SKIN FORUM Presentation, June 26, 2013

A Comprehensive Approach to Topical Bioequivalence

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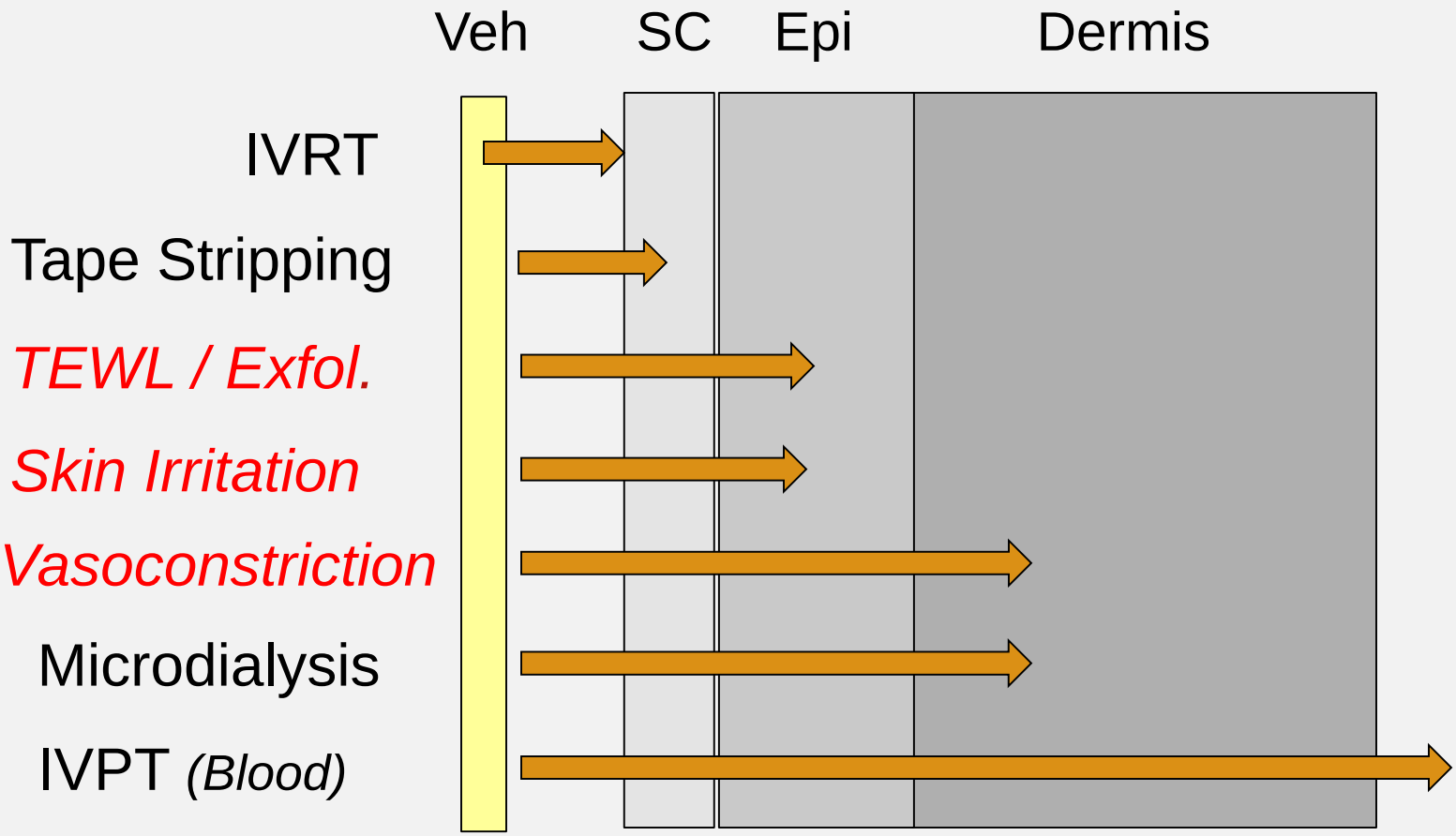
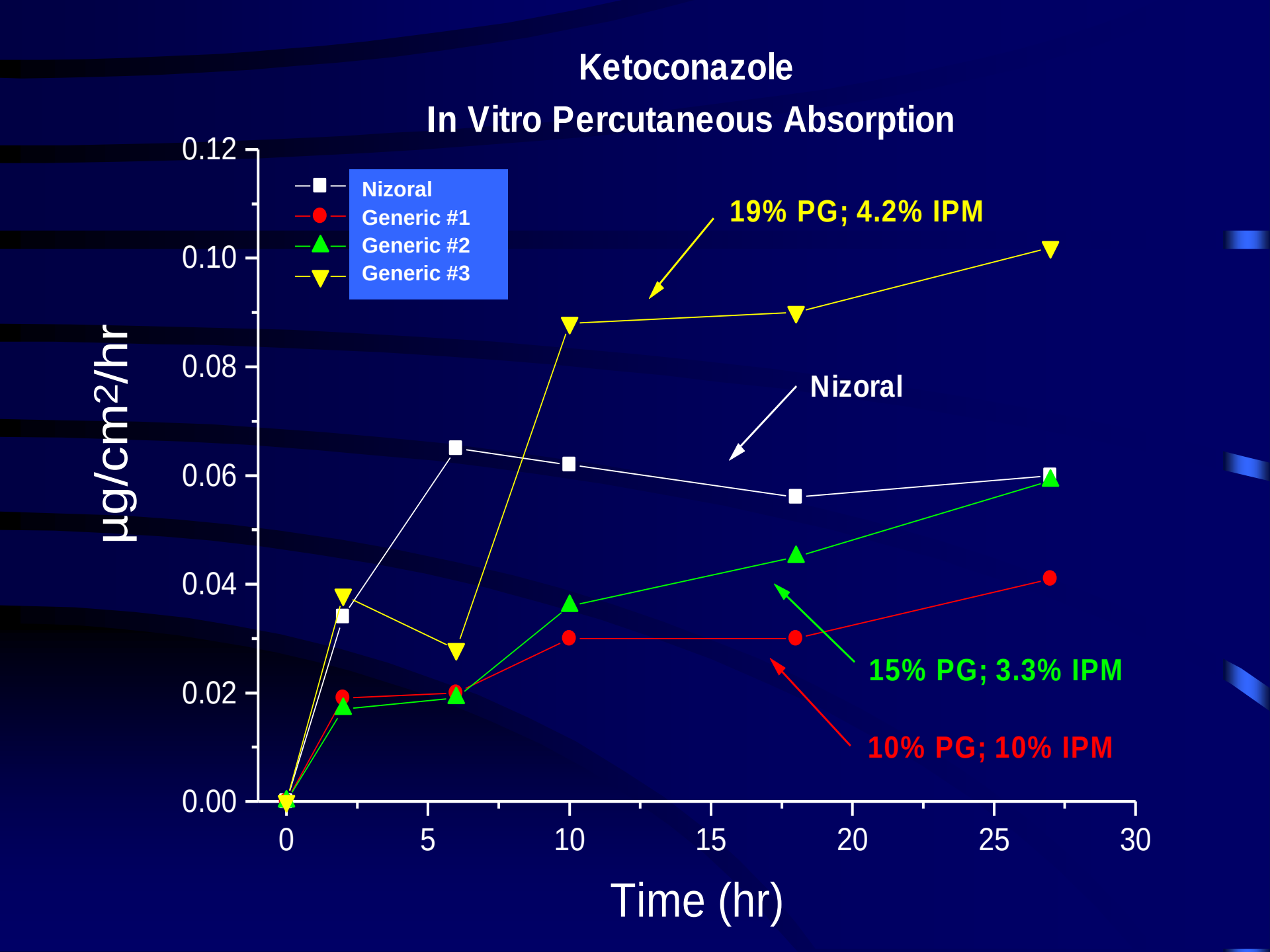
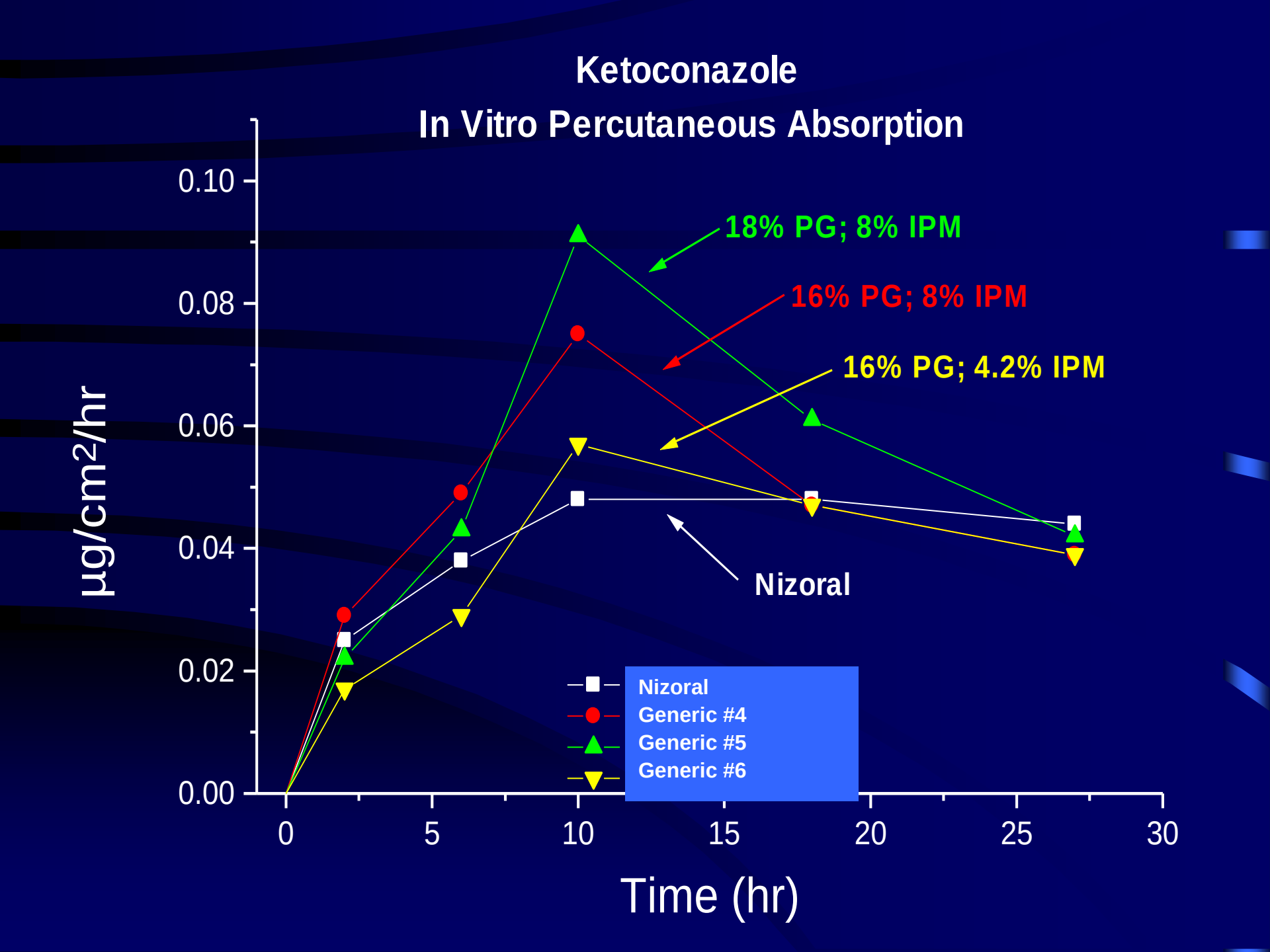
(Partial) Hierarchy of Surrogate Tests

