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Dear Dr. Zeeman:

In response to your October 13, 2003 request, we are pleased to provide comments (enclosure) on behalf of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) on the revised," Draft Guidance Document (No. 34) on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment (OECD, October 2003)." We also acknowledge and appreciate your assistance in obtaining additional time for review and response.

The Committee was pleased to find revisions responsive to a few of the ICCVAM comments submitted on the previous version of this document (OECD, September 2001). In particular, we commend OECD staff for responding to our recommendation to include as annexes the "Solna Principles and Criteria," and the "ICCVAM Guidelines for the Nomination and Submission of New, Revised, and Alternative Test Methods." These additions will ensure ready access to important information highly relevant to the proposed document.

However, we were disappointed to find that many of the ICCVAM recommendations on the previous draft were not addressed or included in this revised draft. We have therefore restated many of our previous recommendations in our current comments and have also provided additional recommendations in response to significant new additions and revisions to this version.

We request that if you disagree with any of the ICCVAM comments, that you contact us prior to indicating such disagreement in the U. S. position that will be forwarded to OECD. If such circumstances arise, we would like the opportunity for interested ICCVAM representatives from the 15 member agencies to further discuss with you the basis for any recommendations that you do not support. Please feel free to contact us if you have any questions or if ICCVAM might be of further assistance. Thank you for the opportunity to contribute to this important document.

Sincerely,

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Enclosure

cc:
ICCVAM Agency Representatives
Dr. Angela Auletta

Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)

Comments on the Revised (October 2003) *Draft Guidance Document No. 34 on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment*

Comments from the ICCVAM are provided below for the OECD document, *Draft Guidance Document on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment* [October, 2003] (hereafter, GD). Based on its extensive experience with validation, independent peer review and regulatory acceptance of test methods, ICCVAM would be pleased to provide assistance to the OECD in revising the GD in accordance with the recommendations provided below.

1. Chapter V (pages 23-39). As stated previously in comments submitted on the September 2001 version of this draft GD, ICCVAM strongly recommends that the GD should describe recent test methods that have been evaluated for their scientific validity and subsequently accepted for regulatory applications. These test methods provide examples of various ways to validate test methods, and how that validation varies with the intended use of the method. ICCVAM has evaluated the validation status of several new and revised test methods for various purposes, including the murine Local Lymph Node Assay (LLNA), Corrositex™, the revised Up-and-Down Procedure (OECD TG425), the Frog Embryo Teratogenesis Assay—*Xenopus* (FETAX), and *in vitro* methods for assessing acute systemic toxicity. Likewise, ECVAM has evaluated the validation status of test methods such as EpiDerm, EPISKIN, and the TER. Each of these evaluations has been followed by publication of a report characterizing the usefulness and limitations of the test method (see references below) and the process used for both validation and subsequent evaluation of the validation status. As previously recommended in November 2001, ICCVAM requests that these important examples be discussed and referenced in the GD.

2. Chapter V (pages 23-38) now apparently describes a specific validation management process advocated by the OECD Test Guidelines Program and fails to recognize or describe validation management processes and approaches used by other organizations to successfully conduct validation studies to characterize the usefulness and limitations of proposed new test methods. ICCVAM recommends that this Chapter describe and emphasize generic processes that reflect the fundamental principles of high quality scientific validation study approaches common to all validation studies (including those used by ECVAM, ICCVAM and other government and non-government laboratories), rather than a description of the procedures OECD recently applied to in vivo endocrine disrupter testing methods. Examples of various approaches that have been used to conduct effective validation studies should be mentioned in the Chapter, and detailed descriptions or summaries of these specific institutional processes, should more appropriately be provided in an Annex or Supplement. These examples should include the validation and/or evaluation

processes used by ICCVAM, the European Centre for the Validation of Alternative Methods (ECVAM), the National Toxicology Program Interagency Center for the Evaluation of Alternative Methods (NICEATM), and other organizations that conduct independent validation studies and test method evaluations.

