January 12, 2005
Sherry Ward
Physicians Committee for Responsible Medicine

Public Comments: ICCVAM Ocular Expert Panel Meeting

Hello, I'm Sherry Ward from the Physicians Committee for Responsible Medicine. I'm speaking today as a member of an animal advocacy organization, and also as a Ph.D. biochemist with a research background in industry and more than seven years of experience in working on the development and validation of human cell-based ocular test methods.

I would like to thank the members of the Ocular Expert Panel (OEP) for all of their hard work in reviewing the data presented to them by NICEATM. I would also like to make some comments regarding the BRD documents, and the overall processes that have become evident during this meeting. I'm asking the panel members to consider the following points before making their final recommendations:

1. Recommendations in the BRDs: Originally, I had decided to not speak to the point of inappropriate influence, because I knew that everyone was aware of the incomplete information and the "leading" recommendations made in the BRDs, and also that several other persons would be speaking to this point. However, after the direction taken yesterday, I think it is very important to revisit this issue again. The issue is whether the OEP can change the direction of their thoughts and conclusions from the original "force" of the negative recommendations made in the BRDs. In spite of all of the information provided at this meeting that demonstrates that at least one or two of the ocular methods are ready for use and validation at this time for the limited application as a positive screen for severe/corrosive materials in the GHS scheme, it is difficult to overcome the original and influential statements to the contrary that were made in the BRD documents. These recommendations do have a lasting influence.

2. Validation and Regulatory Acceptance: Dr. Stokes provided the definition of validation in his introduction as "the process by which the reliability and relevance of a procedure are established **for a specific purpose**." This means that a method can be reviewed and validated by the ICCVAM before it is fully optimized for all or even many product types and chemical classes. A method can be validated for a specific purpose, meaning for one or several product types and/or chemical classes. If the original purpose of the OEP had been presented in the context of mining the existing data to identify which methods and for what applications each method could be recommended to ICCVAM for review at this time, we would be many years ahead of where we are today in getting a method validated for use in the GHS tiered scheme as a positive screen for severe eye irritants.

Although a lot of time was spent in discussing the "clarity" issue yesterday, I do not feel that it is resolved. First of all, in the U.S. a new method has to be validated before it can be

considered for acceptance by the regulatory authorities. That is one of the ICCVAM regulatory acceptance criteria. To say in the U.S. that the data can be "accepted" from a test method, but not move the method to the ICCVAM OTWG for review for validation might be a meaningless process. A method's inclusion in IACUC reviews due to this designation is a minor step forward, and is not sufficient to ensure its use. Also, I'm not clear on why the statement was made that if the methods are validated that they will be required. That has been a policy in the EU, but not in the U.S.

I think a lot of the uncertainty involves a lack of understanding by some OEP members about the regulatory use for which these methods are being proposed. A review of the flow scheme for eye irritation/corrosion in the GHS document (UN, 2003) shows that a material can be labeled as a corrosive/severe eye irritant if it has an extreme pH or if the structure of the compound indicates it is corrosive. The next step involves testing the material in an animal or with a validated in vitro method [there are no validated in vitro methods for this step, and this is where the four in vitro ocular methods would be used – if any of them become validated]. If the material tests positive in the animal [or in vitro if one becomes validated] it can be labeled as corrosive. If it tests negative, it must be further tested in animals. Therefore, even with validated in vitro methods that are not "perfect," an eye irritant would not escape either being labeled as corrosive or being further tested in animals. The structure-activity program(s) that can be used as a positive screen for a corrosive eye irritant in the GHS scheme have never been validated. The Draize test that can be used as a positive screen for a corrosive eye irritant has never been validated. However, for an in vitro test to be used as a positive screen for the same purpose, it has to be validated, and this is the only purpose for which the four in vitro ocular test methods are being evaluated at this time.

3. Regulatory Acceptance of these Methods in Europe: The four ocular methods under review have been used and accepted as positive screens for severe and corrosive eye irritants by many European regulatory authorities [see ATLA 30 (Suppl. 1), 42-43 (2002)]. These methods are long past being ready to be used in the U.S. for the same purpose. We are not aware of any human safety issues from this application of the in vitro test method(s). We, therefore, question why NICEATM failed to include an extensive review of this ongoing regulatory acceptance of these methods in the BRDs.

4. Use of these Methods by Industry: The four ocular in vitro methods are currently used for the entire ocular safety decision-making process in some companies, rather than just as a positive screening assay as proposed in the BRDs. An appropriate discussion of industry's use of these methods in a decision scheme was insufficiently presented in the BRDs, as noted in several of the written public comments. We are not suggesting that you change the purpose of this review, but we want to point out the wide use and utility of these methods. Each of the four methods being evaluated has particular strengths and weaknesses, and if they are all (except the IRE, for reasons noted below) approved for use as screening assays, this will give companies the flexibility they need to choose the proper method or methods that are compatible with testing of their products.

5. Optimization of Test Method Decision Criteria Using Existing Data: As noted by NICEATM, the currently used decision criteria for the in vitro methods could be optimized to reduce over- or under-prediction for any of the methods. There is no need to conduct additional studies to make this evaluation, because the existing data can be used. These analyses, or at least an example, should have been provided in the BRDs to assist the OEP in their evaluation of the test methods. We request that NICEATM provide more information and specific examples of how this kind of analysis could enhance the performance of an assay when the ocular methods are reviewed for validation by the ICCVAM OTWG.

Therefore, we are respectfully making the following **recommendations** to the OEP:

- Our recommendation to the OEP is that they support a retrospective validation of one or more of the ocular methods using existing data without requiring additional optimization and validation, because sufficient data currently exist to make this recommendation. There is no danger that a severe eye irritant would escape the screening process, because any negative testing material is still required to undergo additional animal testing. This would just ensure that regulators could not require a known severe or corrosive material be tested in a live animal, and most companies already adhere to this ethical principle.
- We request that ICCVAM act to validate the methods recommended to them as soon as possible.
- We also strongly oppose ANY animal testing for conducting new optimization or validation studies. In addition to the animal welfare concerns, the CTFA study is an excellent example of why this is not the approach to take. They conducted the best possible study using newly formulated materials and new animal test data. The methods they reviewed were not successful at that time, and I strongly doubt a perfectly predictive method for human eye irritancy would pass the scrutiny of the process as it is now designed.
- And finally, we propose that wording be added to any protocol accepted for the Isolated Rabbit Eye method that prohibits, without any exceptions, the use of laboratory rabbit eyes. Since there are not many suppliers for rabbit meat, and delays in the use of an intact eye would render it unusable for the toxicity assays, there appears to be no justification for investing additional resources in evaluating or refining the IRE test method.