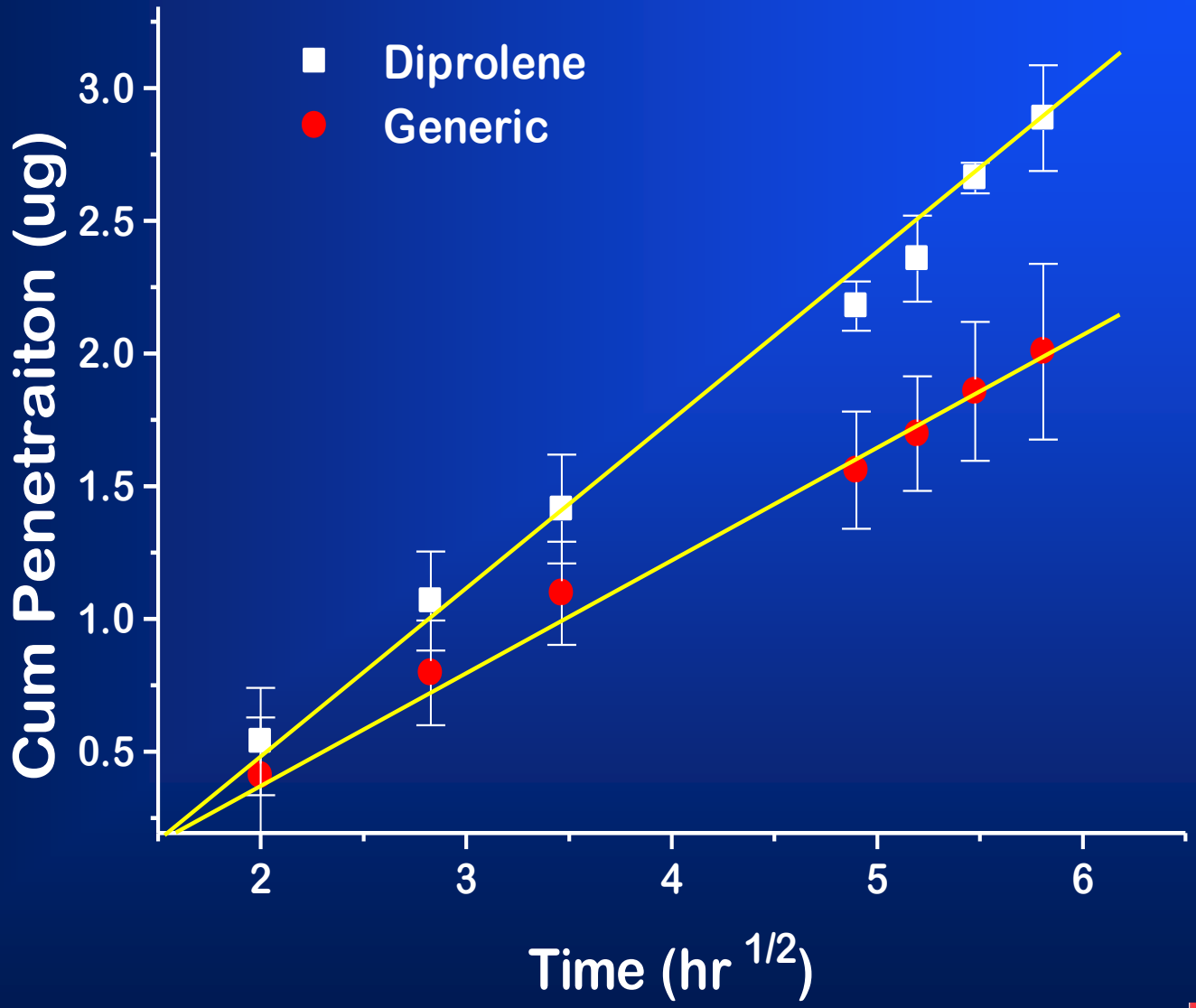



Ketoconazole
In Vitro Percutaneous Absorption
Nizoral
Generic #1
Generic #2
Generic #3
19% PG; 4.2% IPM
Nizoral
15% PG; 3.3% IPM
10% PG; 10% IPM
µg/cm2/hr
0.12
0.10
0.08
0.06
0.04
0.02
0.00
0
5
10
15
20
25
30
Time (hr)


Ketoconazole
In Vitro Percutaneous Absorption
18% PG; 8% IPM
16% PG; 8% IPM
16% PG; 4.2% IPM
Nizoral
Nizoral
Generic #4
Generic #5
Generic #6
µg/cm2/hr
0.00
0.02
0.04
0.06
0.08
0.10
0
5
10
15
20
25
30
Time (hr)

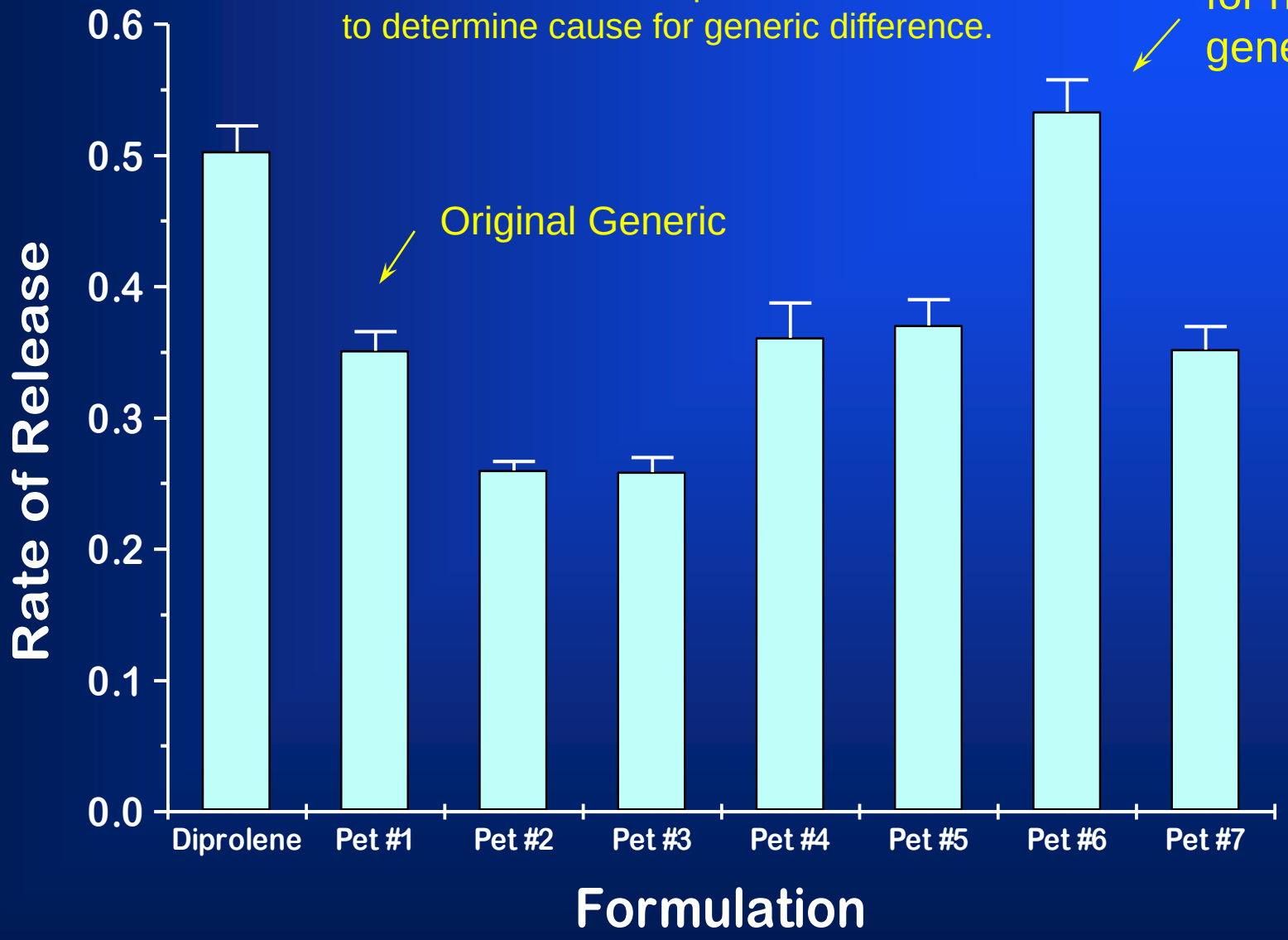
Rate of Release Assay: Diprolene (Betametasone dipropionate)