3. Chapter VI (pages 39-45) "Independent Evaluation of a Validation Study (Peer Review)." In its comments on the previous draft GD (OECD, Septmeber 2001) ICCVAM recommended that a chapter should be provided on Independent Peer Review Evaluation and Regulatory Acceptance Processes. The recommendation was that this Chapter "*should provide practical guidance for independent peer review evaluation and regulatory acceptance processes for new and revised test methods."* However, most of Chapter VI is now largely composed of detailed procedures, tables, and complex figures describing proposed OECD review processes leading to OECD adoption of OECD test guidelines. This material did not appear in the September 2001 draft, and was not presented or discussed at the 2002 Stockholm Conference. Such OECD specific procedures and processes should be deleted from this chapter and either provided as examples in an Annex or Supplement, or more appropriately, incorporated in an updated version of OECD Guidance Document No.1: "Guidance Document for the Development of OECD Guidelines for Testing of Chemicals (1993, reformatted 1995)." ICCVAM recommends that this chapter focus on principles and practical generic guidance, and reflect the salient conclusions and recommendations from the 2002 Stockholm conference. ICCVAM strongly recommends the deletion of paragraphs 114-117, Table 2, and Figures 5, 6 and 7 (pp. 39-44) and paragraphs 123-125. The addition of the following text is recommended to replace the entire section entitled "Mechanisms for Peer Review" (pp. 39-44, paragraphs 114-117, Table 2, and Figures 5, 6, and 7), and paragraphs 123-125 in the section entitled "Peer Review Process" (p. 45):

Pages 39-44: "Mechanisms for Peer Review"

Para 114. Delete current text. Replace current paragraph with the following: It is clear that not all toxicological test methods require the full attention of expert international review and assessment of validation. Certain national regulatory agencies and processes involve the development of test methods to assure the efficacy and safety of individual agents or products that are not applicable to a wide range of chemicals or products. With this type of individual product-specific testing, international harmonization and agreement are not possible for temporal reasons and because of the very specialized nature of the individual product. The specific test method developed may be used for only this product or for a very limited series of products, and therefore expert international review and validation assessment often is not appropriate or desirable.

115. Delete current text. Replace with the following: If test methods will be: 1) used often, 2) for commonly assessed toxicological endpoints, 3) for broad application over numerous categories of regulated products, and 4) for use over extended time periods, an independent evaluation of the validation status of these

tests is extremely valuable to provide information on usefulness and limitations that can assist regulatory authorities with their decisions on the acceptability and applicability of the test method for their regulatory responsibility. Public availability of such evaluations, as well as the opportunity for stakeholders to observe and provide comments for the evaluation will further support international harmonization of test methods and provides greater assurance of its usefulness, reproducibility, and regulatory acceptability.

116. Delete current text. Replace with the following: The sponsor of the test method seeking independent evaluation of the scientific validity of the test method is responsible for contacting one of the internationally recognized organizations; e.g., the European Center for Validation of Alternative Methods (ECVAM) or the US Interagency Coordinating Committee for the Validation of Alternative Methods (ICCVAM) which specialize in validating test methods, to arrange for the process of independent evaluation. The organization to whom the request for evaluation is directed is responsible for assuring selection of panel members who are: independent and free of conflicts of interest, expert in the same or closely related discipline, and knowledgeable in those other aspects of the data review that are deemed necessary to provide a scientifically informed and expert validation review.

117. Delete current text. Replace with the following: It is important for the sponsor of the new or updated test method to carefully assess the quantity and quality of the data available to support the validation review process. A submission requesting determination of validation status should include:

- Rationale for the proposed test method
- Test method protocol components
- Substances used in the validation of the proposed method
- *In vivo* reference data for assessing the method's accuracy
- Test method data and results
- Test method accuracy
- Test method reliability (repeatability/reproducibility)
- Statement assessing test method data quality
- Other pertinent scientific reports and reviews
- Assessment of test method refinement, reduction and replacement
- Evaluation of strengths and limitations of the test method
- References
- Supporting materials

A more complete explanation of the information that should be provided for each of these items is available in Annex III of this document.

118. Delete current text. Replace with the following: Although flexibility in the review process is considered essential, if flexibility would result in a situation that would not meet the standard of a balanced, expert, and fully transparent review, it would be unacceptable.

Page 45: "Peer Review Process"

123. Delete current text. Replace with the following: The international peer review panel should be provided a list of scientifically directed questions appropriate for the nature of the test method being evaluated. These questions can serve as a template for the panel's evaluation. The questions are usually of a standard nature; e.g., has the test method data been collected using studies designed and conducted to comply with appropriate international standards for Good Laboratory Practices? Or may be of a more specific nature to assess the maturity and appropriateness of the protocol components with respect to attaining the objective of the proposed test method. Materials reviewed by the panel should be made available to the public and comments should be invited from the public. These comments should be made publicly available, and provided to the members of the panel for their consideration. Ideally, the panel should meet in public session, with an opportunity for public comments to be made at the meeting. At the end of the review process, the overall assessment of the panel should be determined with regard to the questions directed to the panel. The answers to the questions form the basis for the final assessment of the usefulness and limitations of the test method. It is essential that the basis of disagreements among panel members that cannot be resolved be adequately documented in the panel's report.

