoxyethylene stearate

Q2 Concentrations

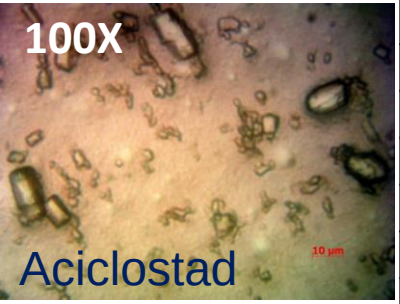


Q3 Micro-structure



Q3 Micro-structure continued

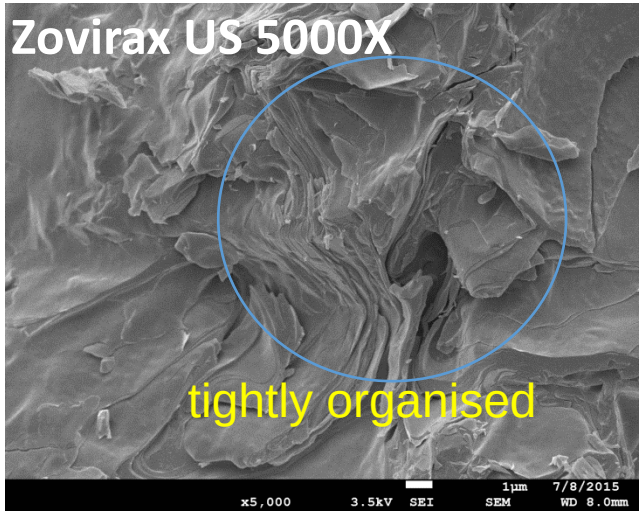
Acyclovir particle size

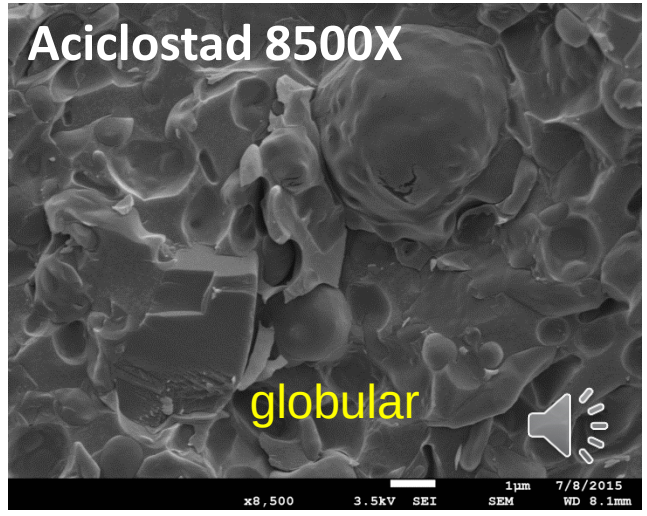


Products	d10 (µm)	d50 (µm)	d90 (µm)
Zov. US	3.63	6.92	16.60
Zov AU	4.00	8.30	29.00
Zov UK (P)	4.00	7.82	18.88
Zov UK (T)	3.52	6.22	19.35
Zov Austria	4.61	8.26	18.34
Aciclostad	2.72	4.38	9.72
Acyclovir 1A Pharma	1.91	2.90	6.24

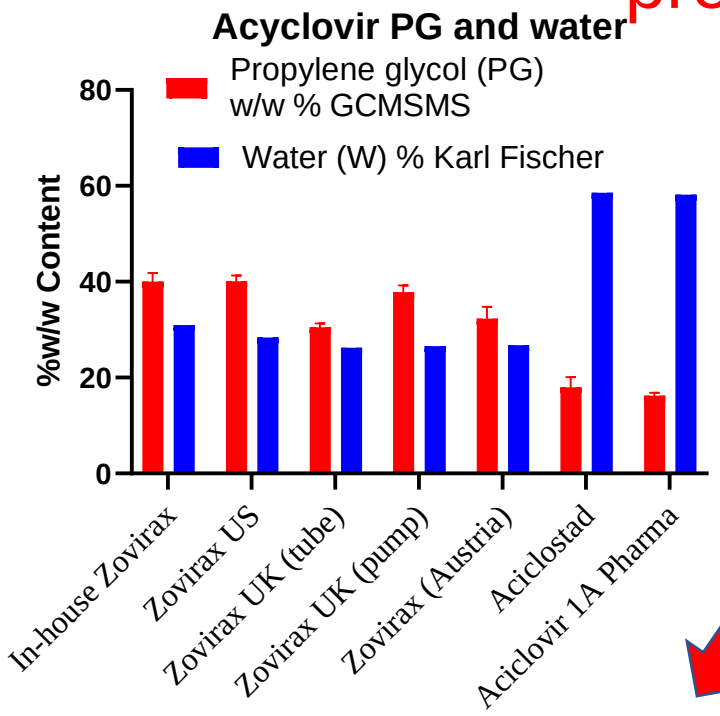
Also differences in phase volumes, solids

Product fabric by SEM





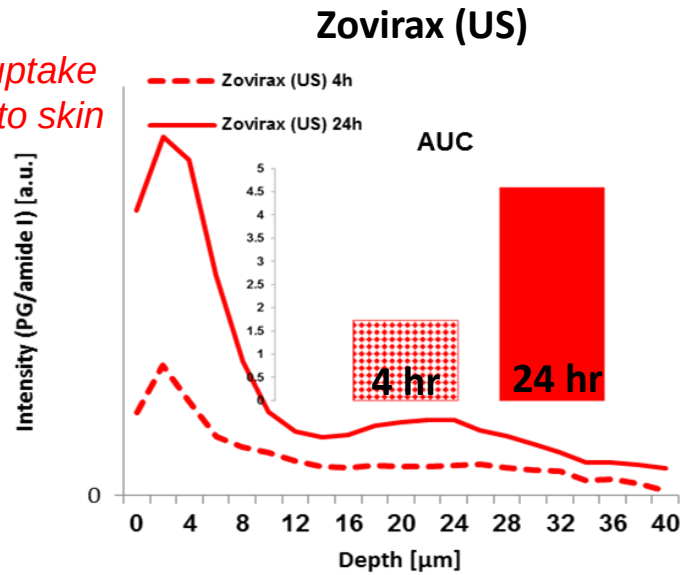
How do differences in Q1, Q2 & Q3 translate into product performance?

