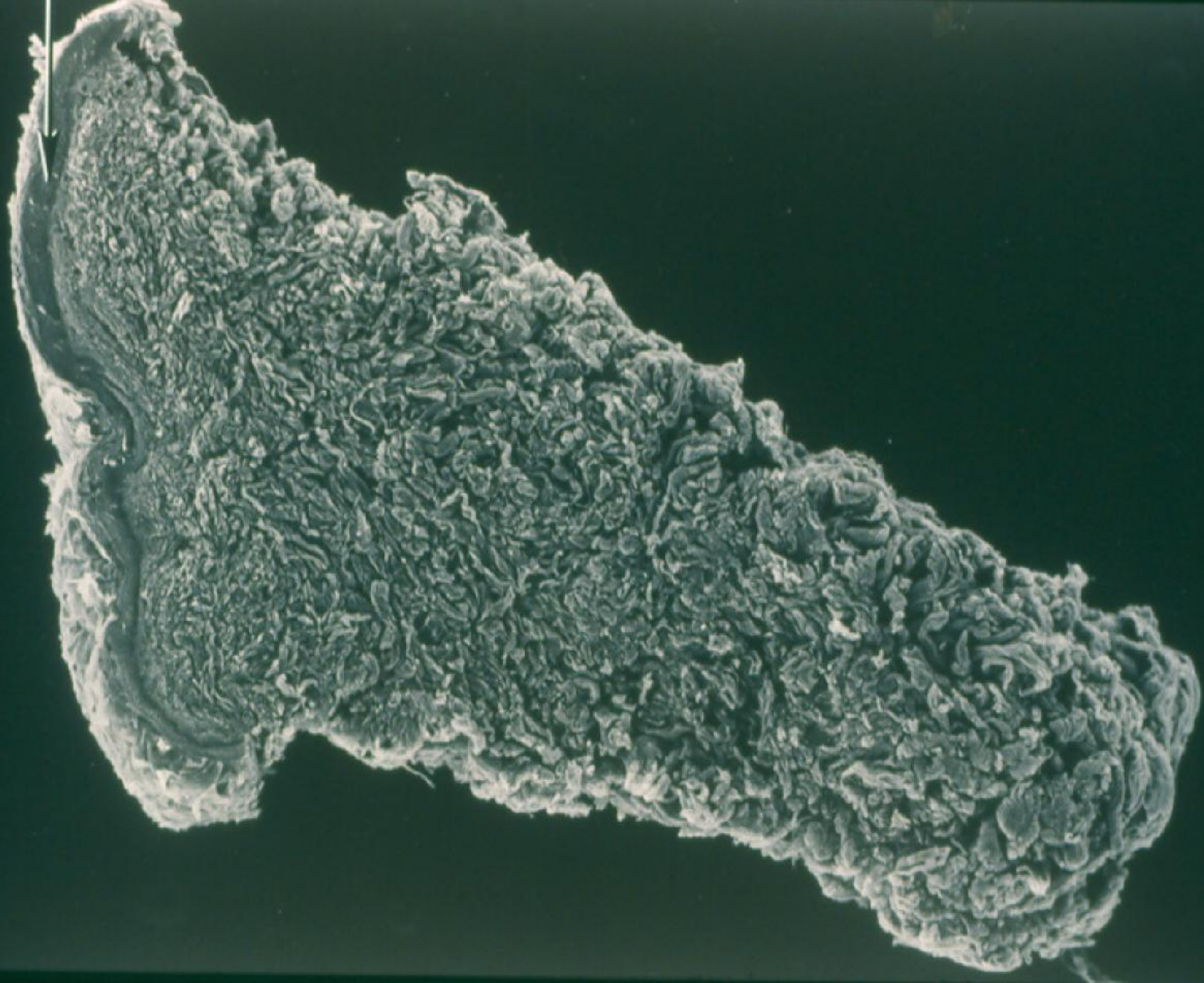


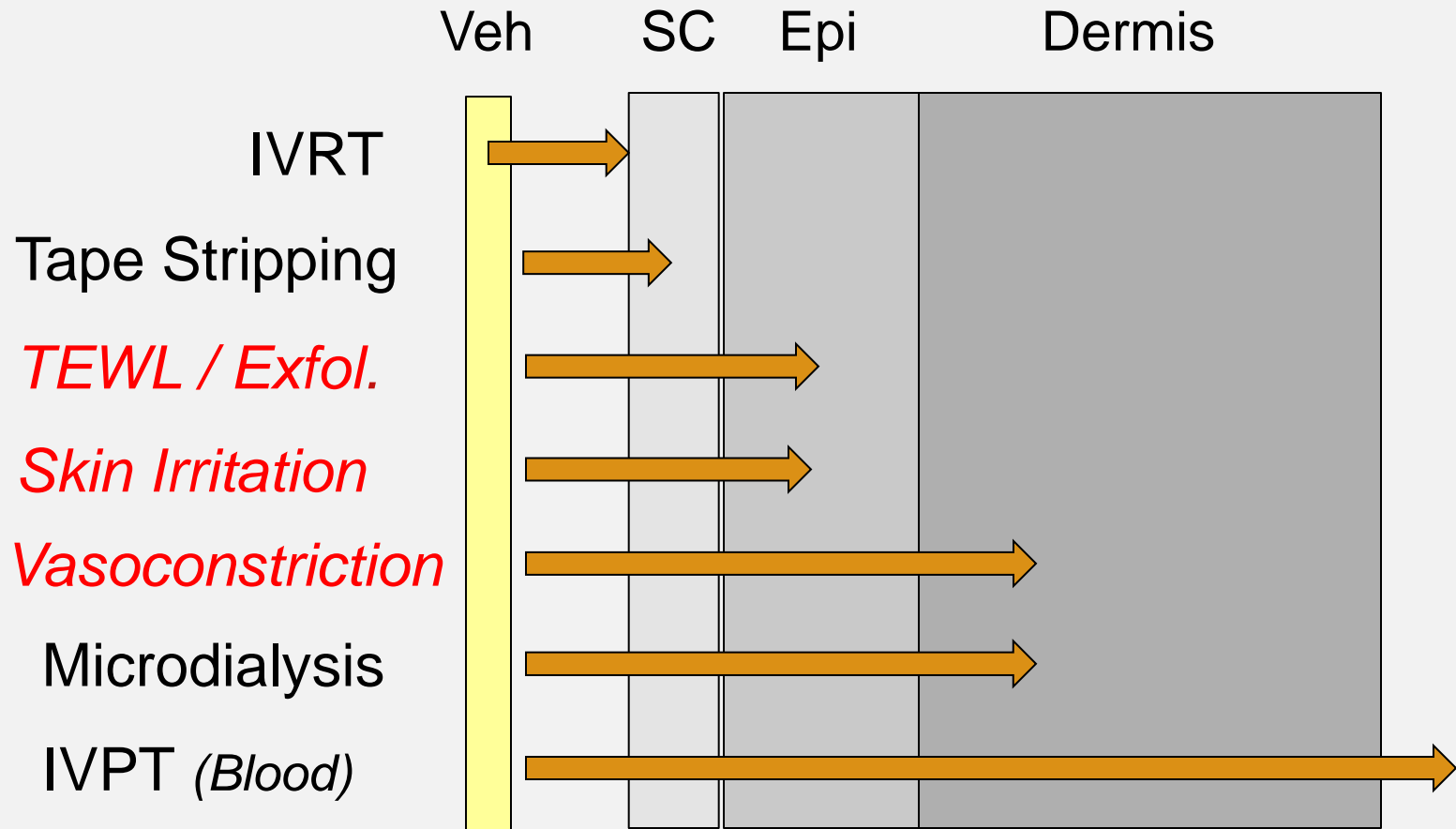


Assessing the BA and BE of Topical Dermatologic Drug Products with Multiple Surrogate Methods

