Adversity Designation and Application to Drug Development

Vincent Meador, DVM, PhD, DACVP (Anatomic and Clinical)
Pacific Tox Path, LLC
Purpose of a Nonclinical Development Study

Regulatory Working Assumption: “Your drug causes toxicity” (Paracelsus)

• “Now determine…..
  – what the toxicity is
  – what dose causes toxicity
  – which tissues or systems are affected
  – how adverse it is
  – what makes it adverse
  – timing
    • when finding(s) occurs
    • if and when finding(s) will go away
  – how finding will be detected if it occurs
  – if possible, the pathogenesis and mechanism
  – and, the finding’s applicability to humans”

Auroleus Phillipus Theophratus Bombastus von Hohenheim (aka, Paracelsus, Grandfather of Toxicology)

Born (1493) in Switzerland of German heritage and died (1541) in Austria

“Poison is in everything, and no thing is without poison. The dosage makes it either a poison or a remedy.”
‘Adverse’ is an Impactful Determination

• ‘Adverse’ forms health-based guidance values
  – No-Observed-Adverse-Effect-Level (NOAEL)
    • Define entry dose for First-In-Human studies
    • Estimate margins of exposure in human health risk assessment
      – Environmental chemicals
      – Food additives
      – Therapeutics

• ‘Adverse’ also contributes to continued development decisions of a molecule through the IND process
  – Nonclinical drug development continues simultaneously with Clinical studies
    • Adds confidence to safety profile for humans
  – Potential Outputs
    • New findings
    • Additional data on prior findings
    • Adjust human exposure levels
    • IND Safety Report initiation
    • Clinical Hold decisions
Recognition of Adverse and Nonadverse Effects in Toxicity Studies

RICHARD W. LEWIS,1 RICHARD BILLINGTON,2 ERIC DEBRYUNE,2 ARMIN GAMER,4 B. LANG,3 and FRANCIS CARPANINI6

1Syngenta CTL, Health Assessment and Environmental Safety, Alderley Park, Cheshire UK SK10 4TJ
2Dow AgroScience, Oxford UK
3Aventis Crop Protection, Sophia Antipolis, France
4BASF AG, Ludwigshafen, Germany
5Syngenta AG, Basel, Switzerland, John Van Miller, Union Carbide, Dunbury, CT, USA, and
6ECETOC, Brussels, Belgium

The no-observed-adverse-effect-level in drug safety evaluations: Use, issues, and definition(s)

Michael A. Dorato a,*, Jeffry A. Engelhardt b

a Toxicology Division, Lilly Research Laboratories, A Division of E·L·R·L and Company, Greenwood, IN 46140, USA
b Preclinical Safety Assessment, Amgen Thousand Oaks, CA 91320, USA

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Identification and Characterization of Adverse Effects in 21st Century Toxicology


Sanofi US, Bridgewater, New Jersey 08807; Dow AgroSciences LLC, Indianapolis, Indiana 46268; Brown University, Providence, Rhode Island 02912; Colorado State University, Fort Collins, Colorado 80523-2001; BASF Corporation, Research Triangle Park, North Carolina 27709-2000; US Environmental Protection Agency, Research Triangle Park, North Carolina 27711; and JSI Health and Environmental Sciences Institute, Washington, District of Columbia 20005-1743

http://www.urbanfischer.de/journals/avtpopath

Session Report from the Joint STP/IFSTP International Symposium “Toxicologic Pathology in the New Millennium”
June 24–28, 2001, in Orlando, Florida

Co-chairman, Consultant, Langendorfer St. 17, Wiltfahr, Germany
Co-chairman and speaker, NYMC, Dept. Pathology, BSH, Valhalla, NY, USA
Speaker, Syngenta Central Toxicology Laboratory, Cheshire, England
Speaker, CHT, Centers for Health Research, Research Triangle Park, NC, USA

Distinguishing between adverse and non-adverse effects

Session summary

E. Karre, G. M. Williams, R. W. Lewis, I. Kimber, and P. M. D. Foster
Basic Issues Related to Use of the Terms “Adverse” and “NOAEL”

• Variable approaches and opinions related to
  – Identifying which effects are “Adverse”, thereby affecting the “NOAEL”
  – Communicating adverse effects from nonclinical studies
    • Report
    • Summary documents
    • Data tables
  – Using adverse effect data and NOAEL in the assessment of human risk
Primary Objective

- Develop recommendations to improve the
  - Identification
  - Communication
  - Utilization

..... of adverse effects found in nonclinical studies

Ultimate Objective

- Contribute to more effective and efficient product development through improved communication and reporting
Recognition of Adverse and Nonadverse Effects in Toxicity Studies

Richard Y. Egan, M.D.
1 Syngenta, RTP, NC, USA
2 Syngenta, Basel, Switzerland

Session Report
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†Sage Publications Inc., New York, New York, USA
‡Department of Pharmacology, University of Michigan, Ann Arbor, Michigan 48109, USA
§University of Wisconsin, Madison, Wisconsin 53706, USA
∥US Environmental Protection Agency, Research Triangle Park, North Carolina 27711; and ††Integrated Health and Environmental Sciences Institute, Washington, DC 20005-1743

