16 | MAR | 2022

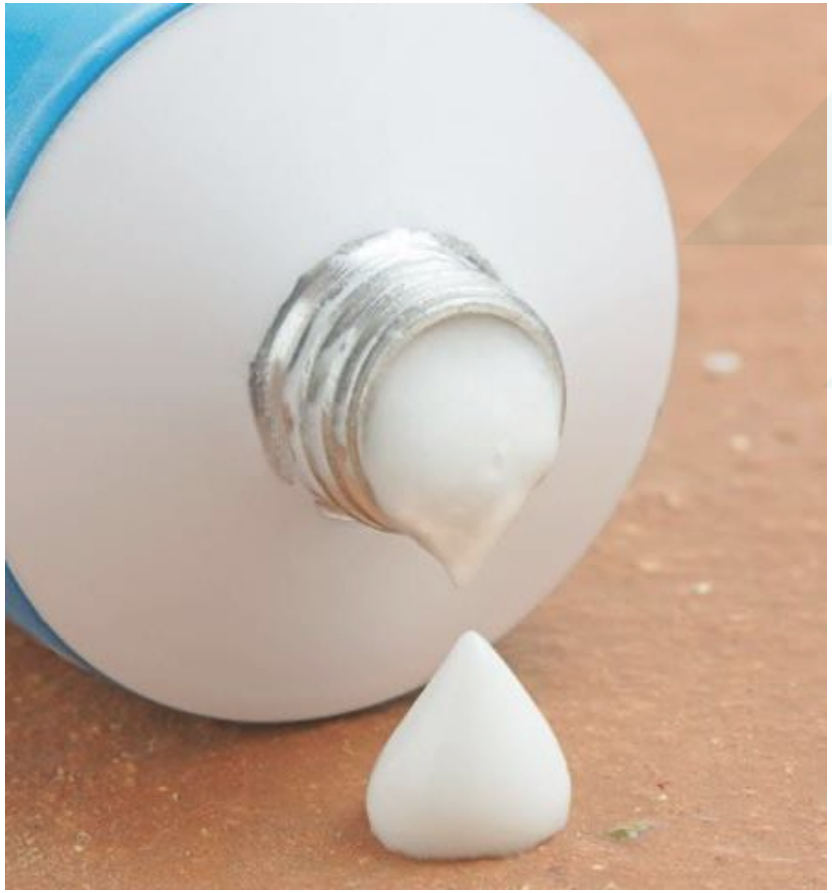
proderm

Phase 1 Studies for Evaluating the Dermal Safety of Topical Products

Our ambition? Excellence.

Klaus-P Wilhelm

Topical Products
General Considerations



- Targeted/ Locally acting
- Reduced/no systemic effects
- Vehicle effect > No true placebo
  - both in terms of efficacy as well as local tolerance
- Formulating challenges
  - Solubility/ Release
  - Delivery of actives into the skin
- Local tolerance
  - active & excipients !

Dermal Safety Testing

Key Objectives

- Aid product development
  - Evaluating different formulas
  - Risk assessment under standardized/maximized exposure

- Regulatory requirements (Phase 1 profile for topical formulations)
  - Cumulative Irritation Potential
  - Sensitization Potential
  - Phototoxicity Potential*
  - Photosensitization Potential*

*If formulation absorbs in UV spectrum (molar extinction coefficient (MEC) greater than 1000 L mol-1 cm-1 (between 290 and 700 nm)

(S10 Photosafety Evaluation of Pharmaceuticals , Guidance for Industry -- U. S. FDA, January 2015 ICH)

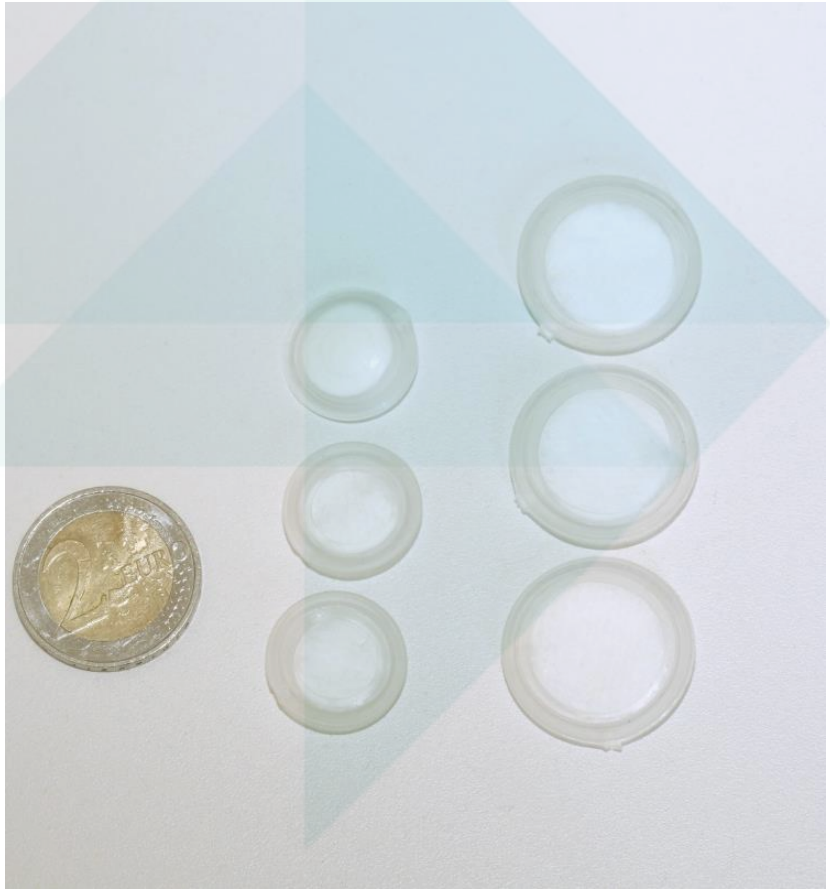
Dermal Safety Testing

General Notes/ Commonalities

- Internationally generally accepted standard study designs
  - Combination studies possible (but not necessarily advisable)
- Patch tests with maximized exposure conditions to detect specific responses
- Intraindividual within subject comparison (allowing to test >1 product/ subject)
- Visual scoring by expert graders (confirmed by dermatologists)
- Single center/ simultaneous inclusion of panel
- Poll 3: Prioritization/ Timing of Dermal Safety Testing in Clinical Development Plan