Thomas J. Franz

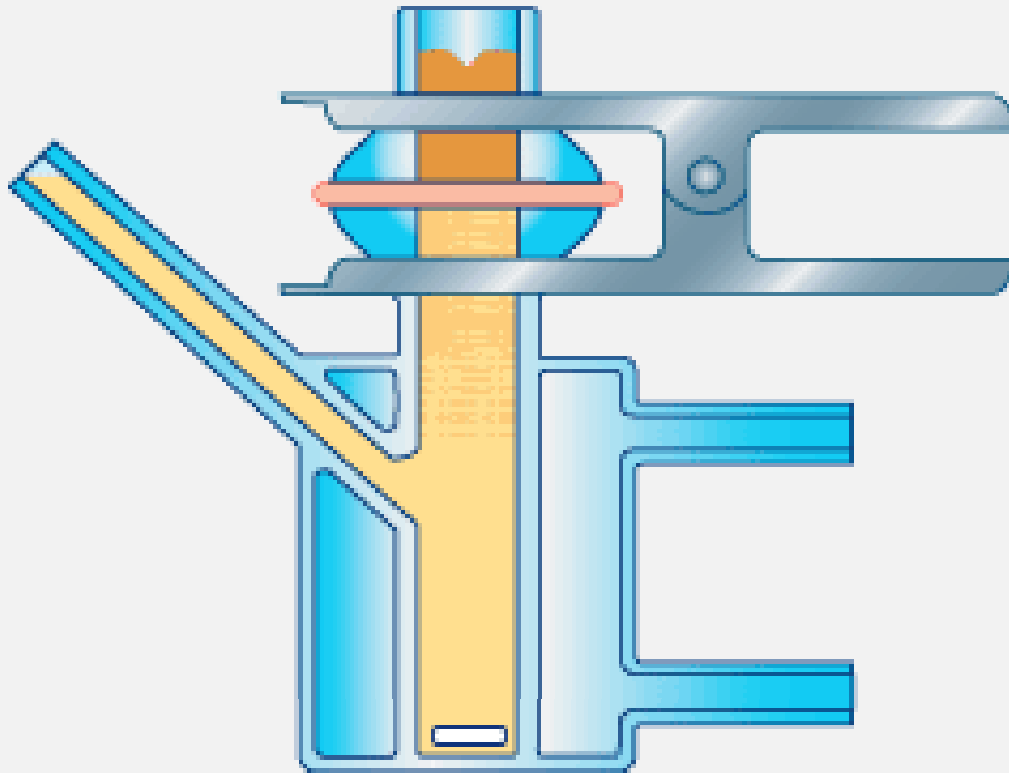


(Partial) Hierarchy of Surrogate Tests



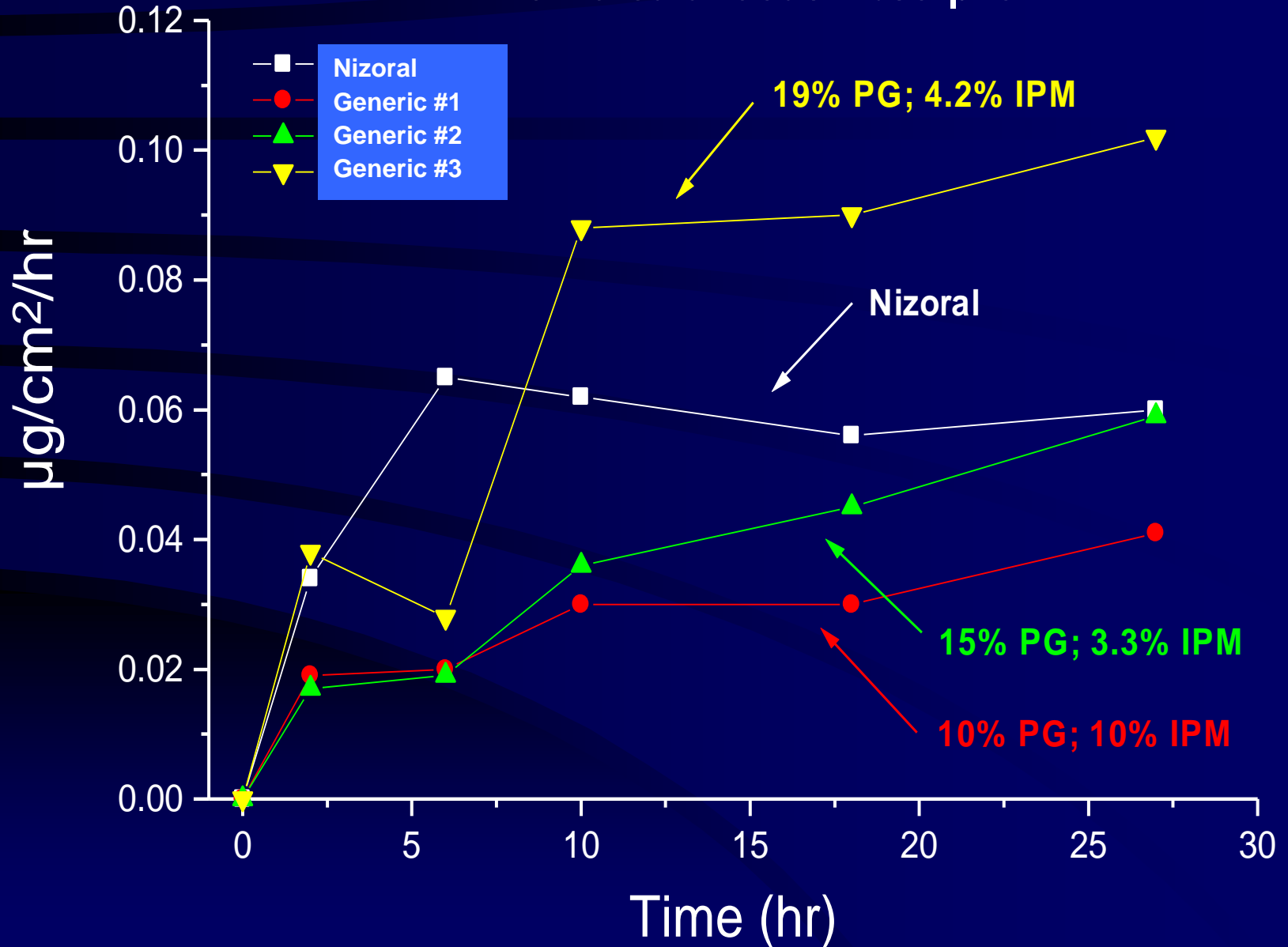
In Vitro Permeation Test

- Diffusion Cell



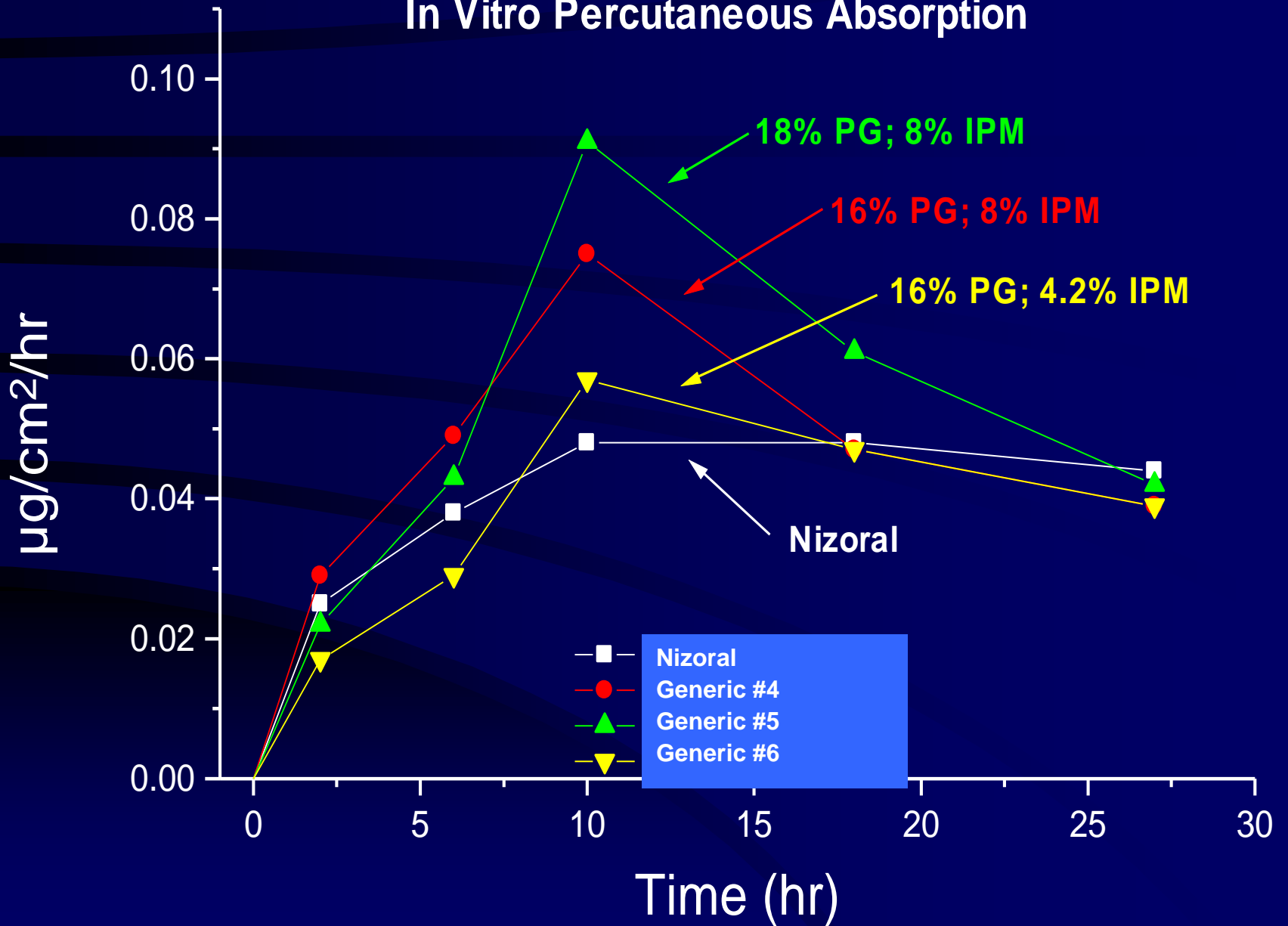
Ketoconazole

