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Specific challenges in the evaluation of irritation and sensitization for transdermal systems: A dermatological appraisal focusing on scoring and application

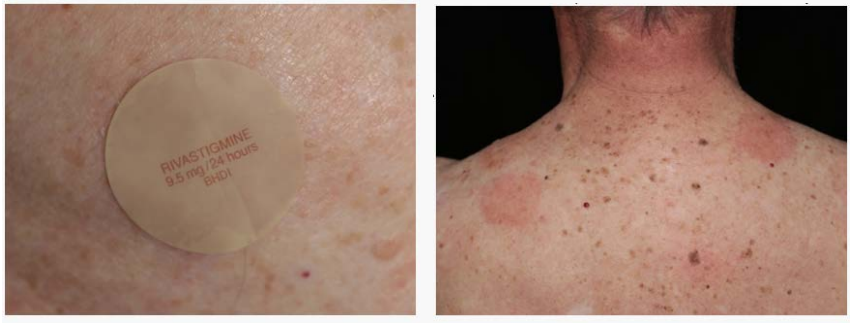
Walter Wigger-Alberti

Generic Drug Regulatory Science Initiatives Public Workshop, FDA White Oak Campus , May 1, 2019

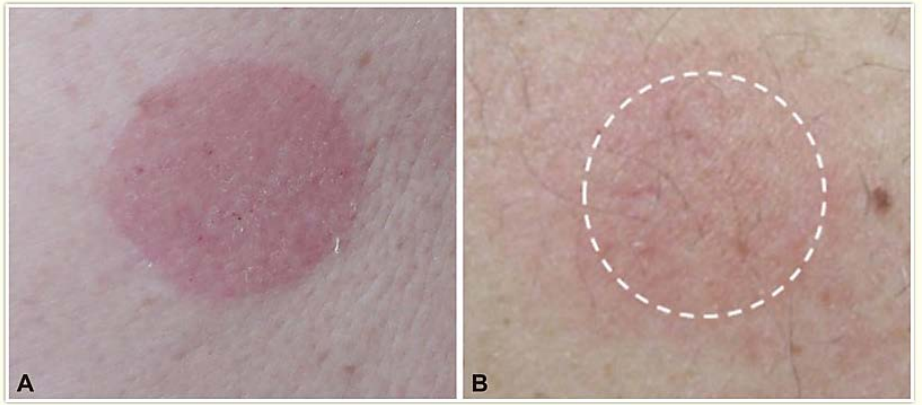
Dermal Tolerability of Transdermal Patches

Transdermal Patches

- once daily
- intact skin
- application site is to be rotated daily
- any application site should not be used more than once in 14 days



Irritant Contact Dermatitis by GM White. www.regionalderm.com

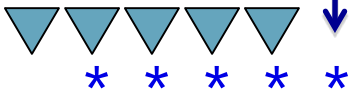


Locations of skin adverse events. A: Limited erythema. B: Extended erythema.

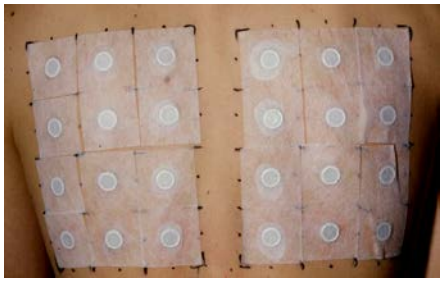
HR Na et al.Dement Neurocognitive Disord 2015;14:31-38