First test of new generic

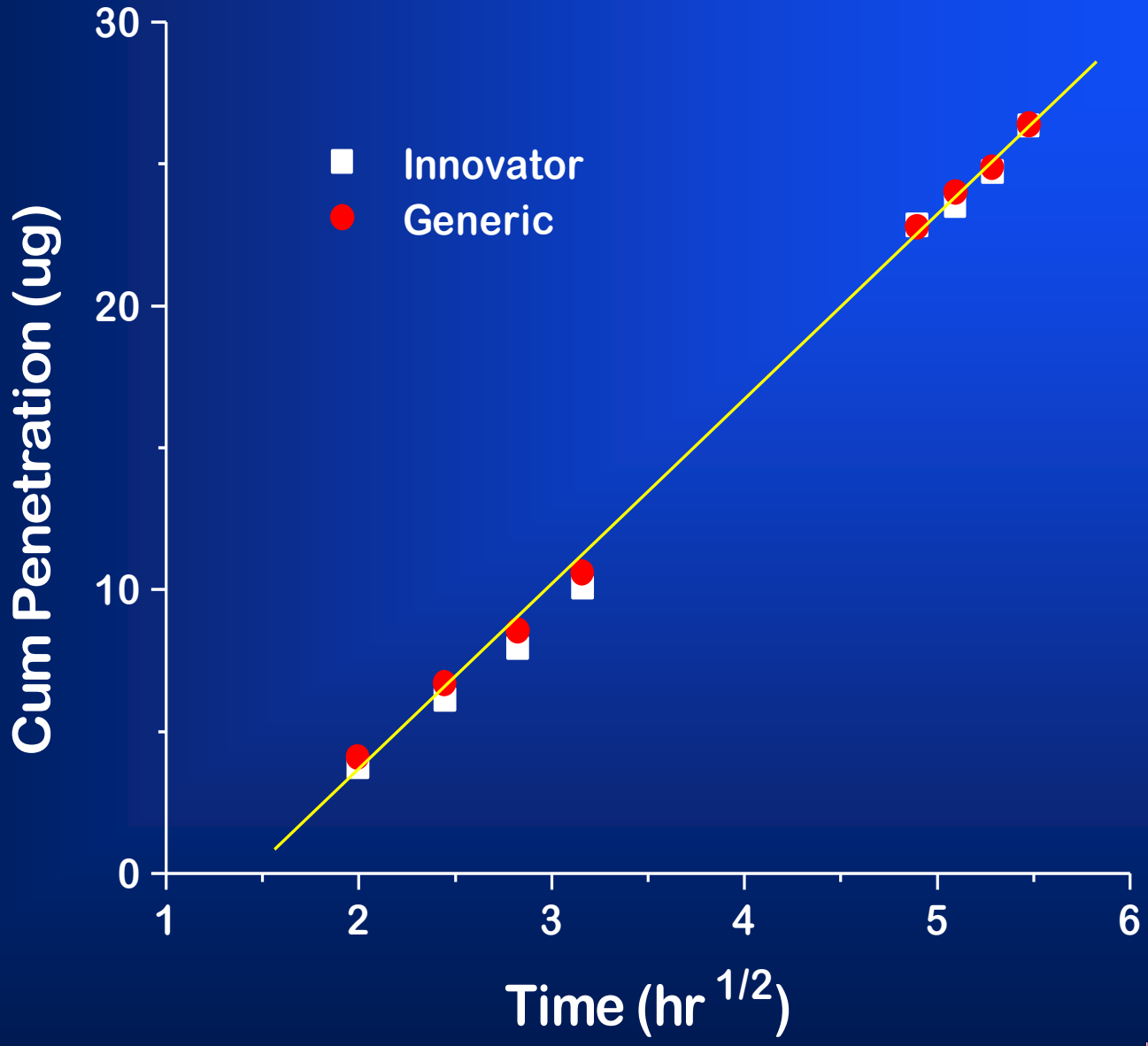


Rate of Release Assay: Diprolene

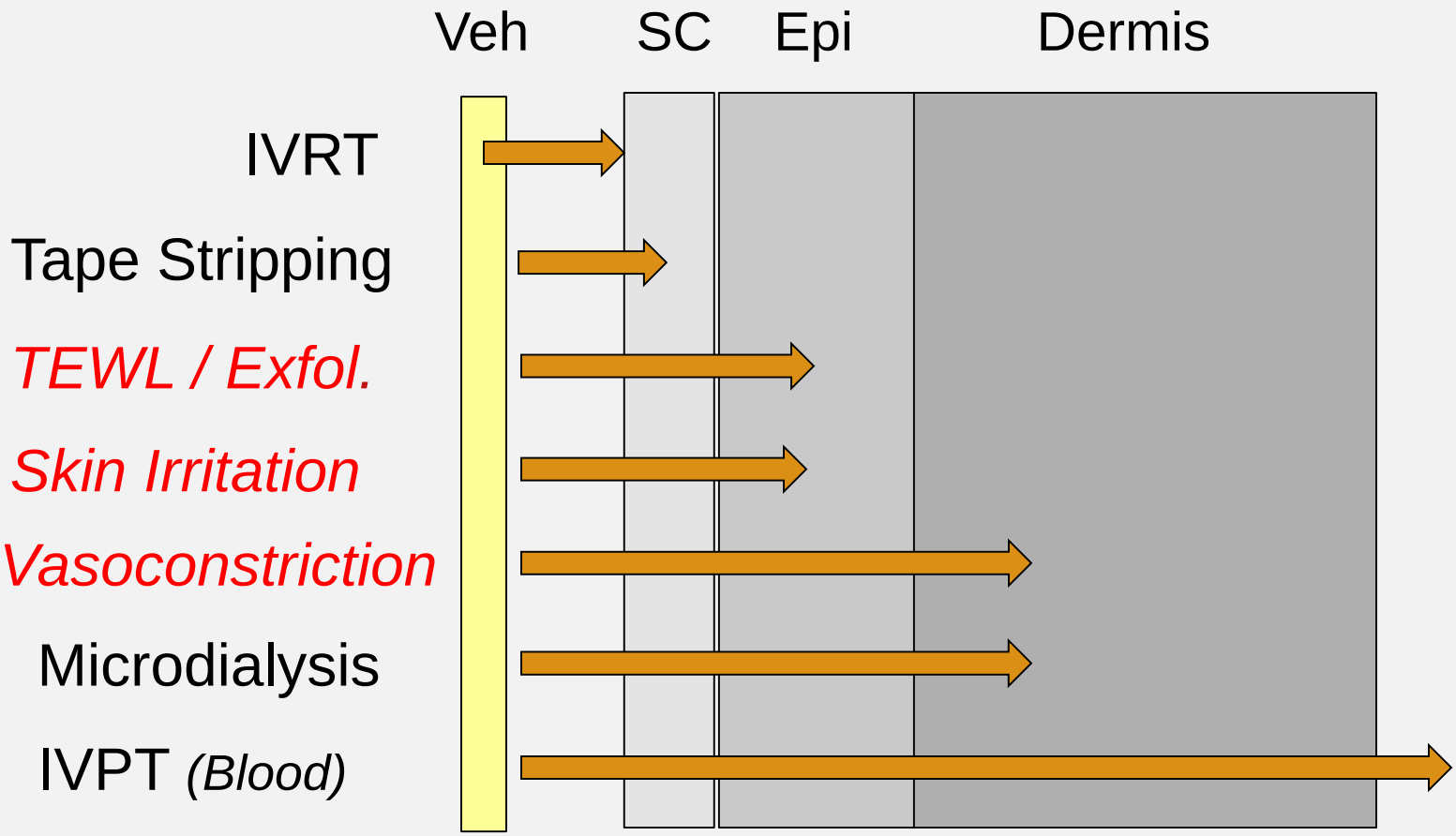
Evaluation of different petrolatum sources to determine cause for generic difference.

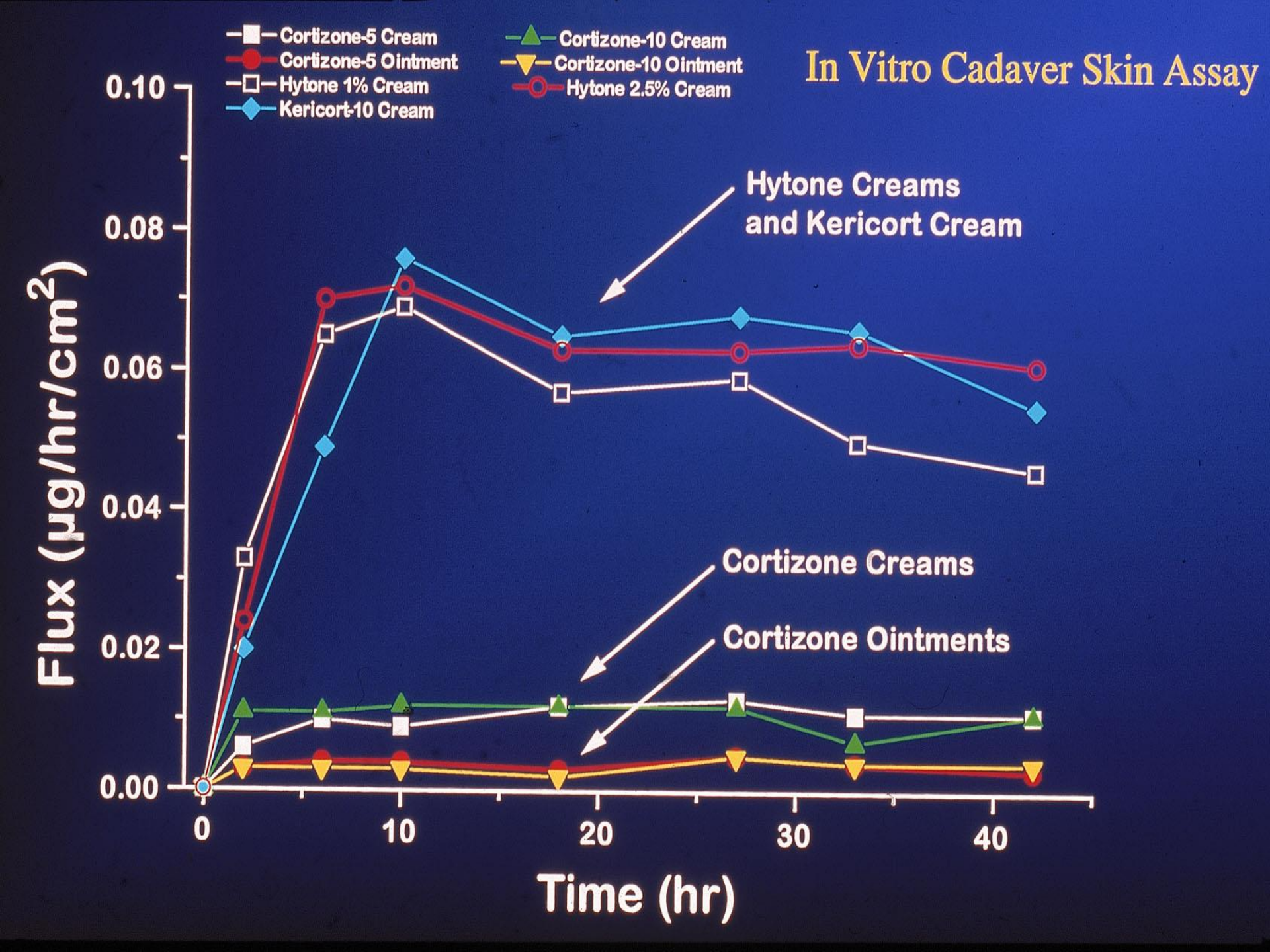


Rate of Release Assay:

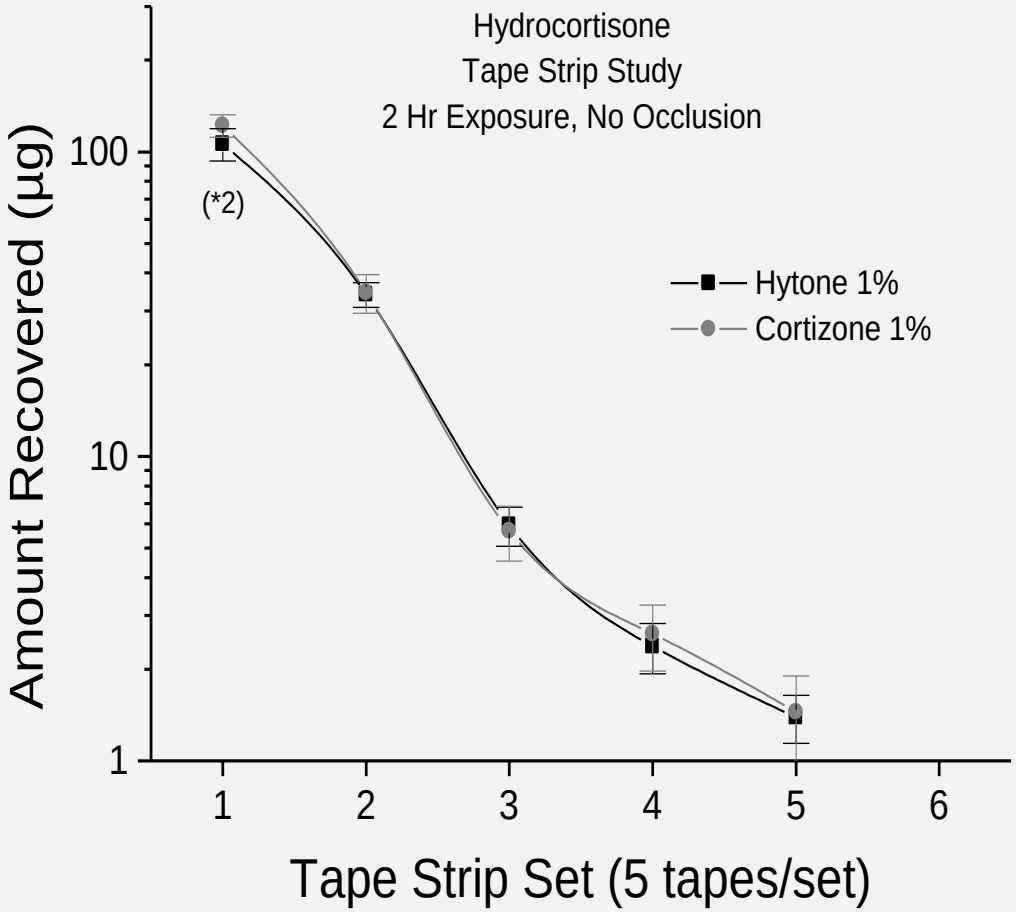


(Partial) Hierarchy of Surrogate Tests




Cortizone-5 Cream
Cortizone-5 Ointment
Hytone 1% Cream
Kericort-10 Cream
Cortizone-10 Cream
Cortizone-10 Ointment
Hytone 2.5% Cream
In Vitro Cadaver Skin Assay
Hytone Creams
and Kericort Cream
Cortizone Creams
Cortizone Ointments
Flux (µg/hr/cm2)
0.10
0.08
0.06
0.04
0.02
0.00
0
10
20
30
40
Time (hr)

