EUROPEAN GENERIC AND BIOSIMILAR MEDICINES ASSOCIATION

Session 3 : Transdermal Products (PK + Adhesion + Irritation/Sensitization)

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Disclaimer

This presentation and session are aimed at facilitating a common interpretation of the guideline requirements and the presentation and session should not be interpreted as regulatory requirements. The contents of this presentation and session are subject to changes and should always be seen in conjunction with more recent official EMA and CMD(h) publications and decisions on the matter

Irritation and Sensitization

Study Design

1. Evaluation of Irritation (1/2)

Appendix I, page 30

"Subjects are assigned to one of two analysis groups (Group 1 and Group 2) and are evaluated for both cumulative dermal irritation and contact sensitization."

Appendix I, page 32

"Dermal response has to be assessed for all subjects in Group 1 and Group 2. Application sites for both groups are evaluated for skin irritation 30 minutes after patch removal (dermal response and other effects scores determined), …"

Both statements indicate that group 2 also needs to be evaluated for irritation.

1. Evaluation of Irritation (2/2)

Appendix I, page 32-33

Group	Phase	Evaluation by observer	Assessment of Test, Reference and Placebo
Group 1	Cumulative Irritation Phase	Dermal Response Score Other Effects Score	• Mean Irritation Score = average of Dermal Response Scores • Total Cumulative Irritation Score sum of Dermal Response Scores • Combined Dermal Response Score sum of Dermal Response Score and Other Effects Score • Mean Combined Dermal Response Score
Group 1 + 2	Challenge Phase (Contact Sensitization)	Dermal Response Score Other Effects Score	-Combined Dermal Response Score 2:2

The table indicates that solely group 1 is to be evaluated for irritation.

Please clarify if group 2 (as defined in Appendix I) needs to be evaluated for irritation or not.

2. Evaluation of Irritation

If both groups are to be evaluated for irritation,

please clarify if the sample size calculated for irritation evaluation should be equally split between groups 1 and 2.

3. Evaluation of Irritation

If only group 1 should be used for irritation evaluation, please clarify how sample size for group 2 should be selected.

4. Evaluation of Irritation (1/2)

Appendix I, page 33

"The primary analysis compares the test and reference treatments for the mean irritation scores (average numeric dermal response over the observations) and the total cumulative irritation scores (sum of the numeric dermal response scores over the observations). A predefined ***statistical evaluation based on a non-inferiority approach*** *is deemed sufficient to support a positive benefit risk evaluation for such a product. The two one-sided t-test method should be used to compare the irritation scores between treatments. For each parameter, least squares means for each treatment are derived from an ANOVA model where subject and treatment are fixed effects. The ratio of the least squares means of the test treatment to the reference treatment has to be calculated, along with its 90% confidence interval. A 90% confidence interval that falls completely* ***within the interval 0.8 to 1.25*** *leads to the conclusion that the two treatments are equivalent."*

4. Evaluation of Irritation (2/2)

The acceptance range 0.8-1.25 indicates that a two-sided test is necessary. However, as stated above as well, a non-inferiority approach is considered sufficient, which means that a one-sided approach would be sufficient.

Please clarify if a one-sided or two-sided test is necessary.

5. Administration Scheme

Appendix I, pages 30-31

The guideline states to apply the patch daily within Group 1

The guideline states to apply the patch 3 times a week within Group 2

- **Is it acceptable not to test the proposed schemes for irritation / sensitization and to follow the application period as proposed in the SmPC for all subjects?**
- **It is not clear as to why 2 groups of subjects with different drug administration schemes are needed for the Induction/Cumulative Irritation Phase.**
- **Can therefore Group 1 be dropped, if irritation is assessed in the bioequivalence studies?**

6. Administration Scheme

Appendix I, page 33

"Group 2 subjects apply test, reference, and placebo patches to randomly assigned treatment areas three times weekly over a period of 21 days (a total of nine applications). … The new patch should be applied to the same site as the previous patch."

The repeated patch re-application onto the same skin site may trigger high drop out rates due to increasing irritation.

Is it acceptable to apply the new patch to another site on subjects in Group 2, if the irritation score is significant (e.g. ≥ 3)?

7. Placebo Patch

Appendix I, page 30

"The study suggested has an active- and placebo-controlled, multiple-dose, three-phase, parallel-group design."

"Test, reference and placebo transdermal patches should be applied to randomly assigned test areas on the back or other parts, if permitted by the SmPC, of subjects in the two groups."

Within the irritation and sensitization study test and reference are compared.

Please clarify why a placebo patch is required and if the placebo can be considered as optional.

8. Strength Selection

Appendix I, page 30

"The strength chosen for the test is determined by considering the following factors:

- ***previous human experience in scientific literature***
- ***previous sensitisation/irritation tests in animals***
- ***safety issues derived from the individual API under investigation"***

"In case simultaneous application of test and reference is impossible as doubled amount of API would be given under off-label use and might have life-threatening consequences the use of a lower strength is acceptable for size proportional formulations."

