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Implementation of the 3Rs in European regulation - activities of Working Group 4 of the European Partnership for Alternative Approaches to Animal Testing I. Impact of liability issues and the precautionary principle, II. Evaluation of statistical reporting for measuring the uptake of 3Rs in regulatory testing

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Abstract
The European Partnership for Alternative Approaches to Animal Testing (EPAA) is an unprecedented collaboration between the European Commission and a number of companies and trade federations active in various industrial sectors. Its purpose is to promote '3R' approaches (replace, reduce, refine) in regulatory safety testing. Working Group 4 (WG4) was established to deal with improving the implementation of 3Rs in European regulatory safety testing and decision making. As part of the overall EPAA approach, WG4 targets optimised approaches along testing and risk assessment strategies in existing and upcoming legislation and their implementation, avoiding double and redundant, as well as unnecessary testing. A suite of workshops including relevant stakeholders provides a platform for in-depth discussion of critical issues and aiming at establishing a basis for implementing the 3Rs in meeting regulatory requirements. Based on the information from the various sectors, the working group also investigates generic cross cutting issues. The results to date of two recent activities of the working group are presented in more detail, I. an investigation of the impact of liability and precautionary principle on the uptake of the 3Rs, II. an evaluation of statistical reporting for measuring the uptake of 3Rs in safety testing.

Keywords: 3Rs, EPAA, statistical reporting, liability, precautionary principle

General Introduction

The European Partnership for Alternative Approaches to Animal Testing (EPAA) is an unprecedented collaboration between the European Commission and a number of companies and trade federations active in various industrial sectors. Its purpose is to promote '3R' approaches (replace, reduce, refine) in regulatory safety testing. Working Group 4 (WG4) was established to deal with improving the implementation of 3Rs in European regulatory safety testing and decision making. As part of the overall EPAA approach, WG4 targets optimised approaches along testing and risk assessment strategies in existing and upcoming legislation and their implementation, avoiding double and redundant, as well as unnecessary testing. This implies the identification of so-called "hot spots", priority areas for action that entail significant animal use and/or provide an opportunity for an effective impact on animal use through application of the 3Rs. Emphasis is also given to the identification and evaluation of main drivers (e.g., safety, liability, precaution, risk acceptance) for regulatory testing requirements. (EPAA Action Programme, 2006[1])

WG4 consists of core group members from the partnership and stakeholders. It calls upon experts from EU-institutions, member states, industry and other relevant stakeholders in sector-specific issues. A suite of workshops provides a platform for in-depth discussion of critical issues and aiming at establishing a basis for implementing the 3Rs in meeting regulatory requirements. A number of sectors were investigated in 2006, i.e. chemicals, pharmaceuticals, agrochemicals and cosmetics[2]. In this regard, a plethora of regulations and guidance has to be taken into consideration, like Directives 67/548/EEC, REACH (Registration, Evaluation and Authorisation of Chemicals)[3], and upcoming GHS legislation

(Globally Harmonized System of Classification and Labelling of Chemicals) for chemicals; 2001/83/EC[4], 2001/20/EC[5], ICH Guidelines[6], 2001/82/EC[7], for human and veterinary pharmaceuticals; 91/414/EEC[8] for plant protection products; 76/768/EEC[9] for cosmetic products; including the various amendments to the directives. Directive 86/609/EC[10] on the protection of animals used for experimental and other scientific purposes, representing horizontal legislation, is of particular relevance to the 3Rs. Analysis of additional sectors like food is envisaged.

Based on the information from the various sectors, the working group also investigates generic cross cutting issues. The results to date of two recent activities of the working group are presented in more detail in the two main parts of this publication, I. an investigation of the impact of liability and precautionary principle on the uptake of the 3Rs, II. an evaluation of statistical reporting for measuring the uptake of 3Rs in safety testing.