124. Delete current text. Replace with the following: The results of the deliberation by the expert review panel should be available in written form subsequent to the final determination of validation status of the test method. This report should be available for widespread public dissemination, and it is preferable that the panel report, or synopsis of the panel report, be published in a peer-reviewed journal.

125. Delete current text. Replace with the following: In certain instances, a previously reviewed test method which has been subjected to further revision or development may be submitted for an additional or subsequent review of its validation status. The level of effort devoted to this subsequent validation review should be commensurate with the degree and importance of changes that have occurred to the protocol components of the test method.

4. It is important to recognize the considerable progress that has been made on the development of nationally and internationally harmonized criteria and processes for the validation and regulatory acceptance of new test methods. Many national and regional organizations have contributed to this progress, including ICCVAM in the U.S., ECVAM in Europe, the Johns Hopkins University Center for Alternatives to Animal Testing (CAAT) in the U.S., the Fund for the Replacement of Animals in Medical Experiments (FRAME) in Europe, the Center for Documentation and

Validation of Alternatives to Animal Experiments (ZEBET) in Germany, the European Research Group for Alternatives to Animal Testing (ERGATT), the National Centre for Alternatives (NCA) in the Netherlands, the Swiss Institute for Alternatives to Animal Testing (SIAT), and the OECD. Furthermore, many countries, including the United States, have established organizations and processes to coordinate validation and acceptance activities and these organizations have, in a relatively brief time period, implemented effective processes for such activities. While the revised GD has included reference to these organizations, descriptions of their experiences and processes remain deficient in the document. ICCVAM recommends that these experience and processes should be discussed and incorporated where appropriate in the GD.

5. The GD should convey that the most important aspect of any test system should be a thorough understanding of its underlying biology and its mechanistic relevance. Short-term tests are generally developed to measure a single biological effect. In the past, extensive effort has been spent trying to determine how well assays that measure single biological effects correlate with health outcomes that result from multiple biological effects. Because of this inherent limitation associated with such short-term tests, it was inevitable that the multi-million dollar, twenty-year effort to develop short-term genotoxicity tests to predict rodent cancer outcomes would fall short of expectations. Hopefully the lessons learned will keep similar approaches from being used for validating alternative assays in the future. The GD should include a discussion about the importance of understanding the mechanistic relevance of test models, and include a discussion of the limitations and usefulness of genotoxicity tests that were learned as a result of those extensive validation studies.

6. Use of the term " Validation Management Group" as the organization that should conduct and manage validation studies suggests that OECD's proposed GD also confers methods validation authority to OECD. OECD has admirably served the purpose of standardizing test guidelines. Studies conducted in accordance with the standardized guidelines can be used by all regulatory authorities to the extent the method achieves their regulatory needs. The newly self-designated OECD role of serving as both a validation authority and, to some degree, a regulatory acceptance authority, could have significant consequences in light of the treaty obligations requiring mutual acceptance of data from OECD accepted methods. This role also raises a potential appearance of a conflict of interest where one organization assumes responsibility for validation, independent assessment and regulatory acceptance. This contrasts sharply with recently enacted law in the U. S. that establishes ICCVAM as the U.S. validation authority (ICCVAM Authorization Act of 2000, U.S. Public Law 106-545). This law also establishes an evaluation process with clear lines of separation for validation study conduct, validation status evaluation and regulatory acceptance. It is therefore strongly advised that caution should be taken not to invoke policy in the GD that may foster trade barriers as some products are regulated under different regulatory mandates internationally. Some mandates require the use of validated alternative assays and others require the use of non-alternative (classical) assays. Such a centralized OECD regulatory acceptance authority could further dilute

the ability to delineate the acceptable criteria of test method validation according to chemical use. For example, OECD test guidelines make no attempt to discriminate the usefulness and limitations of methods for use in testing substances in completely different applications, such as pharmaceuticals, environmental contaminants, or food additives. This was a key element in acceptance of LLNA. Some representatives of ICCVAM member Federal agencies therefore continue to oppose the current draft GD proposed by OECD unless it is revised to clearly state that there is no intent to establish its authority as a formal international methods validation organization, and that it does not intend to expand its current role beyond a methods standardization authority.