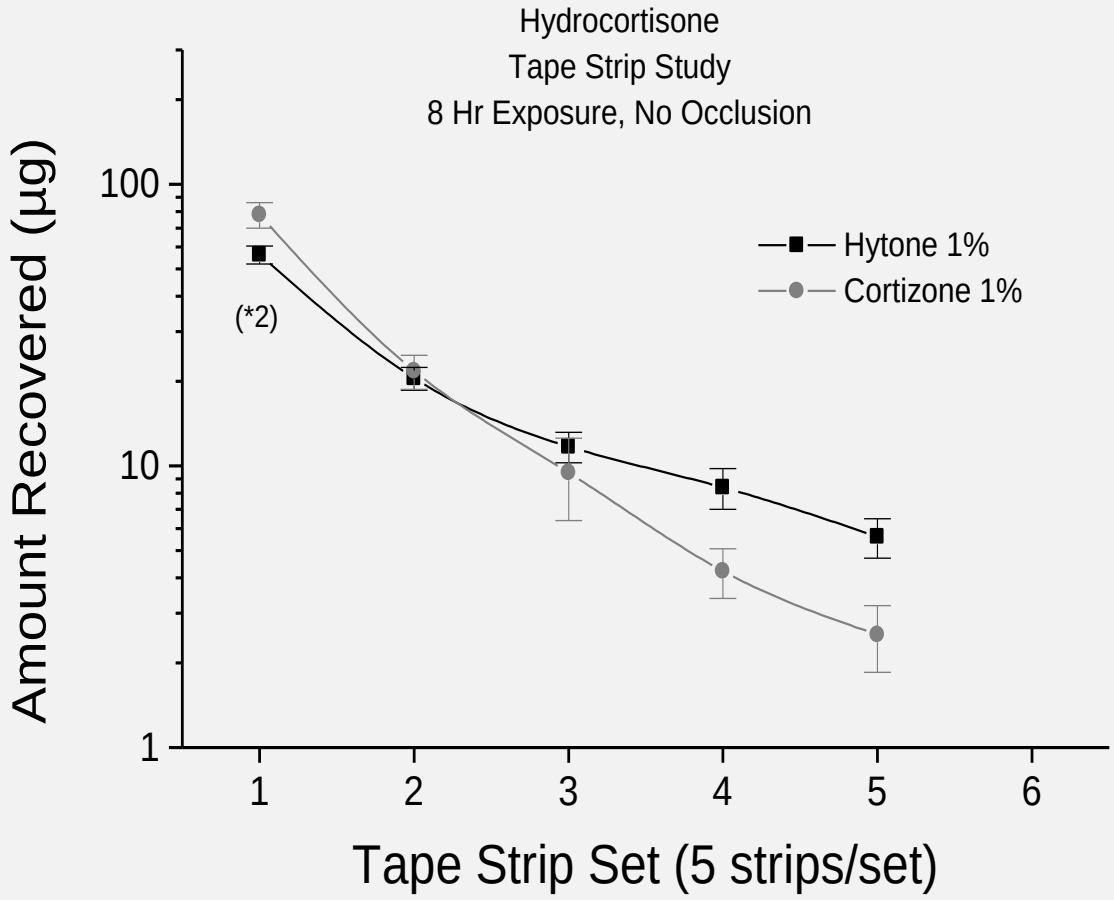
Topical BE: Tape Stripping
(Mean ± SEM)



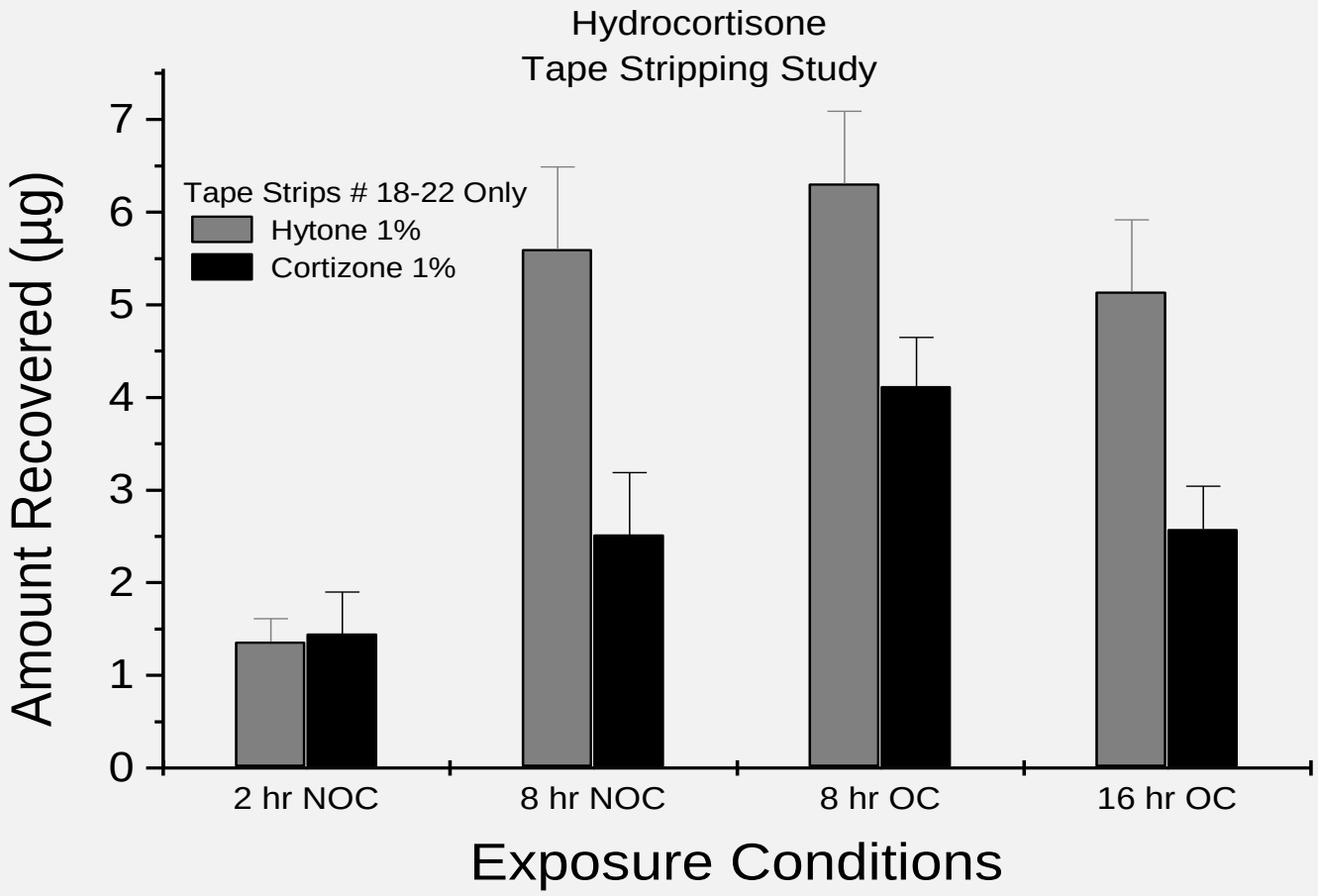
Method

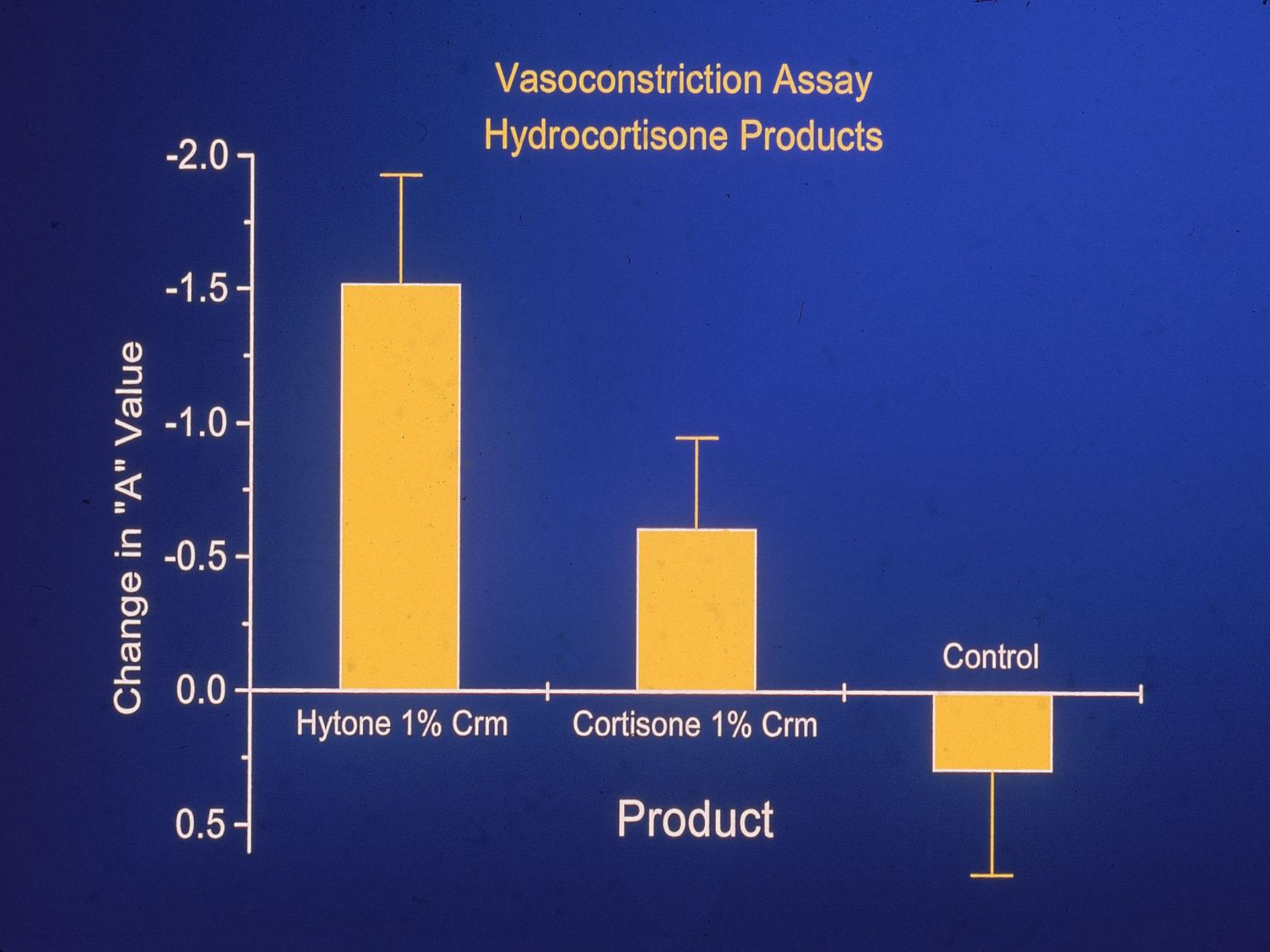
- 6 subjects
- Vent. Forearm
- A = 2 cm x 5 cm
- Dose = 1.9 mg/cm^2
- 1″ Transpore tape,
  22 strips
  pooled (2, 5, 5, 5, 5)
- Extract in methanol
- Assay by HPLC