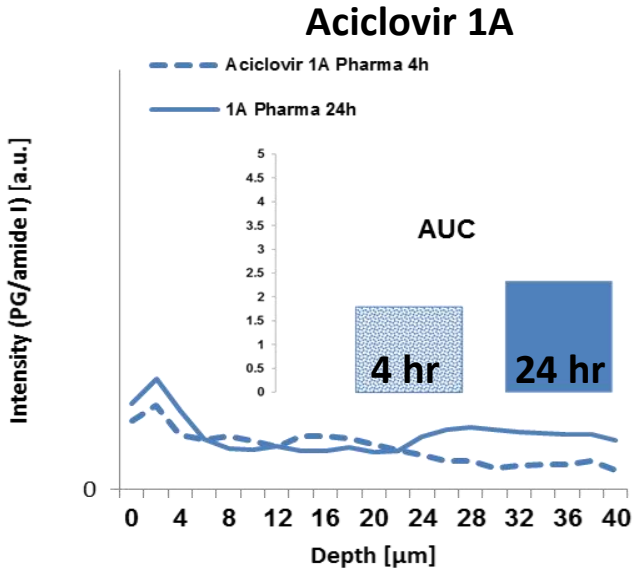


Zovirax (US) has 2.5 times PG & half water content of Aciclovir 1A*

Faster uptake of PG into skin

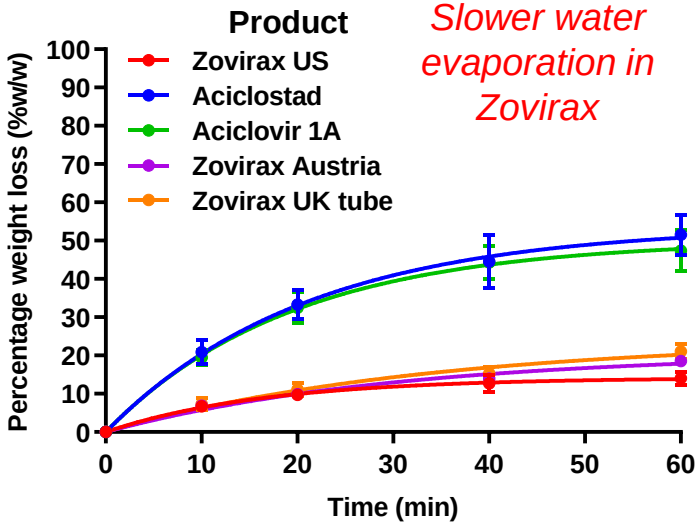
Measure PG in skin by Confocal Raman





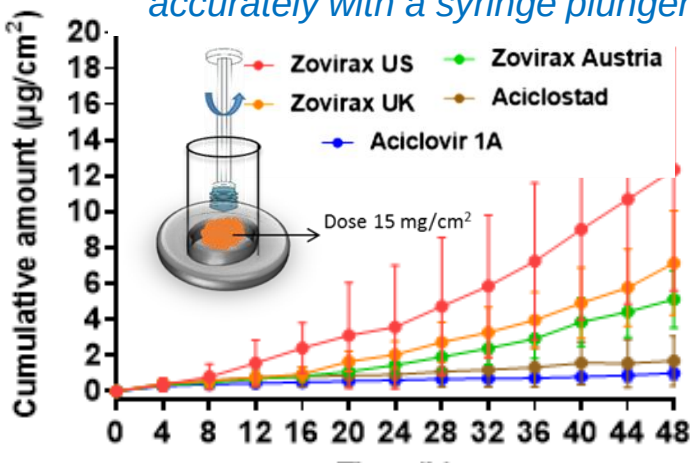
Jung et al Pharm Res 2022: 10.1007/s11095-022-03245-7

Slower water evaporation in Zovirax



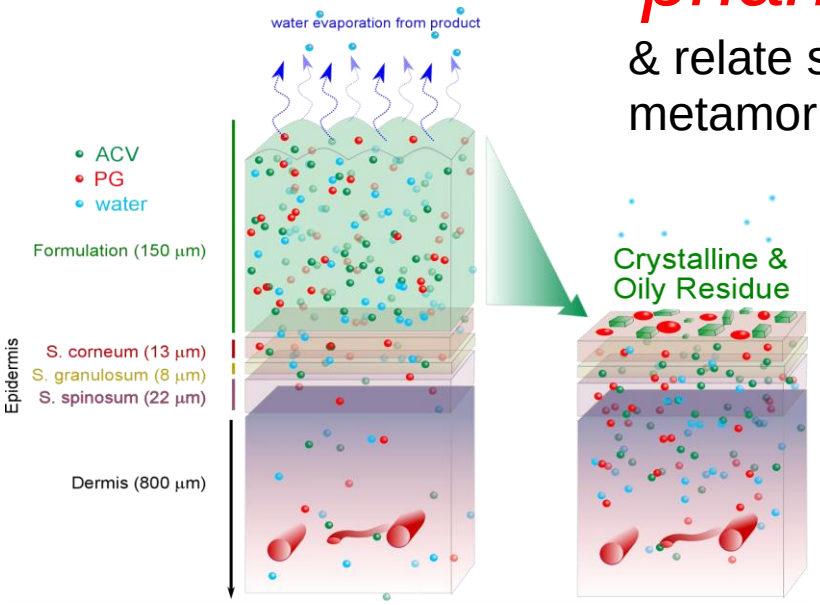
Faster permeation of acyclovir through human epidermis

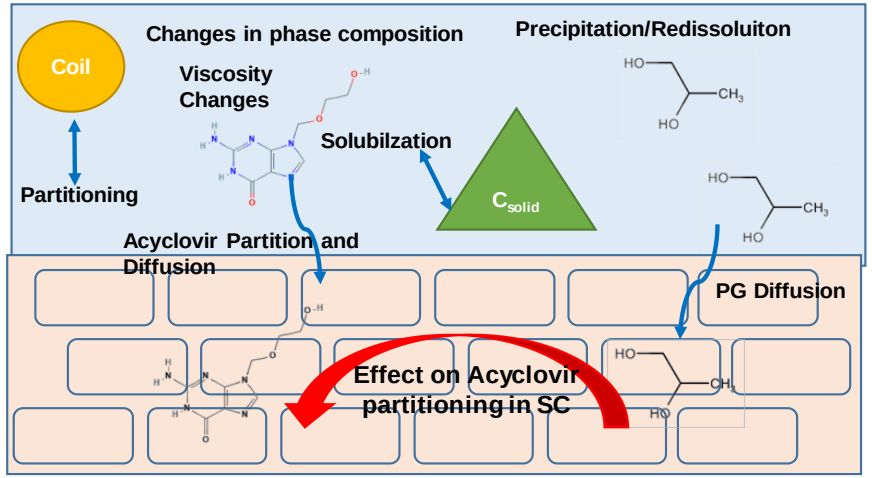
Our group applied 15mg/cm² accurately with a syringe plunger



And now in a combinatorial approach we add In silico pharmacokinetic (PK) modelling