7. The Draft GD provides a recommended generalized framework for the development and validation of hazard assessment test methods prior to acceptance by international regulatory agencies. The guidance is an extension of the criteria developed at the Solna workshop. Although the validation scheme elaborated by the document is generally a useful framework, it is unlikely that the large majority of the tests used by some agencies to comply with statutory responsibilities will or could be validated under the procedure outlined. Therefore we recommend that the following text be added to paragraph 51, "The guidance in this document is intended to be sufficiently flexible so that it can be used for any type of test, regardless of whether it is an *in vitro* or *in vivo* test, or a screening test or a definitive test. Nevertheless, it should be recognized that other validation frameworks and schemes may be necessary and appropriate for hazard/risk assessment test methods that are commonly used in some agencies, such as those dealing with evaluation of biologics safety and efficacy." Some of these test methods are necessarily diverse due to the nature of biologics and the need to evaluate risk in the context of a risk/benefit ratio that is specific for a particular disease and clinical condition. Additionally, because of these inherent fluidities and situations of limited application, it may not be appropriate for some specific methods to undergo generalized validation. Furthermore, paragraph 128 of the document recognizes that "regulatory authorities may still have additional questions on the test beyond its established reliability and relevance, which could affect its regulatory acceptance." Therefore, it appears this wording anticipates that many of the methods validated within the framework will not be relevant to agencies that have specific, focused regulatory concerns which supports the inclusion of the recommended text above.

8. The purpose and perspective of the GD is not clearly stated. If this is supposed to be a document that generally discusses validation, it appears to speak too much from the perspective of OECD itself performing the validations rather than from the perspective of a general guideline for performing validation-related activities by various groups, sponsors, or organizations.

9. Para 24. The “flexibility” described in this paragraph is acceptable provided that it does not impact on the appropriateness of the assay (see also suggested Para 123 under comment #3).

10. Para. 31. In the previous version of the GD, the term " test's position" in a testing program was used that created a point of confusion. Although this paragraph has been revised in an attempt to clarify this term, it still refers to a "test method's position" and this terminology remains unclear.

11. Para 38: As this paragraph is currently written, proof of the ability to comply with GLP can substitute for demonstrated competence in a specific test method. However, these two concepts are independent and not interchangeable. Regardless of how skillful and experienced a laboratory is in GLP, it should not be allowed to participate in a test procedure at which it has no competence or experience. An exception to this would be where a new procedure is being validated and no laboratory, other than the developing lab, has the requisite experience.

12. Para 52: The segment of the scientific community most in need of this guidance is the smaller organizations. It would be useful for a sentence or paragraph to be inserted here to address such a situation. Otherwise, an individual or small organization not involved with OECD, ECVAM, or ICCVAM might believe that this Guidance Document is not applicable to their situation.

13. Para 61/68: The criteria for determining whether a particular protocol is a good potential candidate for supporting the fairly structured data interpretation procedure should be clarified.

14. Para 73: It would be useful to include a statement addressing the fact that the inclusion of a laboratory that does not have the appropriate experience among laboratories that do have experience could seriously affect the determination of inter-laboratory variability and cause the test to appear less reproducible than if only experienced laboratories were involved.

15. Para. 119. The type of philosophical conflict of interest that is to be avoided is unclear. This should be clearly defined, or deleted.

References

ICCVAM. 1999. The Murine Local Lymph Node Assay: A Test Method for Assessing the Allergic Contact Dermatitis Potential of Chemicals/Compounds. NIH Publication 99-4494. National Institute of Environmental Health Sciences, Research Triangle Park, NC. Available on the Internet at: http://iccvam.niehs.nih.gov/methods/invidocs/finalall.pdf.

ICCVAM. 1999. Corrositex: An *In Vitro* Method for Assessing Dermal Corrosivity Potential of Chemicals. NIH Publication 99-4495. National Institute of Environmental Health Sciences, Research Triangle Park, NC. Available on the Internet at: http://iccvam.niehs.nih.gov/corprrep.htm.

ICCVAM. 2001. Report of the International Workshop on *In Vitro* Methods for Assessing Acute Systemic Toxicity. NIH Publication 01-4499. National Institute of Environmental Health Sciences, Research Triangle Park, NC. Available on the Internet at: http://iccvam.niehs.nih.gov/methods/invidocs/finalall.pdf.

ICCVAM. 2001. Guidance Document on Using *In Vitro* Data to Estimate *In Vivo* Starting Doses for Acute Toxicity. NIH Publication 01-4500. National Institute of Environmental Health Sciences, Research Triangle Park, NC. Available on the Internet at: http://iccvam.niehs.nih.gov/methods/invidocs/guidance/iv_guide.pdf.

ICCVAM. 2001. The Revised Up-and-Down Procedure: A Test Method for Determining the Acute Oral Toxicity of Chemicals. NIH Publication 02-4501. National Institute of Environmental Health Sciences, Research Triangle Park, NC. Available on the Internet at: http://iccvam.niehs.nih.gov/methods/udp.htm.