In Vitro Percutaneous Absorption

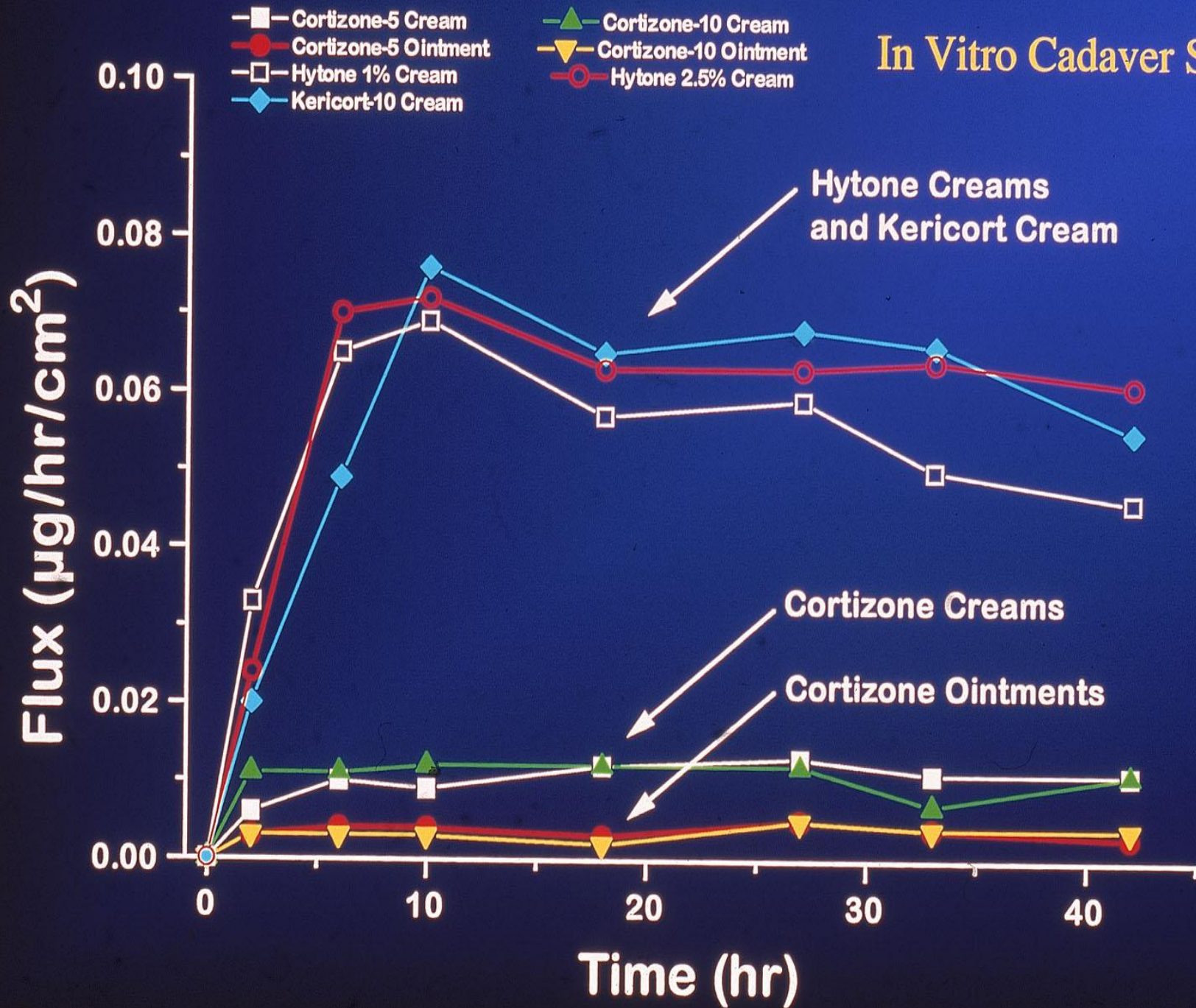


Ketoconazole

In Vitro Percutaneous Absorption

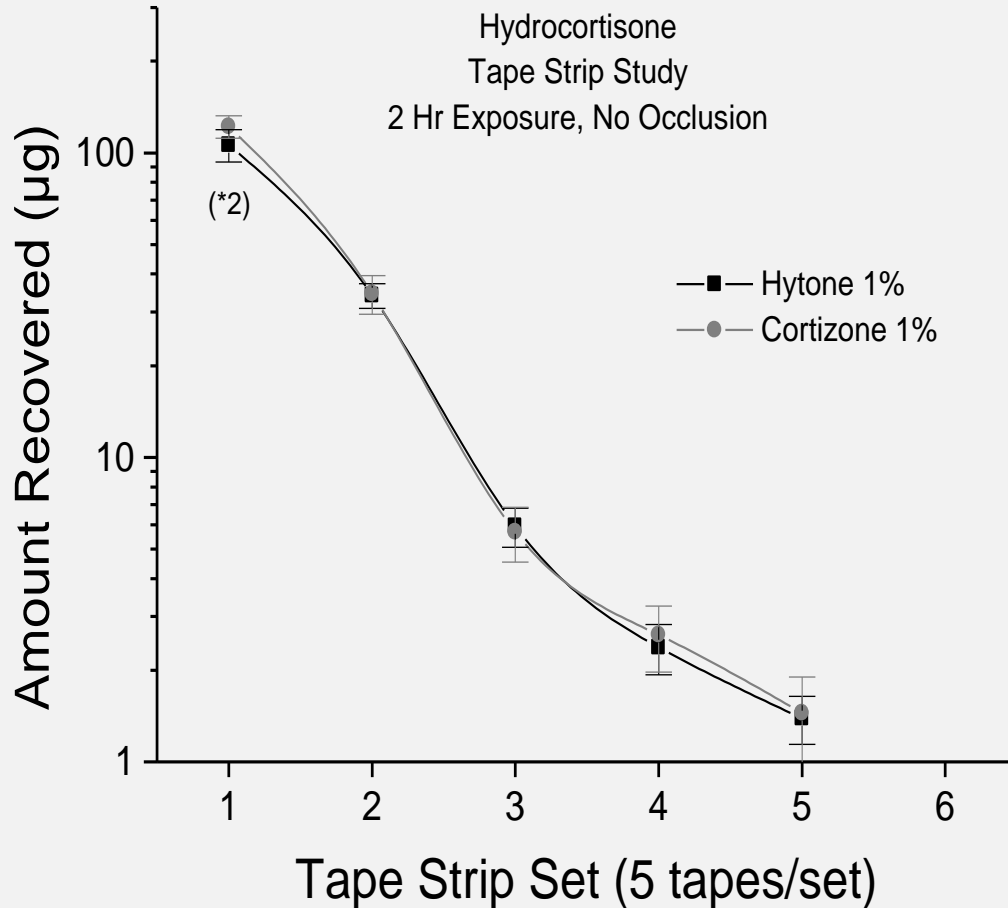


In Vitro Cadaver Skin Assay



Topical BE: Tape Stripping

(Mean \pm SEM)