Part I. Investigation of the impact of liability and precautionary principle on the uptake of the 3Rs

Introduction

Liability has various facets, like product liability, regulatory liability, commercial liability. Product liability in particular is the area of law in which manufacturers, distributors, suppliers, retailers, and others who make products available to the public are held responsible for the injuries those products cause. In the EU, legal provisions are laid down in directive 85/374/EEC[11]. The precautionary principle serves as a guiding principle in a regulatory context of safety provisions. In 2000, the European Commission adopted the Communication on the use of the Precautionary Principle. "The Communication highlights the fact that the Precautionary Principle should be considered within a structured approach to the analysis of the risk and it is particularly relevant to the management of the risk." (European Commission 2000, COM (2000)1)[12]. Some legislation provides an explicit reference. In REACH, for example the precautionary principle is referred to in Article 1.3: "This Regulation is based on the principle that it is for manufacturers, importers and downstream users to ensure that they manufacture, place on the market or use such substances that do not adversely affect human health or the environment. Its provisions are underpinned by the precautionary principle." The burden of proof is with industry, and duty of care is requested (Annex VI: "The Annexes shall thus be considered as a whole, and in conjunction with the overall requirements of registration, evaluation and the duty of care.").

In various sector-specific workshops, liability and the precautionary principle were recognized as potential hurdles for the implementation of 3Rs, and the question was raised how and to what extent in practice acceptance and uptake of 3R methods might be affected. To further investigate these issues, WG4 organised a dedicated session with stakeholders in the context of a workshop on regulatory acceptance of 3R methods and strategies in June 2007. A workshop report and other relevant documents are published on the EPAA website[13]. Three basic questions were addressed to initiate the discussion: 1. How do liability issues affect acceptance and uptake of 3R methods and which specific hurdles can be identified? 2. To what extent are product liability considerations relevant for the choice of testing methods, taking into account that discussions on compliance with regulatory requirements can also result in disputes with supervising authorities, customers or competitors? 3. What is the relevance of sector-specific rules on the burden of proof?

Results and discussion

Since traditional animal testing is widely seen as the "gold standard", this approach is still privileged, which holds true for both regulators and industry. Trust is significantly related to the long standing experience with this type of safety data, nevertheless officially accepted animal methods might also lack a formal validation. At the same time, there is less experience with the use of alternative approaches in risk assessment. Regulators and safety assessors might not accept the results of a method as such, but as a precaution only acknowledge positive results, still requesting animal data to confirm a negative outcome. It is therefore crucial to scientifically demonstrate not only the predictivity for positive, but also for negative outcomes of a method or approach. The discussion has shown that scientific robustness of the method is the key criterion for acceptance and eventually impacts liability. The formal process of the type of validation and need for publication might be driven by additional aspects (provide a full validation path, product-specific validation, or extrapolation of methods across sectors based on interpretation of results).

The character of EU guidance/guidelines was also debated. Unlike regulations or directives, guidelines at EU level do not have a strictly binding character. However, they reflect a consensus statement of authorities, often in cooperation with stakeholders, and any deviation from this guidance must therefore be clearly justified. De facto, guidelines gain an implicitly binding character. A revision of guidelines should therefore be preferred in case an alternative is accepted and/or scientifically recommendable.

Flexible versus mandatory regulatory requirements with regard to the use of specific methods were discussed. Regardless of the nature of requirements, it

was concluded that "one size does not fit all" and that a case-by-case approach is appropriate. Where there is flexibility, the use of the best available method/technology gives highest assurance with regard to liability. Therefore liability questions are inevitably linked to the state of scientific and technical knowledge, and the debate about "best science" and toxicology paradigms.

It was recognized that the acceptance of methods and approaches often differs between regulators in different countries or regions. Therefore, to provide access to an international market, the overall "best level of acceptance" directs the choice of methods. A regional implementation of a 3R approach is usually not feasible. In order to facilitate an international mutual acceptance, more transparency and efficient communication will be needed between regulators, industry and "xCVAMs". Cross-sectoral exchange of data and experience were considered extremely useful. Interlinked processes were recommended, whereas EPAA's role is to provide a platform for communication and information exchange in order to accelerate acceptance and implementation, with a specific emphasis on cross-sectoral links.