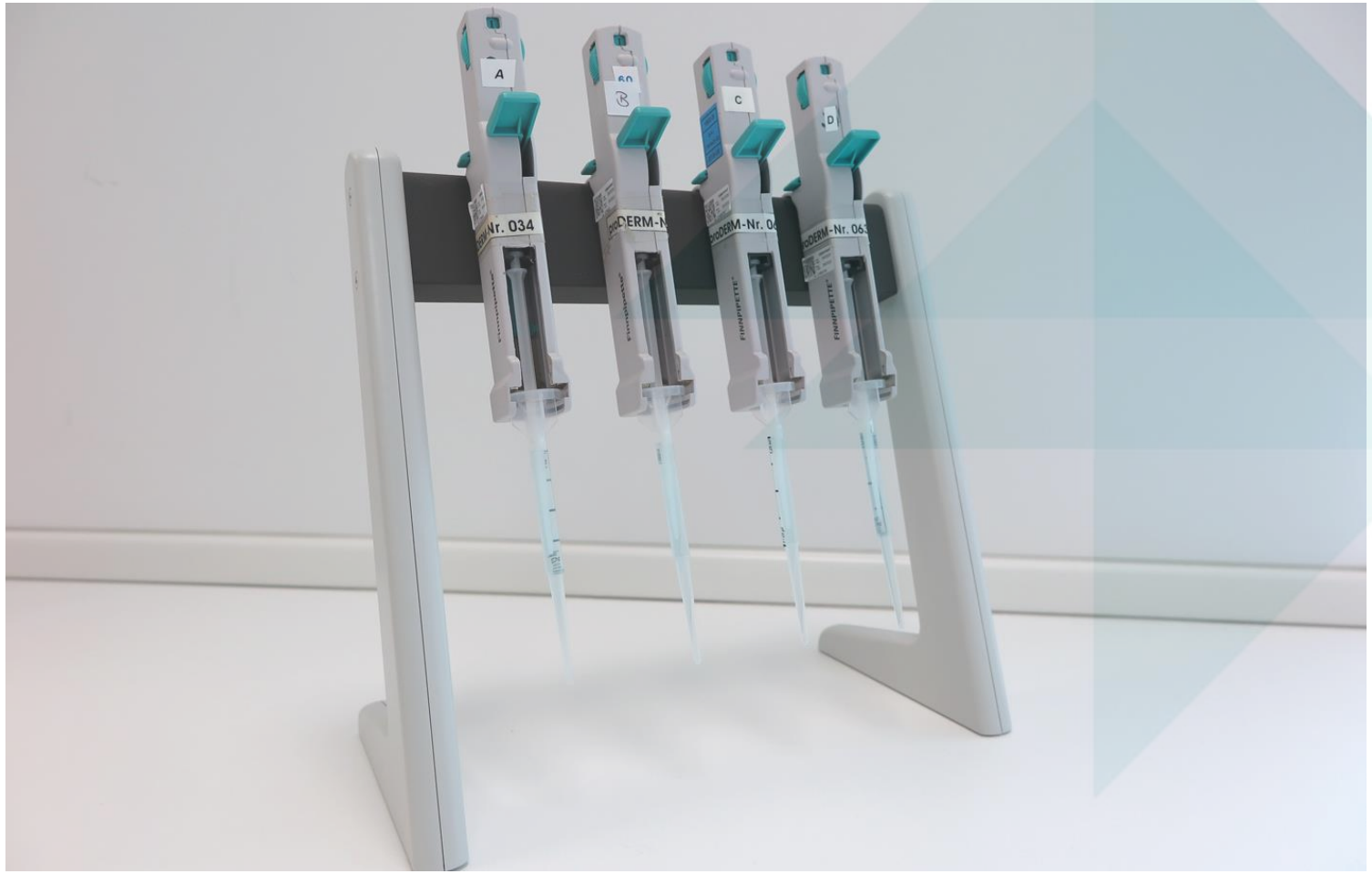
Patch Test Systems

Finn Chambers®



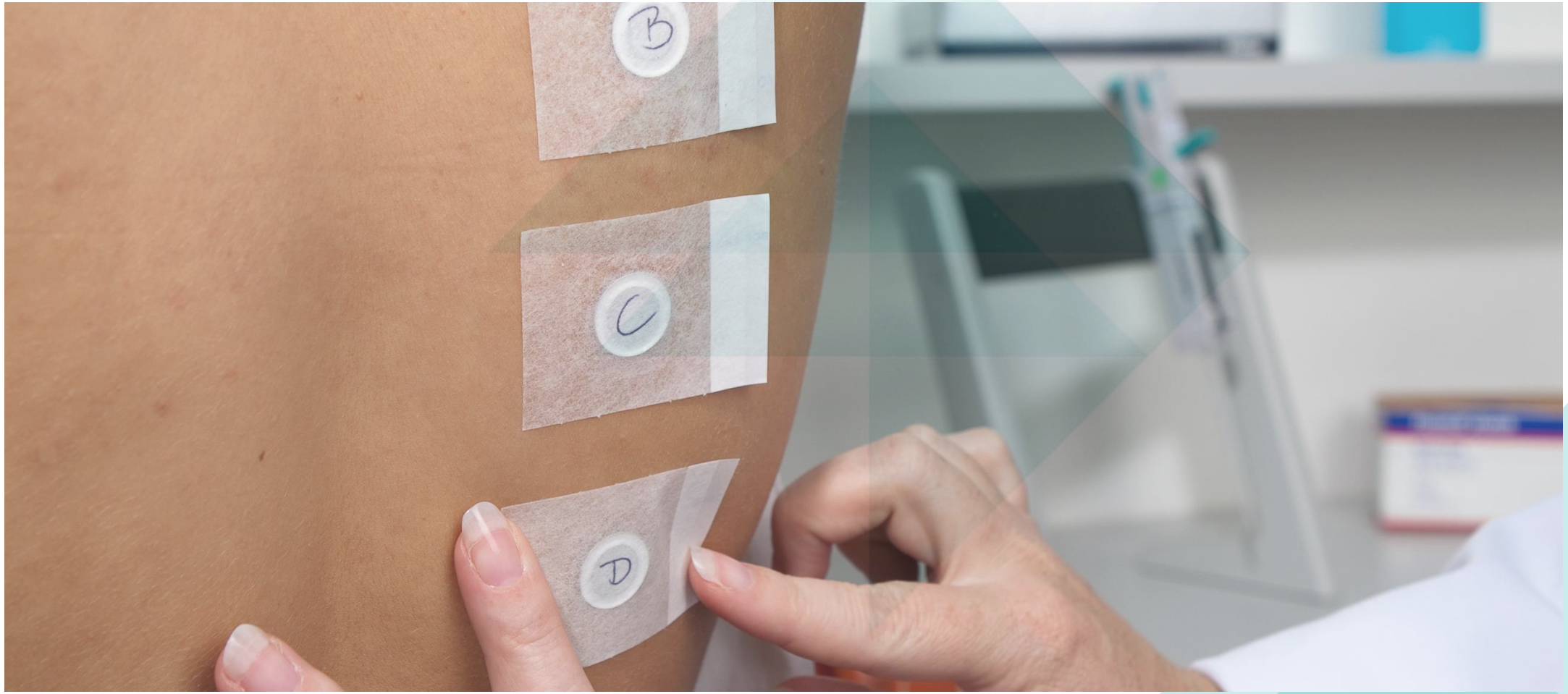
Hilltop Chambers®

Application



- Preferably by Volume, typically 0.2 ml
- Custom tailored Eppendorf Research Pipettes

Application



Clinical Grading / Scoring

Scoring Scales & Procedures

- Global assessment vs. separate grading of various attributes
- All scales are NON-linear (ordinal)
- If score > threshold: discontinued patching and LVCF (alt. max VCF)
- Inter-Grader reliability is paramount
  - Training & annual re-training by Dermatologist, Allergologist
  - Same grader should grade same subject throughout the course of the study (pre-defined backup)
  - Graders need to be blinded (observer-blind)

Clinical Grading / Scoring

Principles & Considerations

- Standard ambient conditions (temperature & lightening)
- Acclimation (rest) period before grading
- Start with overview from slight distance (approx. 1 m) to get impression of general skin pattern
- Grade each site separately
- Palpate (touch) if dermal response (edema, papules are suspected/present)
- Beware of tape-reactions
- Dermatologist: Review of all 'above-threshold-reactions'/grading at select time-points
- Photo documentation of all 'above-threshold reactions' recommended