Topical BE: Tape Stripping
(Mean ± SEM)

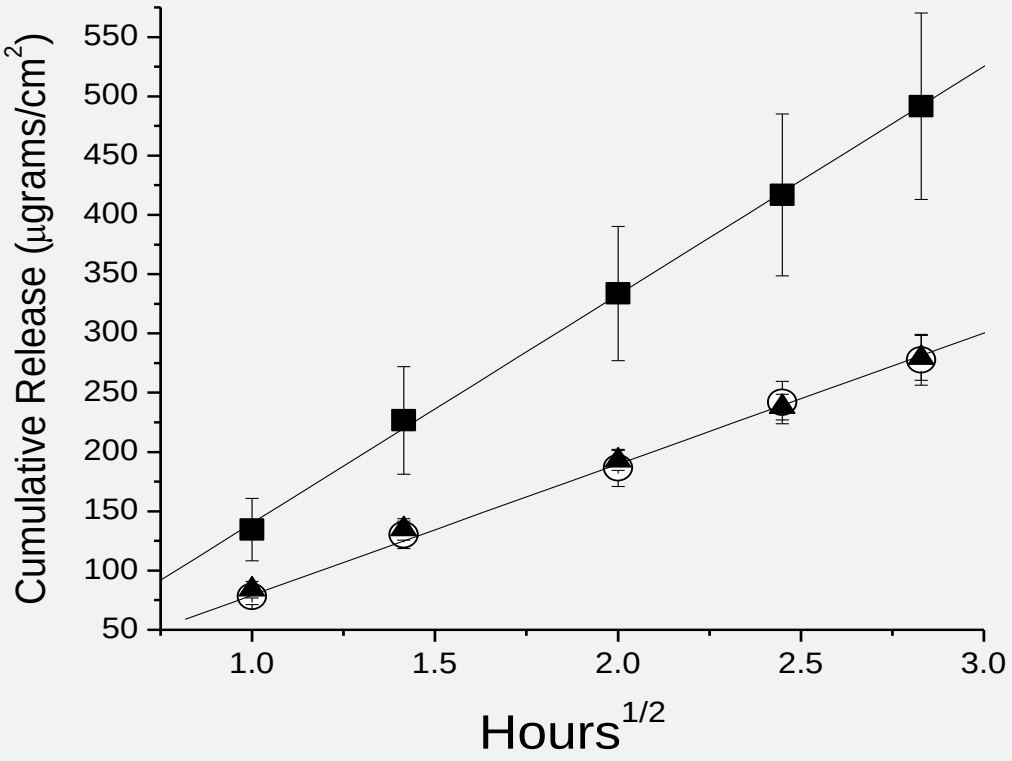


Topical BE: Tape Stripping
(Mean ± SEM)

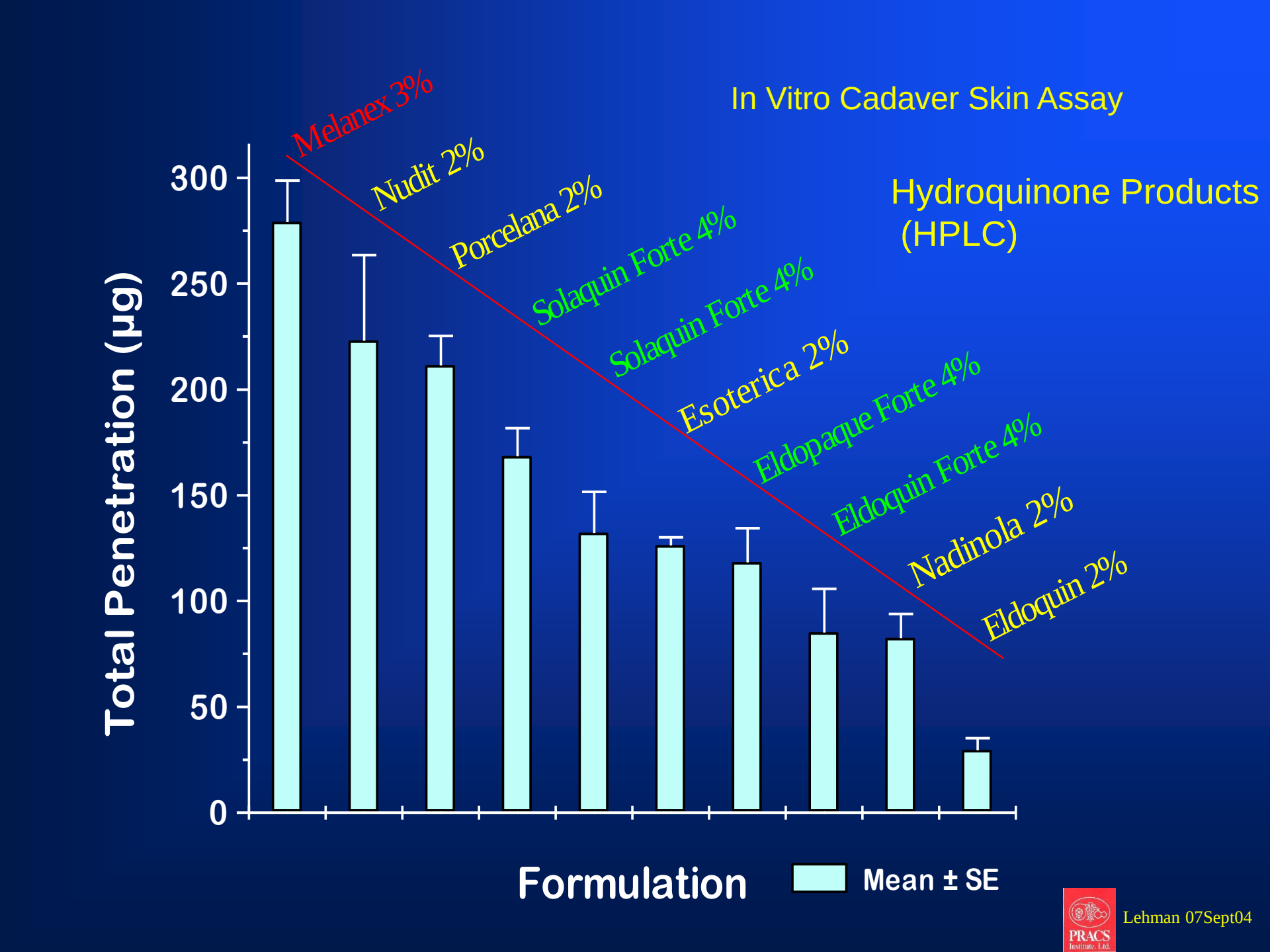



Vasoconstriction Assay
Hydrocortisone Products
Change in "A" Value
-2.0
-1.5
-1.0
-0.5
0.0
0.5
Hytone 1% Crm
Cortisone 1% Crm
Control
Product