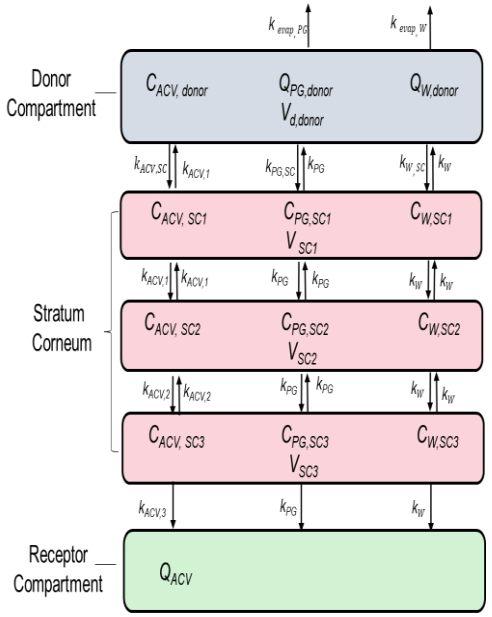
& relate skin IVPT for acyclovir products to product metamorphosis





Propylene Glycol increases the partitioning of acyclovir in skin

PK model



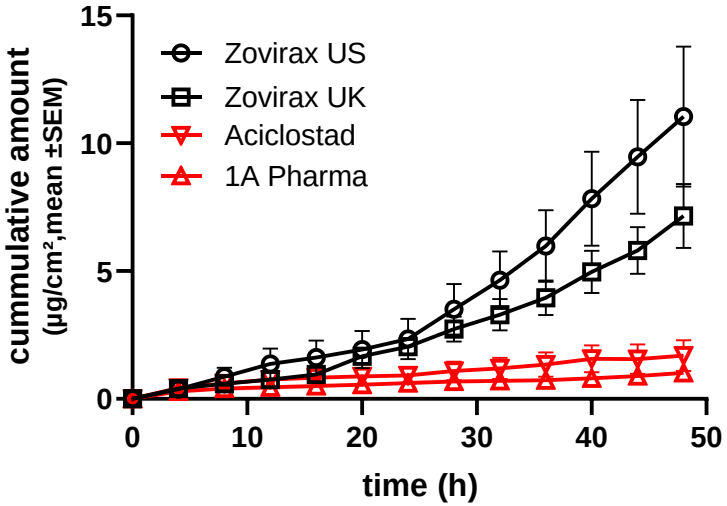
$$K_{acv,SC} = K_{acv,SC,0}(1 + \alpha C_{PG,SC1} + \beta C_{W,SC1})$$

$$D_{acvn} = D_{acv,0}(1 + \alpha C_{PG,SCn} + \beta C_{W,SCn})$$

$$k_{acvn} = 12 D_{acvn}/h_{sc}^2$$

$$k_{SC} = k\, K_{SC}(V_{SC}/3)/V_{d,donor}$$

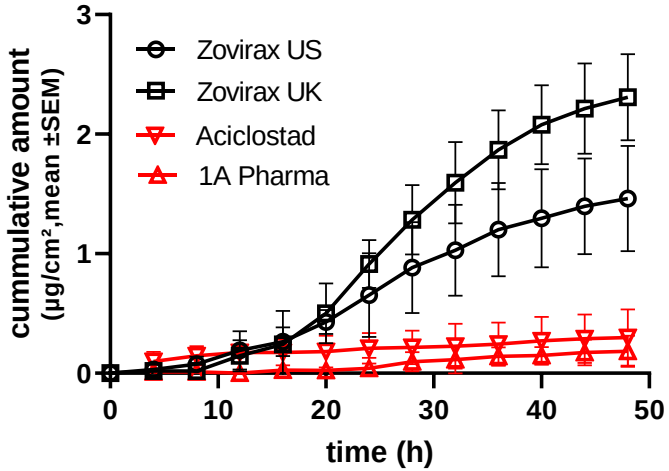
In Vitro Permeation Test (IVPT) our results



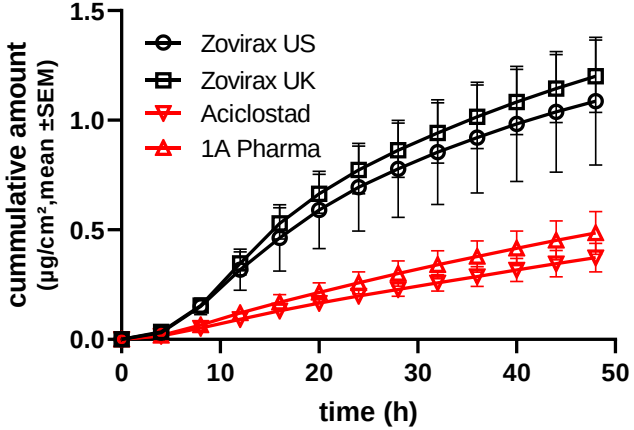
Apply to other Acyclovir studies and predict human *in vivo* outcomes