Cutaneous Safety Testing Irritation and Sensitization Potential

5 DAYS

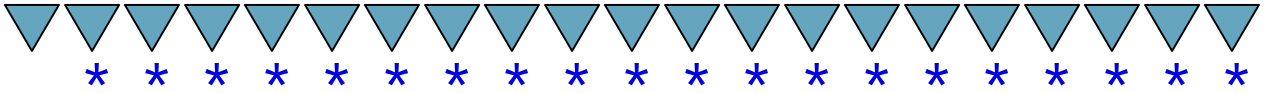


SCORE



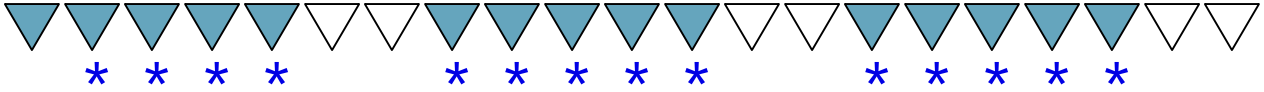
Panel size n = 30-35

21 DAYS – 21 APPLICATIONS



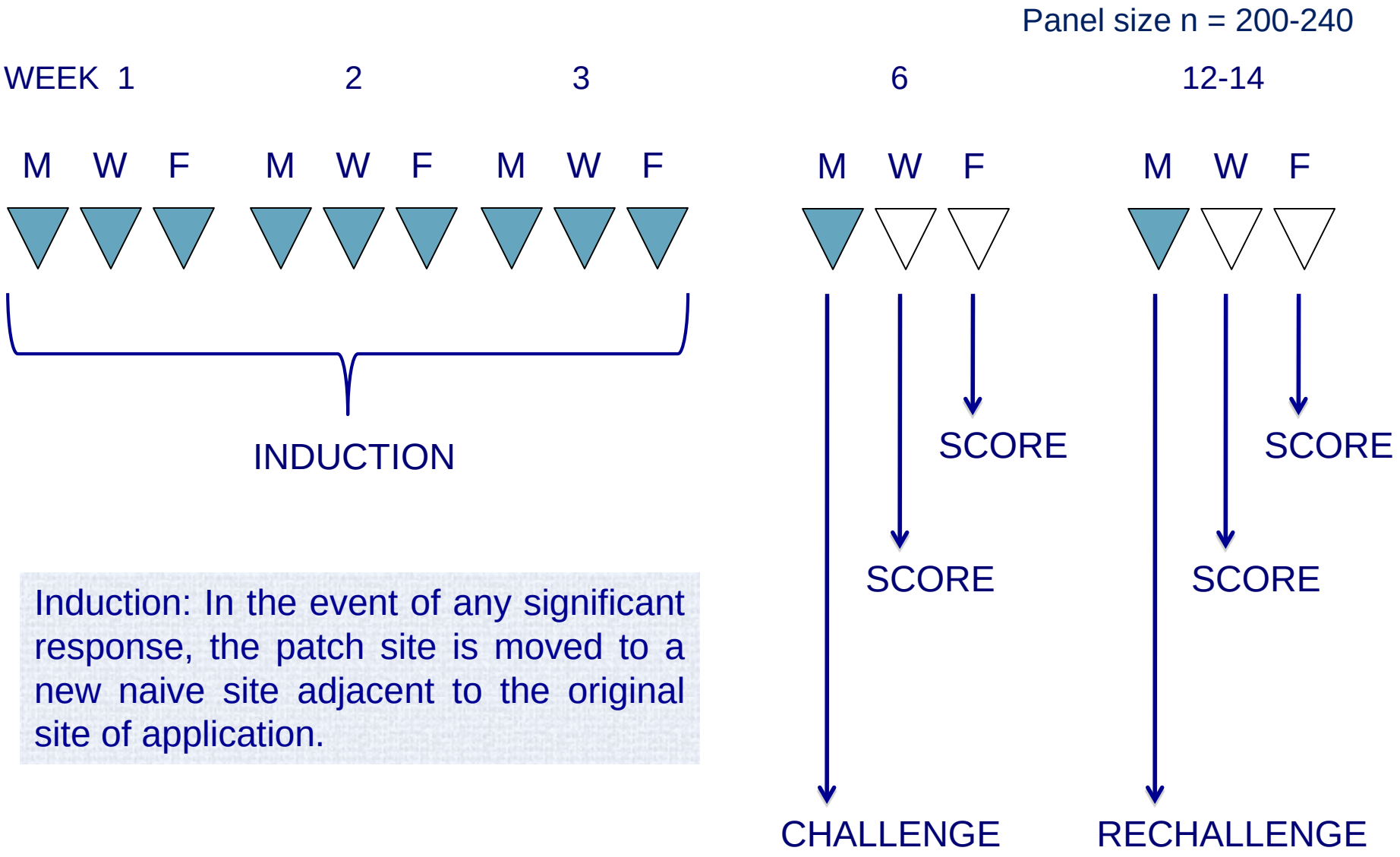
SCORE

21 DAYS – 15 APPLICATIONS



SCORE

Phase I Cutaneous Safety Testing Sensitization Potential - HRIPT



Induction: In the event of any significant response, the patch site is moved to a new naive site adjacent to the original site of application.

HRIPT Interpretation

For example, in the challenge phase if a subject shows scores of:

0,1,0,0

1,1,1,1

2,1,1,0

or similar, these would be indicative of an irritation response

If, for example they show:

3,2,2,2

1,2,2,3

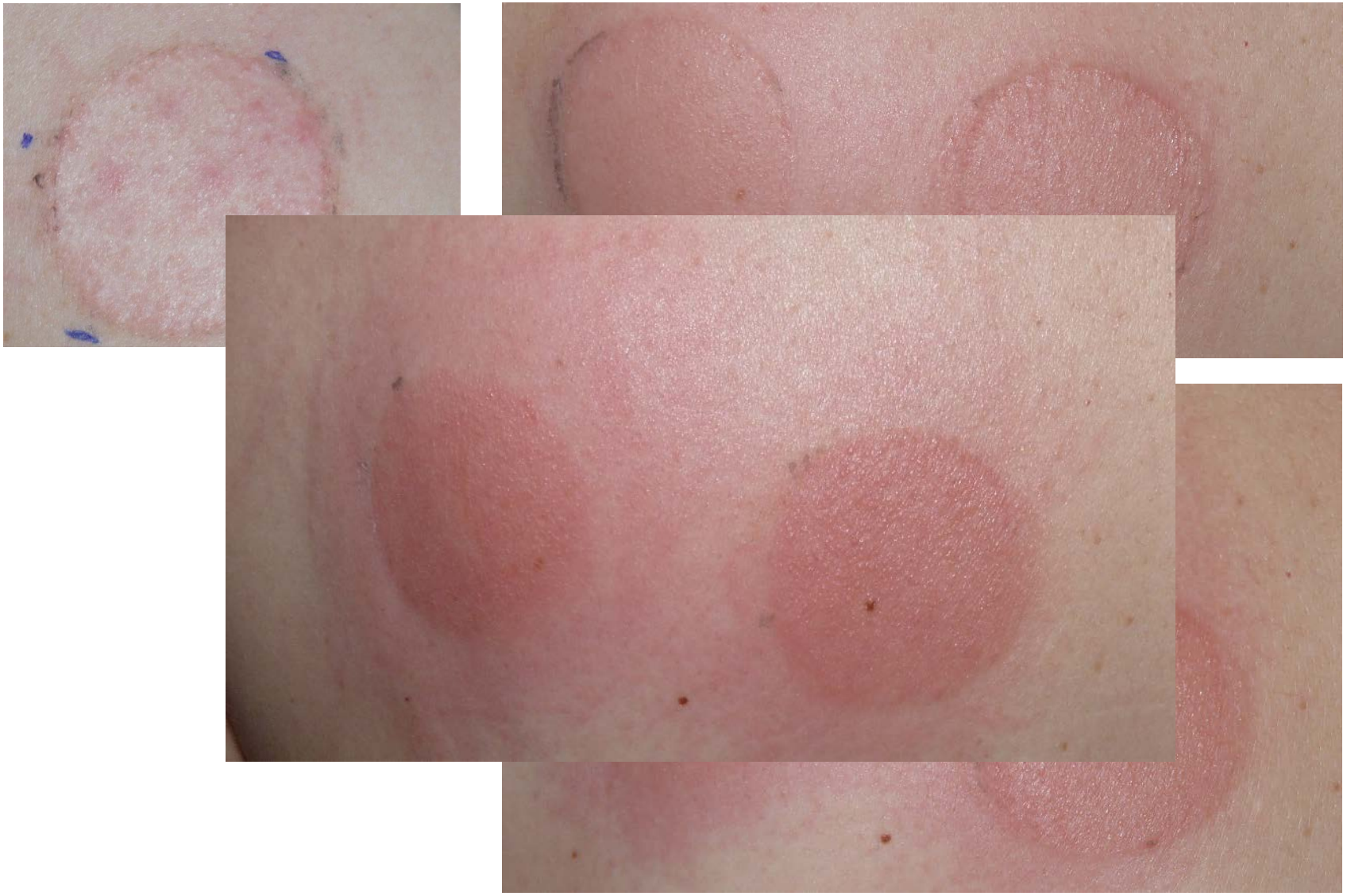
2,2,2,2

or similar, these would be indicative of a sensitization type response

Higher values, and persistence or increase in scores suggest sensitization

McNamee, Api, Basketter et al. Regulatory Toxicology and Pharmacology 52 (2008) 24-34