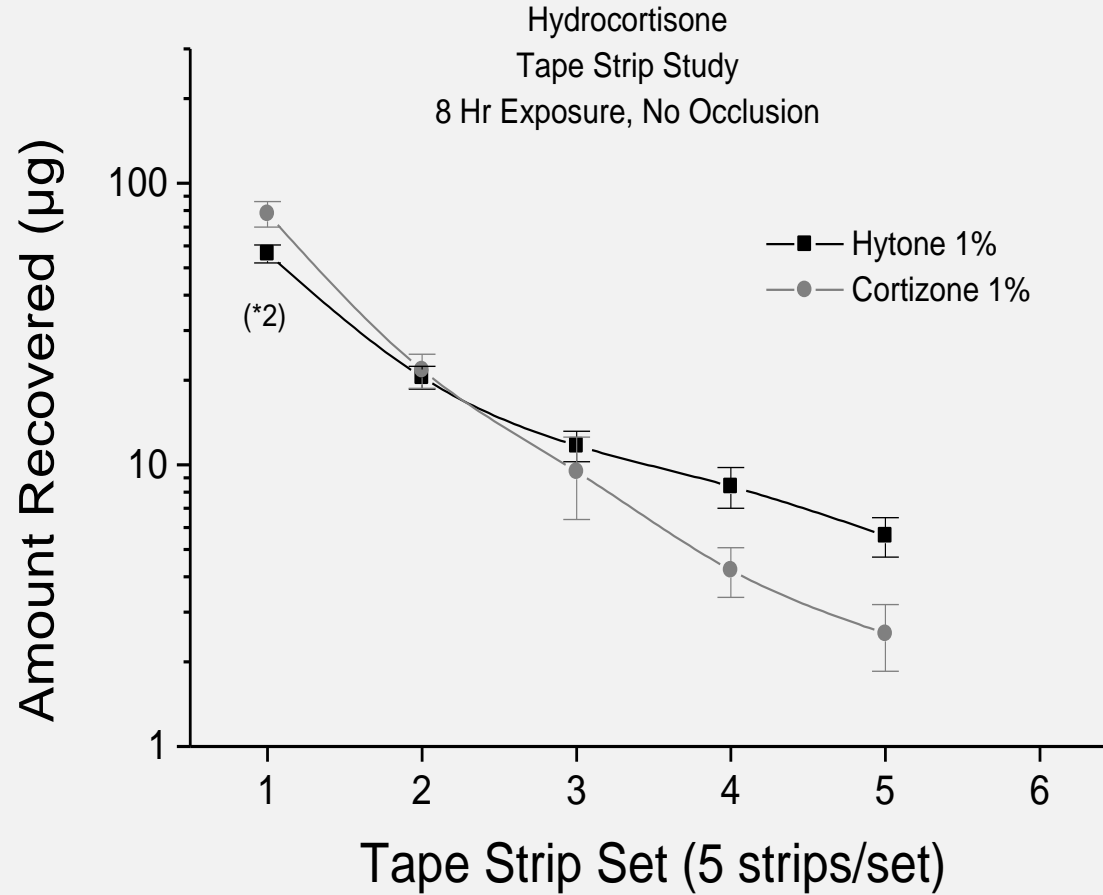


Method

- 6 subjects
- Vent. Forearm
- A = 2 cm x 5 cm
- Dose = 1.9 mg/cm²
- 1" Transpore tape, 22 strips
pooled (2, 5, 5, 5, 5)
- Extract in methanol
- Assay by HPLC

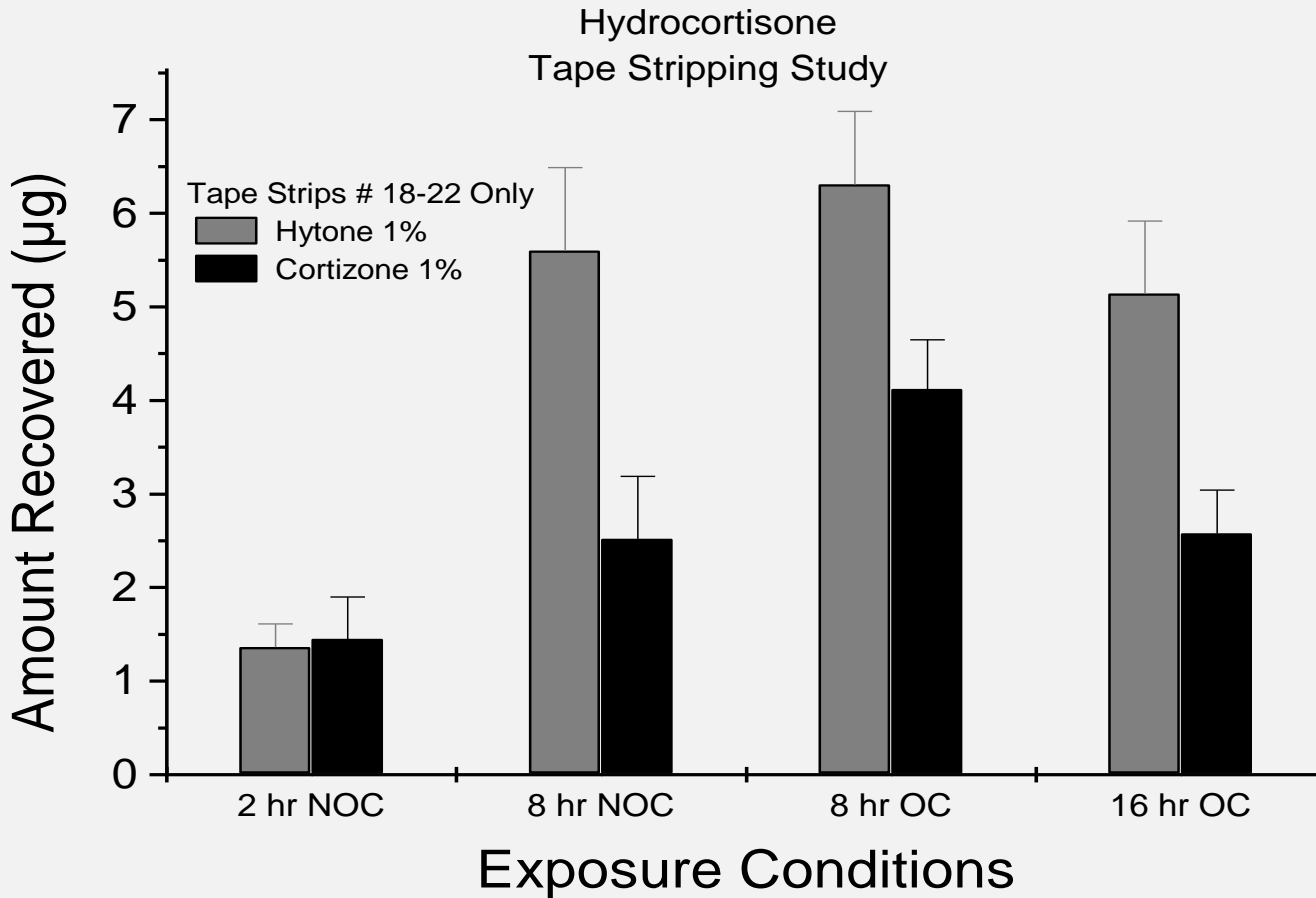
Topical BE: Tape Stripping

(Mean \pm SEM)