In Vitro Permeation Test (IVPT) for other studies from US

Murthy

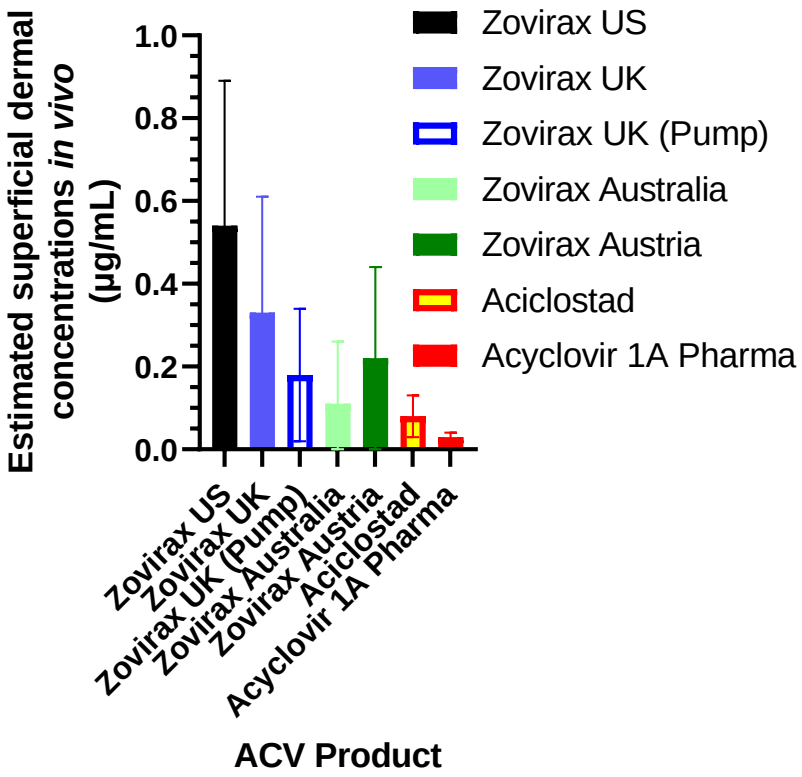


Shin et al

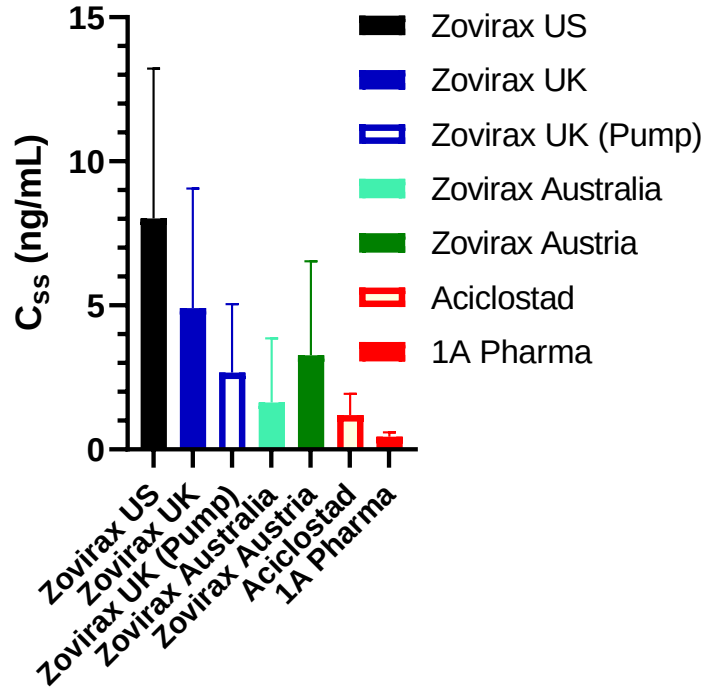


Human *In Vivo*

Superficial dermis concentrations



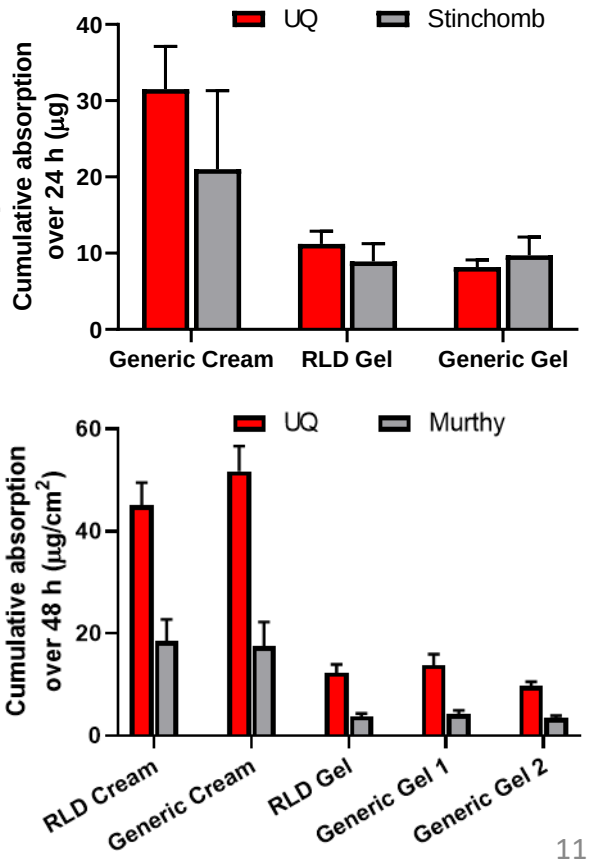
Predicted plasma concentrations (C_{ss})



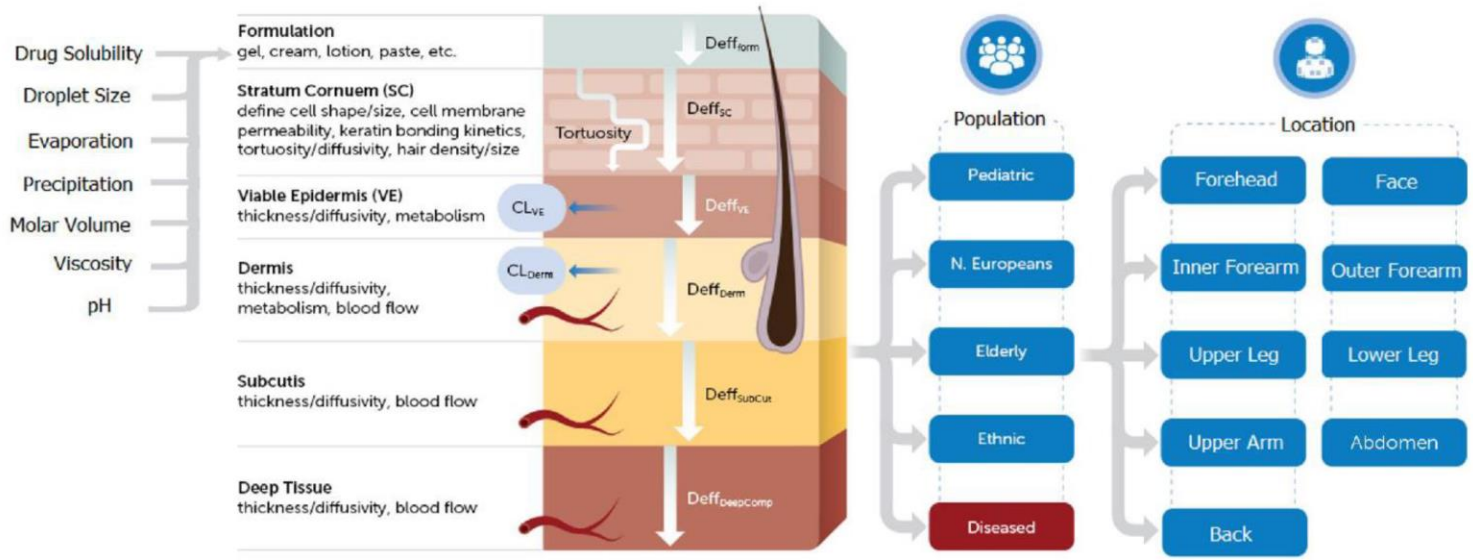
Strengths & limitations in *in silico* pharmacokinetic (PK) modelling

- **Experimental design.** A key benefit of a combinatorial approach is that allows one to do what I call **triangulation**, that is to have at least three independent measures that can confirm and validate bioequivalence.
- **Orthogonal comparisons.** This approach relates to the independence of hypotheses in a given study and can limit $\propto$ if these are clearly defined up front for a balanced design with equal subject numbers in each group. Limiting hypotheses to N-1, where N is the number of treatment groups, gives a frugal design (Klochars http://dx.doi.org/10.4135/9781412961288).
- **Validity and identifiability.** Lastly, as my good friend Michael Weiss has frequently remarked every PK model should be physiologically-based and have both validity and identifiability, which are always obvious by **Visual Predictive Check (VPC)** showing a poor fit of the data and too many parameters, respectively. As Einstein (1934) has remarked *"Everything should be made as simple as possible, but no simpler"*
- **Independent laboratories.** A real strength in the FDA program I have been fortunate to be part of has been a comparison and validation of findings between laboratories in Europe, Down-Under and in the US. My comparison of findings across the three groups for metronidazole products is shown on the right-hand side, where the same trend is seen, but with some variations reflecting differences in the IVPT protocols used.

