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

   This test method is an alternative to the existing Draize test for assessing ocular irritation potency and involves assessing ocular irritation potency of test substances by observing changes in physical properties of an isolated bovine cornea after exposure to a test substance.

   This test method involves assessment of ocular corrosion and strong irritant potency based on measurements of corneal opacity and permeability.

   ICCVAM[1] has conducted an independent peer review based on internationally published academic papers, and an evaluation has been published that included eight reports on a total of 161 validated substances, which indicates that a transparent and independent peer review process has been performed.

   The JaCVAM peer review panel on alternatives to ocular irritation testing based its review on this data.

2. 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.

   The Draize test method is primarily a visual evaluation of the cornea, and this test method, which also evaluates the cornea, is a valid means of predicting ocular corrosion and severe irritant potency.

   Although there are significant anatomical and physiological differences between the corneas of different animals, insofar as the Draize test, which is performed on rabbits, is considered capable of predicting significant damage to the human eye, this test method, which is performed on a bovine cornea, should also be capable of serving that purpose.

   Regarding agreement between the results of this test method and those of the Draize test, no differences were found for substances classified according to GHS,[2] US EPA,[3] or EU classifications, and comparison with GHS classification results showed an agreement of 80%, indicating that this test method is a good predictor.

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

   This test method was developed in order to identify and classify hazards and is therefore useful for hazard assessment, but is not suitable for risk assessment.

   This test method assesses changes in the cornea immediately after exposure but does not assess recovery or other aspects thereafter.

4. 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.

   The supporting validation data for this test method includes a total of 161 chemical substances or products, which are either single chemical substances or commercial products or preparations comprising chemical compounds. Also, a variety of chemical structures, characteristics, properties, and irritation potencies were measured across a clearly defined spectrum of applicable substances.

   This test method is capable of assessing corrosion and severe irritation potency across a wide spectrum of substances. It is not, however, sufficient for predicting potency of alcohol, ketones, or solids.

   This test method assesses changes in the cornea immediately after exposure but does not assess recovery or other aspects thereafter.

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

   This test method, despite minute differences in protocol in the validation tests, provided results with good reproducibility and therefore can be considered sufficiently robust.

   This test method is simple enough to be easily transferable with the proper equipment and training.

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

The cost of this test does not differ significantly from that of the Draize test, but the time required to perform the test is significantly shorter.

Tests using rabbits require from one to 21 days to perform, but this test method can be completed in five to seven hours, provided that eyes are available. In the event a histopathological analysis is also performed, however, there is virtually no difference in time. (Report 1, page 11)

Regarding the usefulness of this test method, it has been proposed that, if used in combination with histopathological observation, a more detailed evaluation of the extent of corneal damage could be obtained, but this would require the establishment of clear criteria for determining effects on tissue morphology. In cases where BCOP is implemented to ascertain corrosion and severe irritant potency of a substance, histopathological observation is not necessarily required.

Although ordinary use in Japan is impracticable at this time, there is an overseas laboratory to which these tests could be subcontracted.

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

This test method is based on existing test methods and is a simple yet suitable means of assessment that is focused on the cornea. Scientifically, it is equivalent to existing test methods for the assessment of corrosion and severe irritant potency.

This test method is ethically preferable to the Draize test method.

This test method could potentially be a more economical alternative to animal testing. At present in Japan, however, due to difficulties in obtaining cow's eyes on a regular basis, testing would be subcontracted to overseas laboratories.

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

This method is capable of assessing direct corrosion and severe irritant potency of chemical substances. Within that limitation, it is suitable for used in a regulatory context.

Based on the above, the JaCVAM Regulatory Acceptance Board has determined that correct application in accordance with all precautions stipulated by the bovine cornea

opacity and permeability (BCOP) test method for assessing ocular irritant potency as an alternative to animal testing is a scientifically-valid means of assessing ocular corrosion and irritant potency of chemical substances.

Notes:

1. Interagency Coordinating Committee on the Validation of Alternative Methods, USA (ICCVAM)

2. Global Harmonized System of Classification and Labeling of Chemicals (GHS)

3. United States Environmental Protection Agency (US EPA)