Phase 1 - Standard Protocols for Dermal Safety

- Cumulative Irritation (21 Day Irritation Test)
- Sensitization (HRIPT)
- Phototoxicity
- Photosensitization

Cumulative Irritation Potential

21-Day-Irritation Patch Test: Test Design

- Subjects: 35 (30 finishing) healthy volunteers
- Duration: 3 weeks
  21 applications for 23 h (alt. 3 x 5 applications for 23 h)
- Evaluations: Daily: 30-60 min after patch removal
- Exposure: Occluded patch or semi-occluded
- Test Products: max. 10: Active, Vehicle, positive & negative Controls, Reference(s) optional
- Variations
  14-day design
  Pre-damaged (tape stripped skin)

Clinical Grading / Scoring

Cumulative Irritation

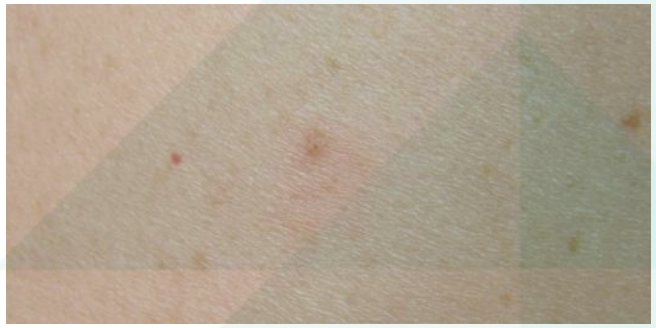
0	=	no apparent cutaneous involvement
0.5	=	equivocal reaction
1	=	slight erythema with or without edema
2	=	moderate erythema, edema with or without papules
3*	=	severe erythema, edema with or without papules
4*	=	severe erythema, edema with vesicles or blisters

* discontinue patching: LVCF

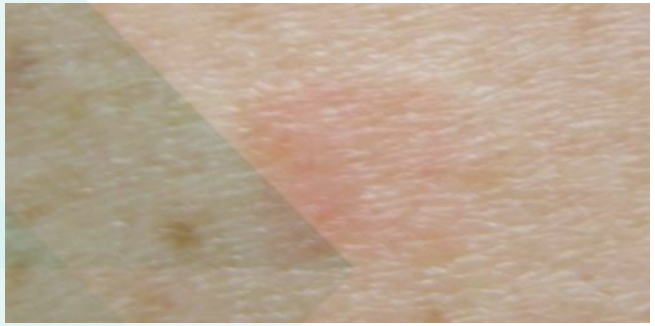
Photographic Scale

Cumulative Irritation Score

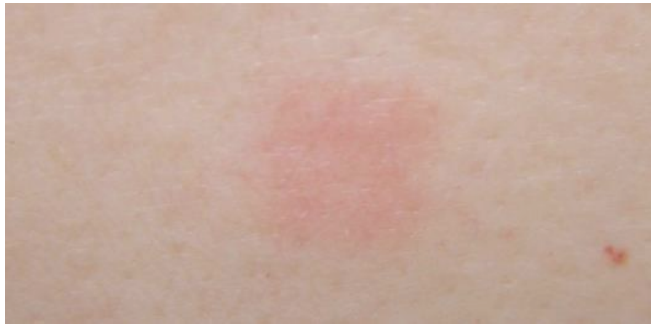
0 = No visible skin reaction



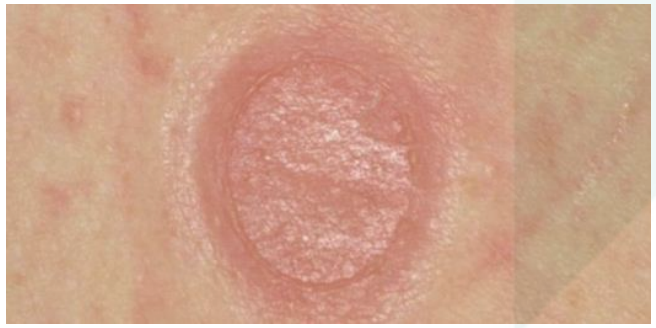
0.5 = Doubtful skin reaction



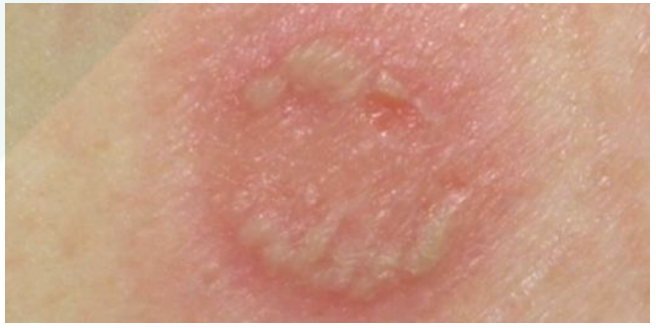
1 = Slight erythema



2 = Moderate erythema



3* = Severe erythema



4* = Severe erythema, edema

Sensitization Potential

Human Repeat Insult/ Epicutaneous Patch Test (HRIPT/HREPT)

- Schwartz, 1941
- Repeat Insult Shelanski, 1951, 1953
- Repeat Insult Draize, 1944, 1951, 1953
- Modified Draize (Marzulli & Maibach), 1973, 1974

HRIPT
Study Design

Phases	Induction							Rest		Challenge					
Week	1 - 3							4 - 5		6					
Days	1 8 15	2 9 16	3 10 17	4 11 18	5 12 19	6 13 20	7 14 21	22	23-35	36	37	38	39	40	41
Patch Application	✔ ✔ ✔		✔ ✔ ✔		✔ ✔ ✔					naive ✔ site					
Patch Removal	- ✔ ✔		✔ ✔ ✔		✔ ✔ ✔			✔				✔			
Scoring	- ✔ ✔		✔ ✔ ✔		✔ ✔ ✔			✔				✔	✔	✔	✔

Sensitization Potential

HRIPT: Test Design

- Subjects: 230 (200 finishing) healthy volunteers
- Exposure: Occluded patch or semi-occluded
- Test Products: max. 4: Active, Vehicle, Reference(s) optional
- Duration: 6 weeks*

*Re-Challenge as needed, > 4 weeks after Challenge

Clinical Grading / Scoring

Sensitization

Skin appearance (dermal response)	Other effects
0 = no evidence of irritation 1 = minimal erythema, barely perceptible 2 = definite erythema, readily visible and minimal edema or minimal papular response 3 = erythema and papules 4 = definite edema 5 = erythema, edema and papules 6 = vesicular eruption 7 = strong reaction spreading beyond test site	N (0) = no other observations A (0) = slight glazed appearance B (1) = marked glazed appearance C (2) = glazing with peeling and cracking F (3) = glazing with fissures G (3) = film of dried serous exudate covering all or part of plaster application site H (3) = small petechial erosions and/or scabs