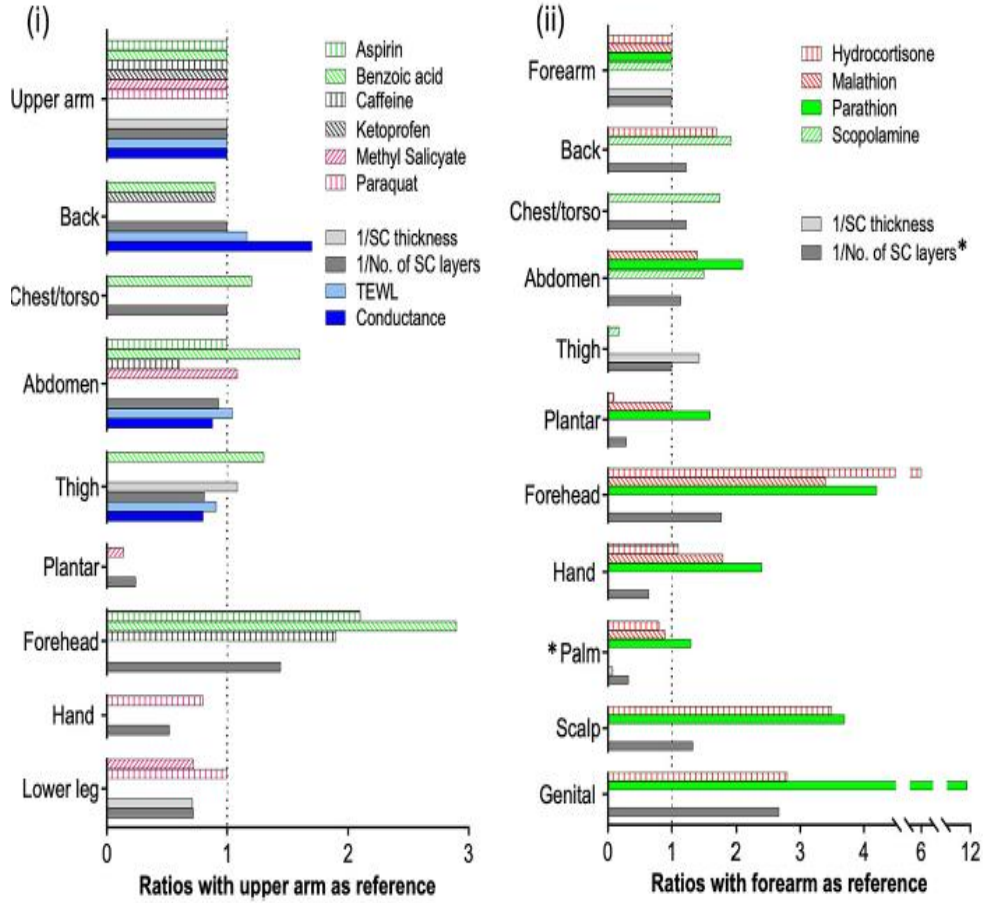
Metronidazole IVPT data



And may extend *in vivo predictions* to other sites and to diseased skin



Certara's MPML MechDermA PBPK model (courtesy Sebastian Polak)

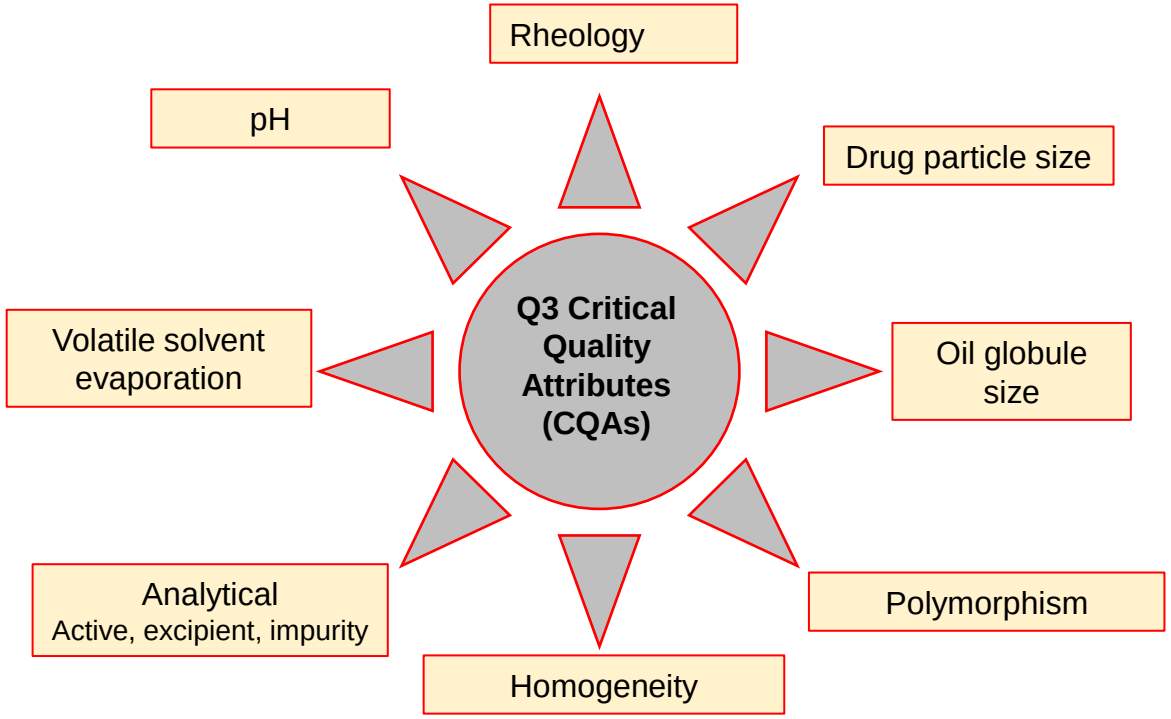


Body site dependence of skin absorption on skin biology (Liu et al 2020)

I now want to consider potential failure modes in the context of formulation & critical quality attributes

Ingredient & Formulation Variables

- Formulation variables
- Manufacturing variables
- Packaging



Failure Modes

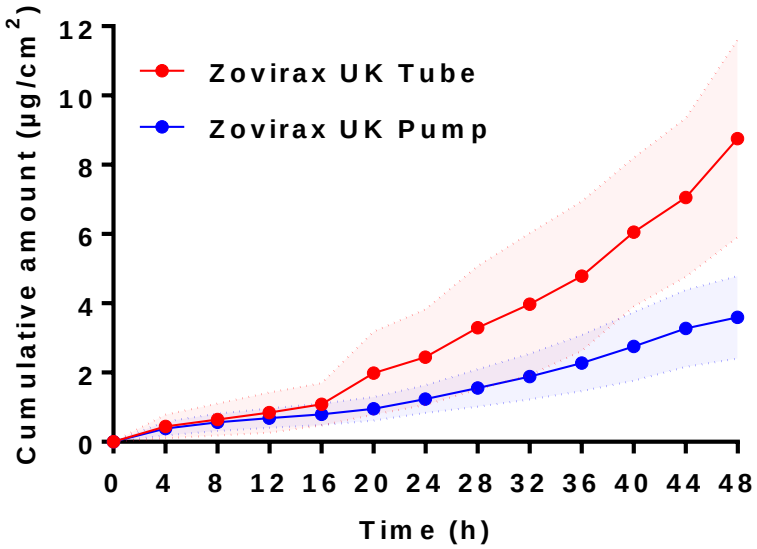
- Physical stability
- Chemical stability
- Performance and compliance

Let us look at two case studies of failure modes:
1. how products are dispensed or applied can matter!

