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## Introduction

### The ICLAS/CCAC International Symposium on Regulatory Testing and Animal Welfare: Introduction and Overview

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The first International Symposium on Regulatory Testing and Animal Welfare (ISRTAW<sup>1</sup>), held June 21-23, 2001, in Québec City, Canada, brought together 160 experts from 22 countries from North and South America, Europe, and Asia.<sup>2</sup> The experts included representatives from national research and regulatory agencies, universities, and industry involved in chemicals, pesticides, and drug safety testing. Representatives from European, Canadian, and US animal welfare groups also participated in the discussions.

The Symposium was organized by the International Council for Laboratory Animal Science (ICLAS<sup>1</sup>) and the Canadian Council on Animal Care (CCAC<sup>1</sup>), with the support and assistance of many sponsors and advisors listed elsewhere in the issue. ICLAS is a worldwide organization whose purpose is to foster international harmonization of animal care and use practices. CCAC is the national agency responsible for overseeing the ethical use of animals in Canadian science. Both organizations are committed to fostering an environment in which global efforts to harmonize testing procedures using animals in a more humane manner can be realized.

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<sup>1</sup>Abbreviations used in this Introduction: ACC, animal care committee; CCAC, Canadian Council on Animal Care; ECVAM, European Centre for the Validation of Alternative Methods; ICCVAM, Interagency Coordinating Committee on the Validation of Alternative Methods; ICH, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use; ICLAS, International Council for Laboratory Animal Science; ISRTAW, International Symposium on Regulatory Testing and Animal Welfare; OECD, Organisation for Economic Co-operation and Development.

<sup>2</sup>This manuscript does not reflect official government agency policy.

The goal of the Symposium was to promote improved welfare of animals used to evaluate the safety and efficacy of pharmaceuticals, biologics, and chemicals. The Symposium sought to build on the ongoing efforts of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH<sup>1</sup>) to standardize methods for the safety evaluation of pharmaceuticals, and on those of the Organisation for Economic Co-operation and Development (OECD<sup>1</sup>) to promote more humane methodologies for the testing of chemicals. The objectives of the Symposium were as follows:

- To identify and agree on available best practices to minimize or eliminate pain and distress for animals used in safety evaluation and testing procedures that should be implemented now, including best practices for reducing and replacing animal use where scientifically possible;
- To identify safety evaluation and testing procedures using animals for which satisfactory best practices do not exist or could be improved, and to develop recommended best practices and/or actions needed to establish best practices; and
- To develop recommendations to improve communications between regulated industry, animal welfare enforcement authorities, and regulatory authorities that require safety evaluation and/or testing.

One of the unique aspects of ISRTAW was the opportunity it presented for the various sectors involved in regulatory testing—pharmaceutical, chemical, and biologicals—to share their common experiences in the development and implementation of best practices for animal care and use. These Proceedings provide the text of the presentations given at the Symposium as well as detailed reports of the discussions of the seven breakout groups and their recommendations to implement best scientific practices in regulatory testing.

The evidence for the unequivocal link between good animal welfare and quality science is highlighted throughout these Proceedings. In 1959, Russell and Burch wrote that the “best animal welfare” results in the “best science” (Russell and Burch 1959). The principles of humane experi-

mental technique—Russell and Burch's 3Rs of replacement, reduction, and refinement—are as relevant now as they were 40 yr ago. In these Proceedings and elsewhere, Jon Richmond (2000, 2002) has described the challenge for us today. Armed with more powerful scientific insights and a better understanding of animal welfare issues than our predecessors, we should be able to ensure that the best animal welfare and the best science drive and shape future developments in regulatory testing.