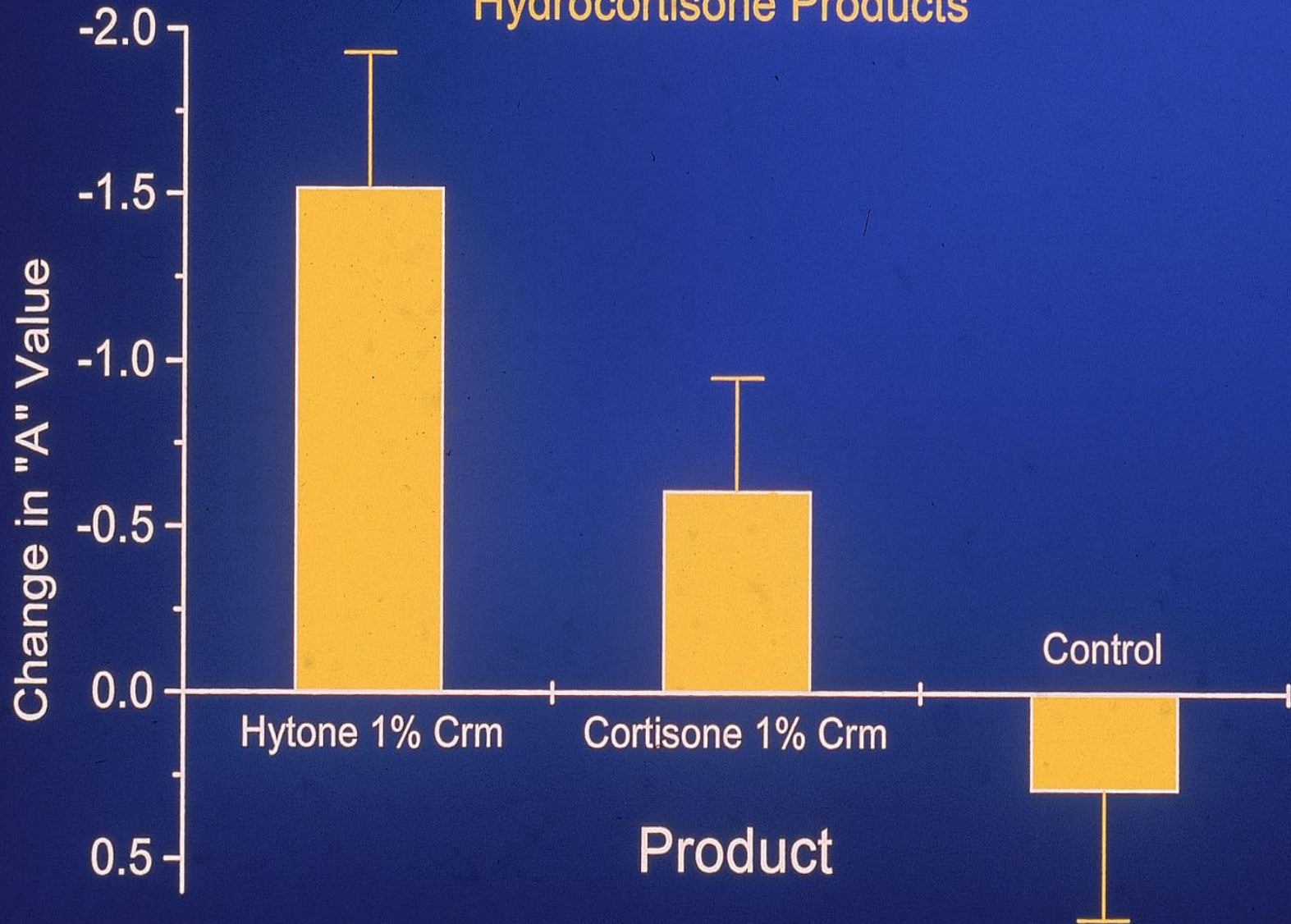


Topical BE: Tape Stripping

(Mean \pm SEM)

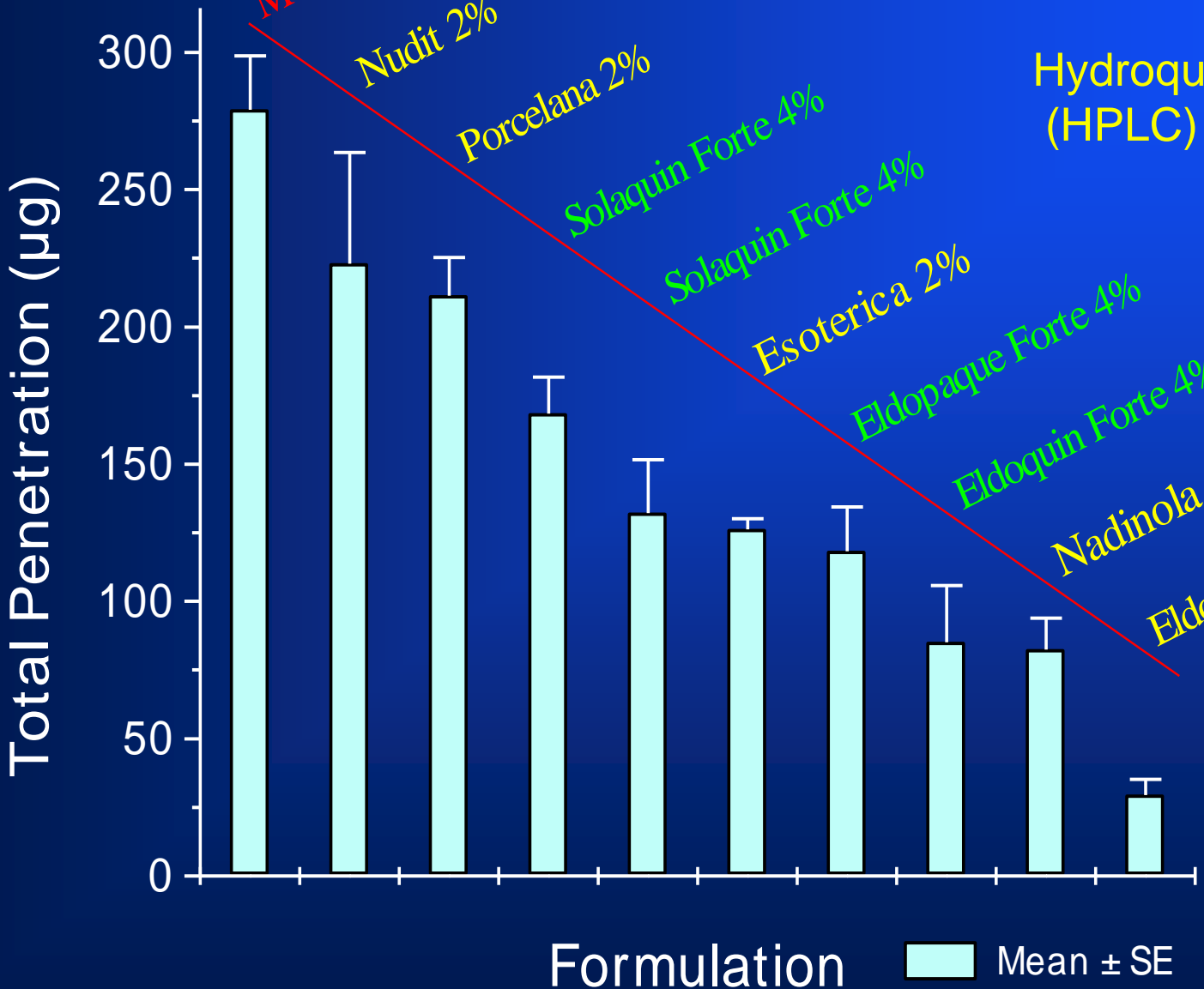


Vasoconstriction Assay Hydrocortisone Products

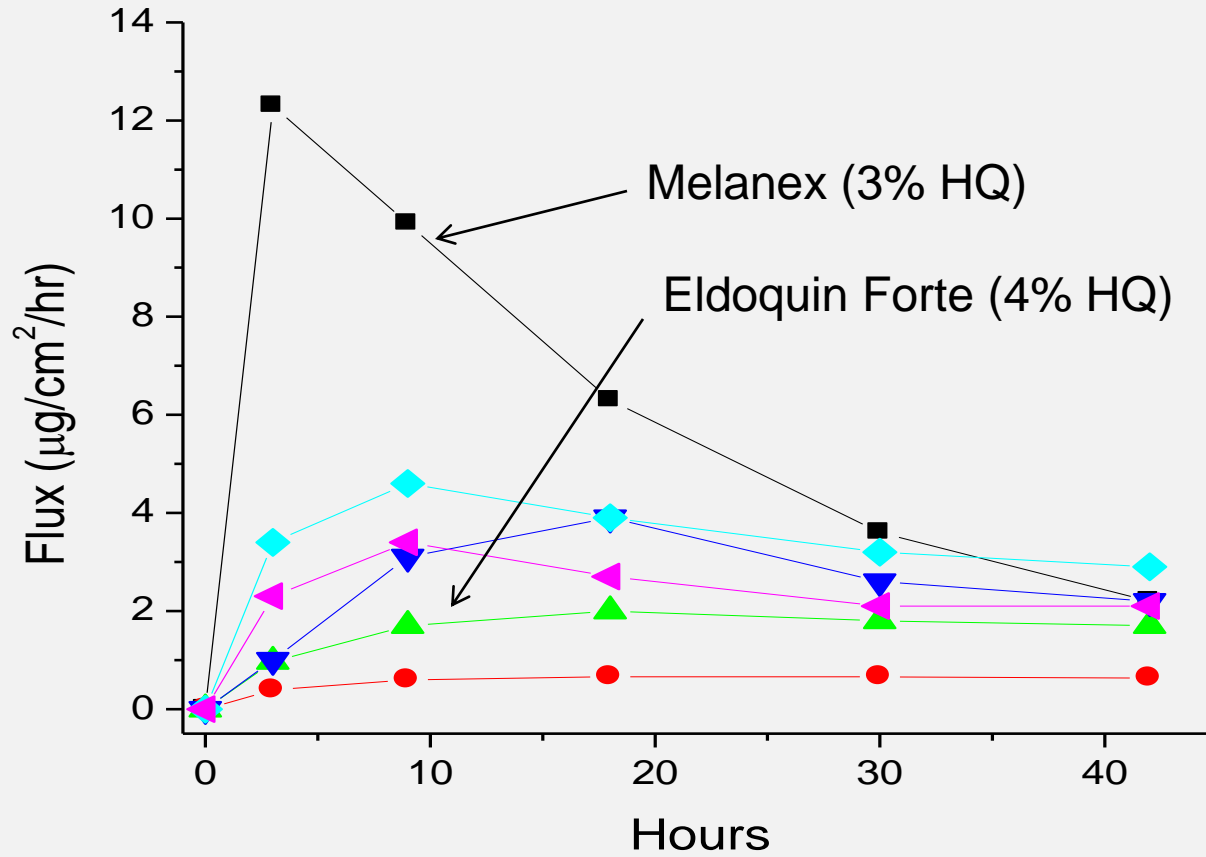


In Vitro Cadaver Skin Assay

Hydroquinone Products (HPLC)