Acyclovir packaged in tube and pump dispenser has the same composition

But, IVPT profiles differ!

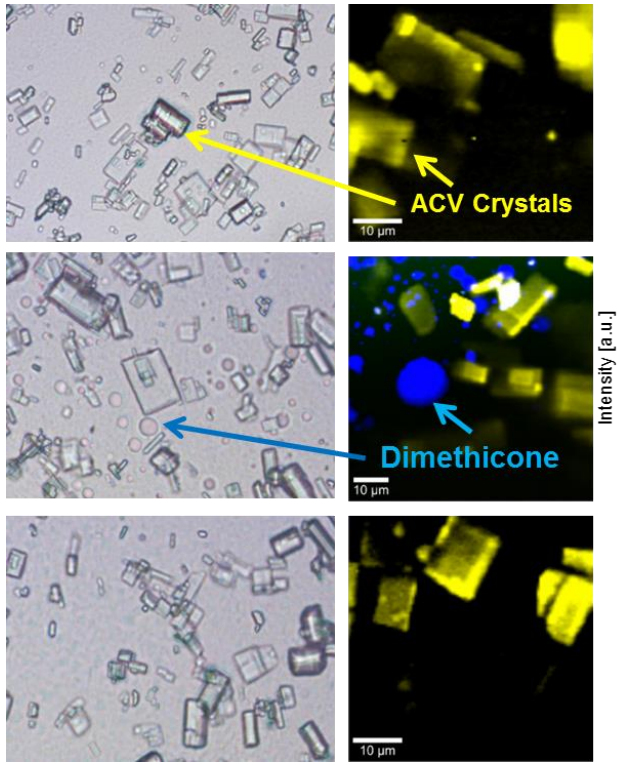
Why?

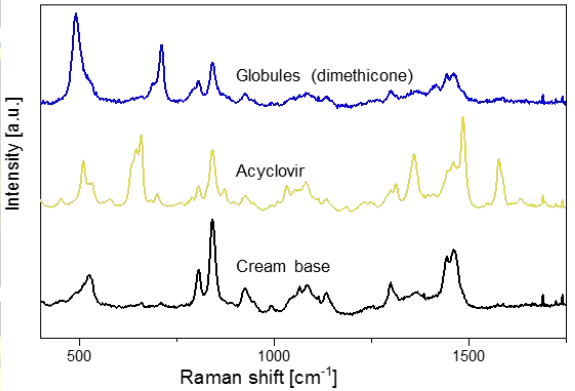


Zovirax UK Tube

Zovirax UK Pump

Zovirax UK Pump (container opened)





Yield stress from strain sweep (Pa)

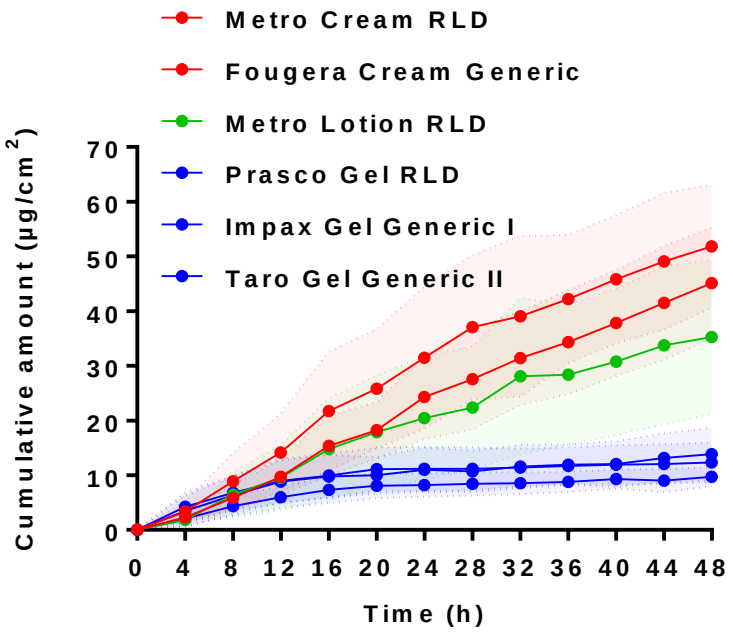
78 ± 1.3 (Tube)

182 ± 0.6 (Pump)

70 ± 10 (Pump opened)

- Confocal Raman: pumping affects acyclovir crystal habit, leading to formation of dimethicone globules
- Rheology: yield stress in packaged tube and pump product is similar but is higher after pumping – due to dimethicone agglomeration?

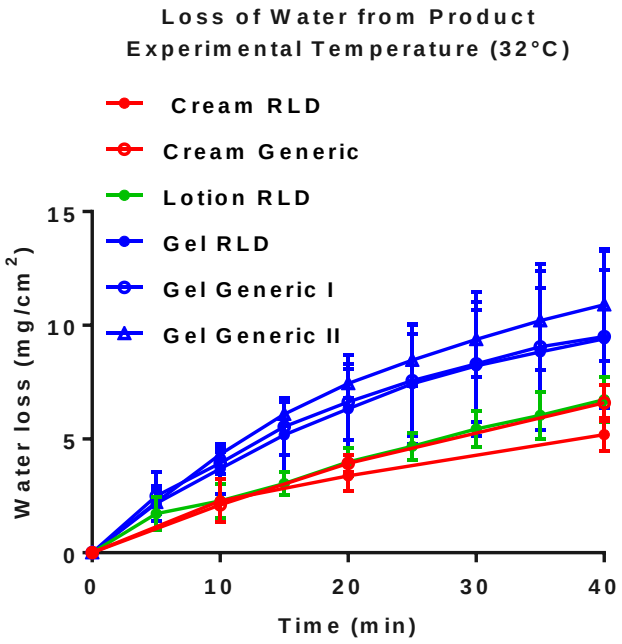
Secondly, let us look at metronidazole Q1, Q2 and Q3 variations between product classes - Does this impact on IVPT?



