Design, Implementation, Monitoring, and Sharing of Performance Standards for Laboratory Animal Use: Summary of a Workshop

DETAILS

128 pages | 6x9 | PAPERBACK
ISBN 978-0-309-37924-3 | DOI: 10.17226/21820

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SUMMARY OF A WORKSHOP

Joe Alper and Lida Anestidou, *Rapporteurs*

Roundtable on Science and Welfare
in Laboratory Animal Use

Institute for Laboratory Animal Research

Division on Earth and Life Studies

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THE NATIONAL ACADEMIES PRESS
Washington, DC
www.nap.edu

THE NATIONAL ACADEMIES PRESS 500 Fifth Street, NW
Washington, DC 20001

This activity was supported by the American College of Laboratory Animal Medicine; American Veterinary Medical Association; Covance Laboratories, Inc.; Genentech; GlaxoSmithKline; Massachusetts General Hospital; National Primate Research Centers; Novartis; Pfizer, Inc.; Stanford University School of Medicine; University of California, Davis; University of Illinois; University of Michigan; University of North Dakota; University of Pittsburgh; and University of Washington. Funding for this conference was made possible, in part, by the Food and Drug Administration through grant 5 R13 FD 005298 - 02, views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government. Any opinions, findings, conclusions, or recommendations expressed in this publication do not necessarily reflect the views of any organization or agency that provided support for the project.

International Standard Book Number-13: 978-0-309-37924-3
International Standard Book Number-10: 0-309-37924-5

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Printed in the United States of America.

Suggested citation: National Academies of Sciences, Engineering, and Medicine. 2015. *Design, Implementation, Monitoring, and Sharing of Performance Standards for Laboratory Animal Use (A Workshop Summary).* Washington, DC: The National Academies Press.

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Acknowledgments

This workshop summary has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Academies of Sciences, Engineering and Medicine Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published workshop summary as sound as possible and to ensure that the workshop summary meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the process.

We wish to thank the following individuals for their review of this workshop summary:

Bonnie V. Beaver, Texas A&M University
F. Claire Hankenson, Michigan State University
Richard B. Huneke, Drexel University College of Medicine
Neil S. Lipman, Memorial Sloan-Kettering Cancer Center and the Weill Medical College of Cornell University

Although the reviewers listed above have provided many constructive comments and suggestions, they did not see the final draft of the workshop summary before its release. The review of this workshop summary was overseen by Stephen W. Barthold, University of California-Davis. Appointed by the National Academies of Sciences, Engineering and Medicine, he was responsible for making certain that an independent examination of this workshop summary was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this workshop summary rests entirely with the rapporteur and the institution.

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Acronyms and Abbreviations

APHIS	USDA Animal and Plant Health Inspection Service
AVMA	American Veterinary Medical Association
AWA	Animal Welfare Act
AWR	Animal Welfare Regulations
Ag Guide	Guide for the Care and Use of Agricultural Animals in Research and Teaching
CCAC	Canadian Council on Animal Care
CCMP	Center of Comparative Medicine and Pathology
CRL	Charles River Laboratories
EU	European Union
FAQ	Frequently Asked Questions
GSK	GlaxoSmithKline
Guide	Guide for the Care and Use of Laboratory Animals
IACUC	Institutional Animal Care and Use Committee
ILAR	Institute for Laboratory Animal Research
IO	Institutional Official
NIH	National Institutes of Health
NRC	National Research Council
NSF	National Science Foundation
OLAW	NIH Office of Laboratory Animal Welfare
PAM	Post-approval monitoring
PHS	Public Health Service
PPE	Personal protective equipment
SCAW	Scientists Center for Animal Welfare
SCWDS	Southeastern Cooperative Wildlife Disease Study
USDA	U.S. Department of Agriculture

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INTRODUCTION[1]

The *Guide for the Care and Use of Laboratory Animals* (*Guide;* (NRC, 2011), developed by a committee under the auspices of the National Academies of Sciences, Engineering, and Medicine's Institute for Laboratory Animal Research (ILAR), defines a performance standard as "a standard or guideline that, while describing a desired outcome, provides flexibility in achieving this outcome by granting discretion to those responsible for managing the animal care and use program, the researcher, and the IACUC (Institutional Animal Care and Use Committee). The performance approach requires professional input, sound judgment, and a team approach to achieve specific goals." Performance standards facilitate good science and animal welfare, explained roundtable Co-Chair Lynn Anderson, Vice President for Global Animal Welfare and Comparative Medicine at Covance Laboratories, and they allow individuals and teams to apply sound judgment, professionalism, and expertise to the problem at hand. As science evolves, the use of evidence-based performance standards will become increasingly important and essential.

To better understand the critical issues pertaining to the concept of performance standards for laboratory animal use, the ILAR Roundtable on Science and Welfare in Laboratory Animal Use held a public workshop in Washington, DC, on April 20-21, 2015. The purpose of the roundtable, Anderson noted, is to promote the appropriate and responsible care of animals in research, to provide a balanced and civil forum for discussion

[1] The planning committee's role was limited to planning the workshop, and the workshop summary has been prepared by the workshop rapporteur as a factual summary of what occurred at the workshop. Statements, recommendations, and opinions expressed are those of individual presenters and participants, and are not necessarily endorsed or verified by the National Academies of Sciences, Engineering, and Medicine, and they should not be construed as reflecting any group consensus.

and collaboration, and to help build transparency and trust among stakeholders (the Statement of Task for the workshop can be found in Appendix C). The roundtable's members determined that an informed discussion of performance standards would further that mission.

Invited speakers at the workshop addressed the challenges of defining, developing, implementing, assessing, and validating performance standards to ensure "optimal practices, management, and operations." Expected outcomes of this workshop included:

- Interactive sessions for the workshop attendees to draft a mock performance standard on post-approval monitoring (PAM) of ongoing research projects with laboratory animals, to better understand the process involved in the development and implementation of performance standards;
- Opportunities for the workshop audience to discuss ways to share performance standards; and
- A rapporteur-prepared summary of the presentations and discussions at the workshop.

In her introductory remarks, Roundtable Director Lida Anestidou, National Academies Senior Program Officer, noted that this is the third workshop the roundtable has held in its 18 months of existence. A workshop on Reproducibility in Research with Animals and Animal Models was held in June 2014, and a workshop on Transportation of Laboratory Animals was held in September 2014. Summaries of the first two workshops will be published, said Anestidou, as would a transportation checklist be developed as part of the second workshop.

Workshop Planning Committee Co-Chair David Kurtz, Veterinary Staff Scientist at the National Institute of Environmental Health Sciences, then explained that developing performance standards is not a one-size-fits-all process. He expressed hope that the attendees would return to their institutions with a better understanding of how to develop and implement their own performance standards.

ORGANIZATION OF THE SUMMARY

The workshop (see Appendix A for a copy of the workshop agenda) was organized by an independent ad hoc planning committee in accordance with the procedures of the National Academies of Sciences, Engineering, and Medicine. The planning committee consisted of Co-Chairs David Kurtz and Patricia Turner, Professor in the Department of Pathobiology and Program Leader of Laboratory Animal Science at the

Ontario Veterinary College, University of Guelph, along with David Anderson, Executive Director of Health Sciences Administration at the University of Washington; Janet Garber, Private Consultant; Andrew Grady, Director of Laboratory Animal Facilities at the University of Mississippi Medical Center; Donna Matthews Jarrell, Attending Veterinarian at the Center for Comparative Medicine, Massachusetts General Hospital; Guy Mulder, Executive Director of Veterinary and Professional Services at Charles River Laboratories (CRL); Randall Nelson, Association Vice Chancellor for Research and Professor of Anatomy and Neurobiology, The University of Tennessee Health Science Center; and Mary Ann Vasbinder, Head of Corporate Responsibility for 3Rs and Training Strategy for Animals at GlaxoSmithKline (GSK).