Challenge Phase Irritant and Allergic Reactions



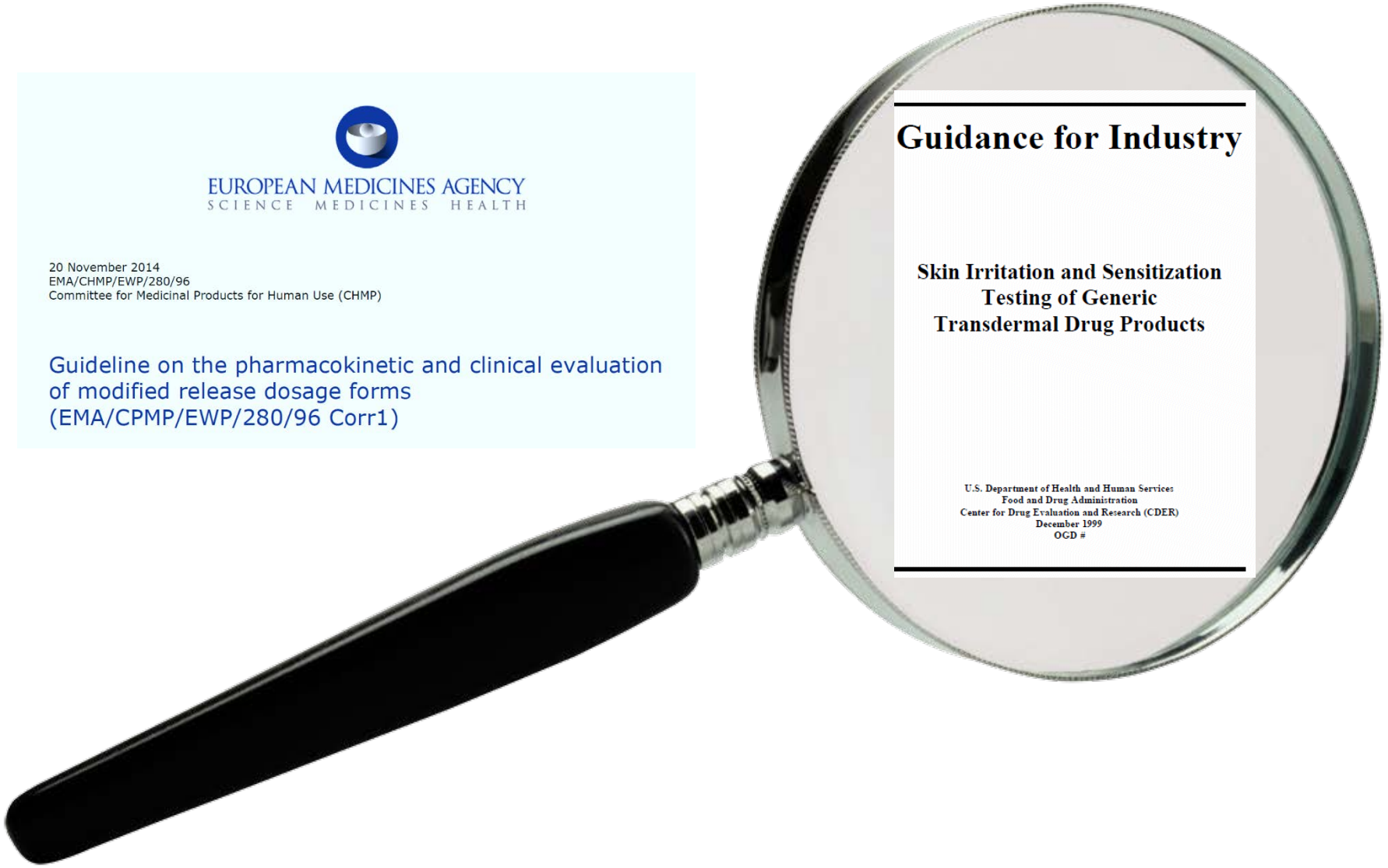
SCORING

FDA Guidance for Industry 1999

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 November 2014
EMA/CHMP/EWP/280/96
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1)



FDA Guidance for Industry 1999

Dermal response:

0 = no evidence of irritation
1 = minimal erythema, barely perceptible
2 = definite erythema, readily visible; 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

Other effects:

A = slight glazed appearance
B = marked glazing
C = glazing with peeling and cracking
F = glazing with fissures
G = film of dried serous exudate covering all or part of the patch site
H = small petechial erosions and/or scabs

* Berger RS, Bowman JP. A reappraisal of the 21-day cumulative irritation test in man. J. Toxicol. – Cut. & Ocular Toxicol. 1982; 1: 109-115.

References for Scoring

A REAPPRAISAL OF THE 21-DAY CUMULATIVE IRRITATION TEST IN MAN

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Rutgers Medical School
University of Medicine and Dentistry (UMD)
Piscataway, New Jersey

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Hill Top Research, Inc.–New Jersey
East Brunswick, New Jersey

Abstract

The standard 21-day cumulative irritation test was reexamined to determine if it could be abbreviated in order to lessen costs and delays and simplify operations. The relative scores on 150 cosmetic-type products were compared at 14 and 21 days. In more than 90% of products studied, we found that we would have made the same decision regarding the level of irritation and the relative ranking of the products at either 14 or 21 days. This high correlation between scores at 14 or 21 days justifies using a 14-day test for many products and for product development comparisons.

*Address reprint requests to: Richard S. Berger, M.D. Hill Top Research, Inc.–New Jersey, 223 Highway 18, East Brunswick, New Jersey 08816.