Data shown as mean ± 95% CI; Each point is the mean of 9* (3 donors & 3 replicates per skin)

- The Gels have a very high water content and therefore evaporate more quickly than other products

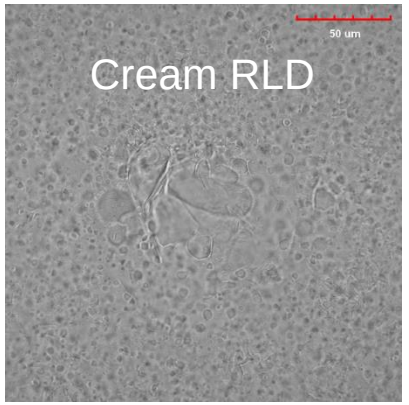
Hence, products may "feel" different after evaporation of products on the skin



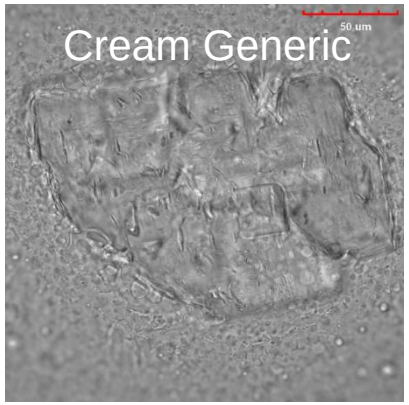
Meaning in parallels?

- IVPT cream ≥ lotion > gel and
- Tribology (friction) cream ≤ lotion < gel

We observed different types of crystals after product drying on the skin surface

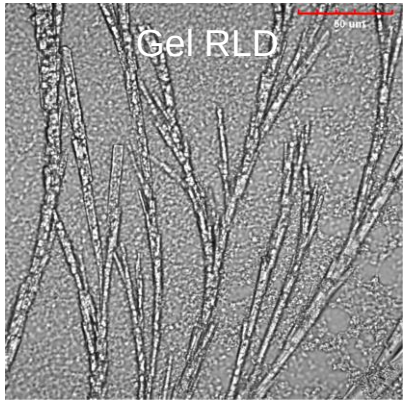


No Crystals



Rectangular Crystals

Rectangular Crystals



Rectangular Crystals forming branched structures

I would suggest that a third potential failure mode is not recognising sensory perceptions associated with topical products – the placebo & nocebo effects

Sensory receptors in the skin

For pressure, vibration, temperature, pain & itching

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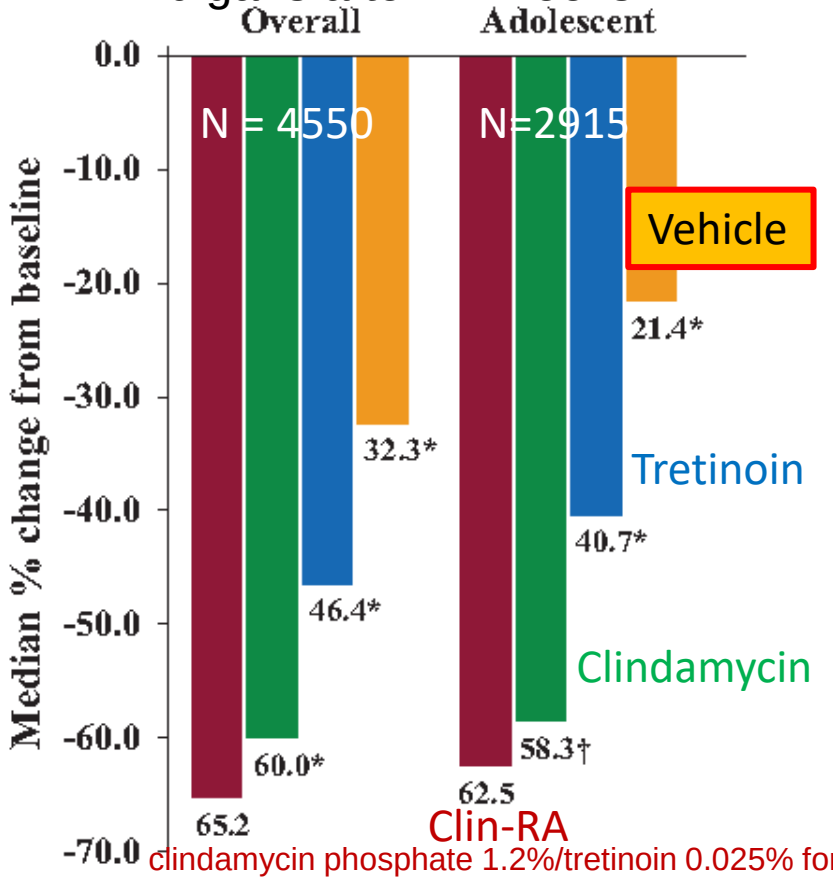
Three pivotal Phase III studies- Change in inflammatory acne vulgaris after 12 weeks.