Hydroquinone Absorption



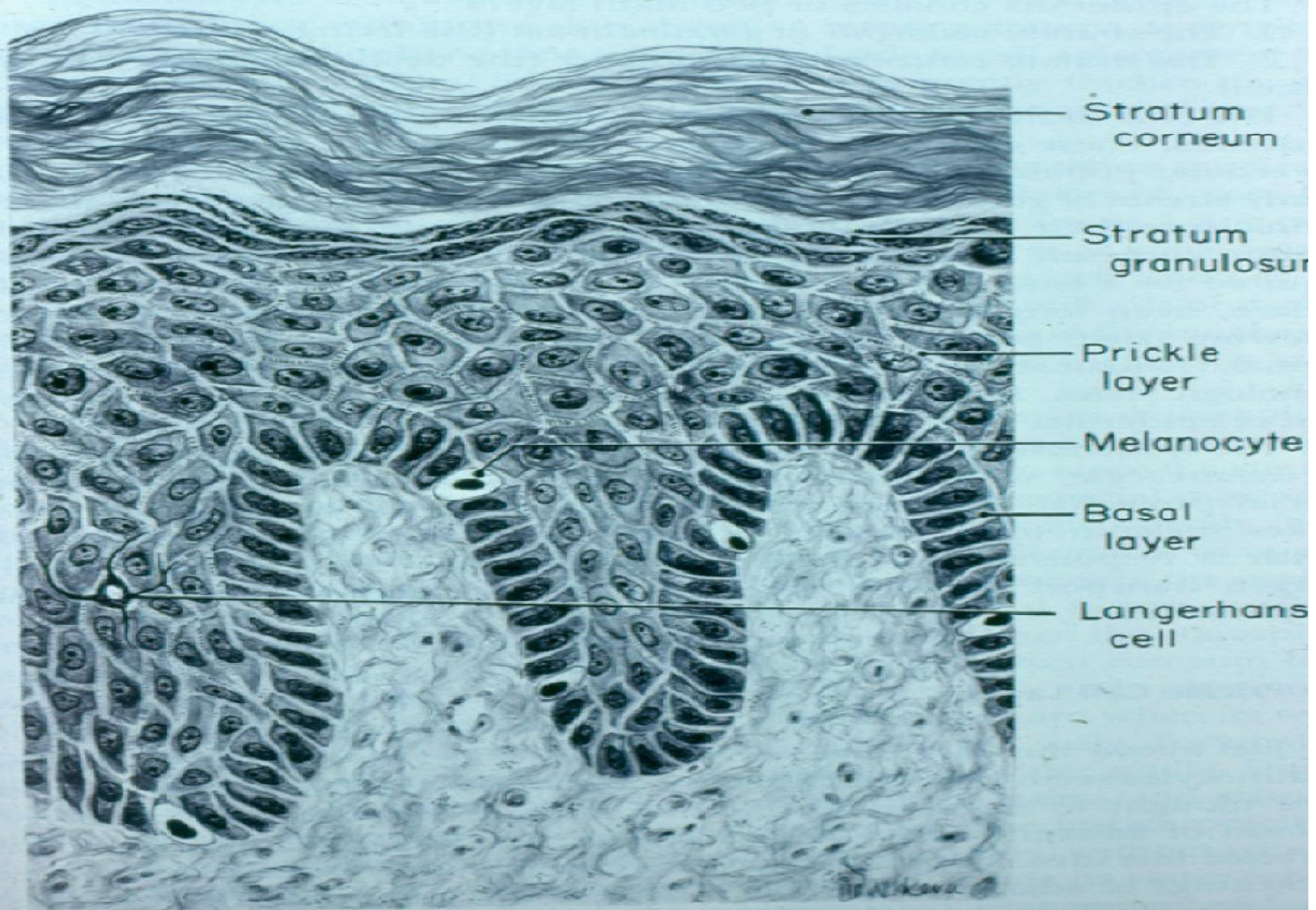
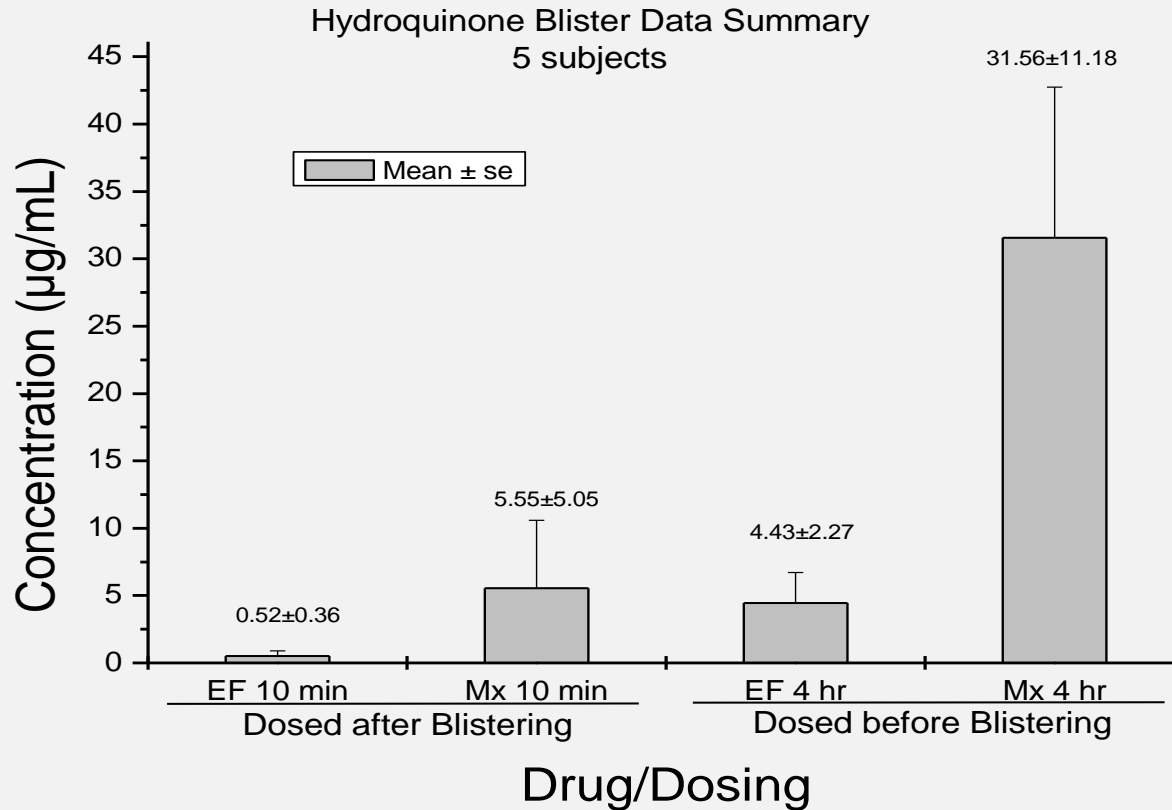


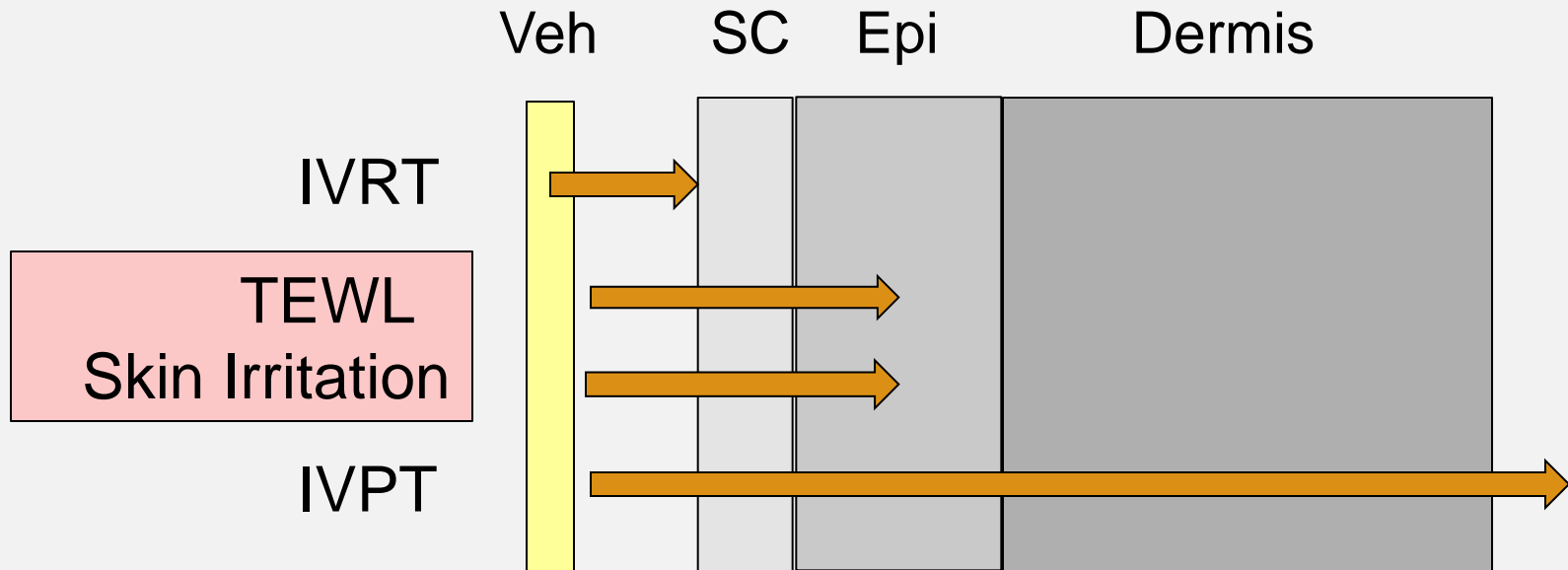
Figure 1-3. The epidermis

The epidermis is stratified. The outer horny layer is dead and made up of cells which are keratinized (the cellular composition of the stratum corneum is not ordinarily evident). The basal layer (the lowest layer) contains the stem or mother cells from which all the other cells ultimately derive. The melanocytes are in the basal layer and frequently look like "clear" cells. The "prickles" are desmosomes.