J. Toxicol.–Cut. & Ocular Toxicol. 1(2), 109-115 (1982)

References for Scoring

The Role of Human Patch Testing in a Product Development Program

1968

BEN MARR LANMAN, M.D., WALTER B. ELVERS, D.D.S., AND CHESTER S. HOWARD, M.D.
Bristol-Myers Products, A Division of Bristol Myers Co., New York, New York

INTRODUCTION

Every dermatologist knows there is nothing so variable and unpredictable in nature as man's reactivity to his environment. As difficult as it may be for the dermatologist to distinguish allergic responses from primary irritations, it is even more difficult for the manufacturer to make the distinction on the basis of his complaint file. By definition, allergic responses are less the responsibility of the latter, and it is to primary irritation that the following presentation is addressed. These reactions to virtually any topical preparation should be a continuing matter of concern to any responsible manufacturer. Dr. Albert M. Kligman put this problem into perspective in a talk delivered six years ago (1) in which he said:

> "Experts are not required to tell us that A is worse than B when A is phenol and B is boric acid. The really practical need is to be able to discriminate among substances which are only mildly active to begin with, and then only for certain persons under certain circumstances. In the modern world of mass production, that is the difference which may decide whether a product is or is not merchandisable. Even if the usual incidence of irritation for a given product is quite low, say, 1 in 10,000 (0.01%), the manufacturer will be harassed by complaints if millions of units are to be sold. He will most certainly alter this product, or replace it with a new one, if he could know beforehand that the incidence would jump to 5 in 10,000. Even if he were prodigal with money, his statisticians would inform him of the futility of safety-

CUMULATIVE PERCENT REACTING

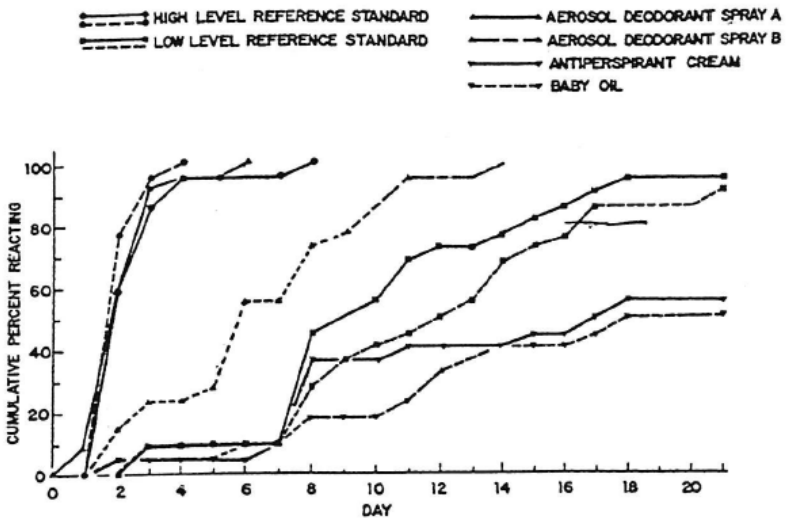


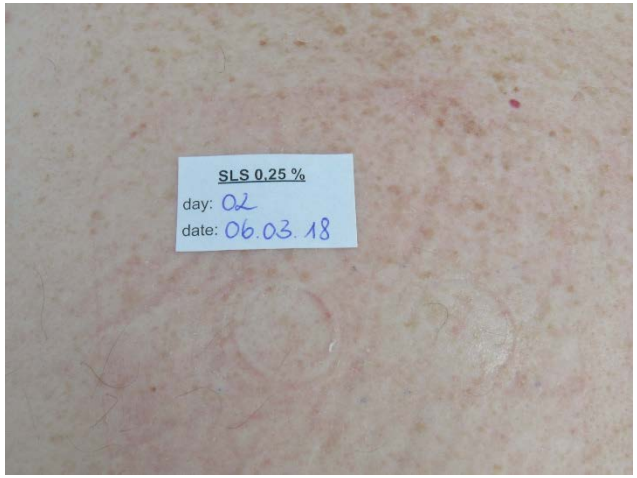
Figure 1. Typical graph of cumulative per cent of subjects

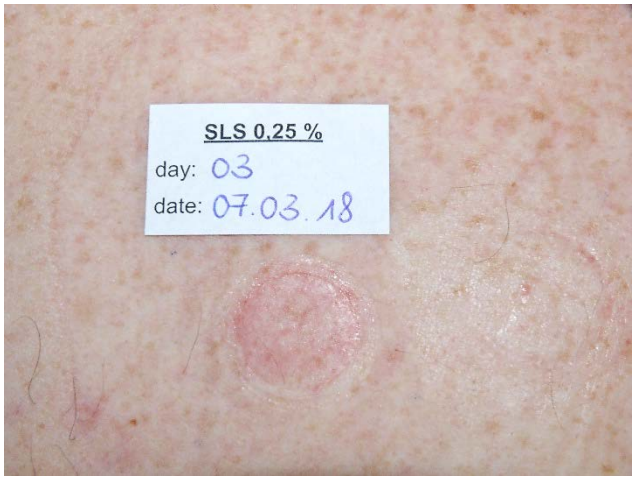
tants could be "tamed" slightly by the use of less occlusive coverings rather than by resorting to dilutions, thereby bringing their behavior into a desirable portion of the response curves. To this end we studied a series of formulas under an occlusive covering (Blenderm), a semiocclusive covering (Dermicel), and a nonocclusive cover consisting only of gauze. We were disappointed to find that the use of the semiocclusive covering not only lowered the absolute response scores for these products but also resulted in a great loss in discriminating ability for the test. The nonocclusive cover was virtually useless for the purpose of studying proprietary products, since there was frequently literally no response to products proven to have an irritation potential in field experience.