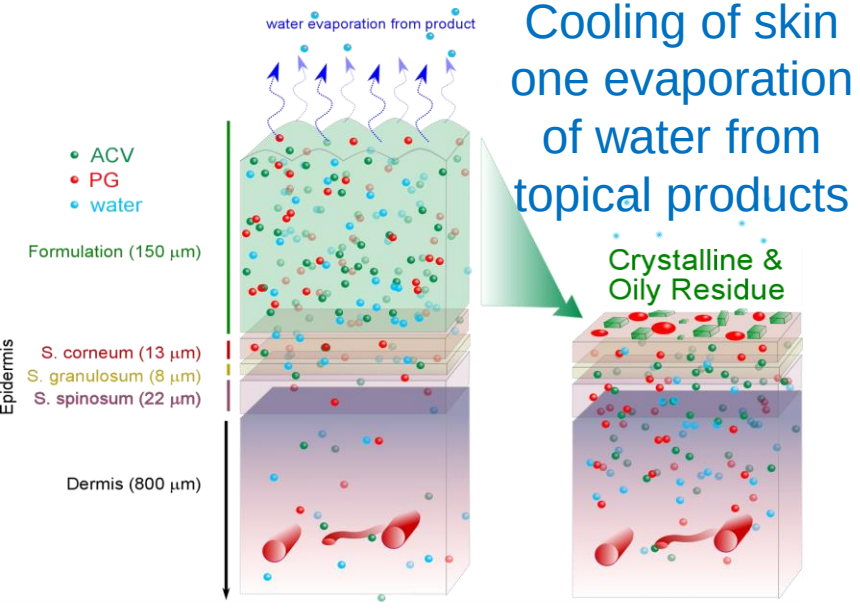


clindamycin phosphate 1.2%/tretinoin 0.025% formulation

Dreno Eur J Dermatol 2014; 24(2): 201-9

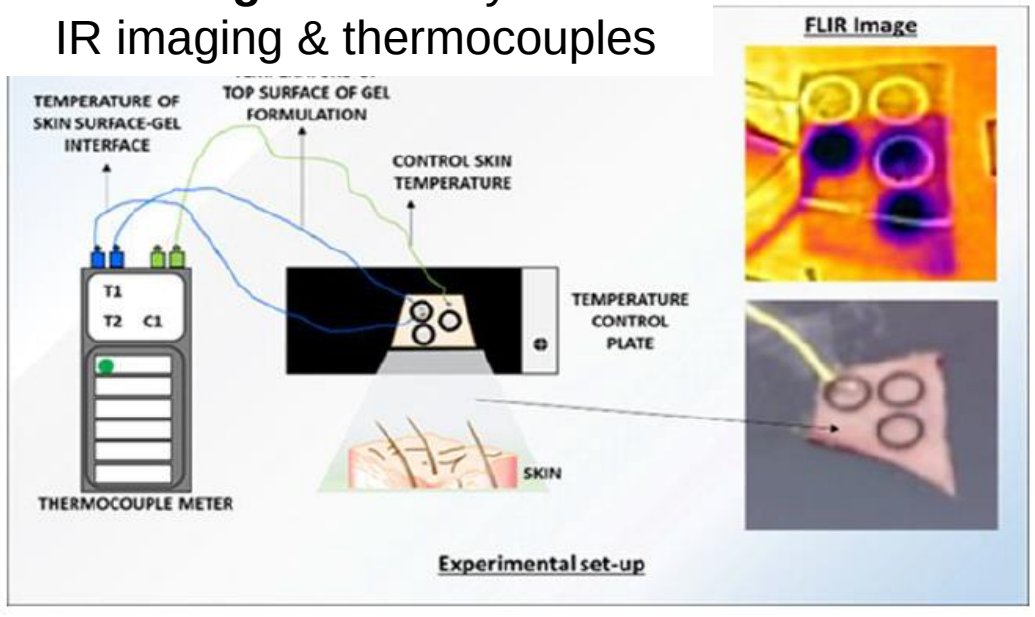
* p<0.0001; † p=0.0002 vs Clin-RA

Can we assess sensory impact of topical products on the skin by instrumental methods?

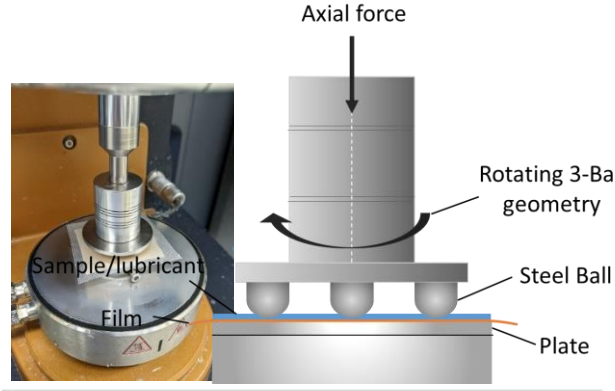


Cooling of skin one evaporation of water from topical products

1. Cooling: Assess by thermal IR imaging & thermocouples

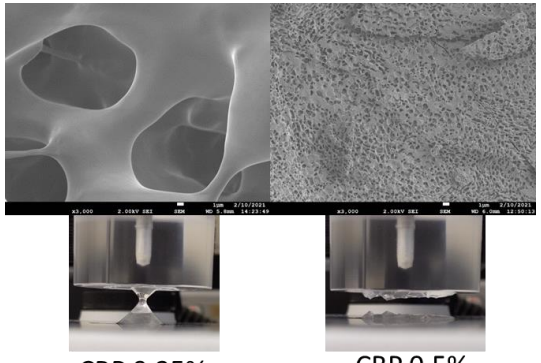


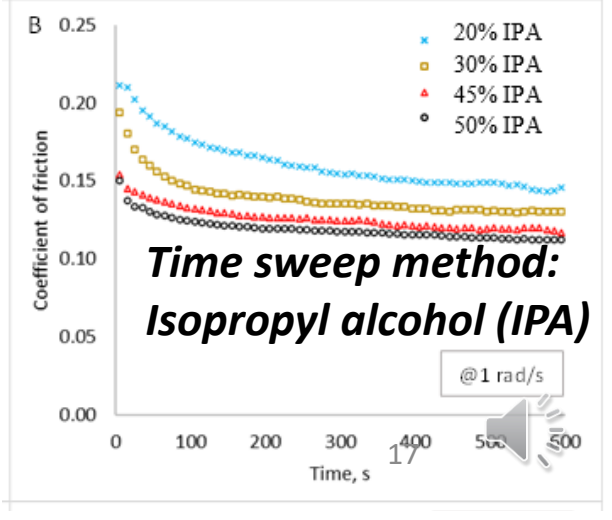
3. **Product Friction & lubrication:** Tribology



2. Texture Profile Analysis

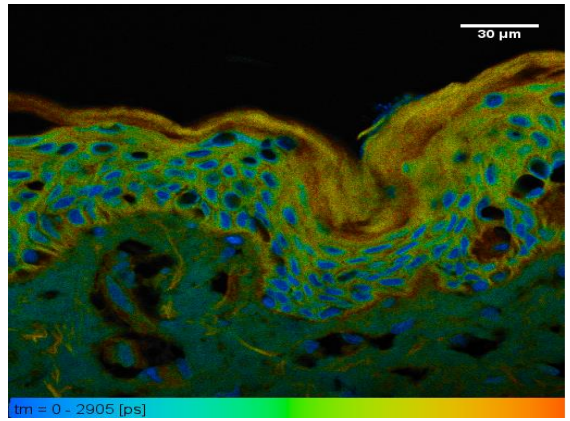
- **Firmness**: Maximum force required for compression to a specified gap
- **Adhesiveness:** Force to withdraw probe to start after compression
- **Spreadability of the gel:** Compressibility
- **Stinginess/tailing:** Distance product still adhered on withdrawal

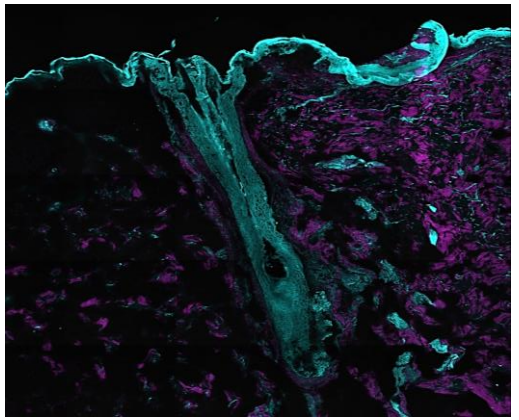




Conclusion

- Evaluation of their topical bioequivalence of generics is on an evolutionary path
  - We have learned a lot about integrating of critical quality attributes for a product with its performance using i*n vitro,In silico* & combinatorial strategies to demonstrate bioequivalence
  - We are now embarking on the journey of virtual bioequivalence in which we can extend results from one body site to others and to disease skin
  - Sensorial effects play an important role in topicals
  - And, lastly, although a quality by design approach using the principles of sameness and similarity (Q1, Q2 & Q3)is the best way forward, there is always the potential of failure.





Restating my key message: This an exciting area where one can make a real difference

Thank you to our team in Australia, especially Yousuf Mohammed, Jeff Grice, Xin Liu & Azedah Alinaghi, to the FDA team and our many collaborators who have made this possible!

And Thank you!

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