FDA Generic Drug Research Public Workshop
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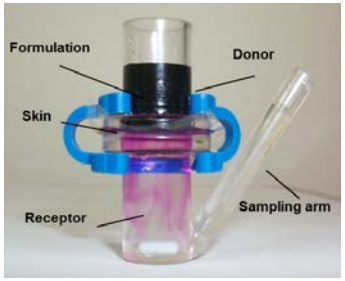
Topical Products: When Does a Difference Matter?



Michael Roberts

The Institute
basil hetzel institute for medical research

UniSA

University of Queensland, Brisbane &
University of South Australia, Adelaide
AUSTRALIA

TRI
TRANSLATIONAL RESEARCH INSTITUTE
AUSTRALIA

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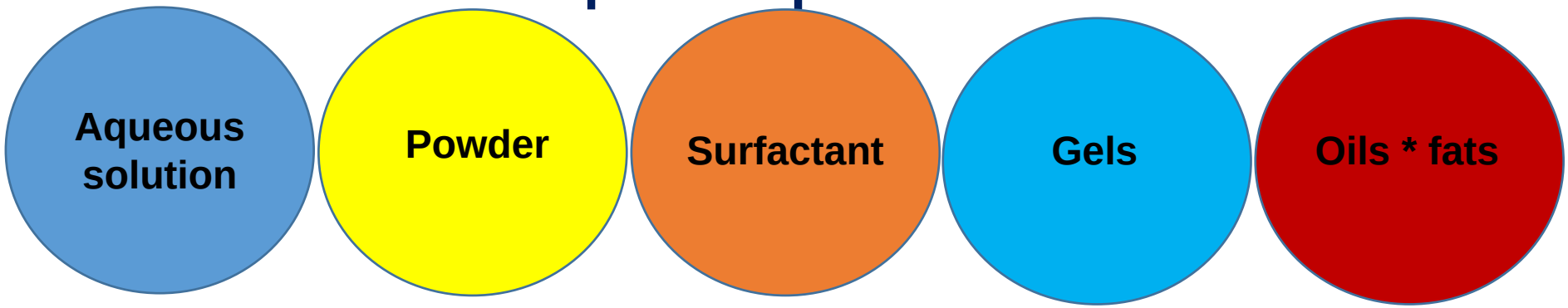
Topical Products: When Does a Difference Matter?

How do topical products differ?



- Can also include preservatives, fragrances, propellants and other excipients to give us the variety of solutions, lotions, pastes, gels, emulsions, creams, foams and so on that we see on our pharmacy shelves today
- Clearly, in terms of feel, smell, look, taste and spreadability, and how the these products feel after being rubbed into the skin, each will be different.
- *But, do these differences matter and when?*

Can one apply a generic product as easily as the innovator?

When do measurable rheological differences translate to perceptible differences for patients?

How easily can we substitute an excipient?

Nitroglycerin ointment for anal fissures

- Topical nitrates have been shown to have initial efficacy in the treatment of anal fissures – 56% for 0.3% nitroglycerin ointment BUT *in (the author's) experience nitroglycerin more often causes a headache than treats the symptoms of anal fissure.*
- A surgeon at my hospital therefore asks the pharmacy to dilute the ointment.
- *Catastrophic result! Patient had the worst ever headache! Why?*
- **Reason: Pharmacy diluted the 0.3% nitroglycerin ointment with petrolatum!**
- *But,* nitroglycerin ointment has excipients in addition to petrolatum
  - Lactose, which adsorbs nitroglycerin
  - Lanolin, a waxy ester in which nitroglycerin is soluble. By contrast, nitroglycerin is poorly soluble in hexadecane – somewhat similar to petrolatum in polarity
- **Take home message - choice of excipient is important in topical formulations**

Hyman NH, Cataldo PA. Dis Colon Rectum. 1999 Mar;42(3):383-5

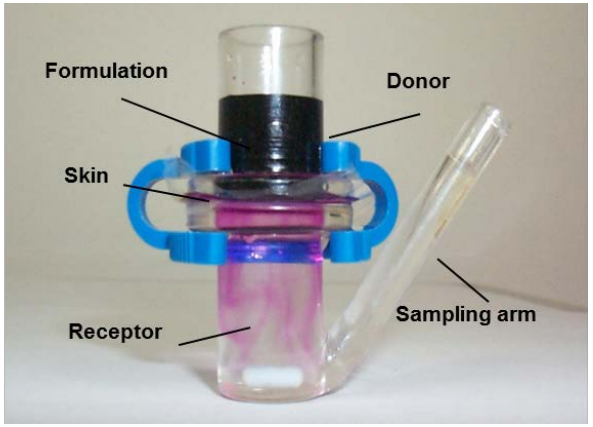
Behaviour of topical acyclovir products is another example of excipients making a difference

Ingredient Name	Zovirax (U.S.)	Aciclovir 1A Pharma (Austria)
Acylovir concentration	5% w/w	5% w/w
Propylene glycol (PG)	**40% w/w**	**15% w/w** *1
Water Content	**≈ 1/3 w/w**	**≈ 2/3 w/w**
Other Ingredients:	Cetostearyl alcohol Mineral oil Poloxamer 407 Sodium lauryl sulfate Water White petrolatum	White Vaseline Viscous paraffin Glycerol monostearate Polyoxyethylene stearate Dimethicone Purified water

