Statement of Arbeitsgemeinschaft Angewandte Humanpharmakologie (AGAH):

Dermal Response Score EMA/CPMP/EWP/280/96 Corr1, Appendix I

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Executive Summary

- The general scoring system currently recommended in the guideline should be modified.
- Increasing score values do not reflect the course of increasing skin reactions.
- It would be much more appropriate to recommend separate scores for irritation and sensitization.
- The irritation score should reflect the increasing level of erythema accompanied by additional criteria such as oedema and papules.
- The sensitization score should reflect the typical setting of allergic dermal reactions.

Origin of the currently used score:

The guideline references a publication of Berger and Bowman from 1982 (Berger, R.S., and .J.P. Bowman, 1982, “A Reappraisal of the 21 -day Cumulative Irritation Test in Man,” Toxicol., l(2); 109- 115). However, Bowman and Berger published that their system was also based on a score used and published by Lanman and co-workers from 1968 (Lanman BM, Elvers WB, Howard CS. The Role of Human Patch testing in a Product Development Program. In Proceedings of the Joint Conference on Cosmetic Science. Washington DC, pp 135-145, 1968.)

That score was developed for in vivo testing of cosmetics, in fact deodorants, antiperspirants and baby oils, using occlusive or semi-occlusive application systems. These products usually include a significant percentage of detergents which may explain the value of a second scoring part (other effect score) focusing on reactions that are typically for detergent based products (glazing, peeling and cracking). Even Bowman and Berger have used this score for their investigation on 150 cosmetic-type products. Understandably, it is also used on the FDA guideline for upgrading category III antiperspirants to category I (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078905.pdf). However, it still remains inexplicable why this score was used for a guideline for transdermals since the pattern of irritant reactions to transdermals are significantly different from those of antiperspirants and deodorants.

Concept of the current guideline:

As part of the guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1) Appendix I lists recommendations for study

design and scoring systems that can be used to test skin irritation and sensitization during development of transdermal products. For both study designs (irritation and sensitization) the same score is recommended: for investigation of sensitization it is used both for the induction phase and the challenge phase. The score itself consists of two parts:, a dermal response score and a so-called other effect score. The dermal response score from 0=no evidence of irritation to 7=strong reaction spreading beyond test site lists various possible clinical features of skin irritant reactions such as erythema, oedema, papules, and vesicles. The other effect score lists mainly additional superficial feautures such as glazing, peeling and cracking.

Evaluation:

Unfortunately, these two combined scores are not practical and do not reflect increasing irritant reactions during a clinical trial with transdermals. Depending on the nature of an irritant, early reactions may start with glazing and/or scaling but this is mainly the case for topical products on the bases of detergents. The leading and most important parameter of skin irritation is erythema that increases with higher level of irritation combined with other phenomenon such as papules and/or oedema and/or eruption. It is critical that the score listed does not reflect an increasing level or irritation with an increasingly higher score since erythema is not assessed for its intensity. In addition a score 4 with definite oedema without any erythema is very unlikely to be observed as a moderate irritant reaction as indicated by a score of 4.

Surprisingly the score has been used over years in various protocols for irritation and sensitization testing both for topicals and transdermals. It is also listed in the FDA guidance for industry for skin irritation and sensitization for testing of generic transdermal drug products from 1999 (http://www.fda.gov/ohrms/dockets/98fr/990236Gd.pdf) which may explain why this score has been copied in so many protocols over years. It was explicitly stated that the scoring system is an example that can be used and that other validated scores can be used.

Taking these aspects into consideration the score listed in the EMA guideline does not seem to be appropriate neither for irritation testing of transdermals nor for the evaluation during the induction phase in sensitization studies but it is even more inappropriate for the evaluation of possible allergic reactions during the challenge phase.

The EMA guideline also mentions possible levels of skin reactions during the challenge phase. “During the Challenge Phase (contact sensitization evaluation), only combined dermal response scores ≥2 are considered a positive response. Strong reactions to the test patch are defined as a dermal response score of 3-7 or any dermal score combined with other effects rating of 4 or greater.” There is no explanation that not only the intensity of reactions discriminates between an irritant or an allergic reaction in the challenge phase but the development of an reaction after removal and the comparison of this pattern with any reactions and their development during the induction phase. A single score never allows to decide what type of reaction is observed. Positive reactions, at challenge, will generally be more intense and persistent than reactions noted during the induction period, particularly those noted early in the test. Characteristically, they may be eczematous (papulovesicular, edematous) rather than strictly erythematous with surface damage. These comparisons,

however, are not always diagnostic and borderline or suggestive responses should be re-challenged. The higher values, and persistence or increase in score suggests sensitization. If the subject shows little or no reaction during the induction phase, then showed these reactions during the challenge phase, this is even further confirmation that the reaction is most likely due to sensitization. An excellent review on how to interpret results during the challenge phase was published by McNamee at al. (McNamee, Api, Basketter et al. Regulatory Toxicology and Pharmacology 52 (2008) 24-34).

In summary, it is doubtful that one single score fits with both, the investigation of the irritant potential and the investigation of the sensitization potential. In particular the score listed was developed for the investigation of cosmetic products, mainly deodorants and antiperspirants, and does not reflect adequately irritant reactions by transdermals.

Proposal for an alternative procedure:

It would be much more appropriate to use separate scores for irritation and sensitization.

For irritation, any score that reflects the increasing level of erythema accompanied by additional criteria such as oedema and papules.

One example is a score published by Robinson. This score refers to erythema and associated symptoms: 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).

For sensitization a score reflecting allergic reactions seems more appropriate.

Allergic reactions are also accompanied by erythema but especially additional papules, vesicles, oedema that may spread beyond the original test field are typical features. An example of such a score is given by the German Contact Dermatitis Group (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, fuer 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) The score consist of 5 items. 0=no reaction; 0.5=erythema, no infiltration; 1=erythema, infiltration, discrete papules; 2=erythema, infiltration, papules, vesicles; 3=erythema, infiltration, confluent vesicles.

AGAH, November 30th, 2015

On behalf of AGAH

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(President elect)

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