This publication summarizes the presentations and discussions that occurred throughout the workshop. Chapter 2 presents an overview of performance standards for the humane care and use of laboratory animals. Chapter 3 discusses the perspectives of four regulatory agencies with regard to the development, implementation, and assessment of performance standards, and Chapter 4 describes how various end-users view the process of developing, implementing, and assessing performance standards. Chapter 5 summarizes the detailed steps involved in the development and implementation of performance standards and includes some examples of how one institution designs new performance standards. Chapter 6 presents the results of the breakout sessions during which working groups drafted a mock performance standard on PAM for ongoing research projects with laboratory animals. Chapter 7 recounts a presentation on the idea that performance standards can increase efficiency and reduce waste and on how the community might best share acceptable performance standards. Chapter 8 provides a brief summary of some of the messages conveyed at the workshop.

In accordance with the policies of the National Academies of Sciences, Engineering, and Medicine, the workshop did not attempt to establish any conclusions or recommendations about needs and future directions, focusing instead on issues identified by the speakers and workshop participants. In addition, the organizing committee's role was limited to planning the workshop. The workshop summary has been prepared by workshop rapporteurs Joe Alper and Lida Anestidou as a factual summary of what occurred at the workshop.

2

OVERVIEW OF PERFORMANCE STANDARDS FOR THE HUMANE CARE AND USE OF LABORATORY ANIMALS[1]

Patricia Turner, Planning Committee Co-Chair, Professor in the Department of Pathobiology and Program Leader of Laboratory Animal Science at the Ontario Veterinary College, University of Guelph, opened the workshop by reviewing how the committee developing the 8th edition of the *Guide for the Care and Use of Laboratory Animals* approached the topic of performance standards. She emphasized that the *Guide,* which was published in 2011, was never intended to be an encyclopedia or even a standalone reference. "Rather, it was intended to be a tool integrated with other pieces of information to develop the best care and use practices at any particular facility," she explained.

The current *Guide* is the first edition that emphasizes the Three Rs – replacement, reduction, and refinement (Russell and Burch, 1959), the importance of animal well-being in ensuring the integrity of animal-based research, and the responsibility of both the institution and researcher to provide humane care to laboratory animals. As a document, the *Guide* was meant to be the starting point for institutions to develop guidelines and policies for the comprehensive care of animals used in research. This process would involve collaboration between the institution, the IACUC, as well as technicians, caregivers, and veterinarians who work closely with animals and research groups on a daily basis, while important concepts, such as cost and efficiency, would not be considered in isolation. In addition, said Turner, the *Guide* was meant to help investigators plan and conduct their studies with scientific rigor.

[1] This section is based on the presentation by Patricia Turner, and the statements are not endorsed or verified by the National Academies of Sciences, Engineering, and Medicine.

The concept of performance standards first appeared in the 7th edition of the *Guide*, published in 1996. The concept proposed that institutions should have the flexibility to structure their programs to fit their own research needs while providing only minimal guidance as to what such flexibility meant and how institutions should accomplish it. When the update process for the 8th edition began in 2008, researchers had produced a wealth of new information, and acceptable practices for the care and use of laboratory animals had evolved. As a result, the committee that wrote the 8th edition was charged by the statement of task to include performance standards as a central feature. The resulting 220-page document provides examples, references, and information on how to implement performance standards.

Engineering standards in the 8th edition are meant to provide a minimum or a starting point for how to best care for animals, Turner explained. This emphasis, she noted, puts a substantial burden on the research and laboratory animal science communities to develop and implement performance standards in tandem, which is not necessarily easy. "While it provides flexibility to institutions, a performance standard approach requires a mature and experienced outlook to know what might be possible and how it can be achieved. It requires knowledge of systems and procedures in the context of each institutional program, and it may require significant research and consultation," said Turner. "In addition, it results in a need for careful planning and for critical and ongoing assessment of how the performance standard is working and whether it is truly benefiting the program and the animals."

Addressing the challenges of developing and implementing performance standards can be frustrating, and after the *Guide's* publication, the committee received requests to "just tell me what to do." Frustrated institutions sometimes default back to engineering standards, said Turner, because it seems easier to do what is prescribed instead of exploring and developing an alternate procedure better suited to the animals, the institution, or the specific research needs.

Turner then defined engineering, performance, and practice standards:

- An engineering standard is a standard or guideline specifying in detail a method, technology or technique for achieving a desired outcome. It does not allow modifications in the event acceptable alternative methods are available, and because of its prescriptive nature it provides limited flexibility for implementation. Engineering standards are helpful for setting a minimum benchmark.

- A performance standard is a standard or guideline describing a desired outcome while providing flexibility in achieving this outcome. When developing a performance standard, it is essential to clearly define the desired outcomes and regularly monitor appropriate performance outcomes to verify the success of the process.
- In the absence of scientific literature or other definitive source, a practice standard is the application of professional judgment to a task or process that over time and experience has been demonstrated to benefit or enhance animal care and well-being.

Performance standards are not exclusive to laboratory animal science, and are often used in other settings such as banking, airline flight tracking, and public safety. Their common feature, said Turner, is that they are not static once developed and implemented. Ideally, engineering and performance standards are balanced, setting a target for optimal practices, management, and operations while encouraging flexibility and judgment. Practice standards, which evolve over time and are widely used and accepted, help define what approaches are and are not acceptable for animal care and use by encompassing a broad base of knowledge, skills, and attitudes. Examples of practice standards in veterinary medicine include collecting temperature, pulse, and respiration during a physical examination; collecting and keeping proper medical records; and collecting informed consent from the owners when enrolling animal patients in clinical trials.

Despite performance standards being at times challenging to develop, there are two good reasons for using them, Turner noted: they provide significant flexibility to institutions to modify and update practices and procedures in response to new information, and they permit timely changes in practice without new regulation or policy. She emphasized that a performance standard both defines expected outcomes and balances the importance of meeting a baseline established by engineering standards with the need for flexibility.

A good performance standard uses what she called "appropriate language," particularly regarding terms such as must, should, and may that appear frequently in the *Guide*. "Must," she explained, indicates actions that the *Guide* committee considered to be imperative and a mandatory duty or requirement for a facility to follow; "Should" indicates a strong recommendation for achieving a goal, while recognizing individual circumstances might justify an alternative strategy; "May" indicates a suggestion to be considered. It is tempting, said Turner, to

make everything a "must" when developing performance standards, but being reasonable is important. "If something is unlikely to be achieved in every instance, then we are setting the facility up for failure. We need to ask, 'Is it absolutely essential in every case to have a certain standard in place for ensuring or enhancing animal welfare or safety?" she said. "Should" and "may," Turner added, can also refer to items that become the norm over time, citing social housing as an example: the *Guide* refers to social housing as a "should" item, but it has become a "must" in the performance standards written by many institutions.

Performance standards can trigger changes in the standard of practice for laboratory animal care and use as individual institutions monitor, evaluate, and validate the success of a specific approach. Toward this end, Turner stressed the importance of sharing changes in performance standards by presenting them at conferences and publishing them in the peer-reviewed literature. Publication, she added, adds to the credibility of the work, makes it easier for other institutions to justify changing their performance standards, and can illustrate an approach with potential utility in other situations. While this evolution can frustrate researchers and institutional officials who may feel the ground is constantly shifting under their feet, it does reflect new knowledge and expectations and increases the level of care for research animals.

Turner then discussed how the *Guide* committee developed certain recommendations related to performance standards. Her first example considered temperature. A *Guide* table lists recommended dry-bulb macroenvironmental temperatures for many species. While it is easy to look at the table for the engineering standard, said Turner, it is important to interpret this information in context with the associated text to get the full meaning of committee's intentions. For rodents, the *Guide* further recommends that dry-bulb temperatures in animal rooms should be set below the animals' lower critical temperature to avoid heat stress, to provide the animals with adequate resources for behavioral thermoregulation (such as nesting materials) and to minimize variations around a set temperature. The *Guide* also lists circumstances requiring additional considerations, such as when animals are recovering from surgery or when the facility houses neonates or hairless rodents.