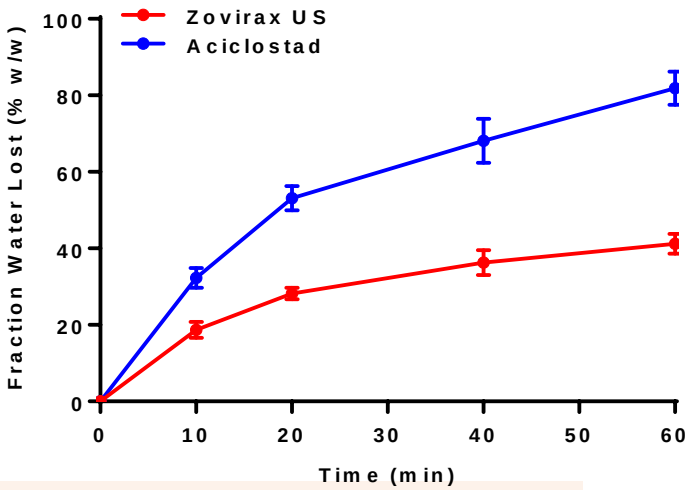
Differences in

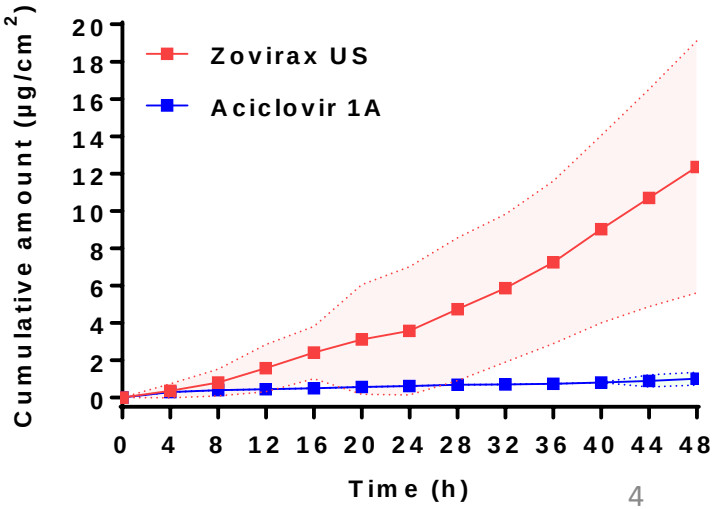
- Q1 (Qualitative – nature of ingredient)
- Q2 (Quantitative - amounts)

In vitro permeation test - IVPT



Product metamorphosis when applied to skin - slower evaporation of water in Zovirax due to PG

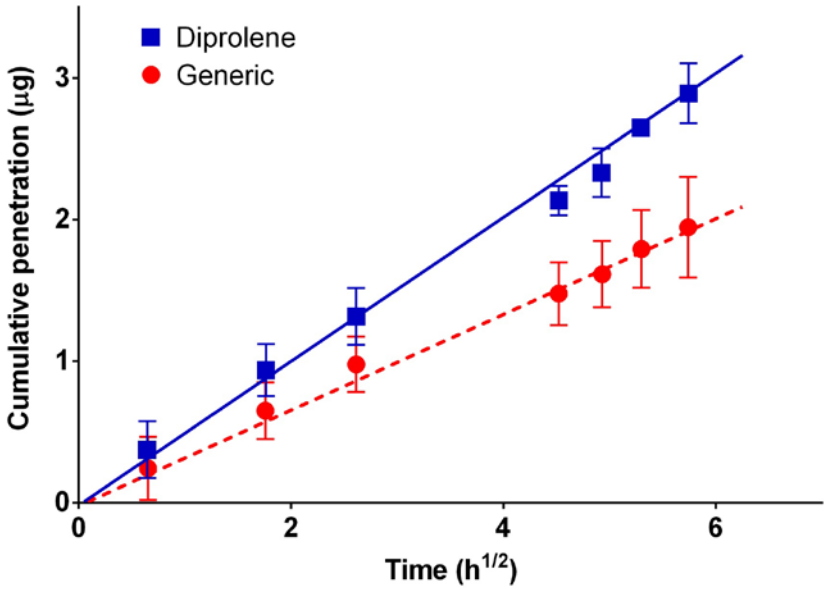


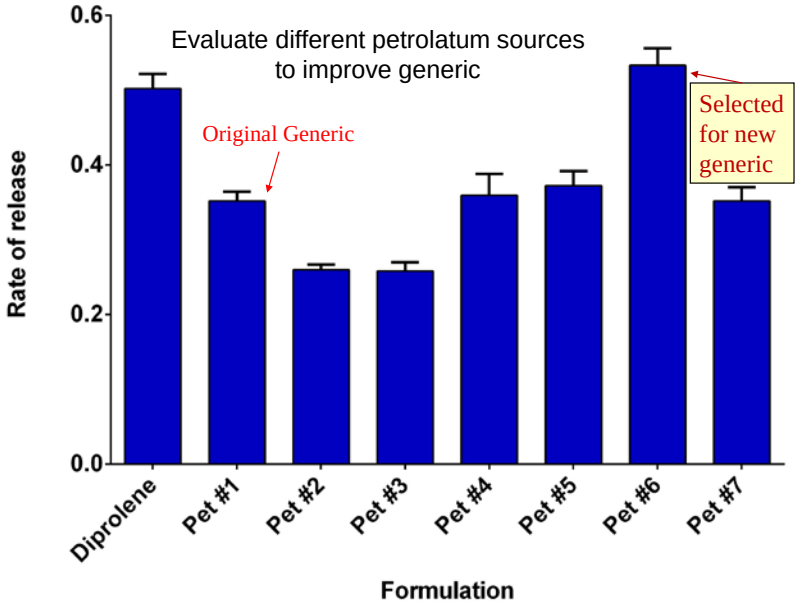


*1 Trottet,LH et al Int J Pharm 304(1-2): 63-71.

