The Regulatory Acceptance Board Report on an alternative skin irritation test method using EpiDerm and SkinEthics

JaCVAM Regulatory Acceptance Board

July 4th, 2012

Having received the Peer Review Panel's report[1] on an alternative skin irritation test method using EpiDerm and SkinEthics, we discussed the following nine items. Items 2–8 are per OECD Guidance Document No. 34.[2] It is our opinion that the use of this test as an alternative to animal testing requires careful consideration of the scope of application.

The Item Discussed

1. The submitted test method should relate to regulations or guidelines in Japan.

This test method relates to skin irritation as stipulated in regulations or guidelines governing chemical substances or products as well as raw materials for drugs, quasi drugs, medical devices, or cosmetics.

2. The submitted test method and supporting validation data should have been subjected to a transparent and independent peer review process.

This test method has been reviewed in a report published by the ECVAM Scientific Advisory Committee (ESAC) in accordance with OECD GD No. 34, which is considered a transparent and independent peer review process.

3. The data generated by the test method should adequately measure or predict the endpoint of interest. For replacement test methods, the data should show a linkage between the proposed test method and an existing test method, and/or the proposed test method and effects in the target or model species.

This test method, which uses a three-dimensional cultured skin model derived from normal human skin cells, involves direct exposure of a test specimen and evaluation based on the survival rate of the exposed skin cells. Thus, it is quite similar to conventional skin irritation test methods using humans or animals. Data obtained in this manner exhibit a favorable correlation with the results of conventional tests in which patches were applied for four hours.

4. The test method should generate data useful for hazard/risk assessment purposes.

This test method is capable of distinguishing between skin irritants (Category 2, score of 2.3 or higher) and non-irritants (no category, score of less than 2.3) per GHS-based EU regulation for classification, labeling, and packaging of substances and mixtures. (CLP Regulation)
This test method is therefore considered useful for hazard assessment of exposure to chemical substances but it is unclear whether or not the method is useful for risk assessment.

5. The submitted test method and supporting validation data should adequately cover a spectrum of chemicals and products representative of those administered by the regulatory program or agency for which the test method is proposed, and the applicability and limitations of the test method should be clearly described.

- A set of 20 suitable test substances was selected per OECD guidelines. In addition, in accordance with the rabbit skin irritation classification system defined per EU CLP Regulation based on GHS, these 20 test substances are to comprise 10 skin irritants (Category 2, score of 2.3 or higher) and 10 non-irritants (no category, score of less than 2.3). This is considered sufficient for identifying the GHS classification of chemical substances. The test, however, is not intended for formulations.
- One limitation on the application of this test method is that, because it uses cell survival rate as an index, it cannot be used to ascertain recovery from skin damage. Also, the use of MTT reduction means that results from this test method could be affected by the use of colored substances or reducing agents.

6. The test method should be sufficiently robust (relatively insensitive to minor changes in protocol) and transferable among properly-equipped laboratories with adequately-trained staff.

Each test method has a well-defined protocol and is robust as long as test parameters are satisfied. The effects of minor changes to the protocol have not been investigated. The test procedure itself, however, is easily transferrable to any laboratory properly equipped for preparing cultures and staffed by personnel adequately trained in the fundamentals of doing so.

7. The test method should be both time and cost effective as well as likely to be used in a regulatory context.

Given that the time required, including that needed for preculturing, is just three days and that costs are acceptable compared with animal testing, this test method is likely to be used in a regulatory context.
The cost of the commercial skin models used in this test are 113,000 JPY for EpiDerm (24 well), unknown for Skin Ethics, and 98,000 JPY for EPISKIN (12 well).

8. Justification should be provided (scientific, ethical, economic) for the new or updated test method in light of existing test methods.

- This test method is quite similar to conventional skin irritation test methods using humans or animals, which provides scientific justification.
- This test method uses no animals, which contributes to animal welfare as a valid alternative method and provides ethical justification.

・ Although it takes time to procure the skin models from Japan and they cannot be stored for long periods of time after purchase, there is economic justification.

9. The test method should be suitable for use as regulatory documentation in the assessment of safety.

・ This test method is used to evaluate potential for skin irritation after a four-hour application and to identify Category 2 skin irritants as defined by GHS, but there is as of yet no sufficient scientific basis for determining its equivalency to conventional tests for evaluating skin irritation after a 24-hour application using animal models as used in Japan for evaluating the potential for skin irritation of quasi drugs and cosmetics.
・ It can be used for hazard assessment of common chemical substances.

Based on the above, the JaCVAM Regulatory Acceptance Board has made the following determination regarding an alternative skin irritation test method using EpiDerm and SkinEthics.
This is a highly ethical test method that when applied under suitable conditions, is useful as an initial step in the evaluation of skin irritants by means of a four-hour application of chemical substances to skin.

Bibliography

1. Peer Review Panel report on an alternative skin irritation test method using EpiDerm and SkinEthics
2. OECD (2005) OECD Series on testing and assessment Number 34, Guidance document on the validation and international acceptance of new or updated test methods for hazard assessment, ENJ/JM/MONO(2005) 14
3. Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), National Toxicology Program (NTP), et al. Background Review Document: In Vitro Cytotoxicity Test Methods for Estimating Acute Oral systemic Toxicity, NIH Publication No. 07-4518