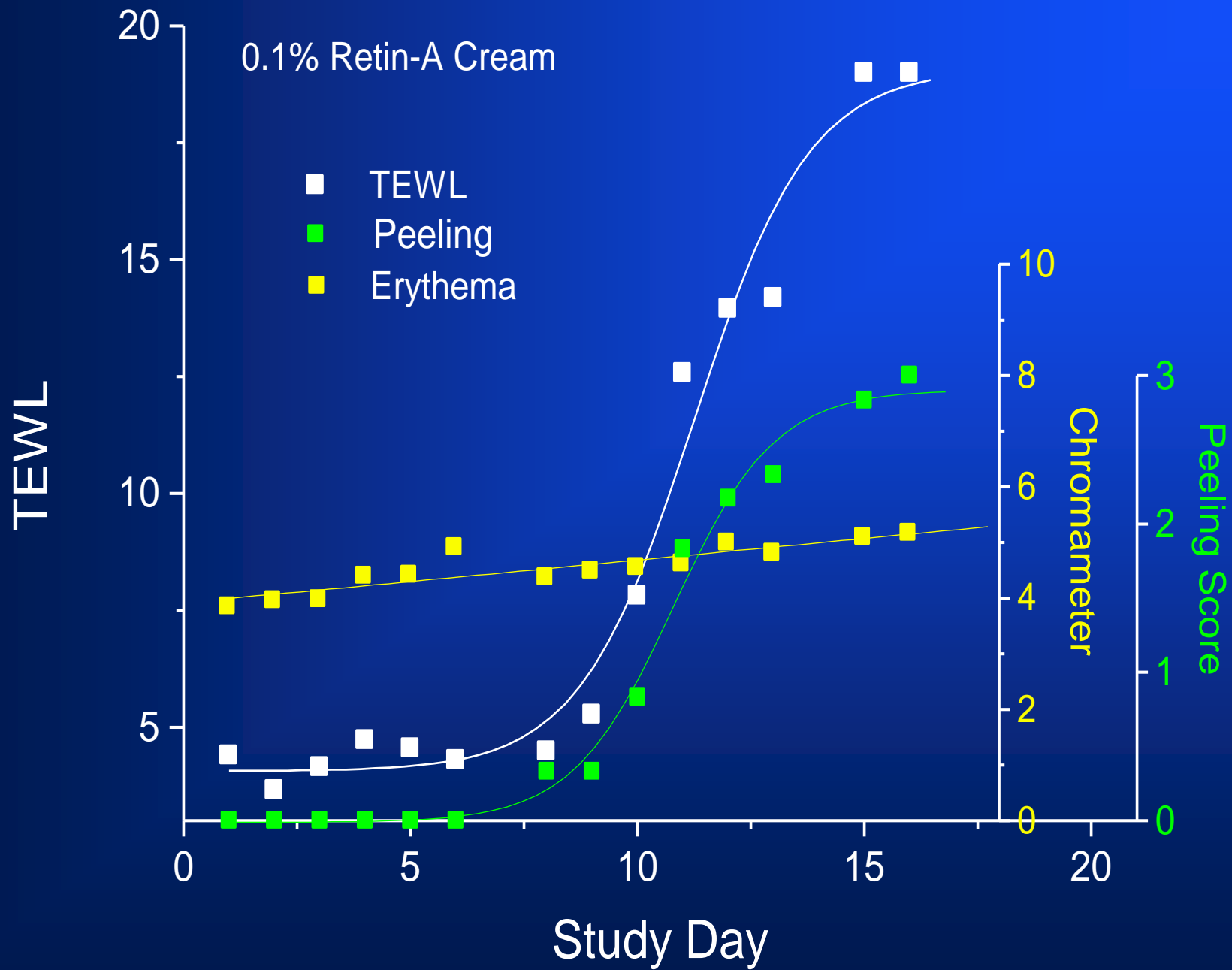
Hydroquinone Absorption



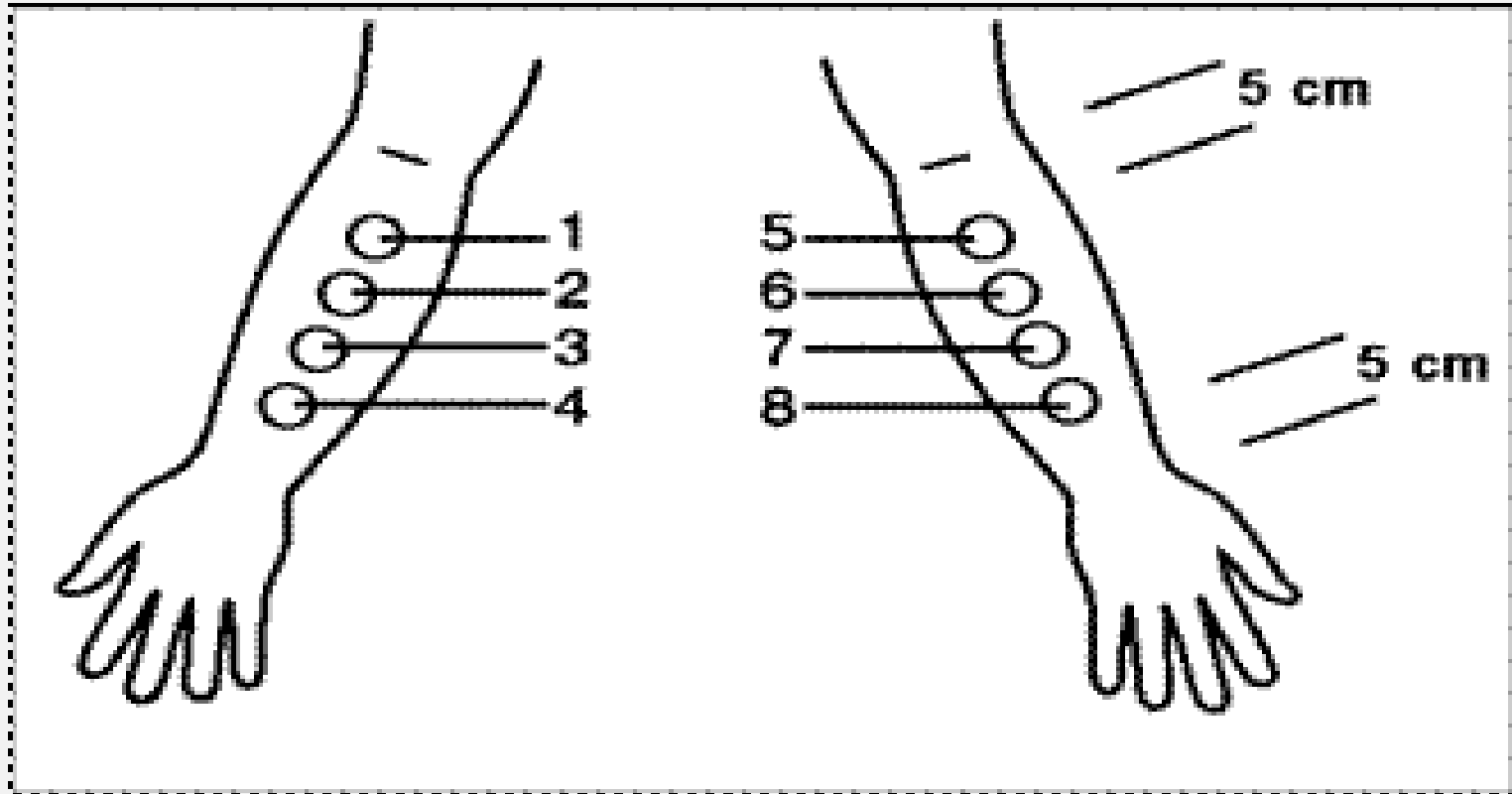
RETINOIDS



Lehman PA, Franz TJ: Assessing the bioequivalence of topical retinoid products by pharmacodynamics assay. *Skin Pharmacol and Physiol* 25:269-280, 2012.