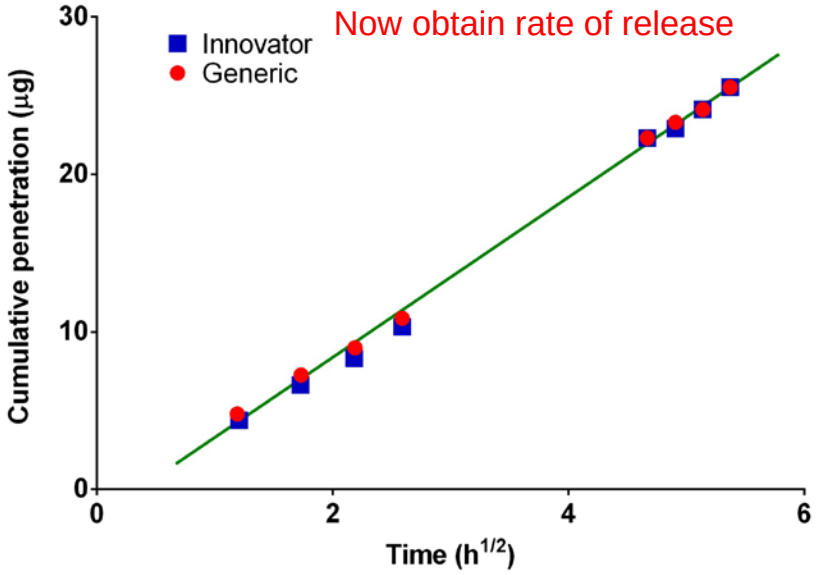
Prospective generic product formulation

Rate of Release Assay: First test of new generic Diprolene

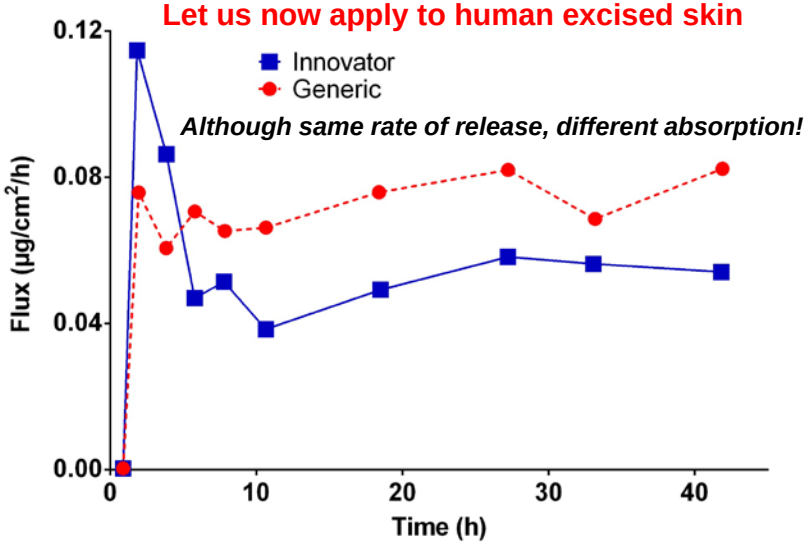




Now obtain rate of release



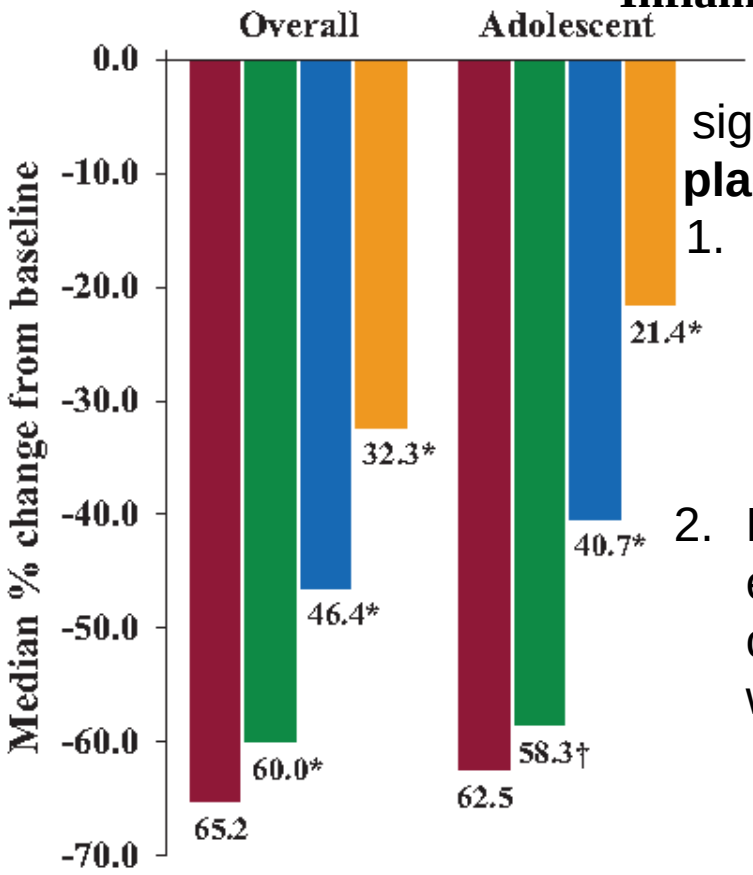
Let us now apply to human excised skin



courtesy Tom Franz & Paul Lehmann

Principles in developing innovator products also apply to generics

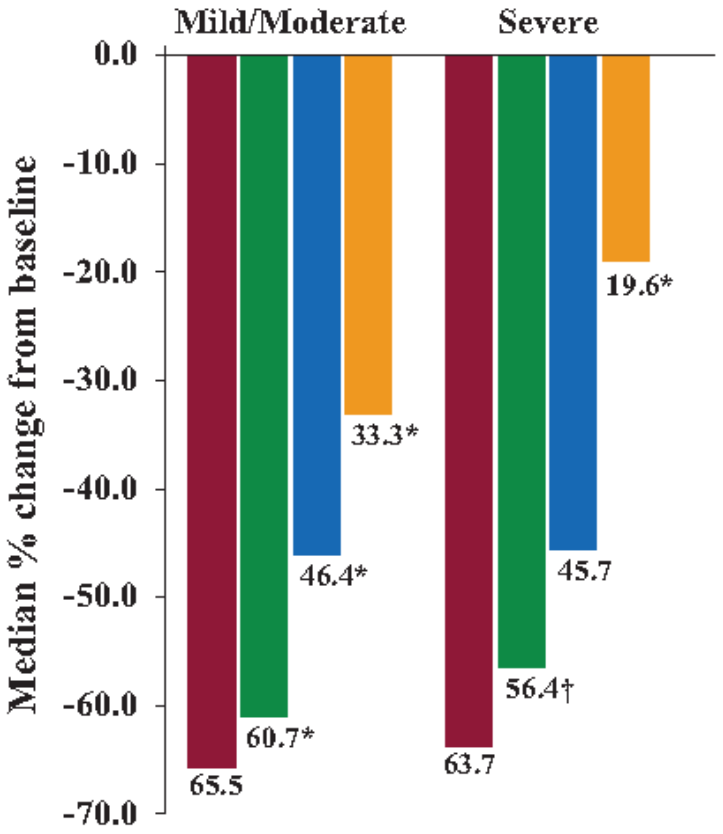
Inflammatory acne vulgaris:



* p<0.0001; † p=0.0002 vs Clin-RA

Note significance of **placebo effect**

1. Age related difference > age related therapeutic response
2. Lesser effect as condition worsens

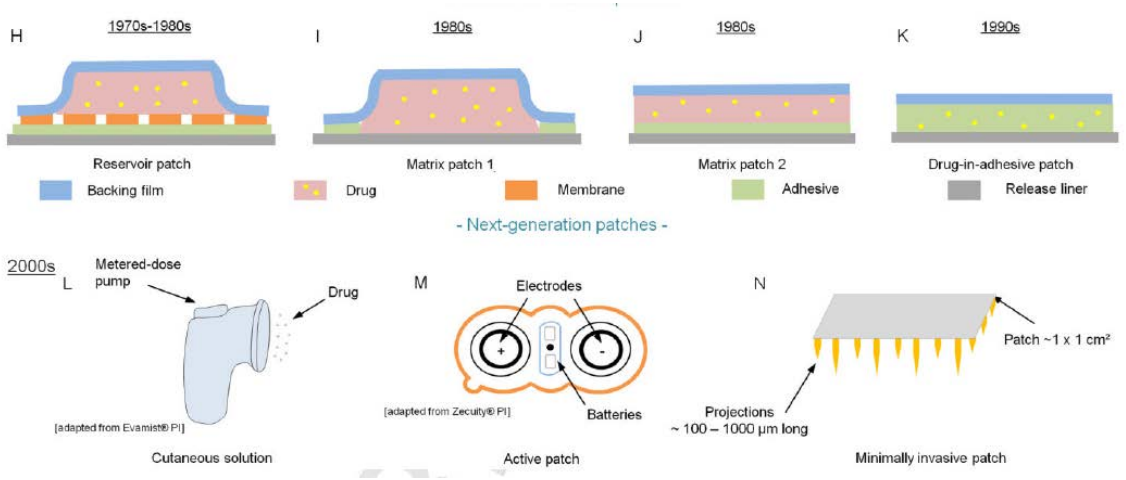


* p<0.0001; † p=0.048 vs Clin-RA

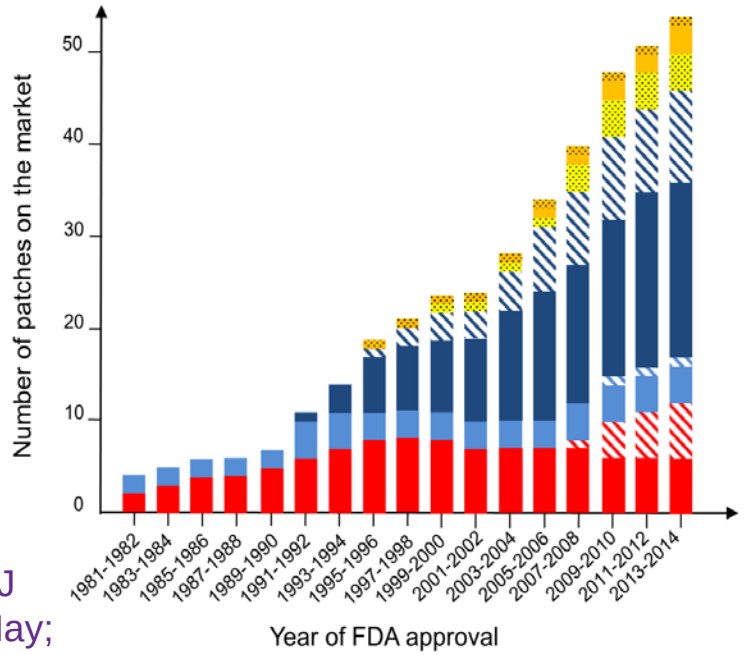
Dreno Eur J Dermatol 2014; 24(2): 201-9

Clin-RA Clindamycin Tretinoin Vehicle

Life cycles in both innovator & generic transdermal patch development



- Lifecycle changes in innovator
- Reduced complexity
- Ease of manufacture
- Less chance of failure
- Easier to use
- Lower cost



Transdermal reservoir: originator

Transdermal reservoir: generic

Transdermal matrix: originator

Transdermal matrix: generic

Transdermal active in adhesive only: originator

Transdermal active in adhesive only: generic

topical patches

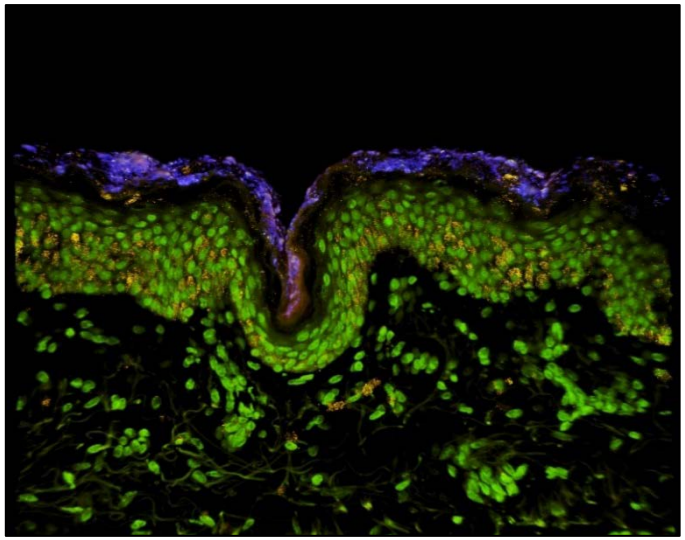
Transdermal next generation

Topical next generation

Pastore et al. Br J Pharmacol. 2015 May; 172(9): 2179–2209.