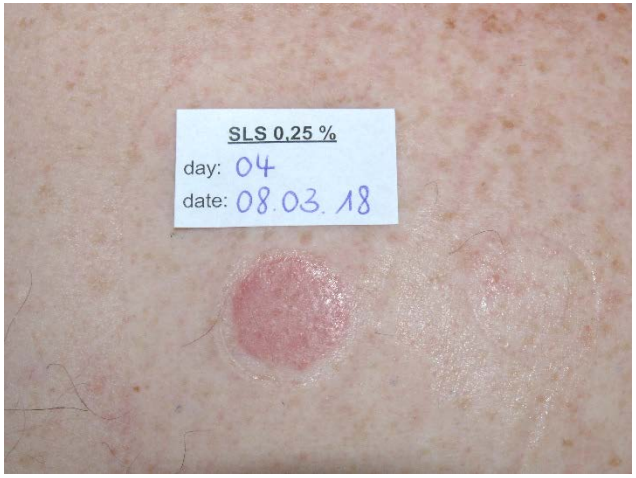
Randomization of the materials applied to patch sites has been recommended to eliminate bias in reading. Aside from the

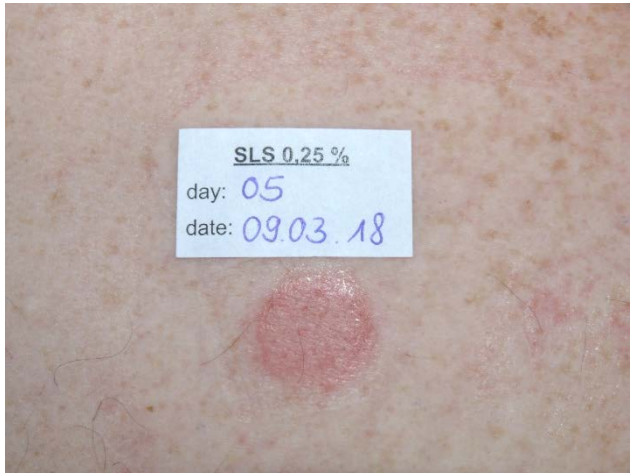
Lanman BM, Elvers EB, Howard CJ, "The role of human patch testing in a product development program". Joint Conference on Cosmetic Sciences, The Toilets Goods Association (currently the Cosmetic, Toiletry and Fragrance Association), Washington, DC, April 2123, 1968.

Phase I Cutaneous Safety Testing Irritation Potential









Symptoms of Irritation in Patch Testing with single application

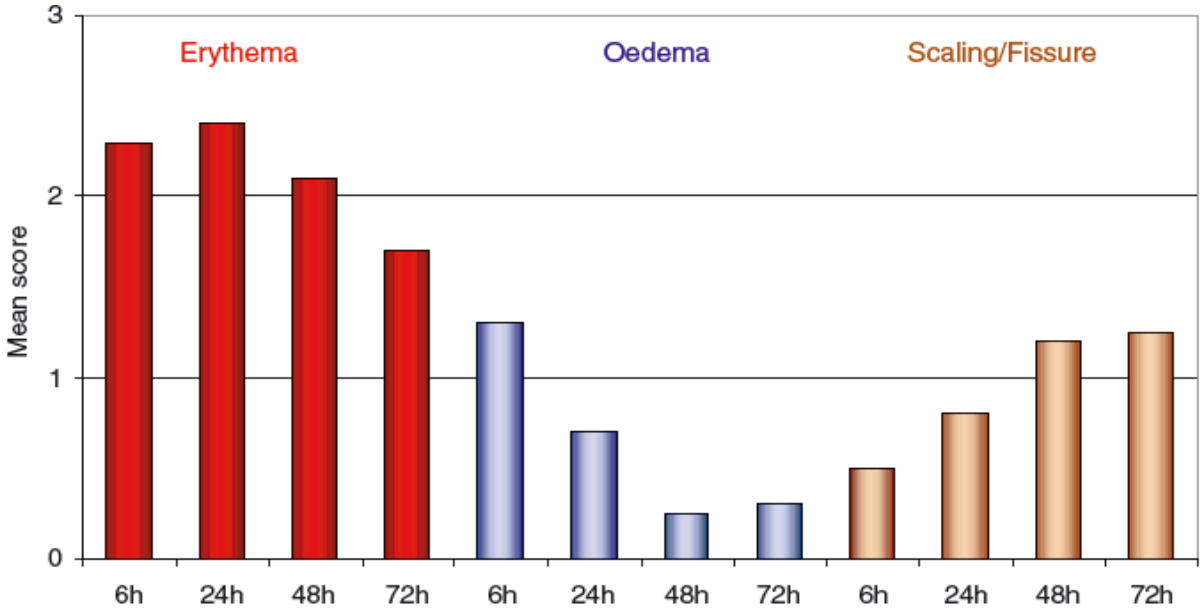


Fig. 1. Kinetics of the development of individual reactions based on the irritation scores. Time points pertain to hours after patch removal. Mean scores for all tested surfactants are shown: red: erythema; blue: oedema; brown: scaling/fissure (error bars were omitted to increase clarity).

Mehling A, Chkarnat C, Degwert J, Ennen J, Fink E, Matthies W, Roethlisberger R, Rossow U, Schnitker J, Tronnier H, Wigger-Alberti W, Wilhelm KP. Interlaboratory studies with a proposed patch test design to evaluate the irritation potential of surfactants. 2010;62(3):157-64.

Alternatives for Scoring - Irritation

0 = no reaction
1 = minimal (barely perceptible) erythema
2 = mild but well defined erythema only
3 = moderate erythema only OR mild erythema plus edema and/or papules
4 = severe erythema only OR moderate erythema plus edema and/or papules
5 = severe erythema plus edema and/or papules OR any vesicular reaction
6 = bullous reaction or any grade 3 - 5 skin reactions that spread beyond the test field

* Robinson MK. Intra-individual variations in acute and cumulative skin irritation responses. Contact Dermatitis 2001; 45: 75-83.

Alternatives for Scoring - Irritation

Table I. Irritation grading scale for exaggerated irritation patch study

Grade	Description
0.0	No apparent cutaneous involvement
0.5	Faint, barely perceptible erythema or slight dryness (glazed appearance)
1.0	Faint but definite erythema, no eruptions or broken skin, *or* no erythema but definite dryness; may have epidermal fissuring
1.5	Well-defined erythema or faint erythema with definite dryness; may have epidermal fissuring
2.0	Moderate erythema; may have few papules or deep fissures, moderate to severe erythema in cracks
2.5	Moderate erythema with barely perceptible edema *or* severe erythema not involving significant portion of patch (halo effect around edges); may have few papules *or* moderate to severe erythema
3.0	Severe erythema (beet redness); may have generalized papules *or* moderate to severe erythema with slight edema (edges well defined by raising)
3.5	Moderate to severe erythema with moderate edema (confined to patch area) *or* moderate to severe erythema with isolated eschar formations or vesicles
4.0	Generalized vesicles or eschar formations *or* moderate to severe erythema and/or edema extending beyond area of patch

Trookman NS, Rizer RL, Weber T. J Am Acad Dermatol. 2011;64(3 Suppl):S16-22.

