**American College of Toxicology Webinar**

**Adversity in Nonclinical Reporting: Myths, Legends, and Reality**

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**About the Speaker:**

Dr. Roy Kerlin is an Australian Veterinarian with a PhD in Immunology. He worked at the University of Pennsylvania in the Department of Biology and the Walter and Eliza Hall Institute of Medical Research in Australia on B lymphocyte biology, including the control of antibody isotype switching. He completed his Residency in Veterinary Pathology at the University of Pennsylvania followed by a Clinical Instructorship at the University of Wisconsin at Madison. Roy is currently employed at Pfizer Inc. as Head of Toxicologic Pathology in Groton, Connecticut. He has 66 publications, including primary papers, reviews and book chapters, as well as innumerable symposium abstracts and platform presentations. Roy is an active member of the Society of Toxicologic Pathologists, recently serving as Chair of the Scientific and Regulatory Policy committee, and Chair and founder of the Regulatory Forum Committee.

Towards the end of 2012, The Society of Toxicologic Pathology (STP) sponsored a working group to address the concept of “Adversity” in regulatory documents through the auspices of the Scientific and Regulatory Policy Committee. Confusion about identifying an “adverse” effect leading to the designation of a “No Adverse Effect Level (NOAEL)” in nonclinical studies has too frequently resulted in misunderstandings and unnecessarily contentious situations. Inconsistent approaches and opinions related to communicating adverse effects in nonclinical study reports, summary documents, and data tables can impede risk assessment and management, and unnecessarily delay progression of beneficial drugs undergoing clinical evaluation. The STP believed that agreement or standardization of basic principles related to “adversity” and “NOAEL” could vastly improve the understanding of nonclinical study results for clinicians and regulators.

Recommendations of the STP paper published in 2016 are presented below in the order they apply in the course of performance and communication of results from a nonclinical study.

1. “Adversity” is a term indicating “harm” to the test animal, within the constraints of the study design (dose, duration etc.)
2. The decision about whether or not test article-related effects (or a group of related effects) in a nonclinical study are considered “adverse” or “non-adverse” should be unambiguously stated and justified in sub-reports and/or the study report.
3. “Adversity” as identified in a nonclinical study report should be applied only to the test species and under conditions of the study.
4. Toxic effects on cells, tissues, organs, or systems within the test animal should be assessed on their own merits
5. Communication of what is considered “adverse” and assignment of the NOAEL in the overall study report should be consistent with, and supported by, the information provided in the study sub-reports.
6. Communication of adverse findings and the NOAEL should include direct interaction between staff within different contributing scientific disciplines
7. The NOAEL for a test article should be communicated in an overview document based upon data from multiple studies.
8. In order to place them in appropriate context, the use of NOAELs in data tables should be referenced to explanatory text.
9. Nonclinical scientists, including toxicologists, pathologists, and other contributing subject matter experts who interpret data from nonclinical studies, should be active participants in assessing and communicating human risk
10. All available data from all nonclinical studies must be evaluated together to define any potential toxicities and to predict human risk.

During the Webinar, these principles will be discussed and a number of case examples will be presented to highlight practical application of these principles.

In conclusion, these recommended practices are intended to produce a more consistent approach to determining, communicating and applying decisions about adversity in nonclinical studies. The identification of an effect as adverse and the resultant NOAEL designation will continue to be based upon scientific interpretation of the available nonclinical data. These recommendations will minimize misunderstandings related to nonclinical study results and their implications for establishing potential human risk.

* The views expressed in this article are those of the author and do not necessarily represent the policies, positions or opinions of Pfizer Inc. or the Society of Toxicologic Pathology.