Skin is a heterogeneous organ

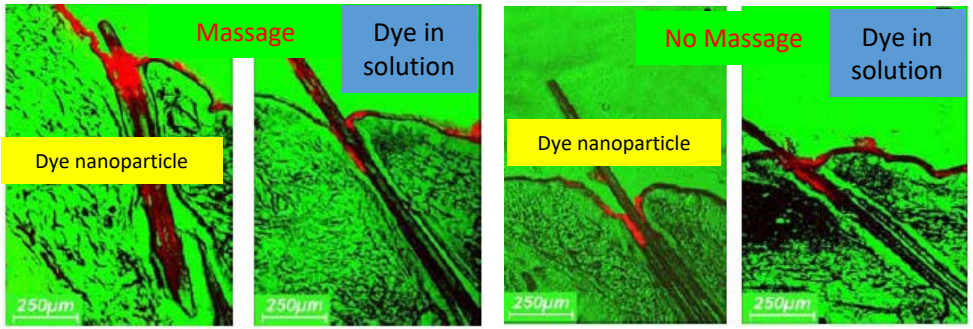
Impact of furrows not well understood



Appendageal pathway often ignored in product evaluation

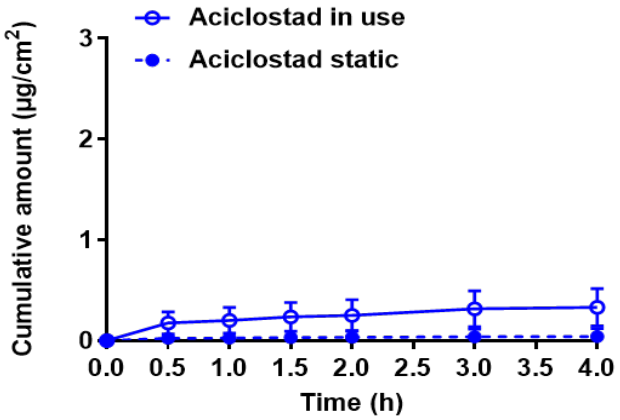
Shelley and Melton (1949) observed perifollicular wheals 5 min after the application of 10 % histamine free base in water.

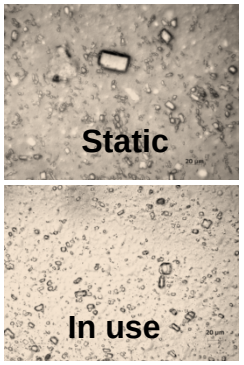
- Histologic studies by **Mackee et al. (1945)** demonstrated follicular diffusion occurring within 5 min.
- Rubbing in of nanoparticles facilitates follicular deposition



Porcine skin *in vitro*: Lademann et al 2006, 2009

Rubbing in of products can also affect product performance (measured by IVPT





Rubbing reduces particle size & may also put more product into furrows

How products are dispensed or applied does matter!

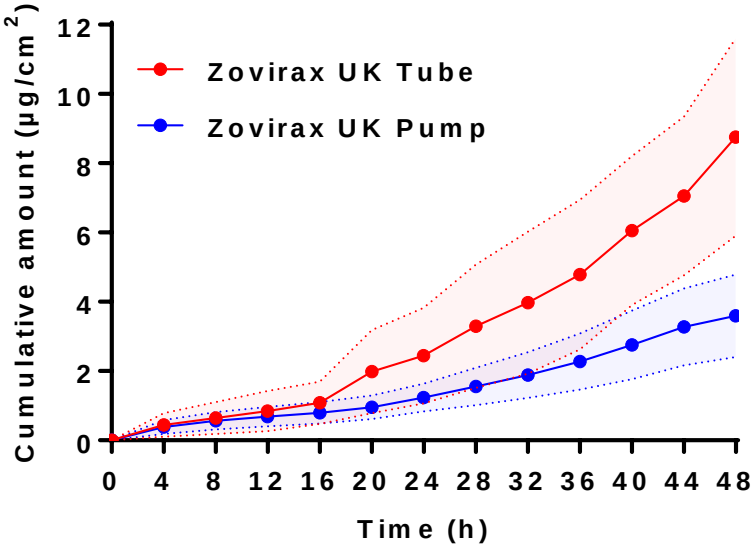
- Acyclovir packaged in tube and pump dispenser have the same composition
- *But, IVPT profiles differ!*

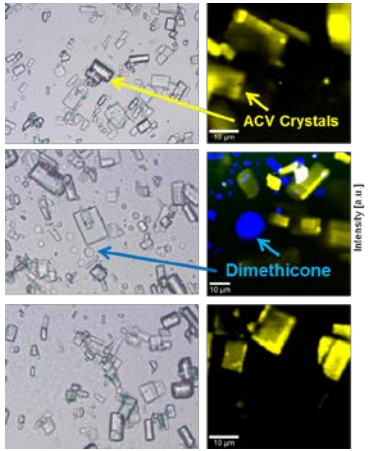
Epidermal flux of oxybenzone depends on the thickness of the applied product

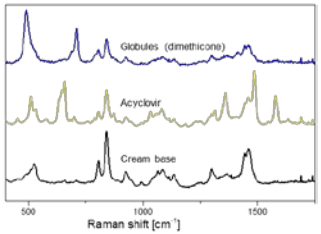
Zovirax UK Tube

Zovirax UK Pump

Zovirax UK Pump (container opened)