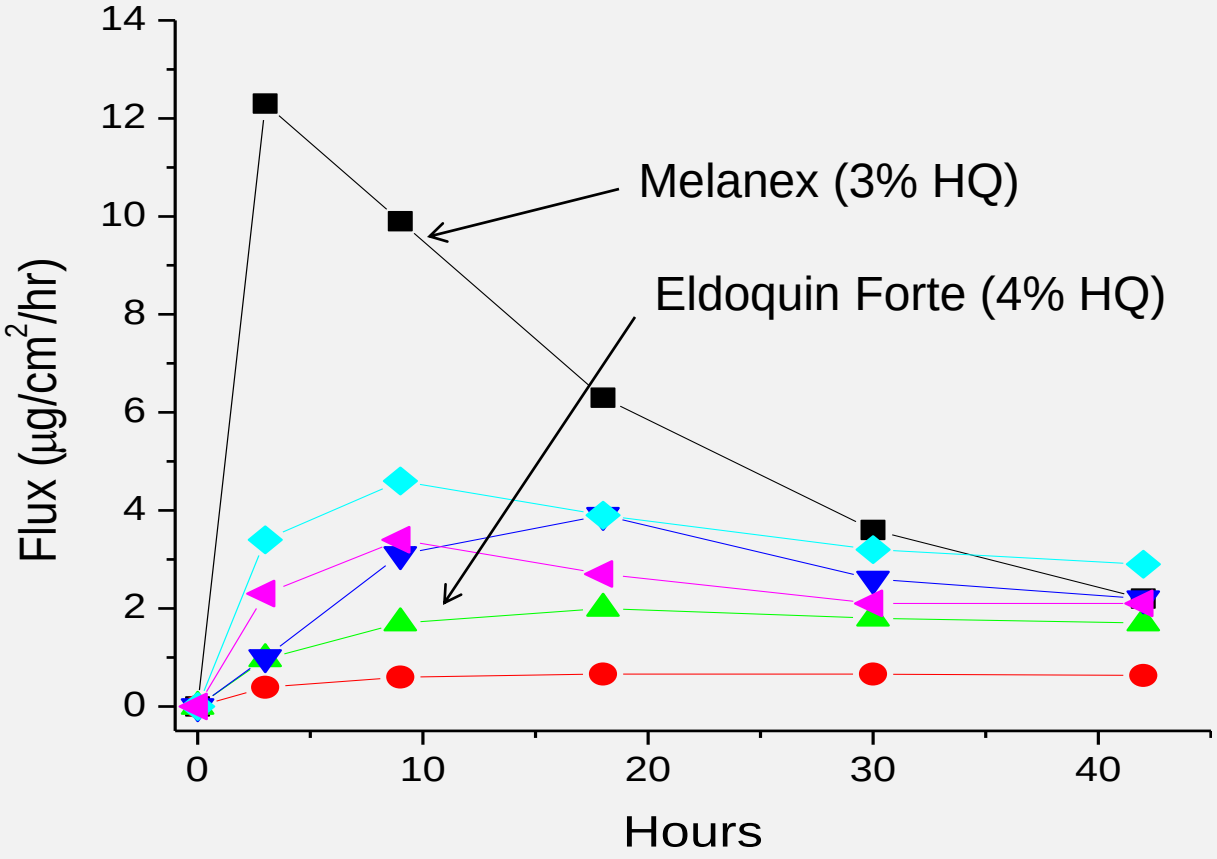
IVRT: Hydrocortisone



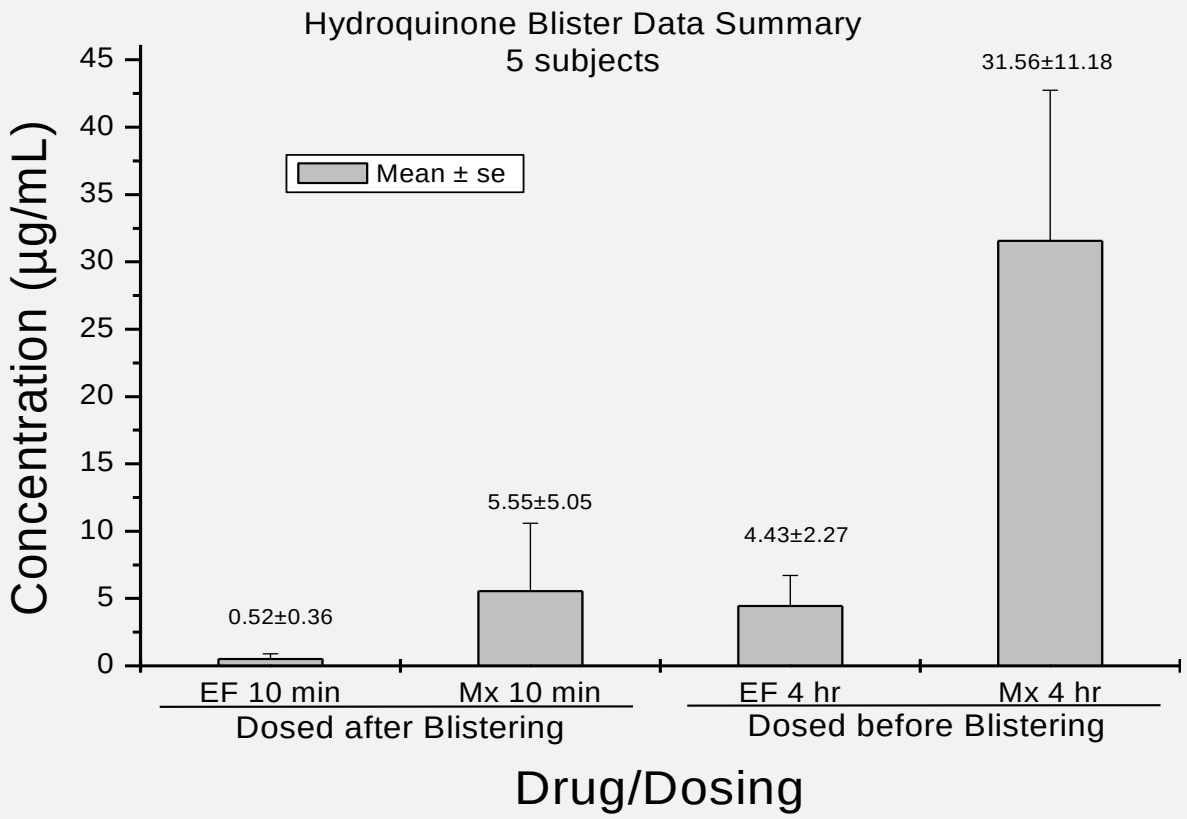
▲ Cortizone 10, ○ Hytone 1%, ■ Hytone 2.5%


In Vitro Cadaver Skin Assay
Hydroquinone Products
(HPLC)
Melanex 3%
Nudit 2%
Porcelana 2%
Solaquin Forte 4%
Solaquin Forte 4%
Esoterica 2%
Eldopaque Forte 4%
Eldoquin Forte 4%
Nadinola 2%
Eldoquin 2%
Total Penetration (µg)
300
250
200
150
100
50
0
Formulation
Mean ± SE