She then discussed social housing. All animals, the *Guide* states, should be housed under conditions that provide sufficient space and supplementary structures and resources required to meet their physical, physiologic, and behavioral needs. Single housing of social species should be the exception and be justified based on experimental requirements or veterinary-related concerns about animal well-being. This performance

standard implies that facilities must have an understanding of species' typical social behavior, including behaviors such as dominance or aggression. It also means the IACUC and veterinarians need to review rigorously and regularly any proposal which includes single housing.

In response to this performance standard, institutions have had to reexamine their ability to socially house certain species, such as rabbits and male mice of different strains. For example, research has shown that BALB/c mice can be housed in isosexual groups for long periods of time with minimal agonistic behavior, but only if those groups are established by five to six weeks of age and only if housed with sufficient environmental resources. Many institutions, noted Turner, are still trying to decide whether and how laboratory rabbits can be paired and group-housed in research settings. "This is a continuing and evolving process in terms of our knowledge of social housing, but without this performance standard requirement, institutions wouldn't be forced to look at some of these practices more closely," said Turner.

Another example of a performance standard focuses on environmental enrichment programs, which the *Guide* states should be reviewed by the IACUC, researchers, and veterinarians on a regular basis to ensure they benefit animal well-being and are consistent with the experiments performed. According to this performance standard, personnel responsible for animal care and husbandry should receive training in the behavioral biology of the species they work with to appropriately monitor the effects of enrichment and identify the development of adverse or abnormal behaviors. Furthermore, it aims to balance the importance of deploying resources and enrichment strategies with the need to support the scientific goals of the study, and it therefore requires a solid understanding of each particular project, said Turner. This performance standard also implies that enrichment should be considered an independent variable that needs to be suitably controlled for in studies.

Turner noted that the cage and pen space performance standard has generated a great deal of comment and interest by the research community. The *Guide* states that "at a minimum, animals must have enough space to express their natural postures and postural adjustments without touching enclosure walls or ceiling, be able to turn around, and have ready access to food and water. In addition, there must be sufficient space to comfortably rest away from soiled areas," and "cage height should take into account the animal's typical posture and provide adequate clearance for the animal from cage structures, such as feeders and water devices." Furthermore, "sufficient space should be allocated

for mothers with litters to allow the pups to develop to weaning without detrimental effects for the mother or the litter." As this performance standard implies, animal space needs are complex, and space allocations need to be assessed, reviewed, and modified as necessary by the IACUC based on performance indices such as health, reproduction, growth, activity, and behavior. For example, the 8th edition provides recommended minimum space needs for rodent females with litters based on current practice standards used by some breeding operations. These are intended to serve as a starting point for addressing the space needs of breeding groups taking into consideration additional parameters such as number of adults, litter size, sanitation frequency, and the age of the pups.

A new performance standard requires validation, and one should never be developed at the expense of animal health and well-being, or in a way that interferes with the science being conducted, said Turner. She added that the principles of the *Guide* are intended to provide an ethical approach for all animals used in research, including fish and cephalopods. However, since there are over 30,000 fish species it would be impossible to include sufficient detail for each of them.

In her conclusion, Turner emphasized that a well-established performance standard, meets the following criteria:

- It supports scientific objectives,
- It supports the health and welfare of the animals,
- It has outcomes set in advance and associated criteria to assess them, and
- It is regularly monitored for success.

The 8th edition of the *Guide* relies heavily on developing and implementing appropriate performance standards to enhance the care and well-being of laboratory animals. This approach, said Turner, allows for institutions to be responsive and to implement actions in a timely fashion while requiring rigor and validation to ensure the outcome is as good as or better than the previous performance or engineering standard.

3

REGULATORY AND ADVISORY PERSPECTIVES

The workshop's first panel session featured four presentations from representatives of agencies that play a role in regulating animal welfare. Susan Silk, Director of the Division of Policy and Education in the NIH Office of Laboratory Animal Welfare, and Carol Clarke, Research Program Manager at the U.S. Department of Agriculture's (USDA) Animal and Plant Health Inspection Service, provided the NIH and USDA's perspectives on performance standards. Gilly Griffin, Director of Standards at the Canadian Council on Animal Care, discussed Canada's view of performance standards, and Judy MacArthur Clark, Head of the United Kingdom's Animals in Science Regulation Unit, spoke about the U.K. perspective and how it fits within the European regulatory system. An open discussion moderated by Planning Committee Co-Chair David Kurtz followed the four presentations.

THE NIH PERSPECTIVE[1]

The NIH Office of Laboratory Animal Welfare (OLAW), explained Susan Silk, oversees the welfare of research animals according to the standards in the *Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals* (PHS, 2015). The PHS policy, first published in 1985 and revised in 2015, incorporates by reference the 8th edition of the *Guide*. It is a tool that enables federal agencies to give legal effect to materials published elsewhere rather than creating a new set of technical standards simply to serve regulatory purposes. Since the *Guide* provides the best-practice standards for biomedical animal care and use programs,

[1] This section is based on the presentation by Susan Silk, and the statements are not endorsed or verified by the National Academies of Sciences, Engineering, and Medicine.

PHS policy requires PHS-funded institutions, including those receiving NIH funding, to base their programs on the *Guide*.

OLAW's interpretation of the *Guide* holds it to be a starting point for how to operate a quality program. The PHS oversight system relies on self-monitoring, self-regulation, and self-reporting, Silk explained, because the NIH is a scientific, not a regulatory agency. This grassroots approach, established by Congress in 1985, supports the development of a culture of compliance and caring. The U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training were promulgated in 1985 (IRAC 1985), and an accompanying report provides Congressional support to OLAW's reliance on IACUCs to oversee PHS-funded animal activities, Silk explained.

PHS's initial policies and guidelines derived directly from the 6th edition of the *Guide*, and the evolution of these policies and the *Guide* has resulted from 26 years of cooperation and careful work supported by documentation and information sharing within the animal research community, said Silk. In 1997, for example, a symposium on performance standards in animal welfare, convened after the publication of the 7th edition of the *Guide*, led to the recommendation that every performance standard required associated measures of assessment; development of such measures is an activity ongoing today.

In 2007, the ILAR Council determined the *Guide* needed updating, and a letter sent to NIH noted the necessity of preserving and perhaps even increasing the performance-based nature of this document. As a result, NIH and other organizations provided funds for ILAR to update the *Guide*. The statement of task to the expert panel charged with revising the *Guide* provided the following instruction: "Where scientifically warranted, the guidance and recommendations of the 1996 Guide will be changed to reflect new scientific evidence, while maintaining the performance standards of the 1996 Guide." NIH, which played no role in developing the *Guide*, took about a year to adopt the *Guide* after its publication and requires all PHS-Assured institutions to implement the new *Guide*.

The *Guide,* Silk noted, is not an operations document, but rather a collection of experts' wisdom assembled "under the benevolent leadership of the National Academies and ILAR, which serves the interest of nonpartisan scientific integrity." She clarified a misunderstanding as to whether federal agencies strongly support the use of performance standards. "Performance standards are the most important component of the infrastructure of PHS oversight of animal programs, and OLAW stands behind this statement. We expect IACUCs to meet their responsibility to ensure humane animal care and use while advancing quality scientific

research through the use of performance standards in the IACUC's oversight of institutional animal programs," said Silk. These statements, she added, are posted on the OLAW website (http://grants.nih.gov/grants/olaw/positionstatement_guide.htm#performance).

OLAW expects PHS-Assured institutions to implement performance standards by enlisting diverse expertise to develop outcome-based performance standards that enhance the quality of animal care and use programs, and to apply professional judgment and experience to develop the policies and procedures needed to maintain a quality program that provides humane care to animals. The 8th edition of the *Guide*, said Silk, supports performance standards that were already in use by most programs, and as a result, OLAW expected few institutions would need to make major changes to quality programs as they adopted the new *Guide*. Institutions not meeting those standards were given a year to develop a reasonable plan and schedule for implementing the *Guide*. OLAW has been holding webinars to help the community understand its expectations regarding well-established performance standards and to address a variety of concerns among members of the community. OLAW has posted the webinars on its website (http://grants.nih.gov/grants/olaw/educational_resources.htm) and is in the process of indexing the comments and questions prompted by these webinars. The website also contains a Frequently Asked Questions (FAQ) section addressing some of the key issues the community has raised, such as on how to assess the adequacy of housing and how to develop performance standards for housing.

