Scientific Advisory Committee Consultation:

ENSURING DATA QUALITY FOR IN VITRO TESTS USED AS ALTERNATIVES TO ANIMAL STUDIES FOR REGULATORY PURPOSES

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EPA plans to adopt the **Performance Standards** developed by ICCVAM as a means of communicating the basis by which each of three validated *in vitro* test methods are deemed acceptable for providing dermal corrosivity data

The FIFRA Scientific Advisory Panel endorsed the **Performance Standards** approach to identify and validate "**me-too**" and "**unique**" in vitro assays

The Panel noted that the approach of using structural and functional equivalence to determine a "**me-too**" test is conceptually feasible

Performance Standards consist of descriptions of:

1) **Essential test method components** which are the essential structural, functional, and procedural elements of a validated test method that should be included in the protocol of a proposed **mechanistically** and **functionally** similar test method

2) A **minimum list of Reference Chemicals**, which is used to assess the accuracy and reliability of the similar test method

3) Comparable **accuracy** and **reliability** values that should be achieved by any proposed test method when evaluated using the minimum set of Reference Chemicals

The Panel concurred that the Performance Standards prepared by ICCVAM are very well described for each of the three tests:

- Corrositex® ,
- EPISKIN™/EPIDERM™ and
- Transcutaneous Electrical Resistance (TER)

and the information should provide a basis to determine whether a test is mechanistically and functionally similar to a validated *in vitro* test method

The approach of specifying a **known level of accuracy and reliability** for a “me-too” test to be considered equivalent to the validated test system was accepted by the Panel.

Panel members suggested that Reference Chemicals be limited to those that have been **tested with sufficient replication**, such that the reliability and accuracy estimates themselves are considered sufficiently precise.

Generic criteria used by ICCVAM for selecting subsets of the Reference Chemicals:

- includes representatives of applicable chemical classes
- measures a range of corrosive strengths
- includes well-defined chemicals that are currently available commercially
- has unequivocal animal or other *in vivo* evidence

The Panel recommended that, generically, the **Performance Standard** should include:

1) a stated minimum number of diverse test chemicals, from all relevant chemical classes

2) a requirement for Reference Chemicals with varying potencies, efficacies, or range of response, ideally within each chemical class, and

3) minimum standards for reliability and accuracy/concordance in the “me-too” test system results when compared to the known properties of the test chemicals for *in vivo* tests

"Although the use of of the entire original Reference Chemical set for validation of a "me-too" test might be considered excessive, it is nonetheless important to carry out a sufficiently broad characterization of a new test to validate its performance."

"Clearly a balance must be struck between maintaining a manageable number of Reference Chemicals and assuring that all relevant mechanistic and chemical classes are included."

Ensuring Consistent Quality and Test Performance:

"**Benchmark controls** as well as **positive and negative controls** should be tested in each new lot to determine the viability and usability of each lot."

"**Benchmark controls** are an important mechanism to assess both the adequacy of the method as well as lot-to-lot variability and should be considered as a standard component of these test methods."

"**Benchmark controls** should include several "classic" responders from different chemical classes/modes of action."