To set the scene for the safety assessment process, Leonard Schechtman and Horst Spielmann describe the current requirements for animal use in the safety evaluation of pharmaceuticals and chemicals, respectively. In these Proceedings, Schechtman (2002a) highlights a number of the scientific initiatives undertaken by the US Food and Drug Administration that have impacted toxicology practices. In particular, he describes the efforts of ICH to harmonize testing practices applied to pharmaceuticals. Although not a primary objective of ICH, the resultant responsiveness to animal welfare issues that address the refinement, reduction, and replacement of animal use has been an indirect consequence of the ICH harmonization effort (Ohno 2002). Differences in national and international test guidelines are unacceptable from the scientific and animal welfare points of view, as well as for economic reasons, as described by Spielmann (2002). Spielmann further points to the fact that in 1982, OECD was the first international organization to agree on harmonization of guidelines for the testing of chemicals. Most importantly, this agreement included mutual acceptance of data produced in member countries in studies conducted according to OECD test guidelines. Sherry Sterling and Amy Rispin (2002) further provide an overview of current practices of the Office of Prevention, Pesticides and Toxic Substances of the US Environmental Protection Agency in implementing the 3Rs, including recognition that many challenges lie ahead and require scientists and policy makers to work together.

The main objective of the Symposium was to identify best practices to minimize or eliminate pain and distress for animals used in safety evaluation and testing procedures. Chemical toxicity and vaccine testing can cause injury, disease, and mortality involving significant levels of pain and distress. Alleviation of pain and distress in animals during testing can be problematic because regulations permit treatment intervention only if it does not interfere with the study. One approach to this problem is to identify criteria that can serve as a basis for the early termination of a test procedure. In 2000, ILAR devoted an entire issue of its journal to the subject of Humane Endpoints for Animals Used in Biomedical Research and Testing (ILAR 2000). In this supplementary issue, Stokes (2002) and Hendriksen (2002) describe approaches for the implementation of humane endpoints for chemical testing and potency testing of biologicals, respectively. ISRTAW participants unanimously agreed that the *OECD Guidance Document on the Recognition, Assessment and Use of Clinical Signs as Humane Endpoints for Experimental Animals Used in Safety Evalu-*

*ation* (OECD 2000) should be regarded as providing initial key "guidance" for defining humane endpoints. Participants also recommended avoidance of extreme endpoints (e.g., signs of severe pain and distress, excessive tumor burden, and moribund condition) whenever possible. Combes and colleagues (2002) report on the recommendations made by the Symposium participants to ensure implementation of humane endpoints for subchronic/chronic toxicity and carcinogenicity testing (e.g., through training and sharing of information). Similar recommendations are reported by Cussler and colleagues (2002) in the area of biologicals, with recognition that monitoring by regulatory agencies can assist in ensuring compliance with the implementation of validated endpoints.

Strategic planning for testing protocols/studies should include the identification of earlier endpoints/markers that can further reduce pain and distress, despite the fact that the inclusion may increase statistical variation and necessitate larger group sizes. Institutional animal care committees (ACCs<sup>1</sup>) can play a key role in the implementation of humane endpoints. For example, ACCs should ensure that frequency of animal observations have been established, that there has been agreement regarding criteria for initiating supportive therapy where appropriate, and that clear and predetermined lines of authority to euthanize are in place. De Haven (2002) further discusses the role of ACCs in his contribution in this issue. In addition, questions that an ACC should ask to ensure that criteria for humane endpoints have been established are detailed in *Guidelines on Choosing an Appropriate Endpoint in Experiments Using Animals for Research, Teaching and Testing* (CCAC 1998).

ACCs have an important role to play in ensuring best practices and public accountability. Recommendations by Symposium participants to improve the functioning of ACCs and animal use oversight are reported by Richmond and colleagues (2002). To facilitate the work of ACCs where regulatory testing is involved, the participants recommend that induction training for ACC members should include a grounding in regulatory requirements and their interpretation. In addition, regulatory authorities should supply ACCs with accessible and easily digestible updates on trends and developments.

Martin Stephens and colleagues (2002) describe future possibilities for refinement in modifying animal-based procedures to decrease pain, distress, and discomfort and to increase animal well-being. Refinement can be applied to all aspects of animal care and use in the laboratory and can improve scientific outcomes as well as animal welfare. ISRTAW participants clearly stated that for any given testing procedure, elimination of pain and distress should be a higher priority than reducing the number of animals used. Nonetheless, important steps can be taken to ensure that animal use is minimized. In this issue, Smith and colleagues (2002) present opportunities for the minimization of dog use in preclinical safety evaluation identified by a European Industry/Animal Welfare Steering Group. Three distinct areas are examined: industrial cooperation/data sharing,

achieving best practice in study design, and assessing the need for a particular study. Additional recommendations concerning the reduction of nonrodent species use are outlined by Weekley and colleagues (2002).