THE USDA PERSPECTIVE[2]

The Animal Welfare Regulations (AWR) mix performance and engineering standards to show there is more than one way to achieve animal welfare goals, explained Carol Clarke. The regulations, for example, require the IACUC to review animal care and use programs and inspect animal facilities every six months, a prescriptive engineering approach with no exceptions and no special circumstances. However, the regulations allow the IACUC to determine the best means of conducting these evaluations. The defined goal is to get inspections done with a flexible, performance approach.

[2] The section is based on the presentation by Carol Clarke, and the statements are not endorsed or verified by the National Academies of Sciences, Engineering, and Medicine.

Housing is another example of where engineering standards prescribe a minimum space requirement for each species. The regulations, however, provide the opportunity to develop innovative cages that may not meet the space requirements but do provide sufficient space and opportunity to allow for provide species-specific behavior. This latter provision creates a flexible, performance-based approach.

Clarke pointed out two important phrases appearing throughout the regulations - "in accordance with established veterinary and medical practices," and "currently accepted professional standards" – that are important because standards and practices evolve. For example, in the 1980s animals did not routinely receive postoperative pain medications after surgery, but this is now a required veterinary practice. At one time, toys were the central feature of efforts to promote the psychological well-being of nonhuman primates, but today's practices require employing innovative social housing and behavioral monitoring. This kind of evolution is important, said Clarke, because it has a direct bearing on what constitutes compliance.

She then dispelled some of the myths associated with AWR. Some believe these regulations are based on specific engineering standards and have not yet incorporated performance standards. To show why this is not the case, Clarke cited the following example: regulations regarding operative procedures on non-rodents call for surgery to be performed only in facilities intended for that purpose and maintained under aseptic conditions. One facility, however, was unable to build a dedicated surgery suite, so it asked USDA if it could use mobile laminar flow hoods for such surgeries. Upon review, USDA ruled that laminar hoods met the requirements of being clean, aseptic, and dedicated to surgery, and approved this request.

Another example concerned naked mole rats, for which there is no species-specific standard. These animals are eusocial and live in underground colonies in a caste system similar to that of ants. USDA ruled that a network of plastic pipes designed to mimic the underground conditions in which these animals live in nature fulfilled the requirement that housing must enable the animals to express their normal social behavior.

The role of the USDA inspector, Clarke then explained, is to ensure a facility is in compliance with the regulations. The inspector understands compliance can be achieved in many ways because of the built-in flexibility of the regulations and variation among facilities. The inspectors can draw upon expertise within the Animal and Plant Health Inspection Service (APHIS), including diplomates from the American College of

Laboratory Animal Medicine (ACLAM) and the American College of Animal Welfare (ACAW), as well as other subject-matter experts. They can also use other references and standards, such as the *Guide* and taxon-specific publications. Clarke encouraged everyone to join the online APHIS Stakeholder Registry to receive updates and notice of future developments.

THE CANADIAN PERSPECTIVE[3]

The Canadian Council on Animal Care (CCAC), established in 1968, oversees the ethics of animal experimentation in Canada, explained Gilly Griffin. It is a non-legislated, peer-reviewed system acting on behalf of the people of Canada. Griffin said there is true public involvement in every aspect of its programs, including members of the public who serve on the Council and on CCAC animal care committees, the equivalent of U.S. IACUCs. The CCAC program, said Griffin, is unique because it both sets standards and maintains them through assessments and certifications. The strong link between assessment and certification programs, she said, creates a learning system that allows the CCAC to adapt to new research realities, incorporate them into the standards, and get information back into the research community.

Canada's approach to its guideline documents is to create modules or chapters that can be updated more regularly than large volumes. Modules are developed by expert subcommittees in a process overseen by CCAC's standards committee (Figure 3-1). After reviewing all of the relevant scientific evidence, an expert subcommittee develops a preliminary draft of a new guideline. Several review steps follow, producing multiple drafts posted on CCAC's website for public comment, followed by a final review. At each point in the process, the standards committee acts as a gatekeeper to ensure each draft is ready for review and aligns with other CCAC guidance documents. The final step is approval by CCAC's board of directors, at which point the guidance document is published. The process takes a long time, Griffin said, but it allows for significant buy-in from the community.

[3] This section is based on the presentation by Gilly Griffin, and the statements are not endorsed or verified by the National Academies of Sciences, Engineering, and Medicine.

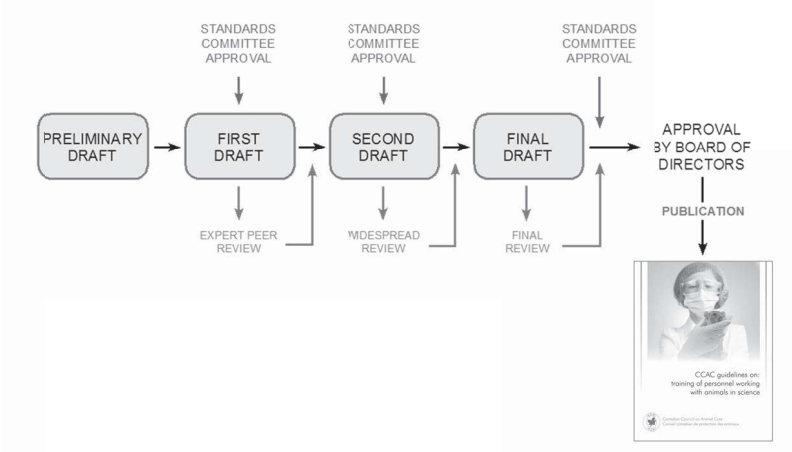

FIGURE 3-1 Canada's animal welfare guidelines development process
SOURCE: Griffin slide 5

This last point is important, she said, because the guidelines are written for several audiences, including:

- Investigators, who write protocols and want to know how their animals are going to be managed;
- Animal care committee members, who review those protocols and ensure they comply with CCAC guidelines and policies;
- Veterinary and animal care staff, who maintain the health and well-being of those animals; and
- Assessment panels, who use the guidelines as their standards during assessment visits and make recommendations based on the guidelines themselves.

As with the *Guide*, Canada's guidelines use "must" for mandatory requirements and "should" to indicate an obligation for which any exception must be justified and approved by an animal care committee based on strong scientific justification for changing that requirement. The guidelines, said Griffin, evolve through an iterative process reflecting how good practices develop into best practices, and they serve as a framework that enables institutions to develop best practices. As an aid for Canada's institutions, CCAC maintains the 3Rs microsite at which it curates best practices documents. CCAC expects these best practices to be published and tested over time and serve as the basis for the next revision of the relevant guidelines.

CCAC's assessment panels, comprising scientists, veterinarians, and community representatives, are responsible for assessing performance standards. These panels do not function as an inspectorate, explained Griffin, but rather as a vehicle to encourage learning and for sharing best practices. After each assessment, the panel prepares a report with recommendations based on CCAC's guidelines and policies, and because CCAC uses a performance approach, these assessments rely heavily on the experience and range of expertise on the panels.

One result of CCAC's historic reliance on a performance approach, Griffin noted, is that the guidelines tend to be a mix of performance standards and more specific requirements. For example, the CCAC guideline on the care and use of farm animals in research, teaching, and testing includes a performance standard stating that flooring should provide a dry, comfortable lying surface, it should allow animals to go through their normal movements and postural changes without slipping, and it should not result in injuries. This performance standard does not specify the flooring material, allowing institutions to choose based on their local circumstances and the types of barns they have. However, the guidelines do include a specific requirement for dairy cattle housed in free stalls mandating at least one stall for each cow within the group. This requirement was based on scientific evidence showing that the more cattle are able to lie down, the lower the chance they will develop hock injuries and lameness while at the same time improving milk production.