For safety reasons it may become necessary to apply lower doses than the smallest available dose.

Please clarify if in this context also "parts of a patch" in case the patches are based on matrix technology are covered.

9. Sensitization and Irritation

Appendix I, page 30

"To fully evaluate the equivalence of a generic transdermal product to the reference product similarity has also to be shown for skin irritation and sensitization unless otherwise justified by e.g. very similar quantitative and qualitative composition."

Possible irritation/sensitization due to the API can be ruled out by the results of the reference and a very low irritation and sensitization potential of a particular technology cannot be further improved.

Would it therefore be acceptable to justify the absence of new studies in cases where a known technology (e.g. same qualitative composition as an approved product) is used that has proven to produce no sensitization or irritation when used in other products (API) even when the composition differs from that used in the reference?

10. Skewed Irritation Scores

It should be noted that the irritation scores are likely to be skewed with many subjects having 0 score. Due to the skewness of the data the suggested parametric approach may be not appropriate.

Please clarify if alternative approaches are accepted, as

- **non-parametric approaches**
- **FDA proposed approach (non-inferiority with the upper bound of the one-sided 95% CI of the mean test product score minus 1.25 times the mean reference product score must be ≤ 0)**
- **bootstrapping.**

Please clarify how to deal with 0 scores if the parametric approach is mandatory.

11.Sensitization (1/3)

Appendix I, page 32

"During the Challenge Phase (contact sensitization evaluation), only combined dermal response scores ≥2 are considered a positive response."

Appendix I, page 33

"The assessment of contact sensitization consists of tabulations of dermal response scores ≥2 during the Challenge Phase. No statistical analysis has to be performed on these data."

11.Sensitization (2/3)

It is not clear which scoring shall be applied for sensitization assessment (“combined dermal response score” or the “dermal response score”).

It is also not clear which evaluation time point(s) post removal of the challenge patch serve as basis for assessment of the sensitization potential. Scores that resolve within 48 hours can be considered to be due to irritation, rather than to sensitization and shall therefore not be used for assessment of sensitization potential.

No statistical analysis has to be performed on contact sensitization data. However, there is no explanation as to what determines equivalence between products.

11.Sensitization (3/3)

- **Please clarify if sensitization potential shall be assessed based on the “combined dermal response score” or the “dermal response score”.**
- **Please clarify which evaluation time point(s) post patch removal serve as basis for sensitization assessment.**
- **Please clarify what determines equivalence with respect to sensitization between products.**

12. Combined Dermal Response

Appendix I, page 33

Group	Phase	Evaluation by observer	Assessment of Test, Reference and Placebo
Group 1	Cumulative Irritation Phase	Dermal Response Score Other Effects Score	• Mean Irritation Score = average of Dermal Response Scores • Total Cumulative Irritation Score sum of Dermal Response Scores • Combined Dermal Response Score sum of Dermal Response Score and Other Effects Score • Mean Combined Dermal Response Score
Group 1 + 2	Challenge Phase (Contact Sensitization)	Dermal Response Score Other Effects Score	-Combined Dermal Response Score 2:2

Please clarify what "2:2" means in the table above.

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Regulatory Aspects

13. Regulatory Aspects

How will new applications (or RUPs) be handled if the dossier includes demonstration of irritation and sensitization that do not exactly follow the requirements of this guideline?

14. Global Product Development

For a Global Product Development, is it acceptable to use US sourced reference product for the Skin Irritation + Sensitization Study, if

- **the SmPCs confirm equivalent qualitative composition**
- **the patch sizes for the respective dosage strengths are equivalent**
- **the drug loading for the respective dosage strengths are equivalent?**

Questions from Attendants

15. Skin Irritation and Sensitization: Screening

Appendix I, page 30

"Screening evaluations are performed within a 14-day period prior to application of the patches."

Having all screening evaluations performed within a 14-day period prior to application of the patches is considered too short per our experience, would a 28 day period be considered acceptable?

16. Dermal Response Score Evaluation

Appendix I, page 32

"Each application site receives a separate dermal response score and other effects score. Dermal response scores require that at least 25% or more of the patch area demonstrate an observable response."

Can one elaborate on the need for a dermal response scores evaluation requiring at least a 25% or more of the patch area demonstrating an observable response.

Couldn't this artificially deflate the response scoring?

17.Irritation Assessment

For irritation primary analysis, the guidance requires only mean irritation scores and total cumulative irritation scores but not combined with other effect Scores?

Should other effect score be considered for Cumulative Irritation Scores for irritation primary analysis?

18. Adhesion Score

To measure adhesion score as the percentage of area that remains adhered to be within 1% is difficult to be done practically. We have been rounding it to be within 10%, please see below for reference. Would this adhesion scoring scale be acceptable?

Adhesion	Score
100%	100
>90% to <100%	95
>80% to 90%	85
>70% to 80%	75
>60% to 70%	65
>50% to 60%	55
>40% to 50%	45
>30% to 40%	35
>20% to 30%	25
>10% to 20%	15
>0% to 10%	5
Fall off	0