Scientific and Regulatory Policy Committee: Recommended (“Best”) Practices for Determining, Communicating, and Using Adverse Effect Data from Nonclinical Studies

Roy Kerlin, Brad Bolon, John Burkhardt, Sabine Francke, Peter Greaves, Vince Meador, and James Popp

Scientific and Regulatory Policy Committee

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STP Adversity Working Group Recommendations

• Recommendations of the STP Adversity Working Group are presented in the order they apply in the course of performance and communication of results from a nonclinical study

• Three sections of 10 recommendations
  – Determining 'Adversity' and “NOAEL” (1-4)
  – Communicating 'Adversity' and “NOAEL” (5-8)
  – Using 'Adversity' and “NOAEL” in assessing human risk (9-10)

Primary driver in ’Adversity’ Process

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Study/Animal Adversity Emphasis Human
Hazard Identification Risk Assessment
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Study/Animal Adversity Emphasis Human Risk Assessment

Hazard Identification
STP Recommendation 1
(Determining 'Adversity' and “NOAEL”)

'Adversity' is a term indicating “harm” to the test animal within the constraints of a given study design (dose, duration, route of administration, etc.)

- Not all test article-related effects are harmful
- Only harmful changes are ‘adverse’
- Test article-related changes that are not harmful are ‘non-adverse’
STP Recommendation 2
(Determining 'Adversity' and “NOAEL”)

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

• A decision regarding a designation of adversity represents an interpretation
• Reasons for the interpretation should be
  – Clear
  – Concise
  – Complete
  – Convincing
STP Recommendation 3
(Determining 'Adversity' and “NOAEL”)

'Adversity' as identified in a nonclinical study report should be applied only to the test species and under conditions of the study

• The study report should address the findings only in regards to the harm to the species in the study
  – Not extrapolated to
    • Other species, including humans
    • Additional studies
      – changed duration
      – different design
      – different model
Toxic effects on cells, tissues, organs, or systems within the test animal should be assessed on their own merits

- Adversity decisions should be based on actual observations and not speculation concerning
  - Pathogenesis
  - Primary, Secondary or Tertiary effect
  - Species specificity
  - Disease indication
  - Reversibility
  - Adaptation
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STP Recommendation 5
(Communicating 'Adversity' and “NOAEL”)

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

• All test article-related changes should be documented in the sub-reports and study report
  – Adverse or non-adverse

• NOAEL should be identified in the study report based on all study data and not identified in sub-reports

• Avoid ambiguous statements (e.g., biologically significant)
  – If use, define and support
STP Recommendation 6  
(Communicating 'Adversity' and “NOAEL”)  

Communication of ‘adverse’ findings and the NOAEL should include direct interaction between staff within different contributing scientific disciplines

- A single toxicity may manifest in different ways to scientists in distinct disciplines and thus be presented uniquely in the various sub-reports
- A complete view of a test-article related effect requires integration of all perspectives within the study report
STP Recommendation 7
(Communicating 'Adversity' and “NOAEL”)

The NOAEL for a test article should be communicated in an overview document based upon data from multiple studies

- Integration is necessary because a NOAEL identified in one study may be discounted as irrelevant within an overview document based on data from another study
- Selection of the NOAEL in the most sensitive species requires analysis of data from all available studies

- Examples of overview documents: IND, CTA, Investigators Brochure, NDA
In order to place in appropriate context, the use of NOAELs in data tables should be referenced to explanatory text

- Rationale communicated in text provides critical insight regarding the basis for the NOAEL
- Use of the NOAEL without an understanding of the effects observed in nonclinical studies can lead to inappropriate drug development decisions
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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

- Individuals who generate sub-reports are best qualified to explain the data set and its interpretation
- Nonclinical scientists from multiple disciplines provide valuable insight in
  - Assisting the study director to weigh the evidence to set the NOAEL
  - Advising the clinical research team with respect to setting the initial dose
All available data from all nonclinical studies must be evaluated together to define any potential toxicities and to predict human risk

- Experimental studies designed to understand the pathogenesis of a nonclinical study finding may profoundly influence the human risk profile
- Assessment of human risk should be based on all available data
  - Nonclinical studies
  - Clinical studies
  - Literature of structurally related or similar acting agents
Summary

• Recommended practices are intended to produce a more consistent approach to determining, communicating and utilizing information on adverse effects noted in nonclinical studies.

• Consistency of approaches will minimize misunderstandings related to the nonclinical effects and the implications of these effects for indicating potential human risk.

Identification of an effect as adverse and the resultant NOAEL designation will continue to be based on scientific interpretation of the available nonclinical data.
Thanks to Drs. John Vahle and Norman Kim on assistance with the presentation, to members of the STP Adversity Working Group: Drs. Kerlin, Bolon, Burkhardt, Greaves, Franke, and Popp.