

Animal care and use programs: Global harmonization through alternatives

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Abstract

The trend toward harmonization of expectations at which animal care and use programs will function is escalating world-wide. Increasingly, scientific collaborations and contracts cross national borders. The need for assurance that the caliber of animal research and animal welfare are consistent and that such animal use is done in a humane and conscientious manner is of concern to the scientific community, the general public, and other stakeholders. As Neil Wilcox, Special Assistant to the Associate Commissioner, U.S. Food and Drug Administration said: "The scientific community and changes in toxicity testing are now international in scope. Everything we do has international implications and whatever we do impacts the international community. Harmonization will reduce wasteful duplication of efforts...." Harmonization has been described as "to bring into consonance or accord" (Merriam-Webster dictionary), "to be in harmonious agreement" (Wiktionary), or "to be in agreement in action, sense, or feeling" (Dictionary.com). Whether one considers "best practices," use of the 3Rs (Russell and Birch 1959), or some other generally accepted approach, consensus is building regarding the way to provide, oversee, and validate that an animal care and use program is at a quality, internationally acceptable standard.

Keywords: laboratory animals, alternatives, harmonization

Why harmonize?

Twelve years ago, Dr. John P. Hearn, then Chair of the International Committee of The National Academies' Institute for Laboratory Animal Research, noted that "...science is about new discovery and knowledge, but it is also about the international adoption and transfer of that knowledge" (Hearn 1995). This global nature of science is reflected in the increasing number of international conferences and international peer-reviewed journals. Thus, harmonization of practices becomes essential due to the scientific need for reproducibility and statistical validity of results intrinsic to quality research and the subsequent inevitable shift researchers and their institutions will make toward requiring commonality in animal care and use practices and standards. And, the often significant scientific and potentially confounding variable resulting from differences in animal care standards can thus be mitigated to a large extent through harmonizing these standards.

As Dr. Hearn correctly summarized, harmonization: "1) optimizes the quality of science; 2) addresses the need for similar standards to govern the care and use of animals in international research protocols, thereby bringing a degree of equivalency to the data or information generated; facilitates the movement and exchange of research animals and animal products; and addresses the need for efficiency in

costs of research." The minimization/elimination of experimental confounding variables and the resulting comparability of studies has a direct impact on reducing the number of animals used worldwide for research—an outcome consistent with the goals of the 3Rs. In addition, such harmonization leads to high animal welfare standards as well as refinements of animal care and use practices—an additional outcome consistent with the goals of the 3Rs. In this manner, both animals and science benefit from harmonization.

There are a number of external influences on animal research that pressure acceptance of harmonized, high quality animal care standards. For example, research collaborations across national boundaries require similarities in the quality of the research animal. Also, institutions that outsource animal-based research want assurance that the work will be done at a level similar to that in the home country of the contracting organization. And, the public has high expectations for science and the way in which it is conducted. Because the public has enhanced information access through the internet and the distribution of consumer products occurs on a global basis, the public is now an international entity that demands the best research practices. So, high standards applied in one country or region of the world are expected to be applied elsewhere around the world. Failure to provide a high quality animal care and use program can lead

to disfavor by the public and even attacks by radical members of animal rights groups.

Harmonization through communication

If harmonization is to be achieved on a global scale, communication of appropriate care and use standards and alternatives to specific animal procedures needs to occur. And, alternatives that may be used successfully on a local or regional basis may not be more broadly accepted and implemented if they are not well-communicated to relevant individuals or governments. Inadequate communication can result in disparate and contradictory approaches to a subject. Inadequate information can lead to misunderstandings and errors in judgment, which in turn can result in flawed research data, less than optimal animal welfare and increased research costs. Interactions between researchers (often from varying scientific disciplines), veterinarians and the animal care staff, regulators and stakeholders are key to this process of communication/information exchange. Conferences such as the World Congress on Alternatives provide important opportunities for such communication networks to be established and maintained.