The welfare cost to the animals used for regulatory testing has two components (Russell and Burch 1959): “direct costs” of the procedures applied and “contingent costs,” which include housing and husbandry. One of the aims of this Symposium was to find approaches for improving animal well-being by focusing on aspects not directly linked to the regulatory test procedures themselves. Fillman-Holiday and Landi (2002) describe current animal care best practices for regulatory testing. Components of best practices common to all species include study design, housing, social contact, diet/feed, enrichment devices, and human interaction. Guitin and Decelle (2002) build on the current situation to consider the most significant future improvements in animal care that might be possible. In the regulatory testing environment, the challenge is to implement care practices that are both practical and science based. For example, discussion at the Symposium and elsewhere has focused on whether enriched environments introduce unwanted variables into a study. ISRTAW participants point to the study of Knight (2001), which concluded that well-implemented enrichment may reduce, rather than increase, variability in a study (Morris et al. 2002).

The use of the test that aimed to identify the single lethal dose of a substance that kills half the animals in a test group—the LD<sub>50</sub> test—should finally be discontinued by the end of 2002 (Botham 2002). Recommendations were made at the Symposium to communicate to those involved in carrying out the tests, or evaluating acute toxicity data, that the three new OECD test guidelines—420, 423, and 425—now provide the current best practices for acute toxicity testing. In addition, ISRTAW participants endorsed the recommendations originating from the US Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM<sup>1</sup>) (ICCVAM 2001) to use *in vitro* data to set the starting doses for acute toxicity testing using any of the three guidelines, thereby minimizing the number of animals involved and providing a more accurate prediction of the lethal dose (Stitzel et al. 2002).

Because ISRTAW participants were drawn from the pharmaceutical testing as well as the chemical testing milieu, there was an opportunity to consider approaches to similar data requirements. For example, it was recommended that a single harmonized study design should be developed to meet the needs for acute systemic protocols for both chemical and pharmacology safety testing (Stitzel et al. 2002). These approaches, if implemented, could have considerable impact on the duplication of testing.

Integrated testing schemes that incorporate scientifically valid nonanimal methods are described by Kathy Stitzel (2002). OECD is in the process of accepting revised test guidelines that include reference to a tiered testing strategy for both eye and skin effects after acute exposure (OECD 2001). Recommendations were made by ISRTAW partici-

pants to encourage the adoption of these guidelines, as soon as some of the areas of ambiguity have been addressed in the accompanying guidance document (Botham et al. 2002). To encourage the use of *in vitro* methods where appropriate, participants recommend the establishment of additional facilities for *in vitro* testing and the provision of hands-on training. In addition, industry should be encouraged to share data so that a reference bank of chemicals can be established and used as a basis for *in vivo/in vitro* comparisons.

Key to ensuring progress in the implementation of the 3Rs within regulatory testing is the timely acceptance of improved methodologies. For this acceptance to occur, new and revised methods must be subject to sound scientific validation. In these Proceedings, Michael Balls (2002) outlines the work of the European Centre for the Validation of Alternative Methods (ECVAM<sup>1</sup>) both in ensuring a sound validation process and also as a process for independent evaluation and scientific acceptance of ECVAM-sponsored and other validation studies. Similarly, Leonard Schechtman (2002b) describes the ICCVAM process and established criteria for the scientific validation and regulatory acceptance of new and alternative methods.

Communication is pivotal to ensuring that the best animal welfare and the best science drive and shape future developments in regulatory testing. In the final paper of these proceedings, Clément Gauthier (2002) reviews the role science advice plays in governmental decision making and provides guidelines as a framework for the development of a science-based decision making process to facilitate government regulators’ implementation of the 3Rs.

The presentations and discussions at this Symposium describe the current best practices for using animals in regulatory testing procedures. Widespread implementation of these best practices will improve the welfare of animals used for safety testing and will contribute to reduced animal use. Nevertheless, some testing procedures still involve unrelieved pain and distress and use large numbers of animals. Progress in addressing these issues is expected from future research, development, and validation studies, including those recommended by Symposium participants. Continued dialogue and communication among all stakeholders will help ensure optimal and improved care and use of laboratory animals for safety assessments.

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