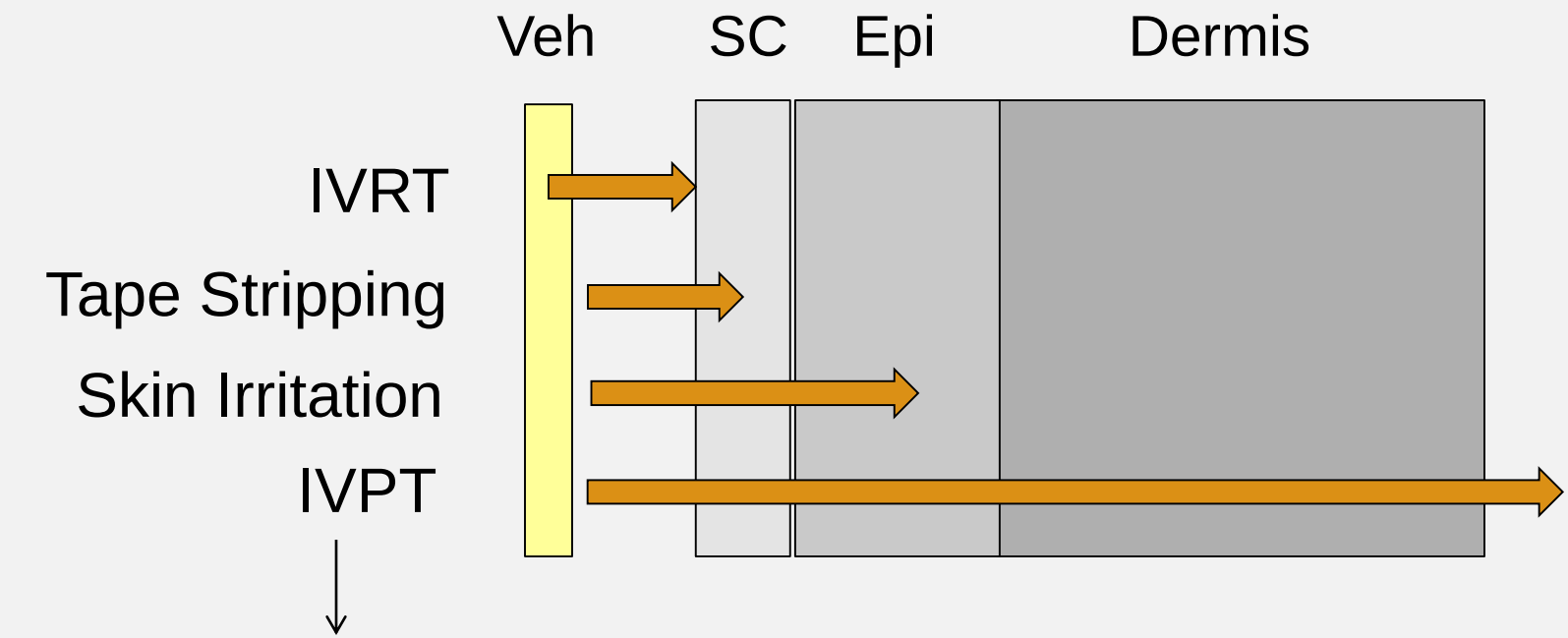
Hydroquinone Absorption



Hydroquinone Absorption



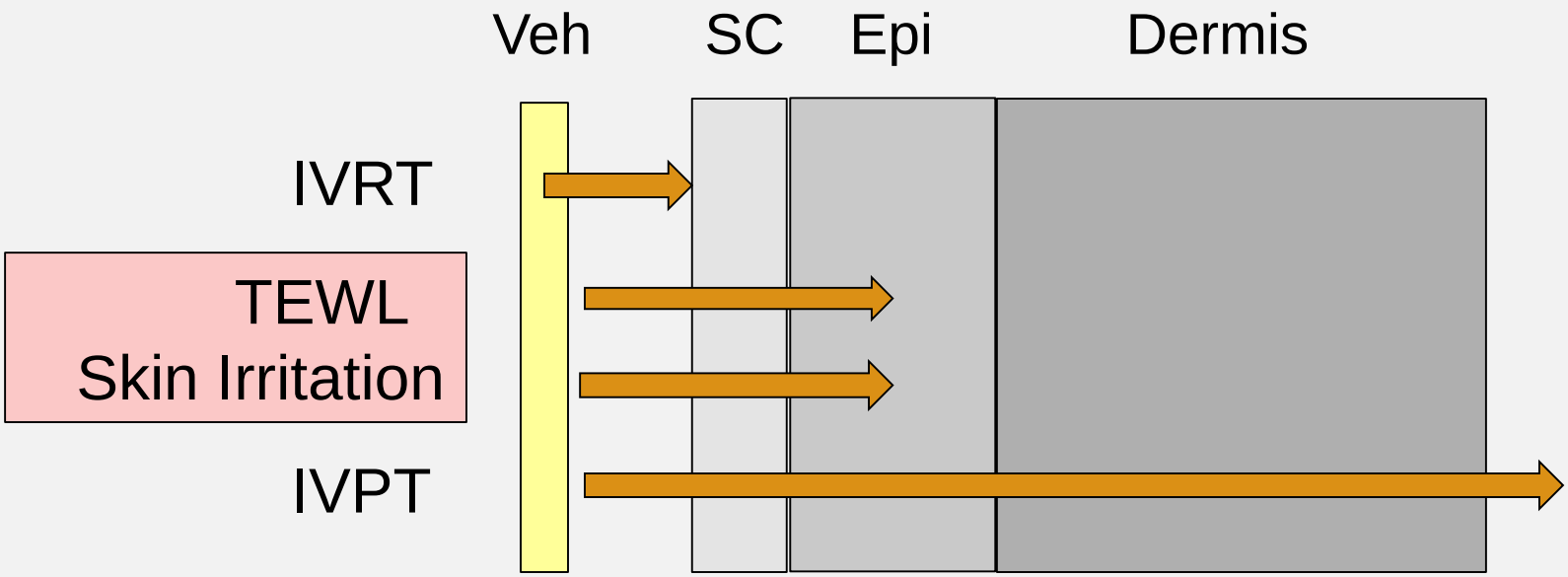
ANTIFUNGALS



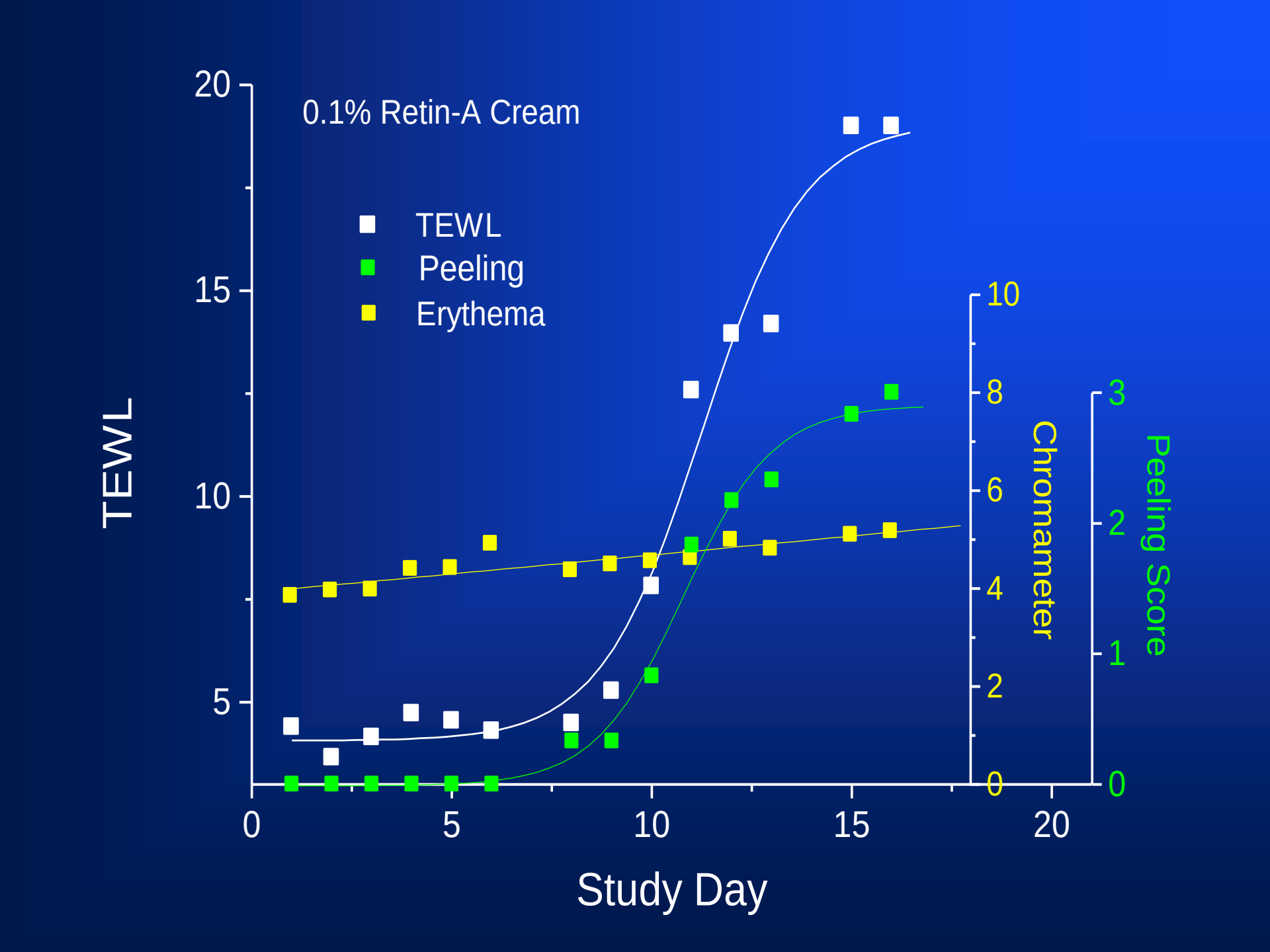
(1) sensitivity, (2) rate + extent of absorption , (3) relative systemic toxicity

Franz TJ, Lehman PA, Raney SG: Use of excised human skin to assess the bioequivalence of topical products. Skin Pharmacol and Physiol 22:276-286, 2009.

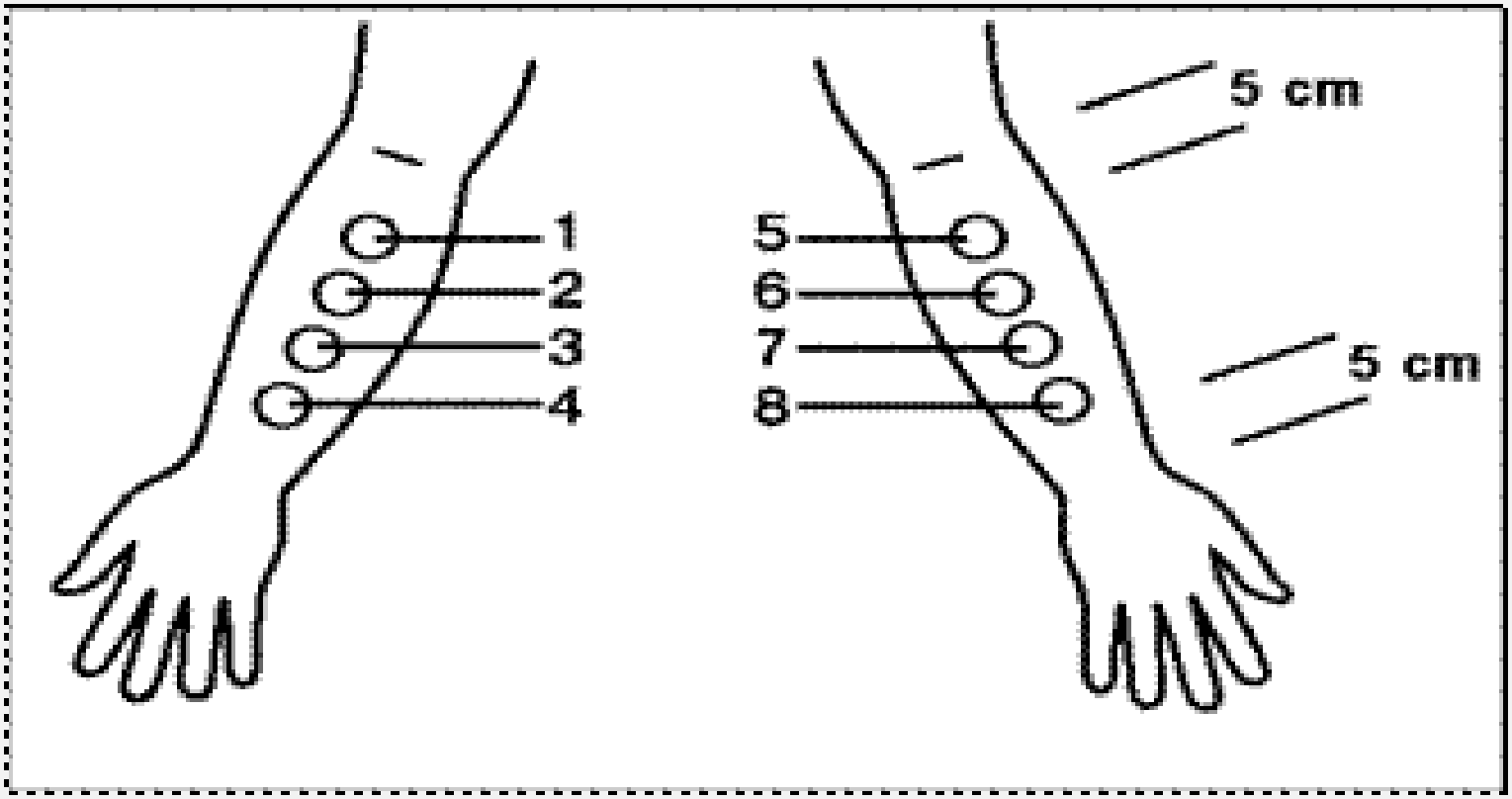
RETINOIDS



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

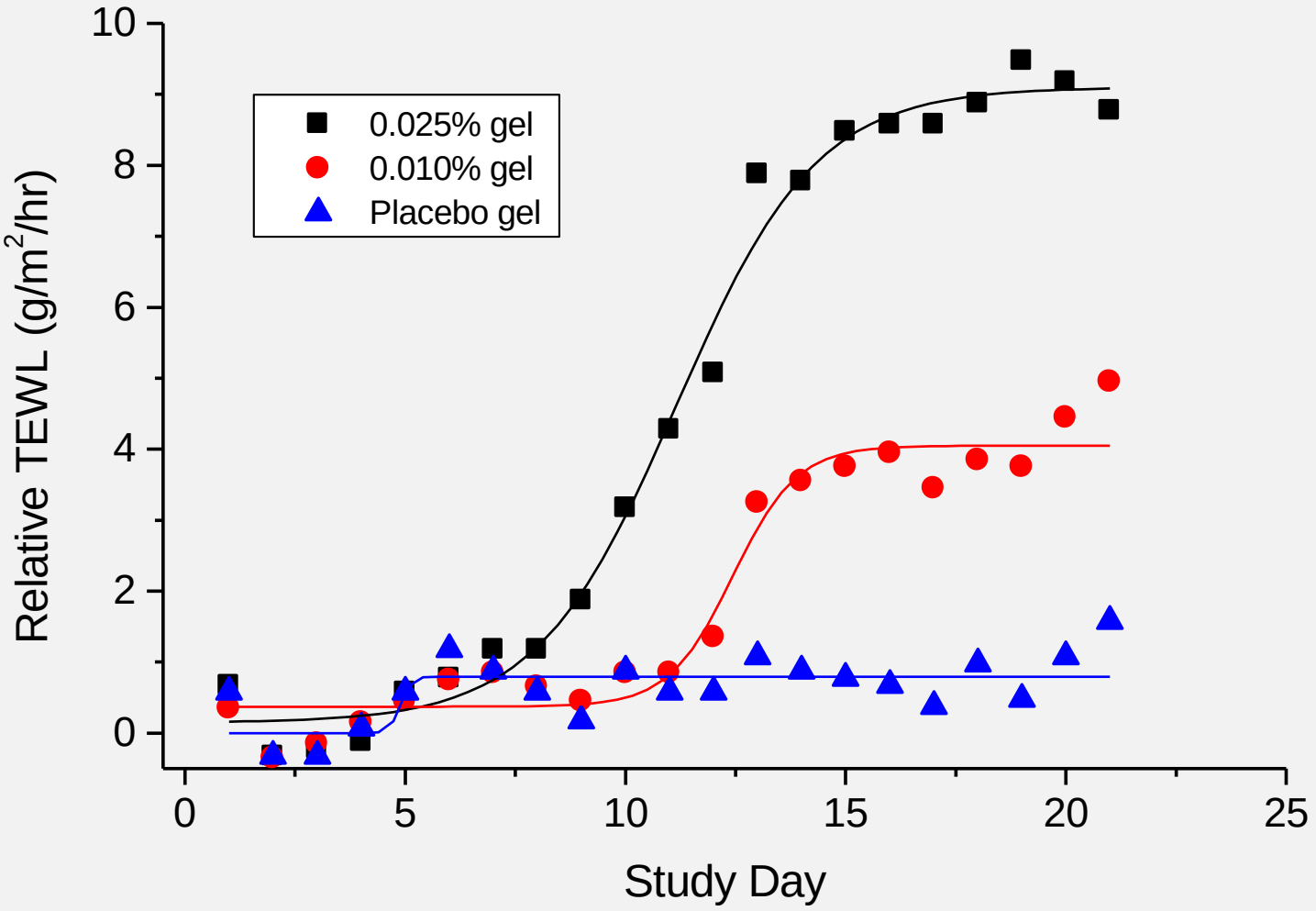

0.1% Retin-A Cream
TEWL
Peeling
Erythema
TEWL
Chromameter
Peeling Score
Study Day
0
5
10
15
20
0
2
4
6
8
10
0
1
2
3