As another example, Griffin discussed CCAC's 2010 guidelines on euthanasia of animals used in science. These guidelines include ten general guiding principles, but also permit animal care committees to accept new methods that conform to these principles. The guidelines include a summary chart of acceptable methods of euthanasia for experimental animals that meet those ten principles, as well as six methods that are conditionally acceptable.

The most recent CCAC guideline, published in March 2015, covers training of personnel working with animals in science and it emphasizes performance standards. The guideline makes institutions responsible for documenting that all personnel involved with animals have the appropriate knowledge, skills, and competency to perform their required tasks, but the document does not prescribe how to deliver programs or record training. As an adjunct to the guideline, CCAC provides a recommended syllabus so that institutions can be certain of what knowledge and skills they need to teach.

CCAC's experience, said Griffin, has been that guidelines often require additional supporting materials, such as implementation tools to help

investigators and animal care committees determine what a performance standard means for the particular animals kept at their institutions. With the euthanasia guidelines, for example, CCAC provides a publication documenting the effects of the different euthanasia methods on research results to help animal care committees look critically at the evidence on the impact of euthanasia methods on common research goals. For the latest guidelines on training, CCAC might provide some information on how to assess and record competency, including a template institutions might use verbatim or as a guide for developing their own way of assessing and recording competency.

THE UNITED KINGDOM AND EUROPEAN PERSPECTIVE[4]

European Union (EU) regulations for the protection of animals used for scientific purposes are stated in EU Directive 2010/63, Annex III (European Parliament, 2010), which lists mandatory standards for application throughout EU member states, explained Judy MacArthur Clark. Referenced in that directive is an EU Commission recommendation based on a document known as Appendix A (Council of Europe, 2006), which is advisory in nature and not mandatory. These two documents – Annex III and Appendix A – need to be referenced with regard to how MacArthur Clark and her team apply EU legislation to U.K. legislation. The result is a set of mandatory standards in compliance with Annex III and what she called delivered advice based on Appendix A.

Regarding U.K. legislation, some parts of the mandatory standards are applicable to all species, and in general, these are performance standards. Other parts of the standards are species-specific, and these tend to be engineering standards. These mandatory standards are published in the *Code of Practice for the Housing and Care of Animals Bred, Supplied, or Used for Scientific Purposes.* The advice component of the U.K.'s code of practice is based largely on Appendix A, but it includes information on how to achieve the performance standards as well as some engineering standards.

In the United Kingdom, engineering standards are defined, measurable parameters with a range of appropriate values. Engineering standards can apply to cage sizes, temperature ranges, photoperiod, trough length, and perch length, for example. Performance standards are outcomes-based parameters, and MacArthur Clark gave two examples:

[4] The section is based on the presentation by Judy MacArthur Clark, and the statements are not endorsed or verified by the National Academies of Sciences, Engineering, and Medicine.

the exposed surface of walls and floors should be made with a material resistant to heavy wear and tear; and noise levels, including ultrasound, shall not adversely affect animal welfare. Engineering standards, she continued, serve as a hard bottom line and tend to be the welfare safety net for individual species. As such, they set clear expectations for both institutions and equipment manufacturers, and they satisfy public expectations. Historically, engineering standards have been the model for compliance monitoring, but in general they are no longer what regulators focus on with regard to compliance. Performance standards reflect the fact that every institution and every experiment is different, and they provide the flexibility needed to accommodate those differences. MacArthur Clark reiterated what the other speakers had noted: it is not essential to mandate how good animal welfare should be achieved given the many ways this can be accomplished.

The challenge with performance standards, she said, is to agree on what is acceptable in terms of animal welfare and who defines the performance outcomes. While growth and reproduction can serve as performance outcomes, for example, there are situations where growth and reproduction do not necessarily measure good welfare. "We need to be open-minded and think carefully about how we are going to measure good welfare," said MacArthur Clark.

U.K. and European regulators, she said, have gone to great lengths to involve a broad range of stakeholders in thinking about how to best measure animal welfare, partly to provide individual EU member states with the opportunity to share ideas and raise their own practices to best practice standards. International expert panels, run by the European Commission, help develop some understanding of performance outcomes, and MacArthur Clark's unit in the United Kingdom develops advisory notes and codes of practice. Often, there are diametrically opposed views on the need for these notes and codes of practice, but getting people with diverse views to talk about their differences and to better understand the role of these advisory documents results in advisories that have broad support.

The cage-side view of the animal care staff, veterinarians, and inspectors is equally important, said MacArthur Clark. Home Office inspectors visit facilities on a monthly or even more frequent basis, depending on the size of the facility, and they serve both as inspectors and as part of the advisory system to share performance outcomes. Strategy and oversight are provided by the Animal Welfare and Ethical Review Boards, the U.K. equivalent of the IACUC. Guidance, she added, helps develop a shared understanding of what is or is not acceptable, and

it provides the flexibility to allow practice standards to evolve. Regulations, on the other hand, are inflexible and require an Act of Parliament. She noted that empowering and assisting institutions with benchmarking drives institutions in their own cycles of self-improvement.

MacArthur Clark explained that her office recognizes that in a normal distribution curve there will be some situations that are at the extremes of the curve and there can be good justification for those situations. In that respect, she said, guidance for performance standards describes what is normally considered appropriate or suitable for a particular species, but also allows for exceptions provided animal welfare standards are maintained. Guidance includes suggestions for enrichment for each species, suggested temperature and humidity ranges, typical species housing needs, typical social needs of a species including those for different sexes and ages, and species-specific dietary advice. All of these items include links to background papers and evidence.

The U.K. Code of Practice contains both engineering and performance standards that are mandatory today and standards that will be mandatory as of January 2017. It also contains non-mandatory advisory information and a bibliography listing a selection of literature supporting that advice. The Code of Practice was published at the end of 2014, and since its publication MacArthur Clark and her team have learned a number of lessons:

- Non-mandatory advice is useful for guidance on how to approach mandatory outcomes and for setting future expectations.
- Users and regulators appear comfortable with the idea that this advice is flexible.
- There is an increased emphasis on institutions justifying their decisions and strategies.
- Institutions prefer performance standards and would like fewer engineering standards.
- Equipment manufacturers and animal welfare groups would like more engineering standards.

Regulators, said MacArthur Clark, are trying to balance these lessons in a way that works best for the animals while recognizing there are other interested perspectives at play. She believes, she said in closing, that engineering standards are providing a welfare safety net for the animals and reassurance to the public, but performance standards provide the opportunity to put animal welfare first. Both types of standards need to be balanced into an effective system, with guidance as an essential

component of the end product to ensure shared interpretation and expectations of what is acceptable performance.

DISCUSSION

To start the discussion, David Kurtz asked the panelists for ideas on how to publish both positive and negative experiences from trying to establish performance standards. Clarke responded that she heard from a group of researchers that there exists an unofficial venue where investigators discuss and share information about what does not work. These researchers told her they were reluctant to make this an official publication, and Clarke wondered if the roundtable could serve as an official venue for resurrecting this idea and getting the community to think about publishing negative results. Patricia Turner said the important characteristic of any data, positive or negative, is that it must be generated by rigorous studies. "We should have a mechanism for sharing information, but we also need to recognize a certain standard for that information. If a study is performed well, even if the results are counter to the hypothesis perhaps that was the initial basis for that work, it should still be publishable," said Turner. Griffin agreed with Turner's statement.

Silk said that OLAW is helping its community implement new standards with significant changes to previously approved animal protocols. OLAW is also encouraging institutions to publish significant changes to their practices on the IACUC Administrators Association website. MacArthur Clark agreed with Kurtz's idea of sharing negative results and said that the field needs a mechanism by which investigators can freely exchange their experiences and get feedback from others in the field, perhaps in the form of a wiki-type environment.