Alternatives for Scoring - Sensitization

Skin irritation score for induction phase

Response	Score
No reaction	0
Slight uniform or spotty erythema	1
Sharply demarcated erythema	2
Severe erythema with infiltrate	3
Severe erythema with infiltrate and/or epidermal defect	4

Tausch I, Bielfeldt S, Hildebrand A, Gassmueller J (1996) Validation of a modified Duhring Chamber Test (DCT) as a repeated patch test for the assessment of the irritant potential of topical preparations.

Alternatives for Scoring - Sensitization

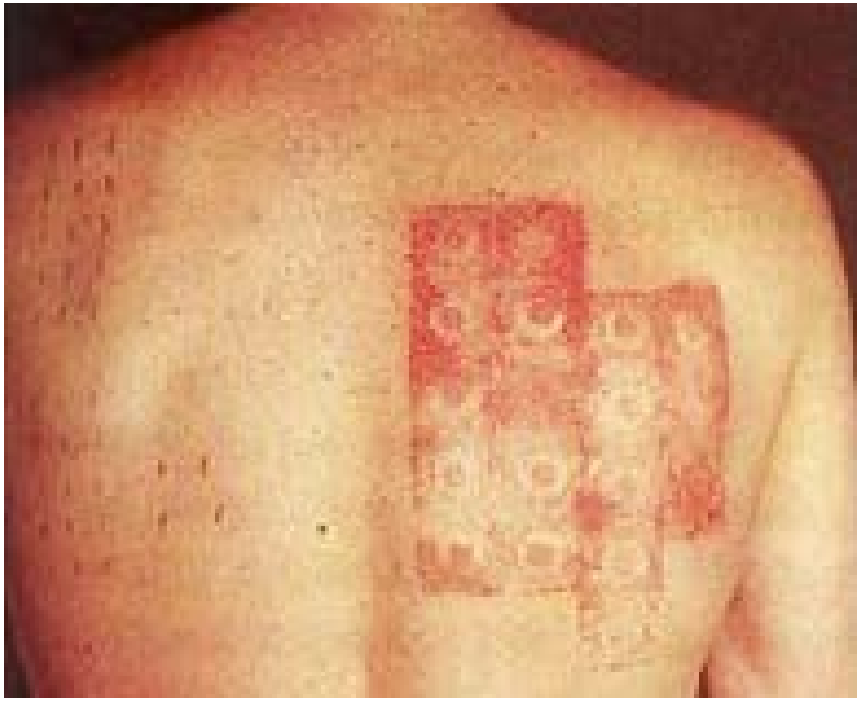
Dermal reaction scores of skin sensitization used in Challenge Phase

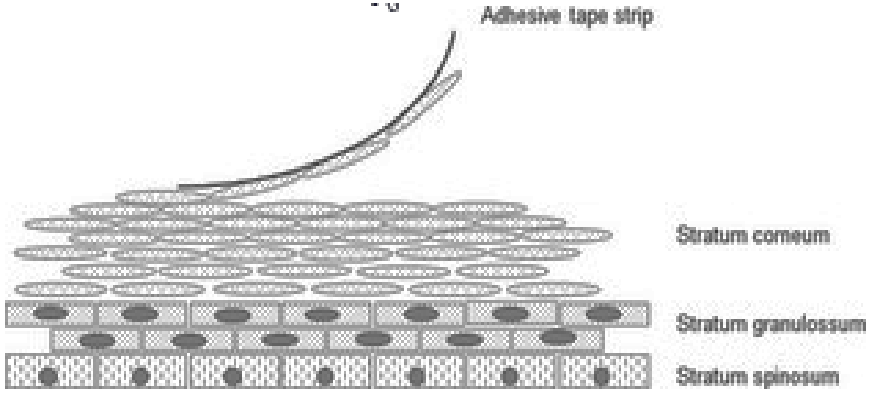
Response	Score
No reaction	0
Erythema, no infiltration	0.5
Erythema, infiltration, discrete papules	1
Erythema, infiltration, papules, vesicles	2
Erythema, infiltration, confluent vesicles	3

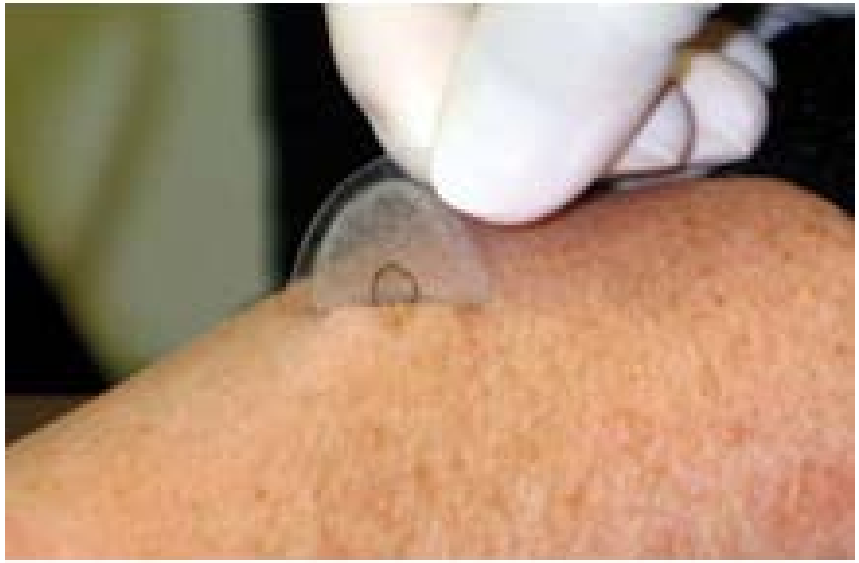
Schnuch A, Aberer W, Agathos M, Becker D, Brasch J, Elsner P, Frosch PJ, Fuchs T, Geier J, Hillen U, Loeffler H, Mahler V, Richter G, Szliska C, für die Deutsche Kontaktallergie-Gruppe (2007) LEITLINIEN DER DEUTSCHEN DERMATOLOGISCHEN GESELLSCHAFT (DDG) UND DER DEUTSCHEN GESELLSCHAFT FUER ALLERGIE- UND KLINISCHE IMMUNOLOGIE (DGAKI) ZUR DURCHFUEHRUNG DES EPIKUTANTESTS MIT KONTAKTALLERGENEN; issued 14.11.1998, updated 4.5.2007