Validation: TEWL Test
Tretinoin Gels

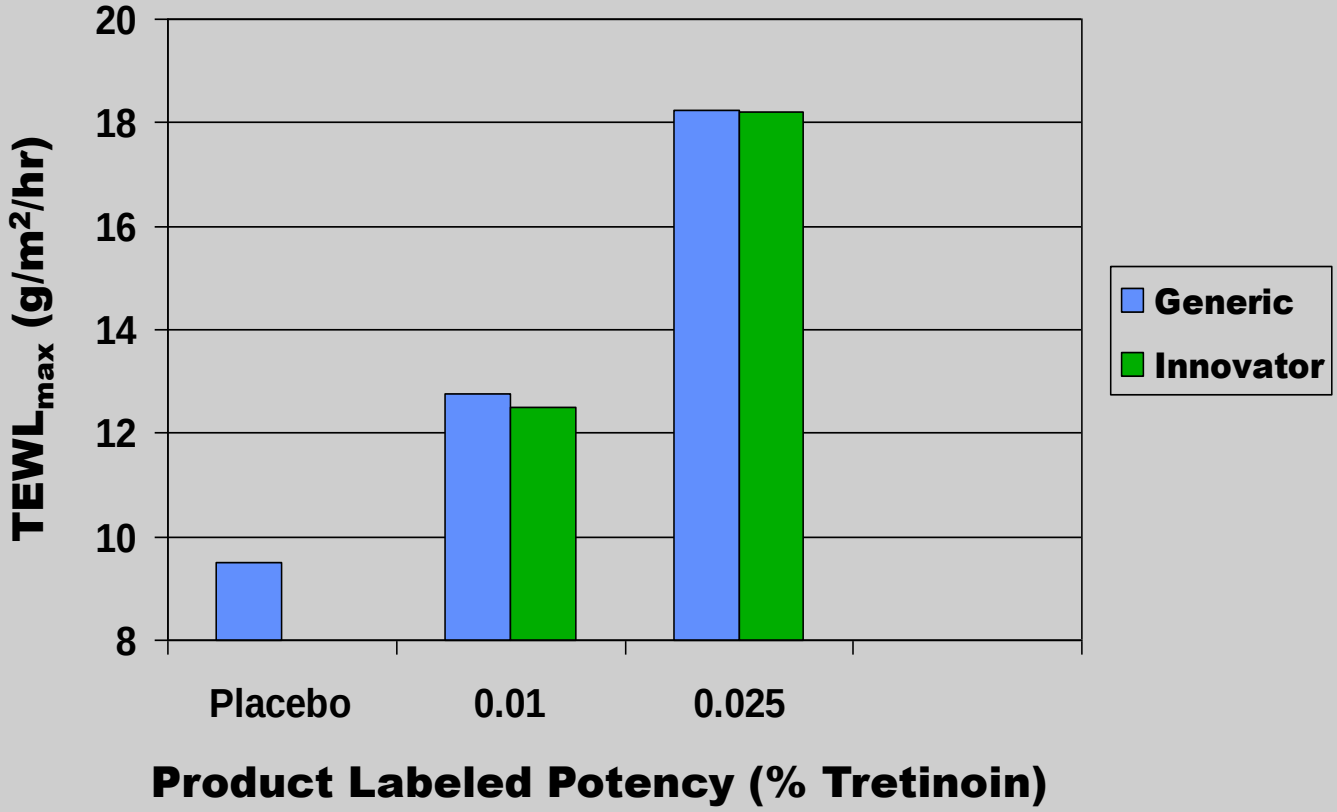


Two Primary Endpoints: (1) maximum transepidermal water loss achieved
(2) days to full peel (DTFP)

Tretinoin Gel: TEWL/Exfoliation



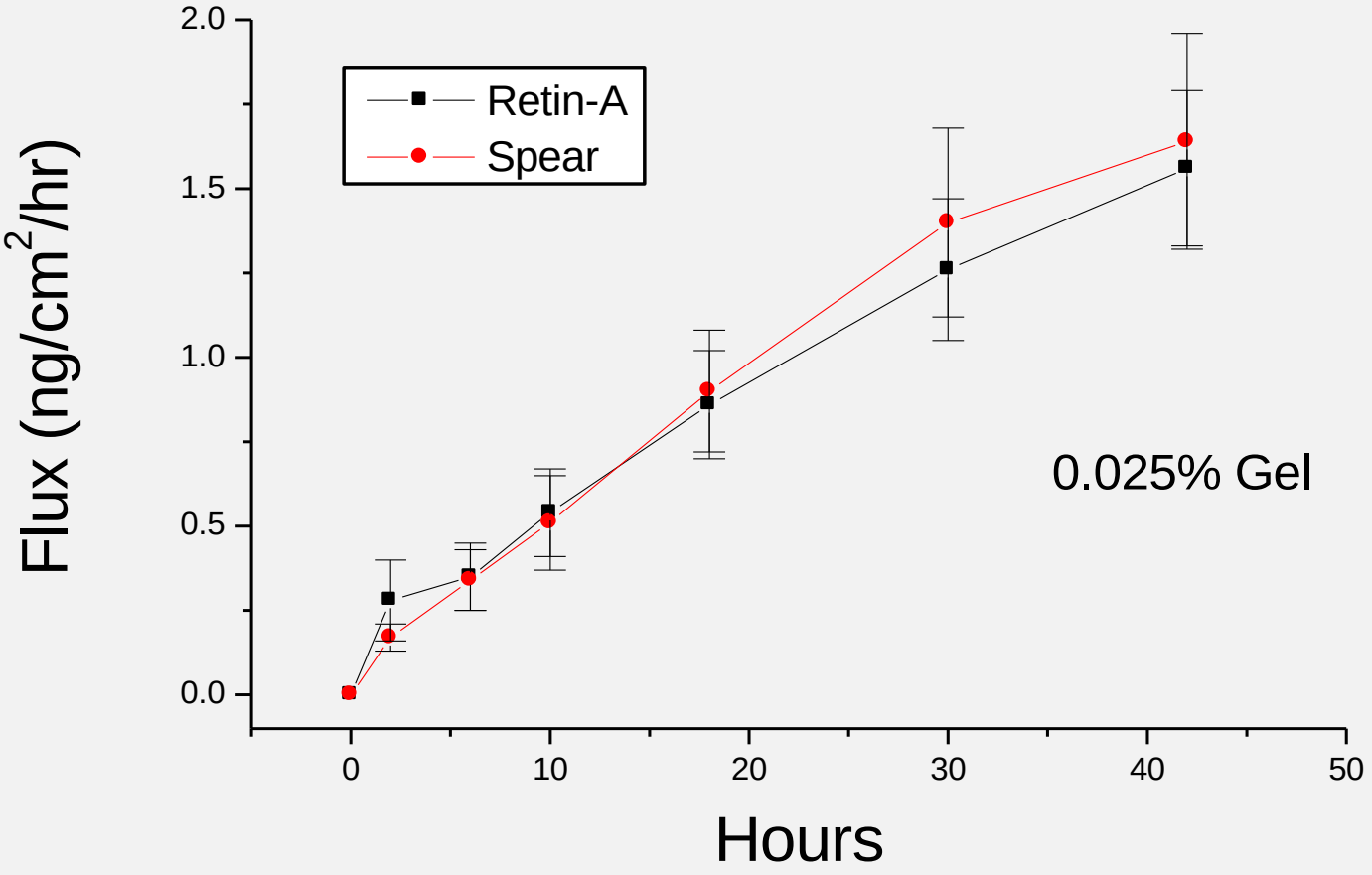
Validation: TEWL Test
Tretinoin Gels Maximum TEWL



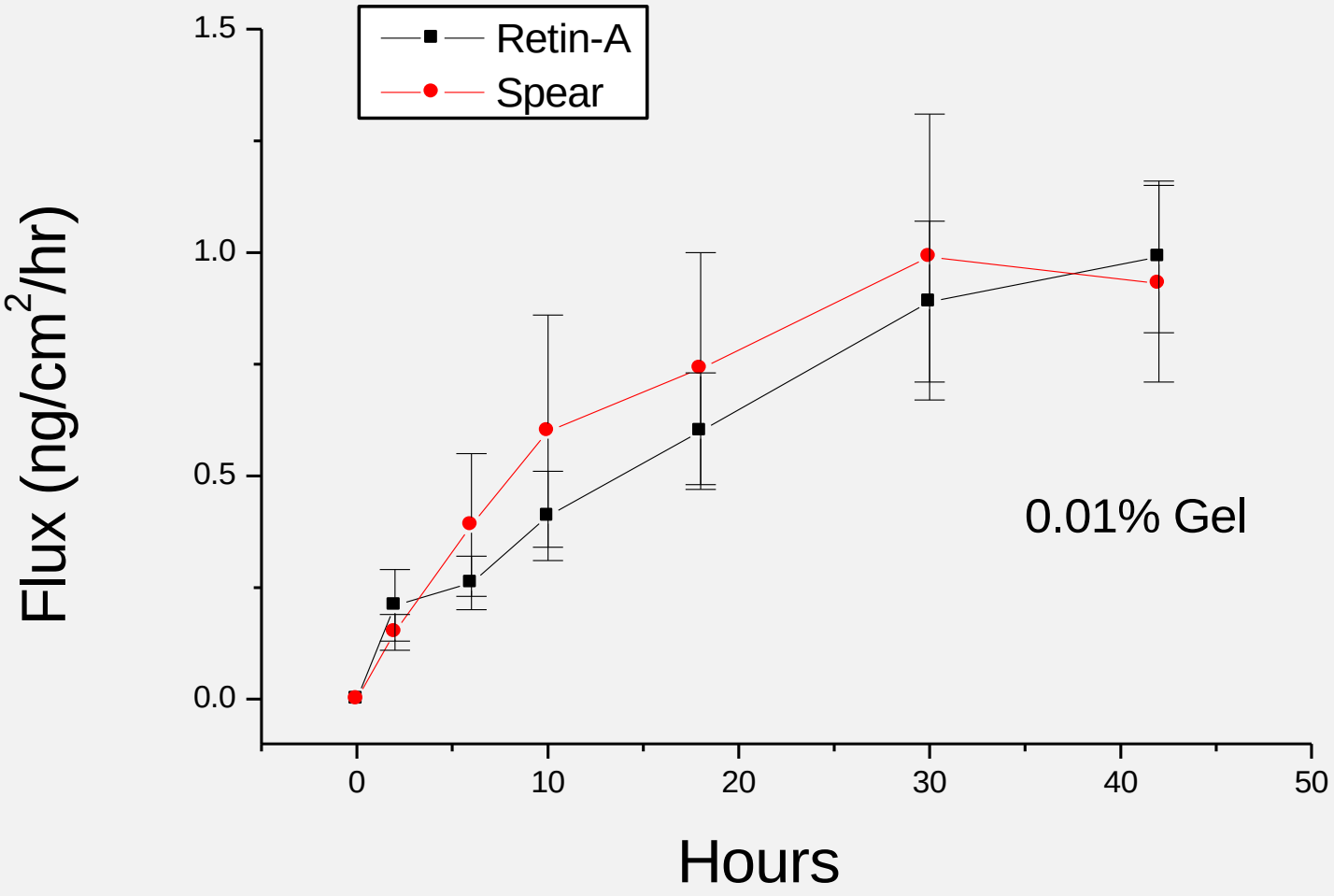
Validation: TEWL Test
Tretinoin Gels Statistical Analysis

- 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%)

Validation: IVPT vs Clinical Trial Tretinoin Gels



Validation: IVPT vs Clinical Trial Tretinoin Gel



Validation: Skin Permeation Test Tretinoin 0.01% Gel

	Mean (Ln transformed data)			90% CI On Ratio
	Spear	Retin-A	Ratio	
AUC	3.0752	3.0072	1.0226	97.07 - 107.46
J_{max}	0.6268	0.6173	1.0378	92.53 – 115.05
T_{max}	3.6118	3.6331	1.0430	92.23 – 116.37

Franz TJ, Lehman PA, Raney SG: Use of excised human skin to assess the bioequivalence of topical products. Skin Pharmacol and Physiol 22:276-286, 2009.

Validation: Skin Permeation Test Tretinoin 0.025% Gel

	Mean (Ln transformed data)			90% CI On Ratio
	Spear	Retin-A	Ratio	
AUC	3.4921	3.4709	1.02798	95.14 – 110.45
J_{max}	0.9058	0.8840	1.11481	95.08 – 127.88
T_{max}	3.6642	3.7248	0.98389	97.26 – 99.52

Franz TJ, Lehman PA, Raney SG: Use of excised human skin to assess the bioequivalence of topical products. Skin Pharmacol and Physiol 22:276-286, 2009.

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.