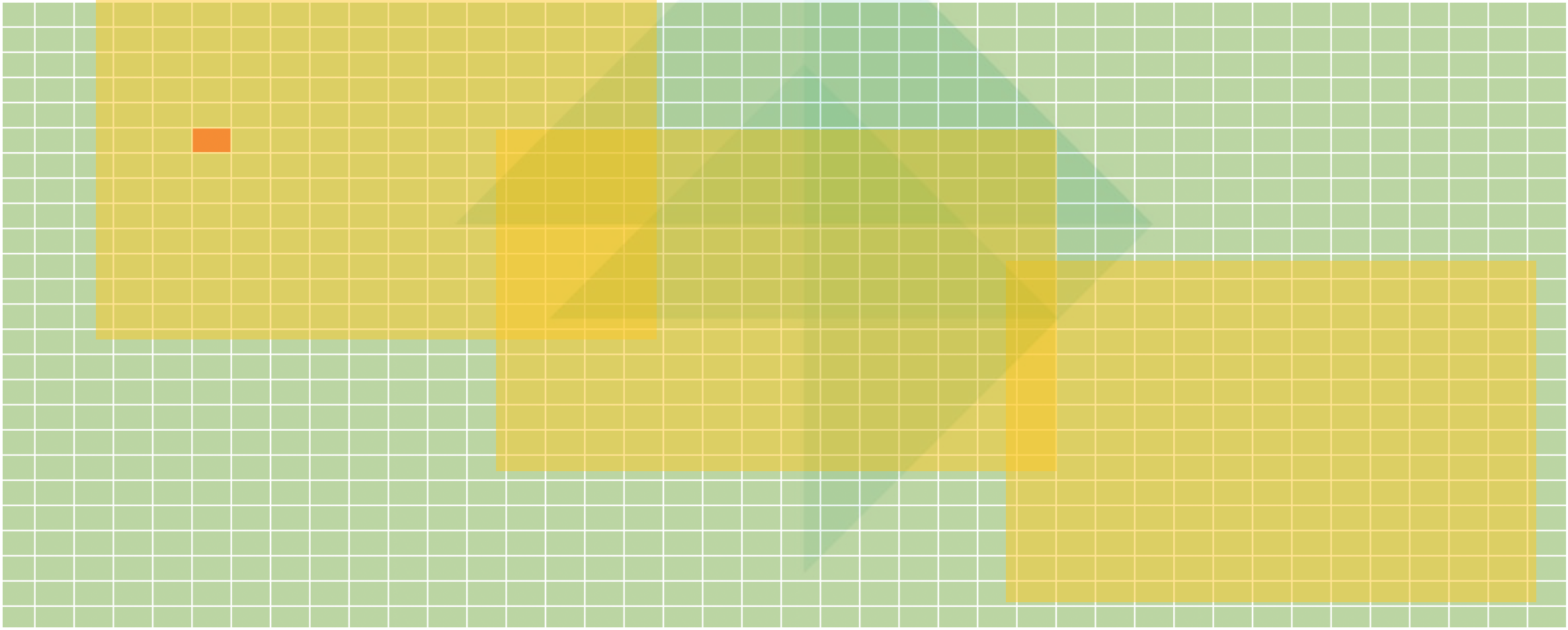
FDA 2018 Guidance for Industry: Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs; Draft guidance

HRIPT: Statistical Considerations

Why 200 Evaluable Subjects

- Only genetically predisposed individuals get sensitized
- Statistical Considerations
  - If an effect (sensitization) is not observed in a study population how certain is this effect absent in the general population ?

HRIPT: Study Population vs. General Population



HRIPT: Statistical Considerations

Why 200 Evaluable Subjects

- Only genetically predisposed individuals get sensitized
- Statistical Considerations
  - If an effect (sensitization) is **not observed** in a study population how certain is this effect **absent in the general population?**
- In the absence of sensitization in a test panel of 200 subjects the 95 % upper confidence boundary for sensitization in the general population would be 1.5 % (double the boundary for half the test panel size, i.e. 3 % !)

Interpretation of Data in a Sensitization Study

Irritation or Sensitization

Klaus-Peter's Rule

- Challenge Score > Induction Score
- Challenge Score @72h ≥3 (papules) (spreading beyond test site)
- Challenge Score @72h (96, 120h) ≥ @48h, i.e. Crescendo reaction
- All of the above: indicative of Sensitization, i.e. no re-challenge necessary

Interpretation of Data in a Sensitization Study

FDA Guidance

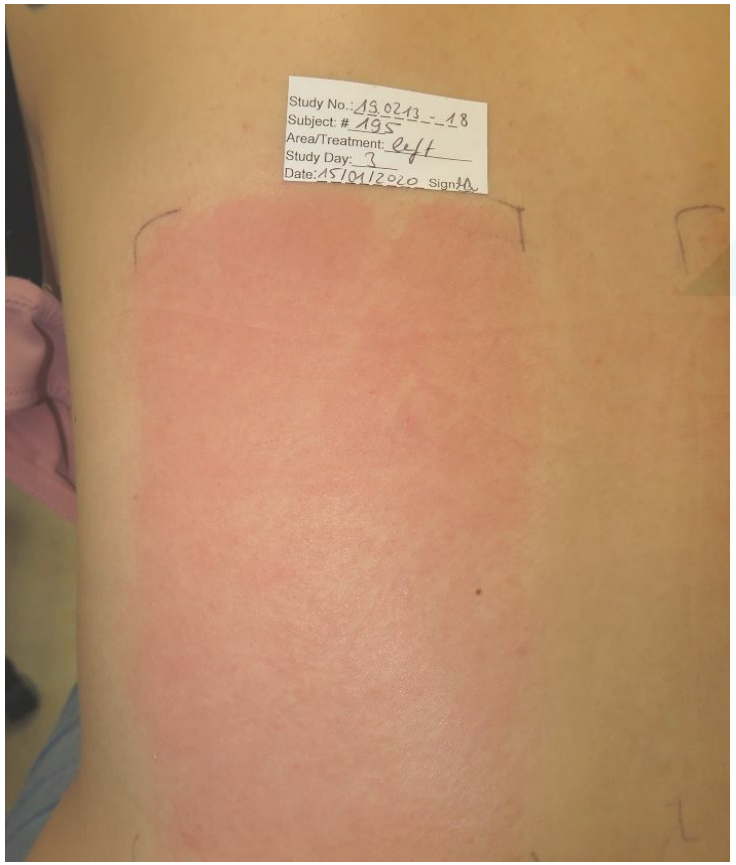
A subject should be considered potentially sensitized if all the following criteria are met