Part II. Evaluation of statistical reporting for measuring the uptake of 3Rs in safety testing

Introduction

Statistical reporting addresses the issue of transparency and public concern. Directive 86/609/EEC calls for the Member States to collect statistical data (Article 13) and the Commission to publish EU statistics to the European Parliament and the Council (Article 26). However, there is no guideline or format for the Member States to follow in the submission process. In 1997, a "modus operandi" was agreed between the Commission and the Member States on a set of 8 harmonised tables for statistical reporting. Although at present their use is not legally binding, Member States in practice implement this agreement.

A question often raised in relation to alternative approaches is whether statistical reporting can indicate progress, or reflect trends in the regulatory uptake of the 3Rs at EU level. To investigate these issues further, a workshop was organized in July 2007 with stakeholders, in particular with representatives from national authorities and companies, effectively involved in statistical reporting, Commission services and interest groups. Documents (presentations, workshop report) are published on the EPAA website[14]. Three major topics were addressed at the workshop: 1. Practical experience with counting and reporting use of laboratory animals, 2. Appropriateness of current structure of reporting, 3. Potential for statistical reporting to measure uptake of 3Rs.

Results and Discussion

A lot of information is collected through statistical reporting, with regulatory testing (quality control and toxicological/safety testing) representing only little over 20% of animal use. The system is complex and it was recognized that it gives rise to different interpretations on how information should be reported, e.g. the counting of pups in reproduction toxicity studies is currently not performed in a harmonized manner. A reason might be that the guidance is not clear enough or not well known. Also, reporting reflects the system in place at a time when the reporting tables were created and is no longer adapted to current needs. Even for transparency reasons, the usefulness of collected information is not clear.

Reporting is currently not harmonized regarding retrospective vs. prospective analyses. E.g., UK is counting prospectively, Netherlands retrospectively, Switzerland counts animals in use during each year, however, the latter are not included in the EU statistics. This issue affects especially the reporting of long-term studies, which will be relevant e.g. for testing under REACH. In prospective reporting animals are counted when procedures are started, whereas in retrospective reporting animal use is counted when procedures are finished. In prospective counting animals appear in the statistics as soon as possible, but on the other hand it does not always reflect the eventual use of animals. Retrospective counting provides more accurate statistics and allows a linkage to reporting of severity, thus providing an opportunity that "refinement" can be monitored. A difficulty with mixing both systems is that prospective and retrospective numbers will not match in a given reporting period and would limit/preclude cross referencing of severity data with other information. As a consequence, at EU level statistics are not really comparable. Harmonised processes would need to be established considering the specific requirements for severity reporting. A feasibility study to assess these issues in detail was run by LASA/APC[15].

It was discussed which indications for the 3R uptake might be derived from statistical data, and it was concluded that very few existing data have the potential to detect 3Rs changes, e.g. in the use of specific methods, changes in testing per product type, switch from "higher" to "lower" species, or severity where it is reported. A comprehensive evaluation is impaired by the fact that other factors than 3Rs uptake can be reflected in statistical numbers, such as fluctuations in research and development activities, outsourcing to third countries, legislative changes or effects from single large scale studies.

With regard to the overall suitability of current statistics, it was recognized that statistics are not a reliable and appropriate tool to measure the success of

alternative approaches in regulatory testing in general. It was recommended that statistical reporting should be improved, for example by providing a clearer, harmonized guidance and definitions and as well a better interpretation of numbers from the bottom up. It should be noted that Directive 86/609/EEC, including the requirements for statistical reporting, is currently under revision.

The role of EPAA - not only in this particular respect - is to monitor the implementation of regulation, highlight issues of concern and scope for enhancing 3Rs uptake, and possibly identify other ways of assessing the uptake of 3R approaches.

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