The value of communication among peers has been articulated by James Surowiecki in his book, *The Wisdom of Crowds* (2004). In it, he states "Large groups of people are smarter than an elite few, no matter how brilliant—better at solving problems, fostering innovation, even predicting the future." Surowiecki suggests four critical elements to the "wise crowd": diversity of opinion, independence in opinion (i.e., individuals are not swayed by the opinions of those around them), specialized knowledge, and a mechanism by which private judgments are woven into a collective decision. A translational model of creating wise crowds (i.e., fostering interactions among knowledgeable individuals from different specialties) that is being used in some companies is the development of Communities of Practice (CoPs). CoPs are groups of people who share a concern or interest and learn how to do it better by interacting with each other. CoPs work through social networking, exchange of knowledge and resources, and collaborating. Membership in a CoP implies a commitment to the subject and a willingness to learn from each other.

An example of how such information sharing can be used to the benefit of both the research animal and the science is provided by the process used by the National Advisory Committee for Laboratory Animal Research (NACLAR) in Singapore. As NACLAR was developing guidelines that would be applied to the animal research enterprise in Singapore, members of the Advisory Committee met with individuals in multiple countries who had experience and/or in-depth knowledge of how their own country had

established standards for research animal care and use. The end result was that the Advisory Committee "cherry-picked" from a variety of different national standards to create the NACLAR Guidelines on the Care and Use of Animals for Scientific Purposes (2004). Input to the Guidelines was derived from the Australian Code of Practice for the Care and Use of Animals for Scientific Procedures (2004); the Canadian Council on Animal Care's Guide to the Care and Use of Experimental Animals, Volume 1 (1993); New Zealand's Good Practice Guide for the Use of Animals in Research, Testing and Teaching (2002); the National Research Council's Guide for the Care and Use of Laboratory Animals (1996); and the U.S. Public Health Service Policy on Humane Care and Use of Research Animals (2002).

Key players in promoting harmonization

International Council for Laboratory Animal Science (ICLAS). In 2004, ICLAS initially convened a Working Group on Harmonization of Guidelines on the Use of Animals in Science. This Working Group identified several subject areas where a harmonization of approach could significantly benefit animal research. These include: euthanasia, humane endpoints, protocol review, animal user training programs, and genetically modified organisms (see www.iclas.org/harmonization). The ICLAS process involves forming ad hoc committees that identify existing guidance on a particular subject of importance that reflects best practices to-date. ICLAS then informs the animal research community in both developed countries and in countries in economic transition that these resources exist and are the basis of a sound program of animal care and use. ICLAS' goal is for these harmonization documents to be accepted and adopted by the international animal research community. Recently, ICLAS published on Principles for Establishment of Humane Endpoints and Principles for Animal Euthanasia (Demers et al. 2006).

It should be noted that other groups have engaged in a similar effort to identify best practices for common animal research procedures. For example, the "Newcastle Report" (Hawkins et al. 2006) is the product of a Consensus Meeting on Carbon Dioxide Euthanasia of Laboratory Animals that occurred among interested individuals (a CoP) that addresses the questions surrounding different methods of rodent euthanasia and to address an immediate need for guidance on the subject. This report (see <http://www.nc3rs.org.uk/downloaddoc.asp?id=416&page=292&skin=0>) summarizes the progress made by researchers on how best carbon dioxide should be administered (i.e., pre-fill the chamber versus providing for a rising concentration) for euthanasia, what humane alternative agents are available, and future research

directions. Such efforts are important in both communicating the current state of knowledge and in supplying a gap analysis for future research efforts. Further, they often demonstrate that there is no single correct methodology and that multiple approaches may be equally acceptable, thereby underscoring the notion that practices and procedures can be harmonized successfully without a need for absolute standardization.