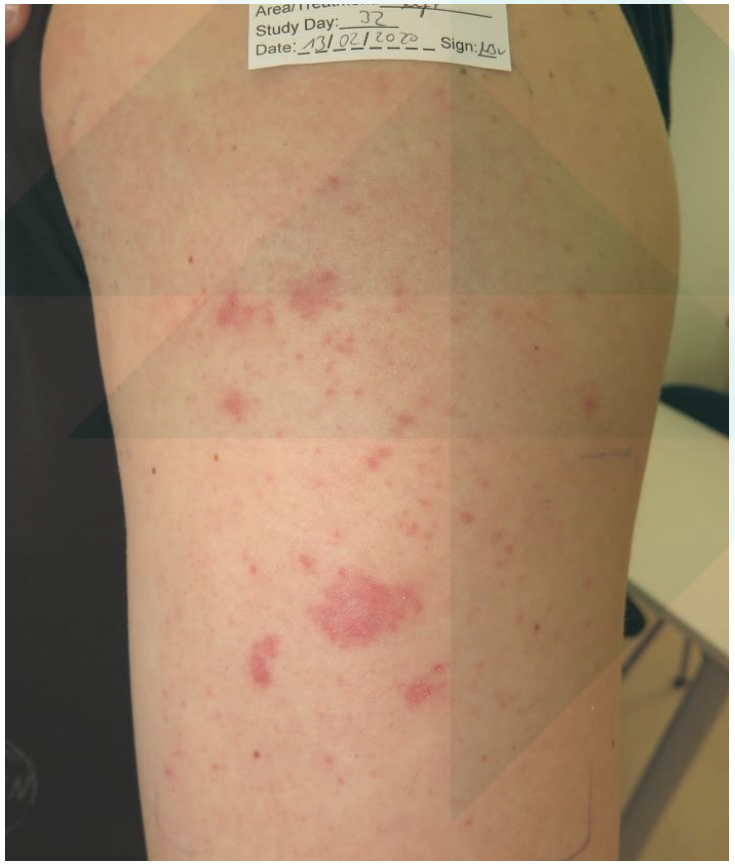
- Skin reactions that resolve before 48 hours are generally considered to be caused by irritation rather than by sensitization
- The subject has a combined irritation score of ≥ 2 at their last evaluation during the challenge phase
- The above two criteria were met during both the challenge phase (and — if performed — during the re-challenge phase)

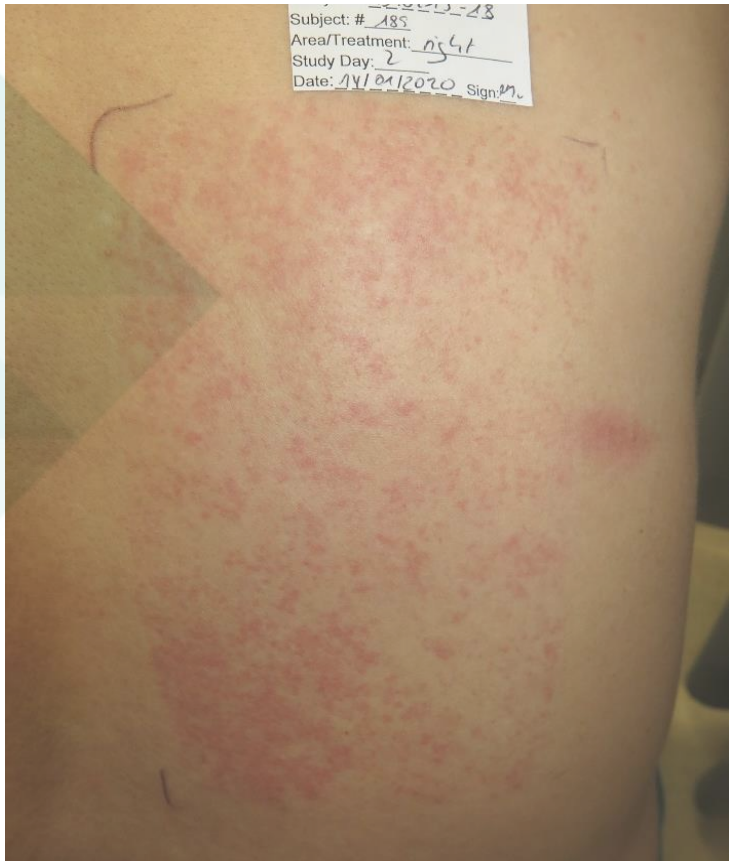
FDA 2018 Guidance for Industry: Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs; Draft guidance

Reactions differ

Photo documentation of positive reactions advisable !