APPLICATION

Reaction on Test Plaster







Tape Stripping increases Irritant Reactions

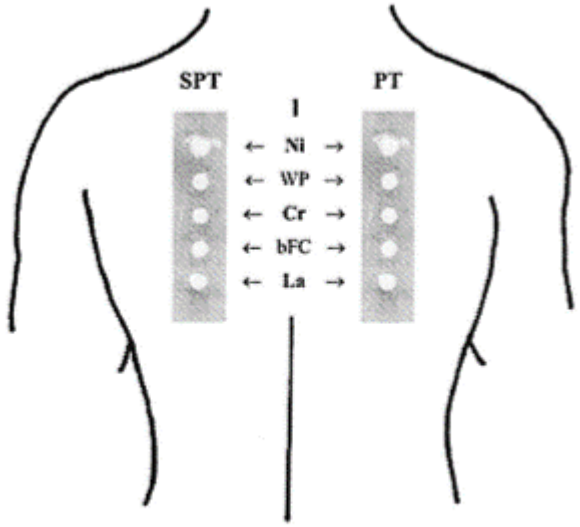


Fig. 2. Position of the test substances and index tests, the latter by randomization. SPT, strip patch test; PT, patch test; Ni, nickel sulfate 5% pet.; WP, white petrolatum pure; Cr, potassium dichromate 0.5% pet.; bFC, blank Finn Chamber; La, lanolin alcohol 30% pet.

Table 3. Reactions to test substances at D3/D4/D5 reading (*N*-tested = 787)

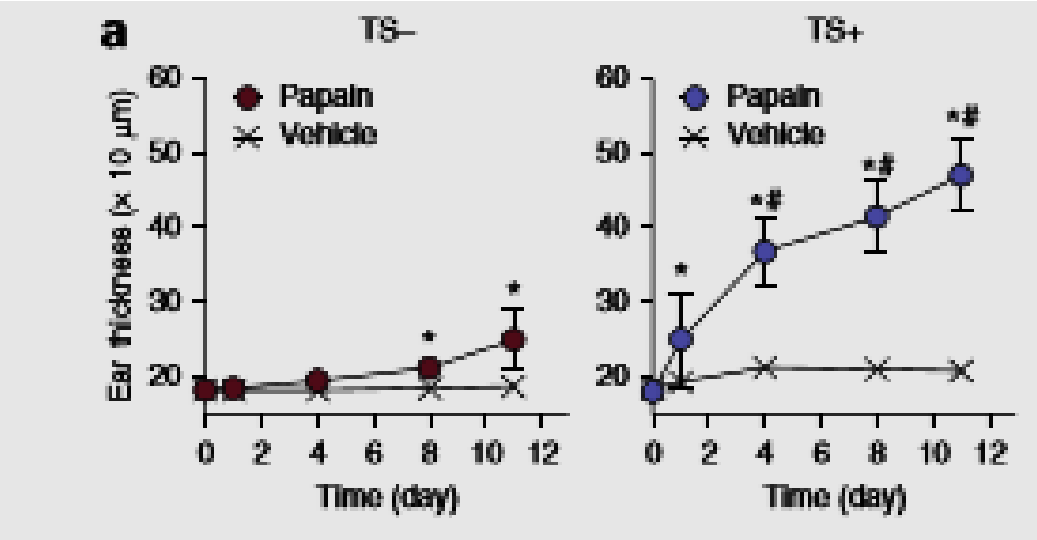
		Reaction					
		+	++	+++	?	IR	Neg.
Ni							
	SPT	88	57	9	14	7	612
	PT	69	38	5	10	3	662
Cr							
	SPT	52	10	4	12	5	704
	PT	25	9	3	14	7	729
La							
	SPT	9	4	0	4	3	767
	PT	6	1	0	3	3	774

Table 5. Main outcomes (*N* = 787)

				Difference	
		SPT	PT	SPT-PT	*P* value
Primary outcome					
Sensitivity, % (95% CI)	Ni	67.2 (58.4–74.9)	50.8 (42.0–59.6)	16.4 (8.7–24.1)	<0.0001
	Cr	60.7 (42.0–76.7)	35.7 (20.4–54.6)	25.0 (8.9–41.0)	0.008
	La	12.5 (1.7–53.7)	0.0 (0.0–31.2)	No convergence	n.c.

Dickel H, Kreft B, Kuss O, Worm M, Soost S, Brasch J, Pfützner W, Grabbe J, Angelova-Fischer I, Elsner P, Fluhr J, Altmeyer P, Geier J. Increased sensitivity of patch testing by standardized tape stripping beforehand: a multicentre diagnostic accuracy study. Contact Dermatitis. 2010;62(5):294-302