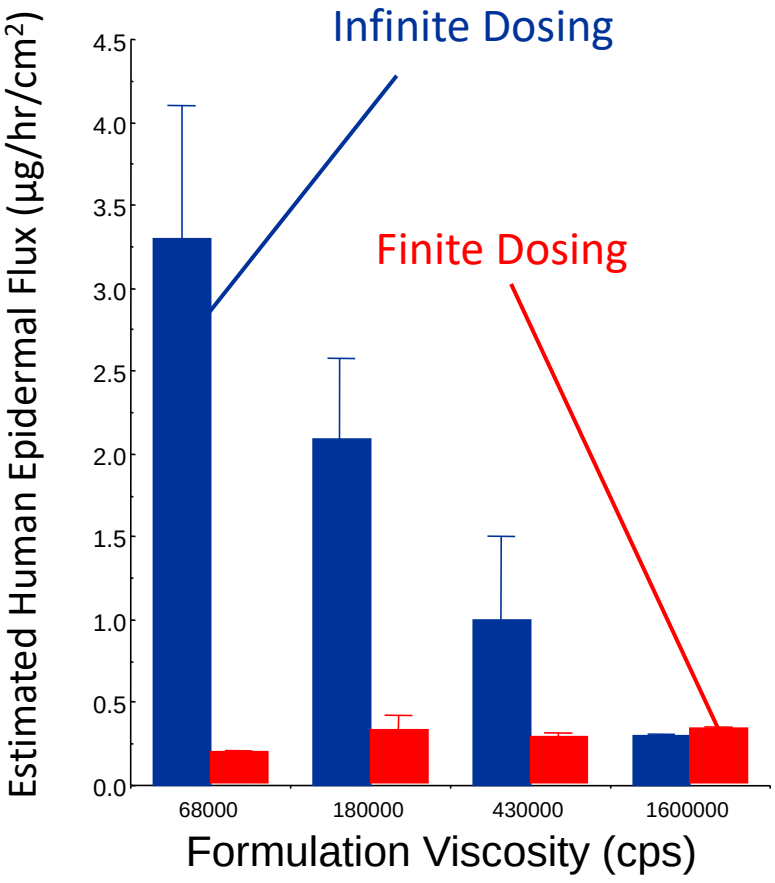


Yield stress from strain sweep (Pa)

78 ± 1.3

182 ± 0.6

70 ± 10

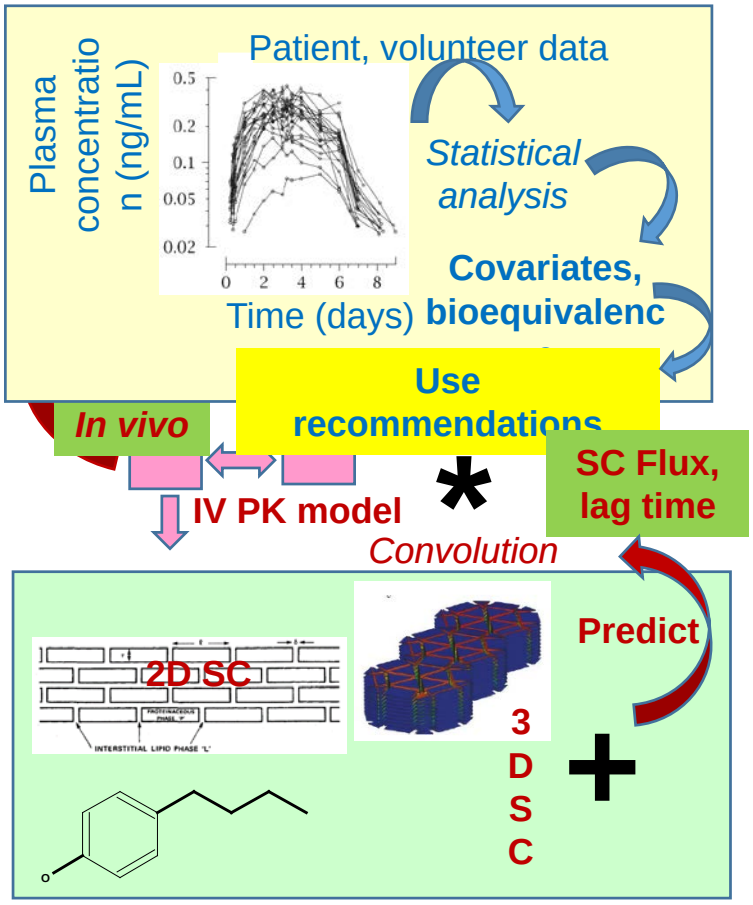


Cross et al, JID, 2001

Characterising skin permeation

Top - down

In vivo human exposure & response data

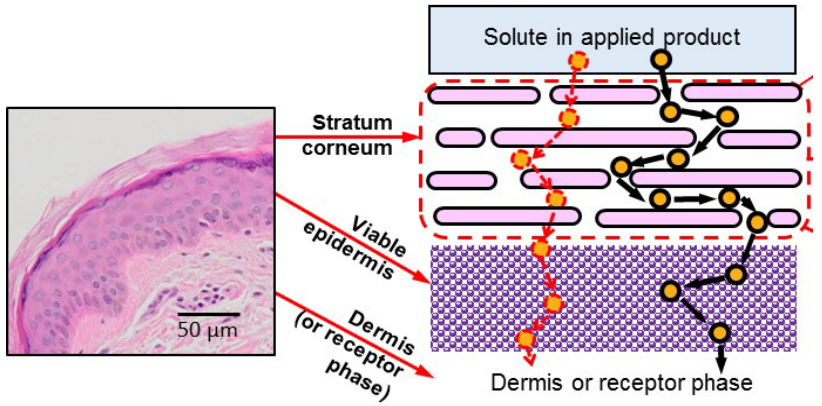


MW, MV, log P, MP, solubility parameters, PSA, H bonding,

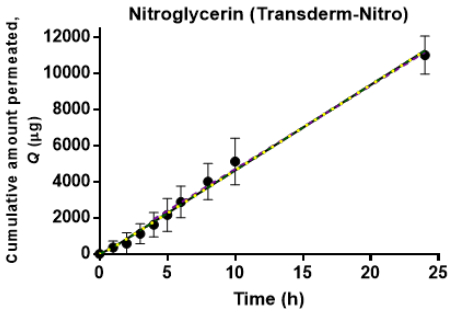
Bottom - up

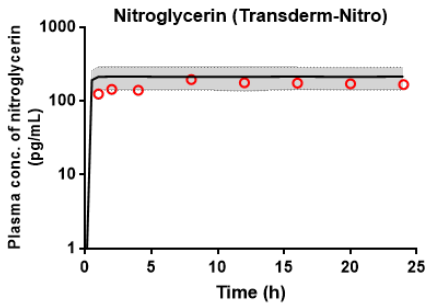
Roberts MS. *J Pharmacokinet Pharmacodyn.* 2010, **37**::541-73.