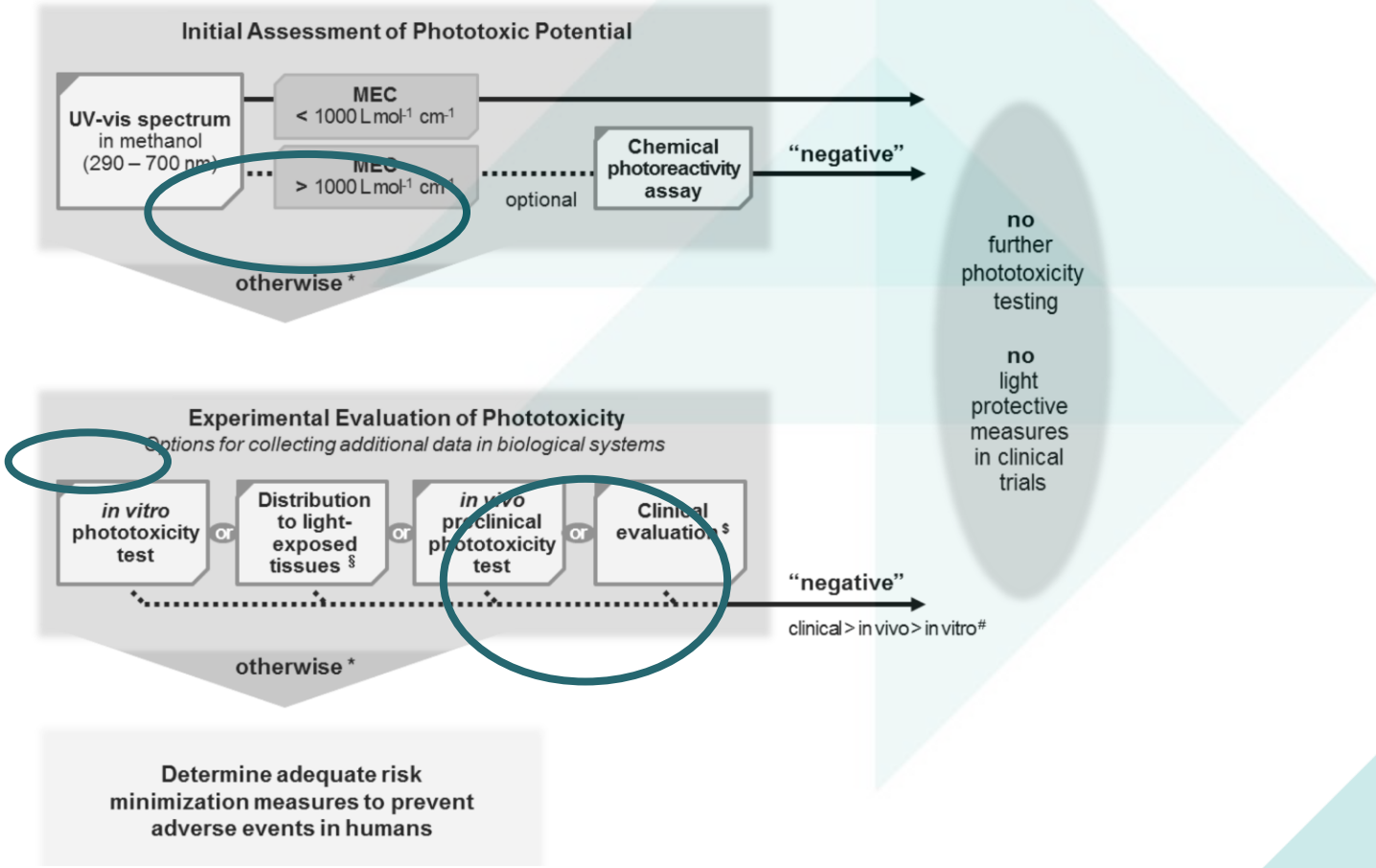






S10 Photosafety Evaluation of Pharmaceuticals

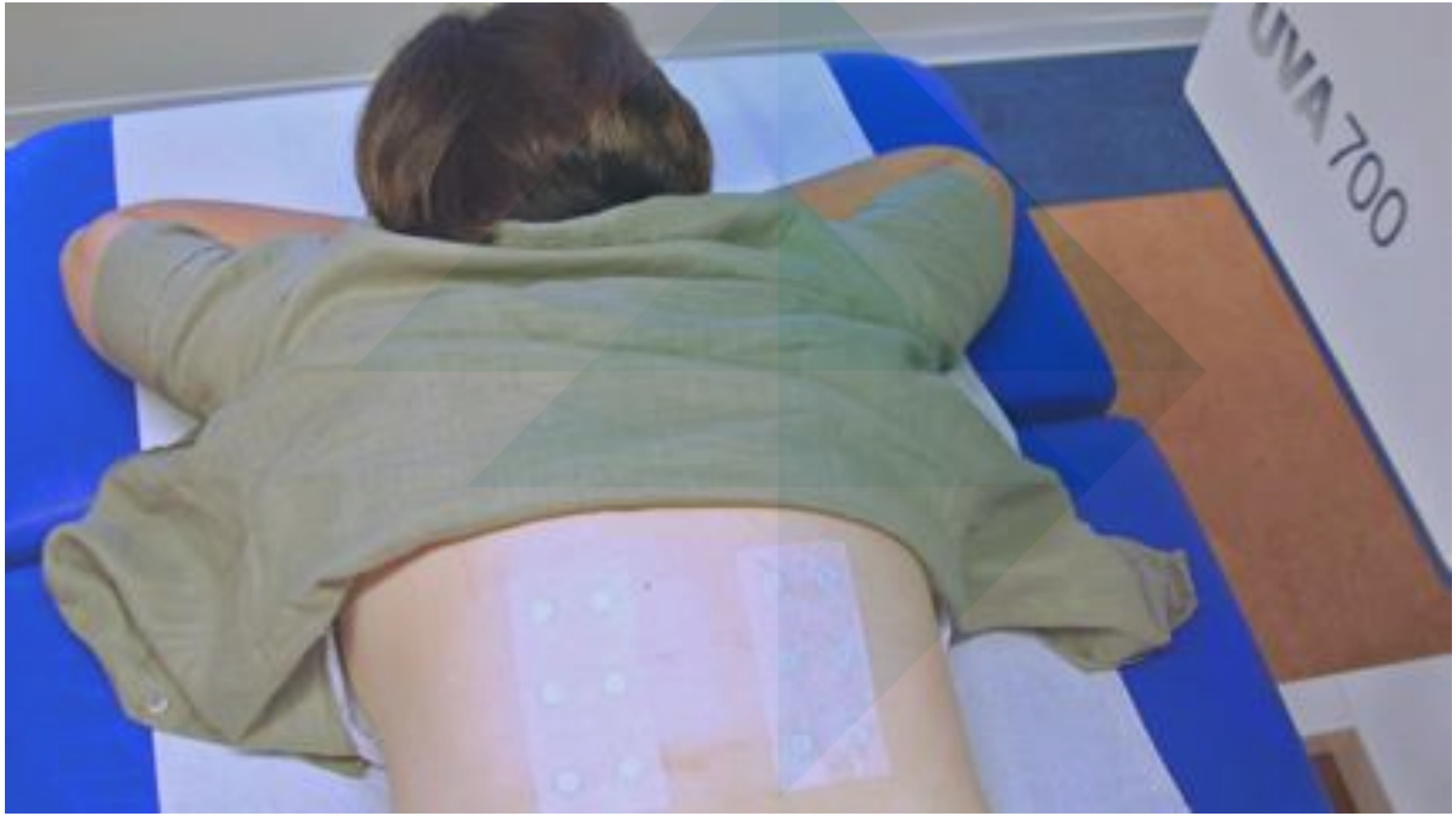
Guidance for Industry (January 2015; ICH)