Paul Locke, from Johns Hopkins Bloomberg School of Public Health, asked Turner to clarify her use of the term practice standard. Practice standard, she replied, refers to what is acceptable in terms of how procedures are done within a facility, and it consists of the appropriate skills, treatment, and attitudes toward animals that occur within an institution. Performance standards, she said, may contribute to the practice of laboratory animal science in the long run and therefore to practice standards that are acceptable.

Locke then asked the panelists for ideas on how to fully engage the appropriate communities and the public to get new performance standards discussed, vetted, and validated.

In Canada, said Griffin, this is done via the assessment panels that share best practices with the institutions they visit. "Our assessments are

a formative experience and an opportunity for institutions to ask questions and get advice and understanding from the panel members, who then go back to their own institutions," said Griffin. Panel members have told her that these assessments have been great learning experiences for them as well as for the institutions they assessed. Griffin also reiterated that CCAC's 3Rs microsite is a place for curating and disseminating best practices, though she acknowledged that operating this site is resource-intensive.

MacArthur Clark said there is no one approach for sharing information that will work for everyone. One barrier her agency faces is that the environment in which it works has been rather secretive and confidential, which does not create an atmosphere that inspires investigators and institutions to share best practices. She is encouraged, though, by the drive over the past four to five years in the United Kingdom to create more transparency, but currently, unlike in Canada, inspectors in the United Kingdom operate under confidentiality and do not share best practices among institutions. One approach her office is considering is to reassign some of its resources to conduct what she called horizontal inspections, which would be thematic rather than institutional and would allow her office to use its annual report and public meetings to disseminate anonymized best practices.

Silk said she is in favor of looking to the people who have contact with the animals every day for ideas to improve what they do to the benefit of the animals. Clarke added that USDA promotes and supports meeting for sharing best practices in an open venue.

Robert Wurtz from the NIH, questioned why regulatory authority over animal experiments in the U.S. was divided among multiple agencies. Clarke explained that every U.S. regulatory agency supports a specific act of Congress, and her agency supports the Animal Welfare Act. Silk noted that USDA is a regulatory agency but NIH is a scientific agency and compliance with its guidelines is entirely optional. "Our guidelines are not laws. We conduct oversight to help you stay in compliance with guidelines that enable you to legally receive appropriated funds," said Silk. NIH has had a Memorandum of Understanding with USDA and the Food and Drug Administration since 1985, she added, enabling the agencies to work closely with one another to harmonize expectations. For example, when NIH publishes its FAQs, it reviews with USDA those questions that concern shared issues. In addition, the two agencies have harmonized their published guidelines.

Regulations impacting the United Kingdom are set at a European level but are then implemented by U.K. legislation, explained MacArthur

Clarke. She noted the implementation process can be tortuous, and in the end, while in theory the regulations of all the EU member states are aligned, in practice each EU member state implements the regulations differently. This creates challenges, she added, when scientists move between countries. Canada, said Griffin, has provincial rather than federal legislation, which requires her office to consider 10 different pieces of legislation when trying to implement a national system of regulation.

An online workshop participant submitted a question asking how to qualify the outcome of no observable effect when using performance standards to assess welfare in the context of trying to reach a good effect or avoid a bad effect. OLAW, replied Silk, encourages its stakeholders to ask questions and it allows its PHS-Assured institutions to suggest different approaches to achieve the objective in a "should" statement in the *Guide*. "If the welfare of the animals is the same or better under the mechanism that they propose, then we would be fine with them going ahead with that," said Silk.

David Anderson, from the University of Washington, asked Silk to comment more on the challenge of being able to accurately assess impact. "Do we really require a demonstrable good effect or is a neutral effect something that is left up to the institution to judge?" he asked. Silk replied that this is a hypothetical question that everyone on the panel faces. "You are not applying performance standards in a large hypothetical universe. You are applying them to particular animals in a particular situation," said Silk. "We would begin to unpack this question by asking specifics about the animals." MacArthur Clark reminded the workshop that the basic operating principle is "first, do no harm," which is why it is important to always assess the outcome of any changes to the performance standard to show there is in fact no harm being done to the animals. Griffin noted the need to put more emphasis on developing good guidance for welfare assessment, something with which institutions often struggle.

Another question submitted online asked MacArthur Clark to comment on the Stop Vivisection European Citizens' Initiative currently in front of the European Parliament and the impact it may have on performance standards in the European Union. MacArthur Clark replied that the United Kingdom is in a pre-election period so she cannot comment about what the future may hold. She did note that it took two years of negotiation involving the European animal welfare bodies as well as the science communities to achieve the current directive, which has been implemented by all 28 member states. The Citizens' Initiative, she explained, is asking for that directive to be abrogated.

Cathy Liss, with the Animal Welfare Institute, said the U.S. system for assuring the welfare of laboratory animals is broken, in her opinion. It is broken, she said, because the safety net is not where it should be given the disparity between the *Guide*, which she said has moved forward and embodies a more thorough assessment, though lacking in specificity that the welfare community would like to see, and the enforcement mechanisms residing with USDA, which does not cover the majority of the animals used in research. She claimed that USDA standards are outdated and do not reflect current knowledge that would improve animal welfare.

She noted, too, that while there is a requirement for primates, there is no requirement for improving the welfare of the other animals. She then asked if there was a chance of revising the standards and revising the Animal Welfare Act so that it embodies more of the principles within the *Guide*.

Clarke replied that there is a mechanism to make revisions to the Animal Welfare Act and that some revisions are going on today. The process, she explained, involves submitting a petition that USDA would then put out for comment. Once the comments are evaluated, USDA would determine if there is a need to go forward and change the standards to which Liss was referring. Though the standards were written some time ago, Clarke said USDA is not standing in the way of progress and is using provisions in the regulations relating to currently accepted veterinary practices to give it flexibility and to allow the standards to evolve. Silk said she does not believe the animal welfare system in the United States is broken. "I think our grassroots approach is providing the best welfare for the animals," said Silk.

Liss asked Silk how OLAW, in the absence of an inspection system, ensures institutional compliance apart from the submission of an assurance. OLAW, Silk reiterated, relies on self-monitoring and self-reporting for every institution receiving PHS funding. The assurance document describes how an institution's animal care program operates and achieves compliance with PHS policy, which incorporates by reference the standards of the *Guide*. Her division within OLAW also helps institutions with education and policy interpretation. "We believe that through education, we prevent non-compliances from occurring," she said. Non-compliances are reported by the institution, by outside parties, or by individuals within the institution. OLAW's compliance division then works with the institution to resolve the noncompliant situation to ensure people and animals are safe and then enacts policies to prevent that situation from occurring again. "I would submit, and this is my opinion, that perhaps our system is more effective than an inspection system,

which is generating a snapshot in time. We are trying to make sure that everyone is working toward a culture of humane care at all times."

Donna Matthews Jarrell, from the Massachusetts General Hospital, said she appreciated the panelists' example of working with institutions to embrace this new approach which emphasizes performance standards. She wondered, though, what these institutions have done after they have evaluated a performance standard, particularly with regard to the schedule on which they continue reviewing these standards. Clarke responded that in the case of the laminar flow hood example, once her office had agreed there were no adverse effects, it became the IACUC's responsibility to monitor the situation on a six-month basis. Silk said OLAW takes the same position – it expects programs to be evaluated semi-annually while deferring to the IACUC's authority to make that decision. If complications did arise during surgery and sepsis developed,

Diane Gaertner from the University of Pennsylvania added, the veterinarians and veterinary technicians who would be monitoring the animals daily would be reporting to the IACUC if there was any doubt that aseptic conditions were being maintained.

MacArthur Clark stressed the importance of the individuals who work in an institution. If the animal care staff is well-trained, well-qualified, and empowered to speak up, there will be adequate protection of animal welfare. Even in the U.K., which has a national inspection system with inspectors going regularly to visit institutions, the strength of the system lies with the individuals within those institutions. Inspections, in fact, are called visits because although there is an inspection component, the inspectors are in essence monitoring the performance of monitoring framework built around the animal care staff.