Permeation through the skin



Scale- up IVPT to *in vivo*





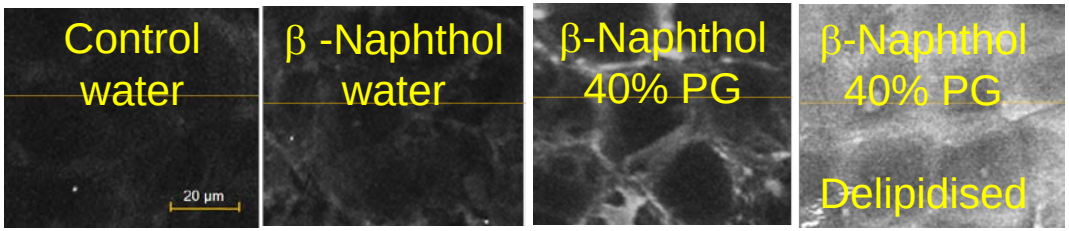
Extraordinary detail on stratum corneum architecture but complicated models unverifiable

Scheuplein Skin Pharmacol Physiol 2013; **26**:199–212

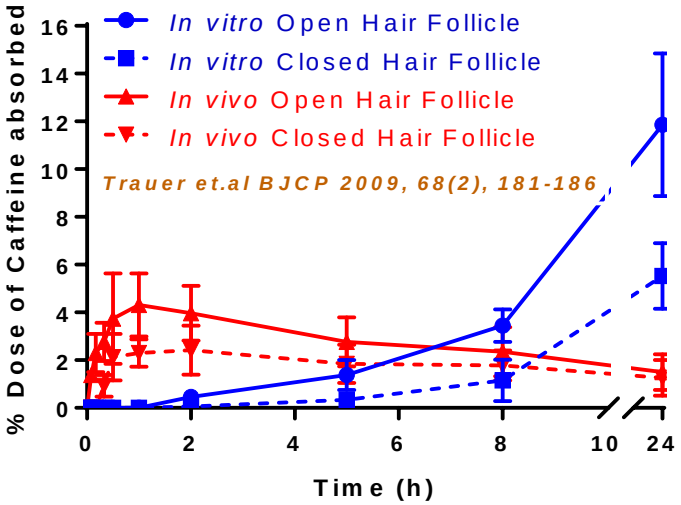
Key messages 1

- Do products feel, smell, look, behave on the skin the same, as well as acting the same? Excipients can make a real difference to both placebo and actual effects!!
- Excipients can have a complex impact on product metamorphosis, drug solubility in the skin and diffusivity in the skin
- Products are in a continuous process of life cyle development that includes generic products seeking to match the efficacy of the newest reference listed drug.
- How much we apply, which dispenser we use and how we apply the product matters
- *In silico* models offer a lot of promise but as Brian Barry said: **Better to be approximately right than precisely wrong! -** Verification of findings with *in vitro* (Q1/Q2/Q3, *IVRT, IVPT*) and, if available, *in vivo* (clinical) data is vital
- *Quality by design QbD concepts dictates comparability of a prospective generic not only in formulation design but also in in silico, in vitro and/or in vivo testing.*
- *Lastly, we must be critical in reviewing & adopting findings*

For instance, how does the formulation affect SC transport? Does choice of *IVPT* skin matter?

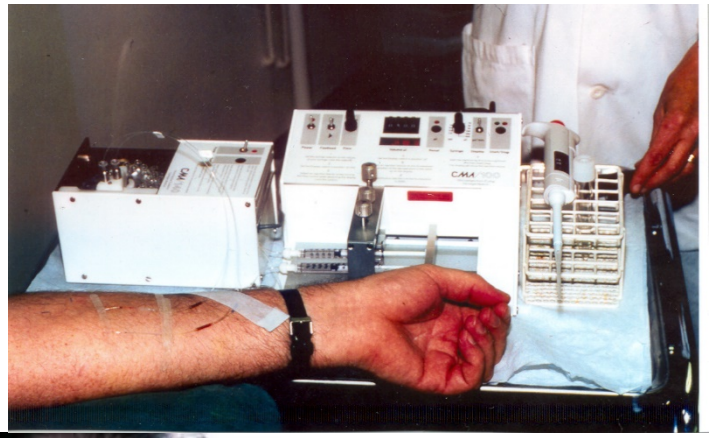


Propylene glycol (PG) increases β-naphthol solubility in SC lipids; β-Naphthol moves into corneocyte interior after solvent delipidisation

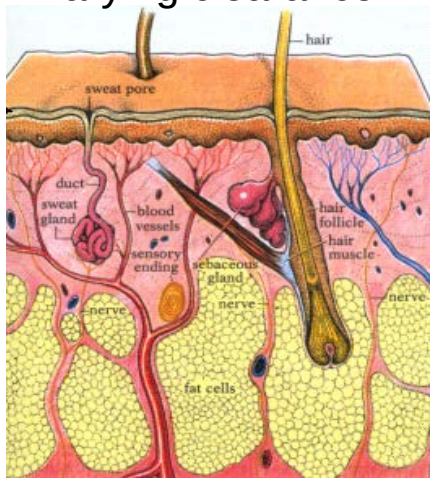


Key messages 2 – what are the differences?

How do we translate data from site of measurement to that at site of action?



What about responses at the different skin target sites, noting also varying clearance?