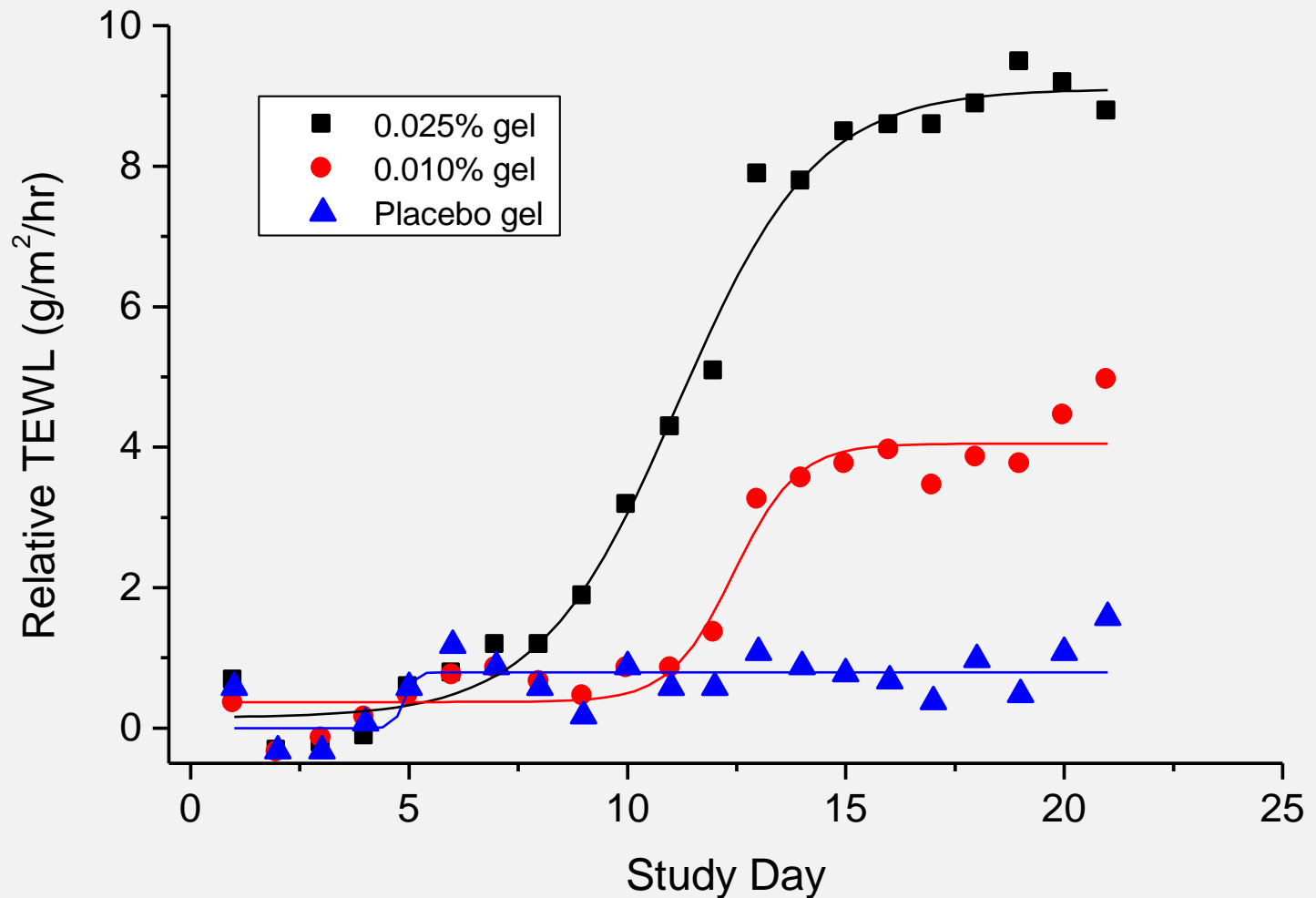


Validation: TEWL Test Tretinoin Gels



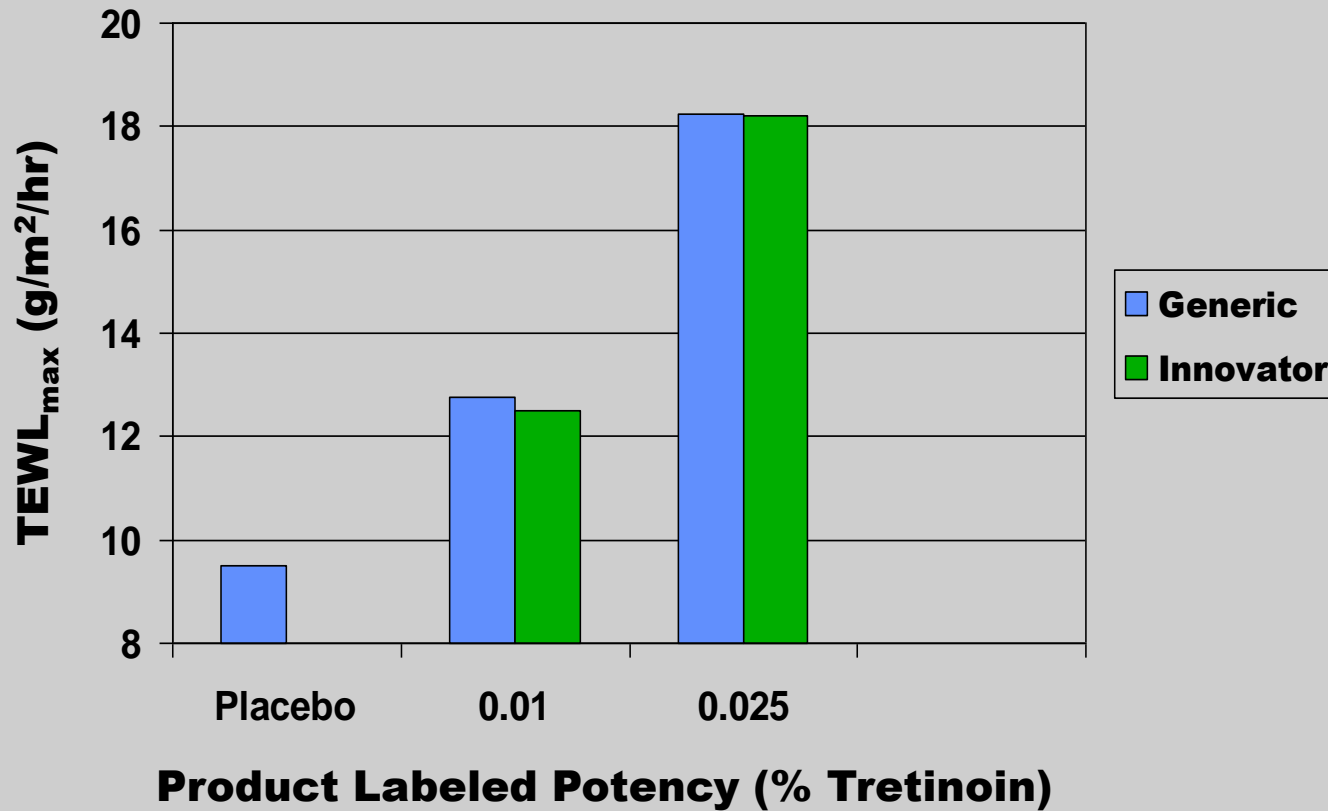
Two Primary Endpoints: (1) maximum transepidermal water loss achieved
(2) days to full peel (DTFP)

Tretinoin Gel: TEWL/Exfoliation



Validation: TEWL Test

Tretinoin Gels Maximum TEWL



Validation: TEWL Test

Tretinoin Gels Statistical Analysis



■ Dose = 0.01%

◆ Classical CI on ratio (test/ref)

✧ TEWL: (93.9%, 114.7%)

✧ DTFP: (95.8%, 103.5%)

■ Dose = 0.025%

◆ Classical CI on ratio (test/ref)

✧ TEWL: (97.8%, 121.03%)

✧ DTFP: (96.3%, 105.2%)

Summary



- Assessment of the BE of topical drug products can be accomplished through the use of appropriately selected *in vitro* and *in vivo* surrogate tests.
- All surrogate tests have limitations but they all don't have the same limitation. The results from one test complement the results of other tests.
- Selection of tests would depend upon the complexity of the formulation and whether the test product is Q1/Q2 equivalent.
- For most products IVRT, IVPT, and irritation testing would be essential.