Steven Niemi, from Harvard University, said he was intrigued by the flexibility USDA affords institutions, and he asked Clarke how the community can find out about these ad hoc interpretations so they may be applicable in similar circumstances at other institutions. Clarke replied these decisions are based on two factors: what is in the literature and what works. If there are no adverse effects to the animals, her office encourages investigators to publish their findings to get the information out to the broader community. Her office has held meetings with research facility veterinary medicine officers at which this topic was discussed and she hopes there will be more such meetings at which information can be shared and discussed.

Saverio Capuano, from the Wisconsin National Primate Research Center, noted that his institution has 194 standard operating procedures, and the University of Wisconsin has a plethora of animal care policies

approved by the IACUC. As a result, his facility's performance standards are not compiled in one place or are even written down in many cases. "When you come to visit me and when I tell you that some of my performance standards are in my head or in the heads of everyone who works at the Primate Center, how do you respond? How does USDA respond? How does OLAW respond to the fact that my performance standards are just everywhere?" he asked. Silk replied that the IACUC determines where performance standards are kept. Clarke added that when a USDA inspector comes and asks why there is a deviation from the regulations, they expect an answer. If the answer is logical, if there is documentation showing the IACUC has approved the modification, and if there are no adverse effects, then there will not be a problem.

4

END-USER PERSPECTIVES

After examining the perspectives of government agencies who oversee the implementation and monitoring of performance standards, the workshop featured two sets of panelists who presented various end-users' perspectives. In the first session, Neil Lipman, Executive Director of the Center of Comparative Medicine and Pathology, Professor of Veterinary Medicine in Laboratory Medicine and Pathology at Weill Medical College of Cornell University, and Laboratory Member of Memorial Sloan Kettering Cancer Center, gave the perspective of someone working in academia; Mary Ann Vasbinder, Head of Corporate 3Rs Responsibility and Training Strategy in the Office of Animal Welfare, Ethics, and Strategy at GSK, provided a pharmaceutical industry perspective; and John Bryan II, Public Service Assistant and Wildlife Veterinarian at the Southeastern Cooperative Wildlife Disease Study (SCWDS), gave a wildlife biologist's perspective. In the second session, Bart Carter, Director of Animal Resources and Attending Veterinarian for the University of Texas Southwestern Medical Center, provided an agricultural perspective; Kenneth Litwak, Laboratory Animal Advisor to the Animal Welfare Institute, spoke from a public interest perspective; and John Bradfield, Senior Director at the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) International, gave the perspective of an international accrediting and assessment organization. Paul Locke, Associate Professor of Environmental Health Sciences at the Johns Hopkins University Bloomberg School of Public Health and Distinguished Visiting Professor of Animal Law and Science at Lewis and Clark Law School, then gave a brief synopsis of the six presentations. An open discussion, moderated by David Anderson, ended the workshop's first day.

THE PERSPECTIVE OF U.S. ACADEMIA[1]

The Center of Comparative Medicine and Pathology (CCMP) is unusual, said Neil Lipman, in that it supports two separate and distinct institutions: Weill Cornell Medical College and Memorial Sloan Kettering Cancer Center, each with its own budget and its own IACUC. Typically, the facility houses a quarter of a million animals on any given day, has about 53,000 rodent cages, and is staffed by some 250 people working in 10 vivaria in New York and Doha, Qatar, with resources smaller institutions may not have. Lipman characterized CCMP as mouse-centric and highly harmonized, as all facilities use the same standard operating procedures. In addition, CCMP has a large multidisciplinary anatomic and clinical pathology laboratory to perform certain types of testing and a postdoctoral training program to provide the labor and skills to develop and assess a performance standard. The culture at CCMP, Lipman added, is to make evidence- and outcome-based decisions, while management is hypothesis and data-driven whenever possible.

From his perspective, engineering standards have both advantages and disadvantages, as previously mentioned. Major advantages include the implementation of a nominal baseline; some level of standardization and consistency; and ease and economy of implementation. Ideally, engineering standards are based on objective, scientific data, which Lipman said is not always the case. In contrast, poor-quality data leads to tight and inflexible engineering standards, which restrict progress and slow the development of new knowledge. They often are empirical and anthropomorphic, he said, and influenced by politics rather than sound information. When not well prescribed, they can also result in unnecessary costs. Performance standards allow greater flexibility to also align with science to improve animal welfare and care. They can be tailored to an individual situation or institution, and they can refine and improve engineering standards. Despite these characteristics, performance standards are expensive to properly develop, a challenge for resource-limited Animal Care and Use Programs. They can also be subjective, making it difficult to objectively determine the appropriate outcomes for assessment.

Lipman discussed two examples of CCMP's operations to illustrate its three primary program drivers: assure animal health and welfare, support science, and provide high-quality customer service. The first involved

[1] This section is based on the presentation by Neil Lipman, and the statements are not endorsed or verified by the National Academies of Sciences, Engineering, and Medicine.

identifying and genotyping pre-weanling mice at an age that permits additional tissue collection. "There are limited methods available to reliably and permanently identify pre-weanling mice, and we have historically used toe-clipping at our institution," said Lipman, who acknowledged that some feel that this technique is not humane. In fact, the U.K. Joint Working Group on Refinement of Production of Genetically Engineered Mice recommended using toe clipping as a last resort and performed under local anesthesia (BVAAWF/FRAME/RSPCA/UFAW Joint Working Group, 2003).

In 2010, two European publications (Castelhano-Carlos et al., 2010; Schaefer et al., 2010) indicated that toe-clipping may be the preferred method for neonatal mice up to age 7 days based on physiological and behavioral observations. These publications were referenced in the 8th edition of the *Guide*, which, Lipman believes, established a de facto engineering standard that warranted further study to create a new performance standard to minimize pain and distress; limit short- and long-term physiologic and behavioral effects; be safe for both animal and operator; be fast, easy, and permanent; and be cost-effective.

Lipman and his colleagues (Paluch et al., 2014) conducted a study to evaluate the effects of toe-clipping on the welfare of pre-weanling animals. Four groups of C57Bl/6J mice were toe-clipped on postnatal day (PND) 7 and four groups on PND 17. One group received and one did not receive a topical vapocoolant anesthetic, while two served as control groups. All were handled and restrained by an experienced investigator. The pups were observed for their reactions immediately after surgery, and at 1, 3, 5, 8 and 12 hours after clipping. The team conducted developmental assessments beginning at PND 6 (to obtain baseline values prior to clipping on PND 7) through PND 21 and behavioral assessments when the animals were adults. The results (Figures 4-1 and 4-2), he explained, showed no observable reactions in the PND 17 group compared to the control, but some signs of distress in the PND 7 group. As shown in Figure 2, the use of vapocolant created difficulties in both age groups. There were no differences in the developmental and behavioral results or weight gain among any of the groups. As anatomical studies showed the digits to be fully innervated and mostly calcified by PND 7, additional pain after PND 7 should not be expected, said Lipman. As a result of this study, CCMP revised its institutional guidelines and established new procedures, eliminating the use of vapocoolant; extending the recommended age for toe-clipping to greater than or equal to PND 17; limiting the procedure to one digit per day; and recommending the toe-clip site to be the distal first third of the first

phalanx. When toe clipping and tail biopsy are both needed, the procedure should be done between PND 14 and PND 17.