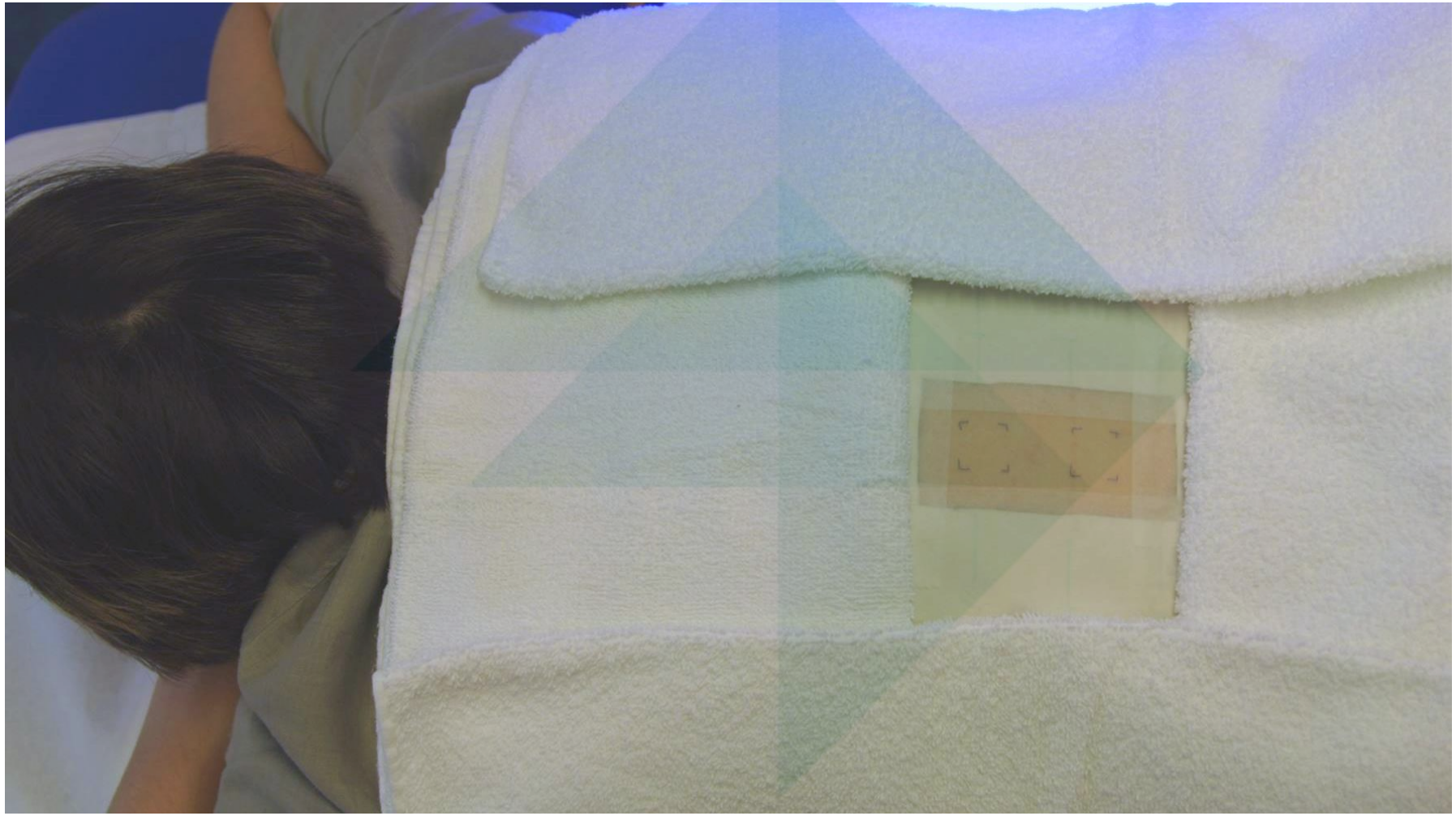


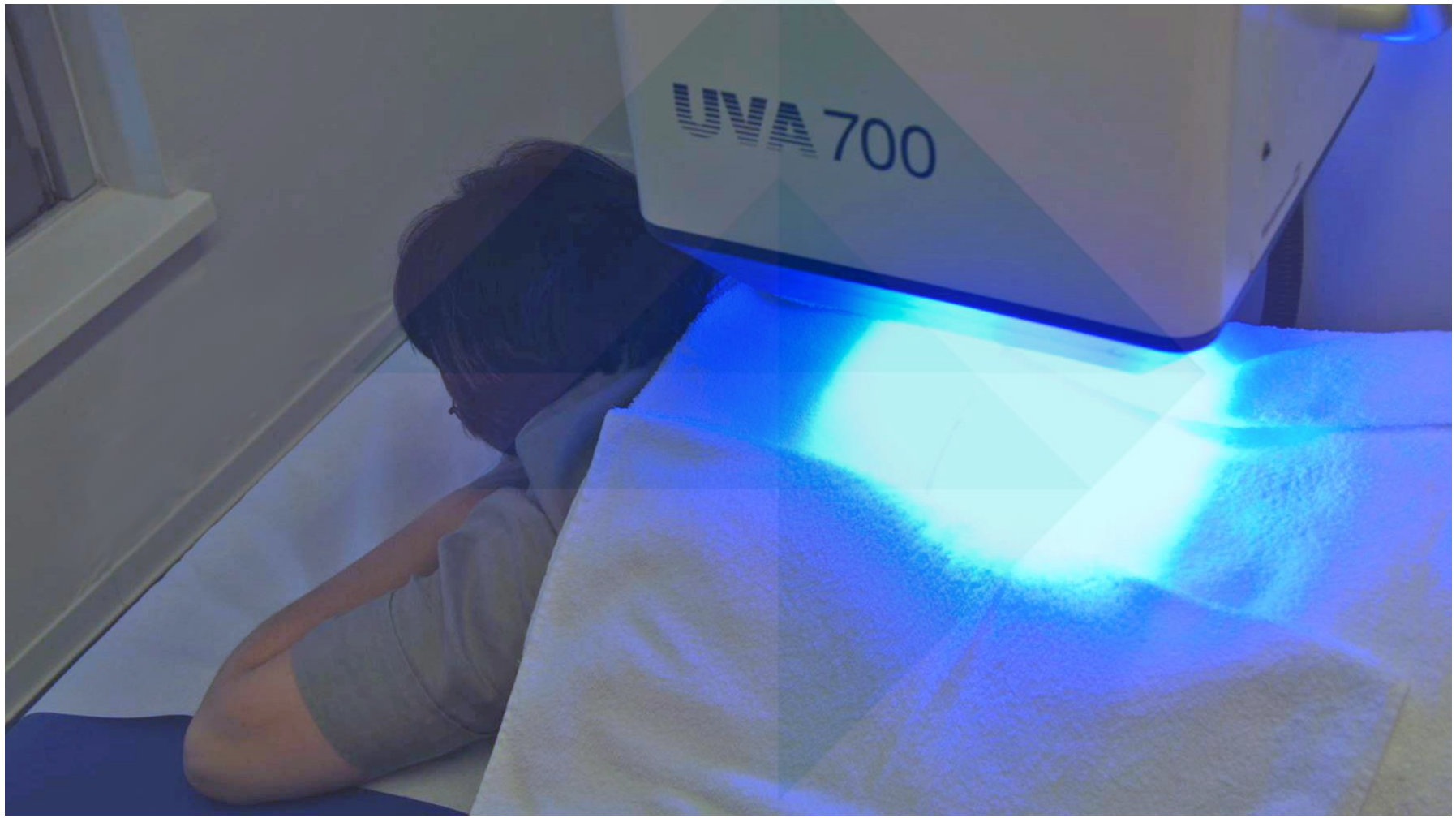
Phototoxicity Potential

Test Design

- Subjects: 35 (30 finishing) healthy volunteers, Fitzpatrick skin photo types 1, 2 & 3
- Duration: 4 Days
  - Day 1: application in duplicate sets (irradiated & non-irradiated) for 24 h
  - Day 2: Irradiation with UV-light (0.5 MED + 5 J/cm2 UVA)
  - Evaluations: Daily: before and 24 and 48 h post irradiation
- Exposure: Occluded patch or semi-occluded
- Test Products: max. 10: Active, Vehicle, un-irradiated Controls, Reference(s) optional
- Note
  No positive control for ethical reasons


UVA 700




UVA 700

Photoallergy Potential

Photosensitization: Test Design

- Subjects: 55 (50 finishing) healthy volunteers
  - 3 weeks induction
    - 6 applications in double sets (irradiated & non-irradiated) for 24 h; Irradiation with 0.5 – 2 MED (UVB+UVA following patch removal

- 2 weeks rest period

- 1 week challenge: 24 h application followed by 0.5 MED + 5 J/cm2 UVA exposure
- Evaluations:
  - Induction: Daily (24 hrs. post application & 24 and 48 hours post irradiation)
  - Challenge: Days 2, 3, 4, 5 / Re-Challenge as needed, > 4 weeks after Challenge

- Exposure: Occluded patch or semi-occluded

- Test Products: Active, Vehicle, un-irradiated Controls (No positive control for ethical reasons)

Special Case: Products for Skin with Impaired Barrier

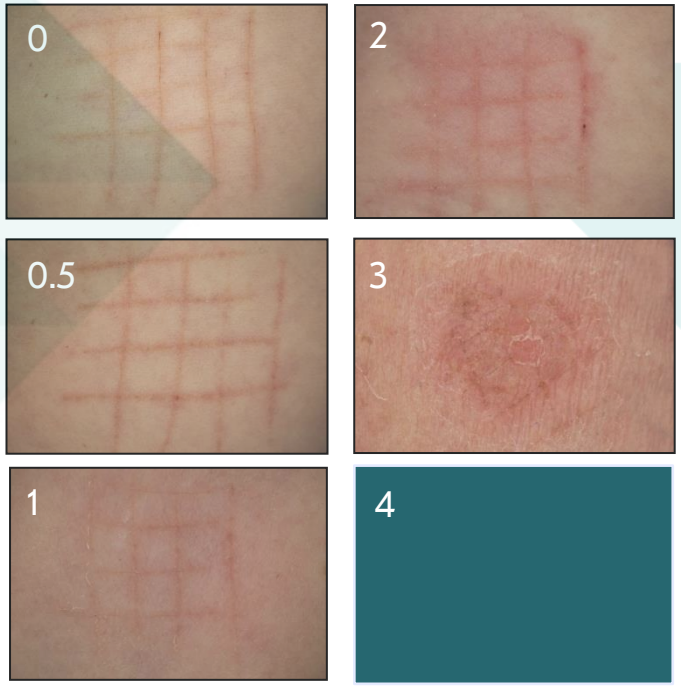
Wound Care, Products for Mucosae

Scratch Chamber Test ('Scarified' Chamber Test)