Tape Stripping increases Allergic Reactions

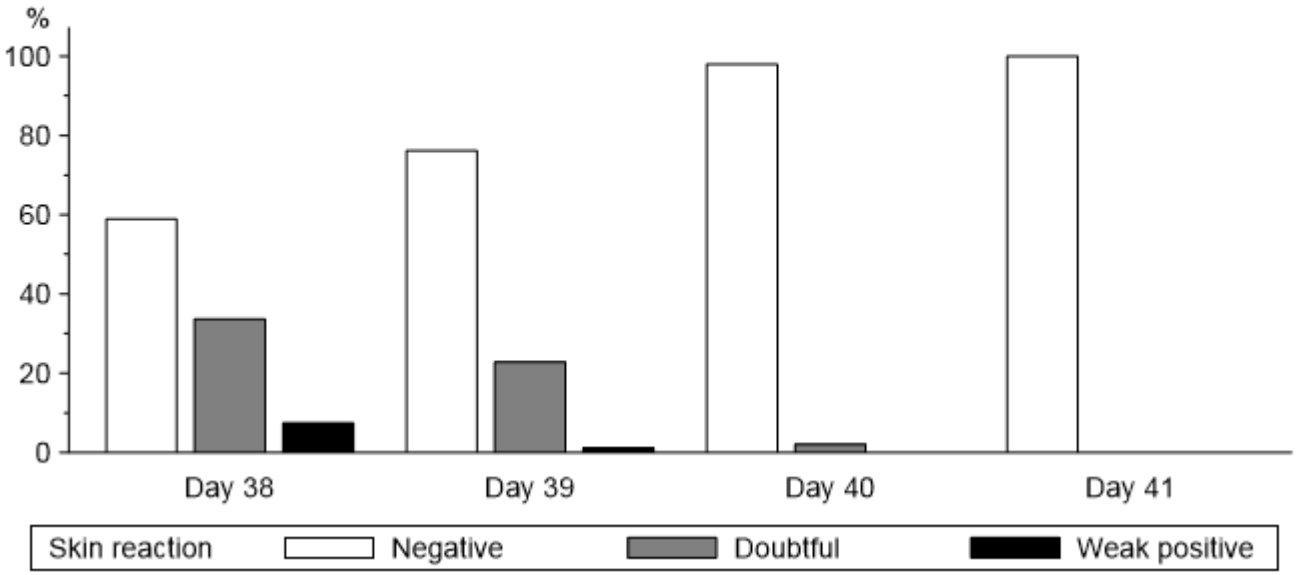


Shimura S et al. Epicutaneous Allergic Sensitization by Cooperation between Allergen Protease Activity and Mechanical Skin Barrier Damage in Mice. J Invest Dermatol 2016;136(7):1408-1417

Rotigotine Patch - Sensitization

Induction phase: 9 applications / 3 weeks

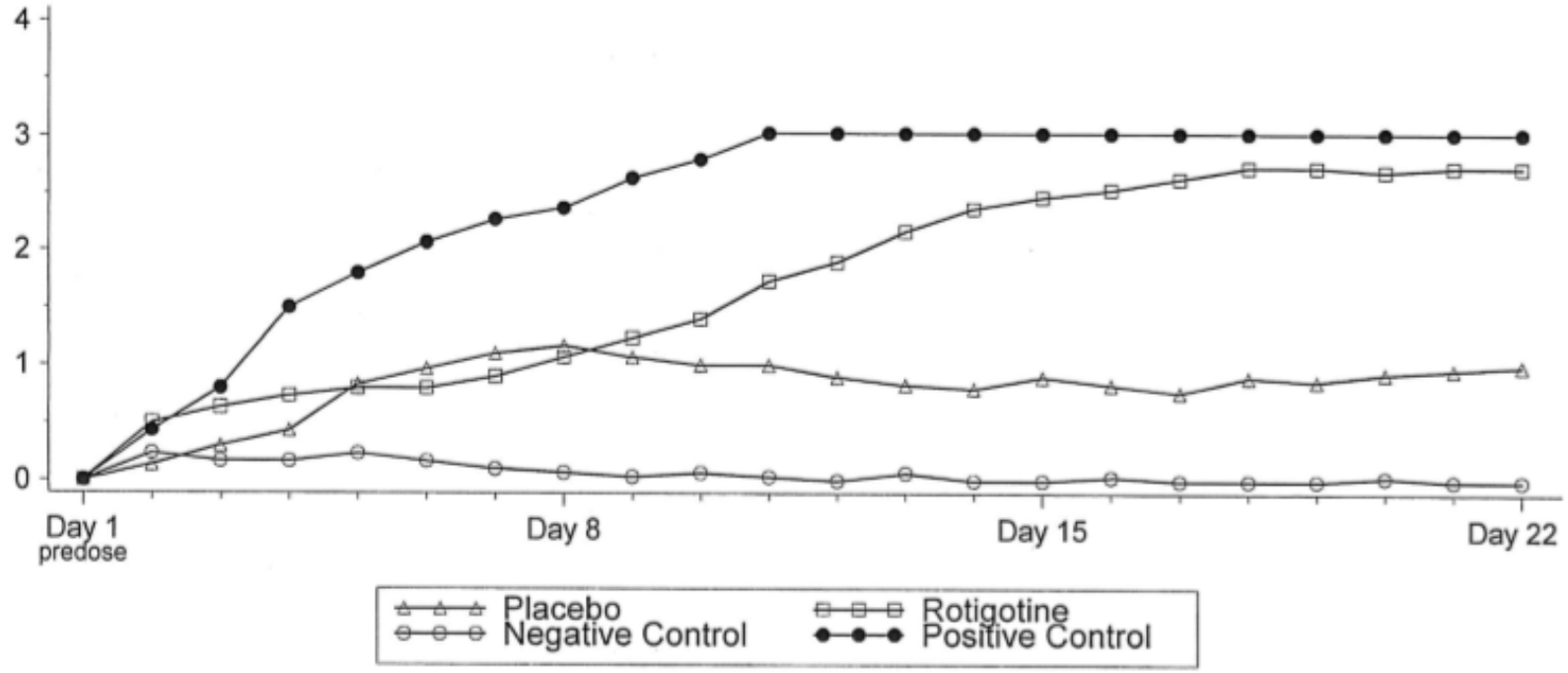
Figure 2.2: Skin Reaction during Challenge Phase: Rotigotine 1.125mg
(PPS N=202)



Rotigotine Patch – Irritation

Irritation: 21 applications / 3 weeks

Figure 1.2: Mean Dermal Skin Reaction Score by Day (PPS (with LOCF))
Repetitive applications



Conclusions

- Recommended score and application scheme is not adaquate for TDS
- Score has been developed for topical formulations, in fact cosmetics
- Leading symptom for irritation is an increasing erythema, for allergic reactions additional symptoms such as papules and oedema
- 21day daily application of TDS causes false positive reactions and includes a higher risk for iatrogenic sensitization

Thank you for your attention

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