The World Organization for Animal Health (OIE). The OIE publishes standards (predominantly on animal health and zoonoses) developed by expert groups on terrestrial and aquatic animals. Animal welfare was identified by the OIE as a priority in its 2001-2005 Strategic Plan. Subsequently, the OIE convened a permanent Working Group on Animal Welfare. This Working Group initially focused on agricultural animal welfare. More recently, laboratory animal welfare was identified as an area of interest. As a result, an ad hoc Committee on laboratory animal welfare was convened with representation from different geographic regions of the world (United States, Canada, Europe, Africa, Asia, South America). The charge to the Committee is to develop baseline standards on laboratory animal welfare for use by the governments of the 173 Member Countries of the OIE.

Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC International). AAALAC International is a non-profit organization that provides assessment and accreditation of institutions using animals for research, testing or teaching. Participation in the program is voluntary. As of this writing, more than 750 institutions in 30 countries are accredited by AAALAC International. A baseline standard, the Guide for the Care and Use of Laboratory Animals (NRC 1996) is used for the assessments, in addition to a list of Reference Resources (see <http://www.aaalac.org/accreditation/resources.cfm>) and the country's own laws and regulations. This global accreditation program provides a "cross-pollination" of information and best practices among the participating programs, resulting in harmonization of practices and procedures and consideration of alternatives to current practices. Details regarding the process by which AAALAC accredits programs internationally are described in more detail by Bayne and Miller (2000) and Bayne and Martin (1998).

Examples of organizations that fund alternatives research

Several organizations fund grants specific to alternatives, while others fund a broad range of proposals related to improving laboratory animal welfare which could include alternatives-specific proposals. A sampling of these organizations and

the types of research they have recently funded are described below. The diversity of subject matters funded by these organizations exemplifies the scope of animal procedures for which alternatives may be identified and implemented.

Center for Alternatives to Animal Testing (CAAT), Johns Hopkins University. Among its numerous programs to promote alternatives to animal testing, CAAT has a grant program to fund 3Rs research. According to the CAAT website (<http://caat.jhsph.edu/programs/grants/index.htm>), projects that have recently received awards include "The use of operant conditioning to acclimate sheep and goats to commonly performed research procedures" (L. Weaver), "The impact of housing conditions on the stress of rats in the laboratory setting" (M. Rose) and "Differential effects of environmental enrichment for mice" (H. Markowitz and C. Roberts).

European College of Laboratory Animal Medicine (ECLAM)/European Society of Laboratory Animal Veterinarians (ESLAV) Foundation. The ECLAM/ESLAV Foundation funds grant applications from both European and non-European countries. Examples of funded projects listed on the Foundation's website (<http://www.eclameslavfoundation.org/reports.htm>) include the "Effects of social housing and testing order on novelty-induced behaviour in male and female mice of 3 strains to ensure a scientific basis for housing and husbandry standards," "Reducing rat numbers by use of a purified diet instead of a natural-ingredient diet," "Characterization of isoflurane and sevoflurane for anesthesia of mice and optimization of effective analgesia and balanced anesthesia," and "Determination of minimum concentrations for loss of consciousness and abolition of reflex withdrawal during euthanasia with carbon dioxide."

National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs). In addition to hosting conferences, networking with animal using organizations and publishing information on the 3Rs, the NC3Rs funds research that promotes the 3Rs. Examples of funded and published studies of alternatives include the development of a non-invasive alternative technique to identify rodents by use of earprints, rather than tattoos, ear clips or transponders (Cameron et al. 2007). Similarly, the use of a technique for collecting blood samples from the sublingual vein in rats has been proposed as an alternative to sampling from the orbital plexus or tail vein (Zeller et al. 1998).

Conclusions

The increasing on-line availability of guidelines from several countries around the world, as well as information regarding best practices, alternatives, and other refinements to animal research will certainly lead to harmonizing of animal care

and use procedures, with both the quality of the research and welfare of the animals benefiting from this harmonization. Recognizing the value of communicating with colleagues, and actively participating in such dialogues, will further advance productive harmonization efforts.

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