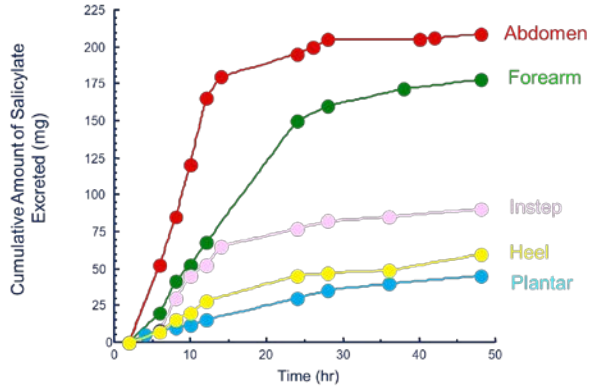
Can we use skin physiology data?

Data for a 20 year old male

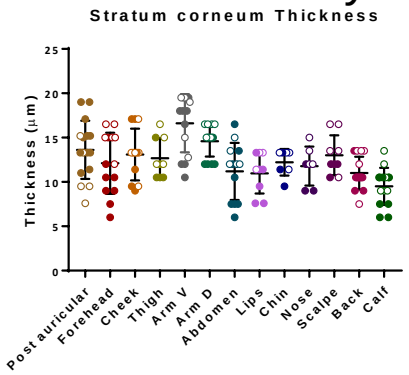
Body site	Forearm	Palm	Leg
SC thickness µm	26	74	20
Corneocyte Size **H** µm	23	14	18
Corneocyte Size **W** µm	20	28	20
TEWL g m^{-2} h^{-1}	6.42	77.68	6.46

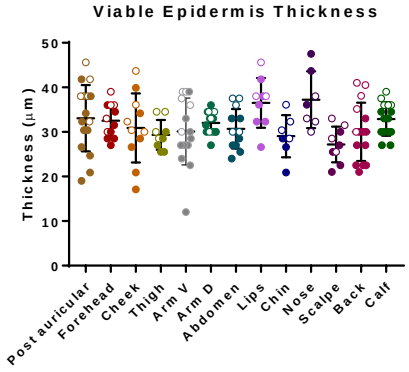
Can such data be use to predict *in vivo* absorption?

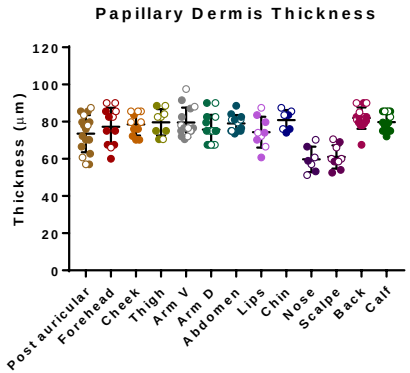
Urinary excretion of salicylate *(5g methyl salicylate product / 50cm² for 10 h)*



And can we adjust for individual variability?



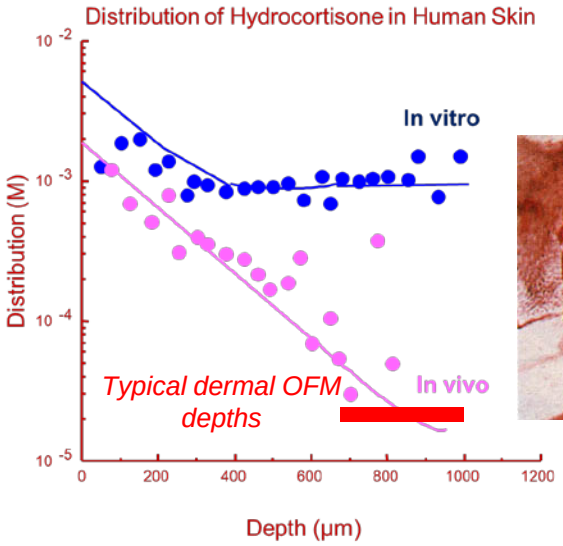


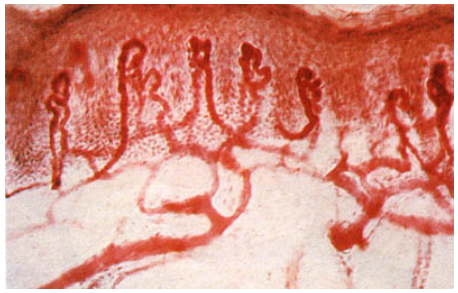


Key messages 3 – what are the differences?

Measure at sites of action better than we do now?

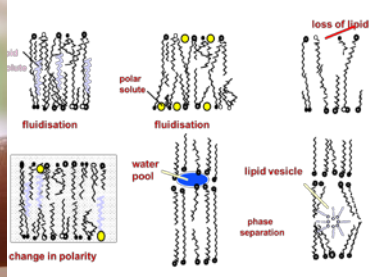
Dermal sampling site for microdialysis, micro-perfusion (*in vivo*) & *in vitro* dermatomed skin





Schaeffer et al, 1996

- What is the impact of **local events** (e.g. binding that can prolong effects, active transport by transporters & metabolism) in both viable epidermis and dermis?
- **What is the clearance?** Steady state levels at **site of action** depends on both skin flux to site and **clearance** from site – important to have realistic *in vitro* and *in silico* models of clearance!!



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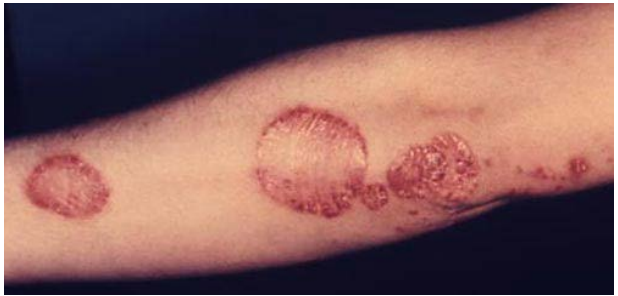

*In my view, the holy grail in **topical product development** is unchanged, i.e. to maximise its effectiveness by understanding and applying **drug - product - skin & skin sensorial interactions** at the **affected skin site** for the **person being treated**.*

Thank you

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