Day	1	2	3	4
Scratching	x			
Application of test materials	x	x	x	
Patch removal (23 h after the last application of test materials by subjects)		x	x	x
Visual evaluation (24 h after the last application of test materials by a trained evaluator or, 1 h after patch removal)		x	x	x

Scratch ("Scarified") Chamber Test

- 0 = No visible skin reaction
- 0.5 = Faint, definite or diffuse erythema (greater than 0, less than 1)
- 1 = Mild erythema in test area, maybe stronger within the scratched sites
- 2 = Moderate erythema in test area, maybe stronger near the scratched sites or broader bands of increased erythema with or without rows of vesicles, pustules or erosions
- 3* = Strong erythema in test area, maybe stronger around the scratched sites OR severe erythema with partial confluency with or without other lesions
- 4* = Confluent severe erythema sometimes associated with edema, necrosis and bulla formation
- * No further application of the product for the duration of the study. In that case the last value of the respective product(s) will be carried forward for the rest of the testing period.



Contact Dermatitis, 1996, 34, 181–184
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CONTACT DERMATITIS
ISSN 0105-1873

Reproducibility of the chamber scarification test

KLAUS EJNER ANDERSEN
Department of Dermatology, Odense University Hospital, Denmark

	Negative Control	Positive Control
Median	2.1	9.6
25 % CI	1.9	9.0
75 % CI	2.9	10.2
Least/Most irritating product	12/13	11/13

Cumulative Irritation Potential

21 Day Cumulative Irritation Test

Journal of Toxicology: Cutaneous and Ocular Toxicology

A Reappraisal of the 21-Day Cumulative Irritation Test in Man

S. Berger Richard & P. Bowman James

- The standard 21-day cumulative irritation test was re-examined to determine if it could be abbreviated
- The relative scores on 150 cosmetic-type products were compared at 14 and 21 days
- In more than 90 % of products studied, authors found that one would have made the same decision regarding the level of irritation and the relative ranking of the products at either 14 or 21 days.

Cumulative Irritation

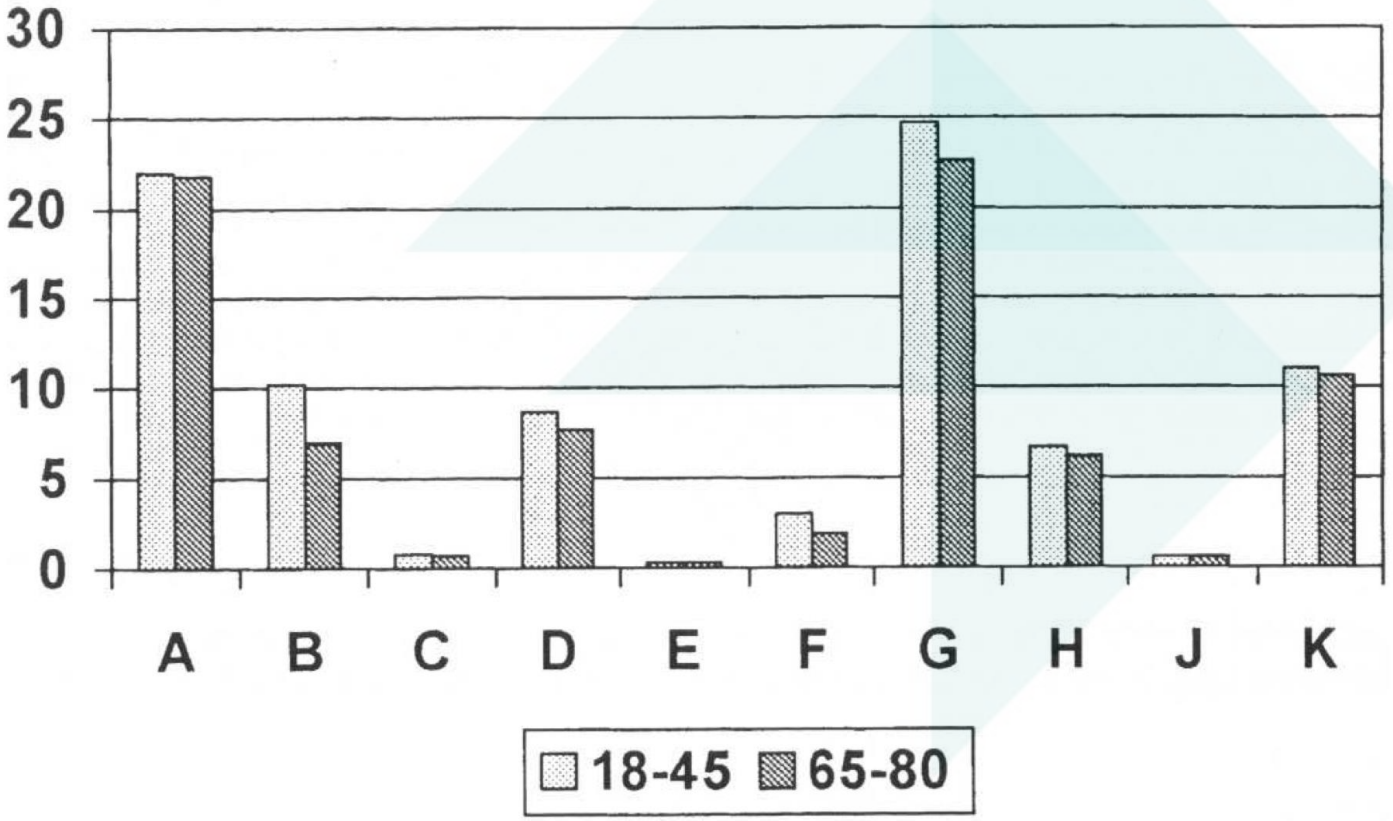
Influence of Geographical Location

	Arizona	Florida	Manitoba
Cumulative irritation (0 1% SLS)	30.3 ± 2.7	29.9 ± 1.0	29.9 ± 2.5
Cumulative irritation (saline)	1.2 ± 1.0	0.1 ± 0.1	1.2 ± 1.3
Temperature (°C)	24.1 ± 10.4	21.0 ± 5.52	-2.4 ± 20.5
Relative humidity (%)	32.7 ± 17.8	71.7 ± 5.3	72 ± 10.7
Dew point (°C)	4.3 ± 4.4	15.5 ± 5.4	-3.98 ± 19.2

Trimble MW, Kaul N, Wild JE, Bowman JP, J Cosmet Sci, 58: 519-525, 2007

Cumulative Irritation

Influence of Age



Bowman JP Kligman AM, Stoudemayer T, Nicholson, J Cosmet Sci, 56: 213-218, 2005

Dermal Safety Testing

Summary

- Timing: Prior to or in parallel with phase II / III
- Pilot Study ahead of main panel advisable if concerns re. tolerance present
- Single center, block enrollment, parallel execution enables expedient timelines
- Intraindividual comparison possible
- Vehicle Control mandatory, esp. with anti-inflammatory active
- Regular training and experience of graders necessary
- Specific dermatologic expertise for oversight & interpretation of results mandatory