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GUEST EDITOR'S NOTE: BIOSTATISTICS IN PRECLINICAL STUDIES

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PRECLINICAL studies are not as clearly defined as clinical studies with their Phase I-Phase IV classification. Moreover, the statistical methodology varies more in preclinical studies depending on the rather different nature of the studies. This may be one reason for the underrepresentation of statisticians working in this field as well as of the number of papers published on this topic, again, in comparison with clinical trials. Pharmacology, toxicology, substance screening, bioassay, stability testing, and so forth, however, play an important role in the drug development process.

It is difficult to find statistical publications in the nonclinical area, because they are widespread in biostatistical papers, for example, in Biometrics (1), in toxicological papers, for example, in Mutation Research (2), and in pharmacological papers, for example, in Regulatory Toxicology and Pharmacology (3). Several books were published in the last seven years, for example, Kirkland (4), Hothorn (5), Krewski and Franklin (6), Vollmar (7), and Morgan (8).

In toxicology, for example, two objectives of biostatistical work can be distinguished: academic—to find the most sophisticated approach—and practical—directed by the so-called "regulatory toxicology," that is, the toxicological studies defined by national and international guidelines or recommendations in the industrial drug development process. These studies, performed in either pharmaceutical companies or in contract research organizations, are routine in character. If, for example, hundreds of Ames assays a year are analyzed in a laboratory, using very different substances with different mechanisms in the same assay, this is done due to the need for cost minimization. Therefore, statistical approaches should be as robust as possible against real data configurations, as simple as possible for physicians to interpret, as clear as possible in relation to the false positive/false negative rate, and available as validated software. One dilemma is that the bandwidth of approaches for design and analysis of toxicological studies is too broad from the above viewpoint. Moreover, some of the International Conference on Harmonisation (ICH) documents and national guidelines on toxicological issues include facts relevant to statistics. Unfortunately, these seem to be largely written by nonstatisticians. Therefore, there is a need for recommendations on statistical analysis. Two such papers were developed in preparation for the DIA meetings in Brugge (March 1996) and Tokyo (August 1996): one on mutagenicity studies (9), the other on repeated toxicity studies (10). A third paper, on animal carcinogenicity studies, is still under preparation by an international team under the supervision of W. Fairweather.

The DIA workshop held in March 1996 in Brugge (Belgium), consisted of five sessions which included:

- Animal carcinogenicity studies,
- *In vivo* and *in vitro* mutagenicity studies,

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- Toxicokinetic studies,
- Testing principles in toxicity studies including dose-response analysis, and
- Pharmacological studies and other preclinical applications.

The goal of the workshop was to bring together statisticians from the pharmaceutical industry, academia, and regulatory bodies, to provide an open forum to discuss the appropriateness of the biostatistical methods described in new toxicological guidelines and related ICH documents (or drafts) and important issues of current interest to statisticians involved in nonclinical and toxicological drug development. The program committee consisted of co-chairpersons Drs. William R. Fairweather (Chief, Statistical Application and Research Branch, FDA, USA), Gerald Hajian (Director, Schering Plough, USA), Dieter Hauschke (Senior Statistician, Byk Gulden Pharmaceuticals, Germany), Ludwig A. Hothorn (Professor, University of Hannover, Germany), Toshij Igarashi (Director, Eisai Co. Ltd., Japan), and Paul Koopman (Senior Biostatistician, Solvay Duphar, The Netherlands).

The PSI gave a book prize for the best paper. Professor Isao Yoshimura (Science University Tokyo, Japan) was selected as the winner for his excellent paper "Performance comparison of maximum contrast methods to detect dose dependency," published in this issue of the DIA journal.

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