ADVANCING 3RS IN REGULATORY TOXICOLOGY
CARCINOGENICITY TESTING WORKSHOP

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The European Partnership for Alternative Approaches to Animal Testing

Brussels, Belgium, February 28th 2013

EPAA WORKSHOP ON CARCINOGENICITY TESTING: SCOPE FOR HARMONISATION AND ADVANCING THE 3RS

The EPAA project on Advancing the 3Rs in Regulatory Toxicology has been in progress since the end of 2011. The aim is to identify opportunities for improving the science behind the regulatory testing of medicines and chemicals through the application of the 3Rs. Among the seven sectors that EPAA is gathering, the ones involved primarily in this project are those concerned with the development of human medicines, veterinary medicines, and crop protection products.

The overriding principle behind the project has been to look at how each sector approaches the issue of regulatory toxicology and to identify opportunities for cross-sector alignment on best practice and on the introduction of new methodologies advancing the 3Rs. Alignment has two aspects: industry alignment on testing methodologies, and regulatory harmonization both across sectors and across global regions. Thus the project aims not only at identifying possibilities but also how these might be translated into regulatory practice.

"Identify opportunities for cross-sector alignment on best practice and on the introduction of new methodologies advancing the 3Rs"

The Project Team initially conducted a survey of regulatory requirements in the various sectors and then sent a questionnaire to the relevant EPAA member associations (EFPIA, IFAH-Europe and ECPA). This asked for more detailed information on the scope for variation in study design within the existing guidelines, on regional variations in regulatory requirements, on individual company practice, and on the development of alternatives that could advance the 3Rs. The questionnaire was distributed to the member companies of these three organizations and the results collated and analyzed by the Project Team. It was clear that there is considerable divergence in practice within sectors, between sectors and between geographical areas, despite the existence of international harmonization bodies such as ICH and VICH. Moreover, differing practice was as likely to be a result of tradition as a result of the application of science.

Following these discussions, the Project Team selected the area of carcinogenicity testing as one that offered great potential for the project: all sectors need to consider the carcinogenic potential of their products, sector practice is quite divergent, the scientific value of some study designs is currently being questioned and the introduction of in vitro methods offers the possibility of a more targeted and progressive approach to animal testing.

In order to appreciate the current state of the field, a workshop was held in Brussels on February 28th 2013 to understand the opportunities for introduction of new methods, for harmonization and rationalization of current practice and for furthering the 3Rs. It was attended by 29 experts* from the three original sectors (human and veterinary medicines, crop protection), the chemicals and cosmetics industries, regulatory bodies, the European Commission, EURL ECVAM, EPAA and the UK National Centre for the 3Rs. Both the public and private sectors were represented and the international dimension was enhanced by US speakers from Bristol Myers Squibb and the Environmental Protection Agency.

Speakers from each sector described the nature of the regulatory regimes in which they operate currently, but more importantly, they spoke about the status of discussions on the introduction of new methods with 3Rs implications. These include the waiving of in vivo

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tests through weight of evidence approaches, analyses of adverse outcome pathways, the introduction of in vitro alternatives, the use of genetically modified animals, and new ideas on experimental design to minimize animal numbers and suffering. Several things were clear to all: first, that much of the current regulation is based on traditions going back decades that have not evolved in response to scientific advances; second, that differences between the regulatory guidelines from one sector to another are not necessarily based on a clear scientific rationale; and third, that different sectors are often unaware of practice in others.

"The potential for advancing all the 3Rs through harmonization between sectors and adoption of new methods is considerable"

This means that the potential for advancing all three of the Rs through harmonization between sectors and adoption of new methods is considerable e.g. replacement of in vivo tests by alternatives, refinement through better approaches to dosing and reduction through waiving of some current tests.

The information disclosed and discussed at the workshop, together with the results of the analysis carried out last year, will be the subject of a paper comparing sector practice, pinpointing anomalies and inconsistencies, and recommending areas for further work to advance the 3Rs and improve the science of carcinogenicity testing. The day after the workshop, the Project Team discussed the outputs of the meeting to plan its work for the year ahead.

There are now several work streams under consideration: a project to analyze data on pharmaceuticals for human use to see whether outcomes of the mandatory two-year carcinogenicity study in rat can be predicted from the six-month repeat dose toxicity study supported by other pharmacological data; an extension of this project to include other sectors to examine whether carcinogenicity testing in a second rodent species adds any useful information; and a project to look at alternatives to the use of the Maximum Tolerated Dose in dose selection for carcinogenicity testing and other chronic studies.

The Project Team has not forgotten other areas of regulatory toxicology and will continue to look for new opportunities. However, the workshop confirmed that for the time being, the Project Team has more than enough work to do in the carcinogenicity field, and that it made a good decision to focus on a topic that not only has strong ethical implications, but has the potential to encourage better science, streamline regulatory practice and improve human safety.

Participating Organisations

Abbvie, Germany
BASF, Germany
Bayer, Germany
BfR (Bundesinstitut für Risikobewertung), Germany
Bristol Myers Squibb, USA
CBG-MEB (College ter Beoordeling van Geneesmiddelen Medicines Evaluation Board), Netherlands
Cefic (European Industry Chemistry Council), Belgium
Dow AG, UK
EC, DG Enterprise, Belgium
EURL ECVAM (European Reference Laboratory for Alternatives to Animal Testing), Italy
EFSA (European Food Safety Authority), Italy
EPA (Environmental Protection Agency), USA
EPAA, Belgium
GSK, UK
Johnson & Johnson, Belgium and Germany
Karolinska Institute, Sweden
NC3Rs (National Centre for the 3Rs), UK
RIVM (National Institute for Public Health and the Environment), Netherlands
Syngenta, UK
ECPA (European Crop Protection Association, represented by ToxAdvice, Switzerland)
IFAH-Europe (International Federation for Animal Health Europe, represented by TSGEurope, UK)
University of Tübingen, Germany

CONTACT

epaa The European Partnership for Alternative Approaches to Animal Testing

entr-epaa@ec.europa.eu
www.epaa.eu.com
+32 (0)2 29 52 014