HESI GLOBAL NON-CLINICAL/CLINICAL SAFETY CORRELATIONS TECHNICAL COMMITTEE

Mission

The Non-Clinical/Clinical Safety Correlations Technical Committee was organized to develop an improved understanding of the extent to which various types of human toxicities manifested during clinical trials could be predicted from standard non-clinical toxicology studies.

2007 Committee Participation
Amgen, Inc.
AstraZeneca AB
Boehringer Ingelheim GmbH
Hoffman-LaRoche, Inc.
Institut de Recherches Internationales SERVIER
Johnson & Johnson Pharmaceuticals
Novartis Pharmaceuticals Corporation
Pfizer, Inc.
sanofi-aventis
University of North Carolina School of Medicine
US Food and Drug Administration
US National Cancer Institute

Publications:
Olson, H., Betton, G., Stritar J., and Robinson, D. The Predictivity of the Toxicity of Pharmaceuticals in Humans from Animal Data – An Interim Assessment, Toxicology Letters, 102-103: 535-538, 1998. Olson, H., Betton, G., Robinson, D, Thomas, K., Monro, A, Kolaja, Lilly, P., Sanders, J., Sipes, G., Bracken, W., Dorato, M., Van Deun, K., Smith, P., Burger, B., and Heller, A. Concordance of the Toxicity of Pharmaceuticals in Humans and Animals. Regulatory Toxicology and Pharmacology, 32: 56-67, 2000.

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Fact Sheet

ILSI Health and Environmental Sciences Institute

NON-CLINICAL/CLINICAL SAFETY CORRELATIONS TECHNICAL COMMITTEE

MISSION

The Non-Clinical / Clinical Safety Correlations Technical Committee was organized to develop an improved understanding of the extent to which various types of human toxicities (HTs) manifested during clinical trials could be predicted from standard toxicology studies.

OBJECTIVES

The objectives of the Non-Clinical / Clinical Safety Correlations Technical Committee are to:

- provide an opportunity for review and discussion of the database and its findings;
- develop analyses of correlations between toxicity data in humans and laboratory animals;
- identify gaps in understanding and deficiencies in current types of studies based on database analyses;
- make recommendations regarding future study design; and
- describe future opportunities for method development (in vivo, in vitro, models, etc.).

BACKGROUND

There is a widespread perception and assumption that laboratory animals are appropriate models for predicting the adverse effects of chemicals in humans. For many classes of chemicals, testing this assumption is not practical. By contrast, for pharmaceuticals, an extensive body of relevant data exists to explore the validity of this assumption. These data come from substances evaluated both in animals and in humans; however, the data lie largely unpublished in the files of pharmaceutical companies.

Publicity has been given to those cases of drugs that are dropped from clinical trials or withdrawn from the market for reasons of toxicity that were not predicted from animal studies. However, little attention has been given to the successful predictions from animal data, and there has been no comprehensive and systematic evaluation of the utility of the tests conducted.

Furthermore, whether the range of preclinical tests performed produce data that are relevant in the design and/or interpretation of human studies has not been addressed. In the face of continuing regulatory, industry, and public pressures to increase the efficiency of the drug development process, this is an opportune time to conduct an evaluation to examine the value of animal studies as surrogates for predicting toxicity of drugs to humans and to address how non-clinical tests can be optimized to improve drug safety.

ACTIVITIES AND ACCOMPLISHMENTS

To meet these goals, the Non-Clinical / Clinical Safety Correlations Technical Committee has developed an internet-accessible system to facilitate the entry of proprietary compounds into a database to evaluate the concordance of animal toxicity and safety pharmacology data with actual human toxicities (HTs) for a number of pharmaceutical agents exhibiting clinical toxicity during Phase I, II or III clinical trials. Members gain access to the database through a secure server where compounds can be entered in a confidential manner.

ACTIVITIES AND ACCOMPLISHMENTS

The current project is a follow-up to the initial stage of the program. The first stage of the project has been extended into a second stage to broaden the scope of the data collected and to generate additional data in a prospective manner.

To establish a more comprehensive measure of the true predictivity of non-clinical animal studies for human risk assessment, the proposal for the Stage II program includes the following features:

1) The project is a *prospective* study of compounds entering the *in vivo* toxicology stage of drug development. This will ensure studies have been conducted according to modern guidelines.

2) The details of toxicity manifested in animals considered to be counterparts of the human clinical toxicity profile will be fully documented beyond the organ system level.

3) Toxicokinetic and metabolic interspecies comparison data is being collected.

4) All consecutive projects from contributing companies will be entered to ensure an unselected comprehensive dataset is generated.

5) Additional areas for predictivity assessment may also be incorporated, e.g. SAR expert systems, toxicogenomics, HTs detected post-marketing.

To date, the database includes approximately 95 separate human toxicities arising in clinical trials to evaluate over 150 compounds. The database contains compounds for which development programs were started after 1998 to ensure that studies were performed in a manner consistent with good laboratory practices (GLP). The details of toxicity manifested in animals considered to be counterparts of the human
clinical toxicity profile will be fully documented beyond the organ system level. The database includes very detailed compound information including toxicokinetic and metabolic interspecies comparison data.

The committee hosted an international workshop on September 20-21, 2007 in Washington, DC to comprehensively review the contents of the database. The workshop provided an opportunity for the assembled experts to use the database to assess the utility of pre-clinical animal studies for predicting human outcomes. The outcome of the workshop will be a consensus report describing the findings from the database relative to a number of specific toxicity endpoints, and assessing the animal-human toxicity correlations for each endpoint. The report will also identify gaps in understanding and deficiencies based on the database analysis. The workshop proceedings will be published in the peer-reviewed literature.

Publications include:

Olson, H., Betton, G., Stritar J., and Robinson, D. The Predictivity of the Toxicity of Pharmaceuticals in Humans from Animal Data – An Interim Assessment, Toxicology Letters, 102-103: 535-538, 1998.

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LEADERSHIP AND INFORMATION

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Vice Chair.....Dr. Edmund Kadyszewski

HESI Staff.....….....Dr. James Kim

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AstraZeneca Pharmaceuticals
Boehringer-Ingelheim Pharmaceuticals, Inc.
Johnson & Johnson Pharmaceuticals
Novartis Pharmaceuticals Corporation
Pfizer Pharmaceuticals
Roche Pharmaceuticals
sanofi-aventis, Inc.
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U.S. National Cancer Institute

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