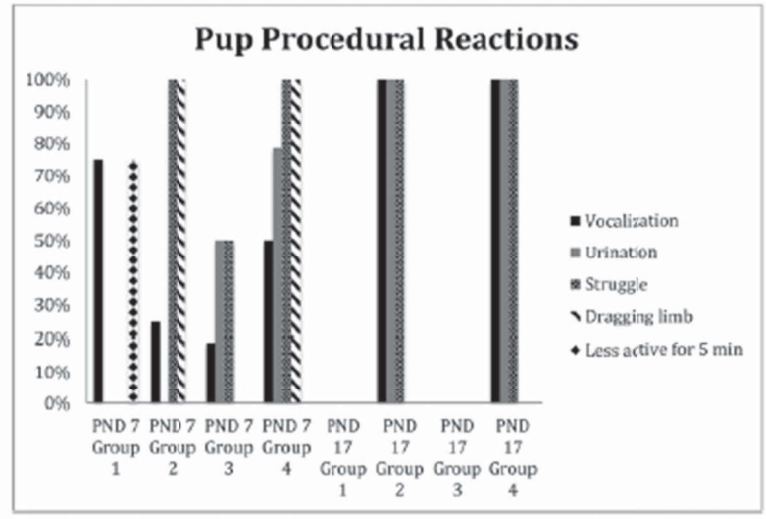

FIGURE 4-1 Immediate post-clipping observations (note: no reactions were observed in PND 17 groups 1 and 3)
SOURCE: Lipman slide 14

	Toe-clipping	Vapocoolant + Toe-clipping	Vapocoolant
Signs of distress	PND 7: ~60% vocalized, ↓'d activity PND 17: little reaction	PND 7: dragging of sprayed limb post-clip PND 17: vocalization, urination, limb withdrawal	
Bleeding	PND 7 & 17: immediate clotting	PND 7 & 17: Delayed profuse bleeding	N/A
Ease of procedure	PND 7: Difficult to clip small toe size	PND 7 & 17: VC causes toes to stick together → hard to isolate toe → clipping difficult	
Post-procedural observations	No maternal rejection PND7: swelling of HP ≤ 12 h PND 17: no abnormalities	No maternal rejection PND 7 & 17: swelling of paws ≤ 12 h	No maternal rejection PND 7: swelling of paws 5 ≤ h PND 17: swelling of paws ≤ 12 h

FIGURE 4-2 Additional data from post-clipping observations
SOURCE: Lipman slide 18

The second example Lipman discussed focused on developing a humane, safe, and efficient method of euthanizing mice that would induce rapid unconsciousness and death; avoid excitement; minimize fear, distress, and anxiety; minimize changes in the animal's environment; and would be efficient and reproducible. At CCMP, staff worked with a caging manufacturer to develop a sophisticated engineering paradigm based on the use of a single type of ventilated cage that allows room air to be replaced with carbon dioxide. This system was validated, including videographic behavioral assessment, and has now been used successfully for over nine years (McIntyre et al., 2007). Since the release of the latest edition of the Guidelines for Euthanasia by the American Veterinary Medical Association (AVMA 2013) a conflict exists with regard to the optimal flow rate for carbon dioxide used to euthanize rodents that CCMP employs. "We have a system that we have validated that does not meet this recommendation, so what do we do?" said Lipman. The CCMP team compared its performance with the AVMA Guidelines recommendation and showed that the CCMP system produced significantly lower distress levels in both mice and rats.

Even though this information was shared with the system's manufacturer, this performance standard was not widely adopted because it was not compliant with the AVMA guidelines, Lipman noted. The CCMP team then developed a new protocol for introducing carbon dioxide into the cages at a lower displacement rate to meet the AVMA guidelines. Today CCMP can use either standard.

In Lipman's opinion, research funds to develop science-based standards for the care of laboratory animals have been few and are getting fewer. To answer some of the larger questions, such as those about cage space, it will be necessary to create multi-institutional consortia to secure the funds to pay for these large studies, he added.

THE PHARMACEUTICAL INDUSTRY PERSPECTIVE[2]

A unique feature of the pharmaceutical industry, said Mary Ann Vasbinder, is its obligation to answer to multiple regulatory organizations worldwide, creating a dynamic working environment, particularly given that views on animal welfare differ across the globe. As a result, a pharmaceutical company has to consider what kind of performance standards are maximally applicable across global operations, have the flexibility to accommodate its needs across all of the markets in which it operates, and have aligned outcomes so there is a sense of satisfaction from doing the right thing for the animal.

One difficulty in developing a performance standard, she said, is getting everyone involved to agree on outcomes and expectations, particularly when those can change over time. At GSK, an acceptable performance standard is outcomes-based, has associated metrics for success, and derives from facts and data. When there are not enough facts and data, expert advice comes into play, but using experts comes with its own challenges, said Vasbinder, particularly when experts have different opinions based on their culture and background. At GSK, areas considered for performance standards include veterinary care, environmental enrichment, and acclimation to study, training, exercise, and socialization.

As an example of how GSK develops and implements a performance standard, Vasbinder reviewed a project on dog housing, which the company undertook because every site within the company handled the issue of cage size differently. After developing a management plan for a

[2] This section is based on the presentation by Mary Ann Vasbinder, and the statements are not endorsed or verified by the National Academies of Sciences, Engineering, and Medicine.

project that would examine dog housing, exercise, socialization, and environmental enrichment, her team lined up sponsors who provided research funds and agreed to build the cages the team would design based on the research findings. The team also created a communication plan to convey information to its key stakeholders on a regular basis and get buy-in as the project proceeded. After completing a literature review, talking to others in the community to learn what they had done, and developing a benchmarking system, Vasbinder and her colleagues conducted pilot studies with flexible housing options suitable for dogs and miniature pigs. From these pilot studies, the team realized it needed advice from behaviorists and people experienced with caging, so Vasbinder recruited five individuals to list and then prioritize the things they thought would be most valued to a dog in its home environment. Social interaction, both between dogs and between dogs and humans, the opportunity to exercise, and the ability to have environmental enrichment were perceived to be more important than cage size.

Using the experts' recommendations, the team built cages that would increase visibility for the dogs, optimize interactions with staff, and have a softer look than with standard cages. The trial cages incorporating these features were built to accommodate between four and six dogs, based on unpublished studies suggesting this number created a good balance between social interactions and fighting behavior. The cages were also designed, based on a strong recommendation from a behavioral expert, with enough space to enable dogs to trot within their enclosure. To benefit staff, the cages had to be easily cleaned and sanitized.

Vasbinder's team then looked at the different exercise programs the company's facilities were using and decided they wanted a dedicated area outside of the kennel and the main room for exercise. They also decided the dogs needed access to complexity – to be able to climb on things, to interact with toys, and have social interactions with people and other animals and with enough space to run. The team developed a performance standard for exercise of 15 minutes based on observing that when staff let the dogs out to exercise, the dogs were all lying on the floor or interacting socially rather than exercising after 15 minutes. Currently, the team is working on a performance standard regarding acclimation to the environment and another on how to introduce new dogs into the facility and condition them to a study.

The resulting cages have horizontal bars to increase visibility; Dutch doors to allow staff to pet the dogs, medicate them, and give them treats without letting them out of their cages; and benches the dogs can jump onto to further increase visibility. The cages have what Vasbinder called

alleyways through which dogs can see other dogs, and the cages can be connected to one another. The team further found that flooring with some grip to it improved the health of the dogs' feet. The cages also have areas where a dog can escape social interactions and be on its own should it need a break.

Assessments of the first generation of cages led to some modifications that further improved animal health and reduced stereotypic behavior. Vasbinder noted that staff morale improved as well. Even though these new cages took longer to clean, staff enjoyed the ability to interact more with the animals. In reviewing the project, she said the performance standards she and her team developed have worked well and the outcomes from this project were positive, despite the lack of published literature on which to base some of the decisions the team made. Many of the decisions came down to observations, listening to the advice of experts, and applying common sense, but Vasbinder wondered if common sense is an acceptable rationale for making decisions on performance standards.

GSK, she explained, has a set of core principles and policies for animal care driving much of what she and her colleagues do to create a better environment for the dogs and for the people who care for them. GSK, she said, is studying the characteristics of good exercise for dogs and plans to publish the findings.

THE WILDLIFE PERSPECTIVE[3]

Most wildlife research, John Bryan noted, is done for the sake of the wildlife and is not about using animals as a model for human biology. As a result, the methodology used to develop performance standards in the wildlife setting is different than in the laboratory setting. As a wildlife veterinarian, Bryan believes the definition of a performance standard that Patricia Turner presented fits nicely with the performance standards that are used in wildlife veterinary medicine, particularly because that definition includes the word "discretion."

What ties wildlife research to biomedical research, he added, is the desire to develop the best possible standards reflecting the beliefs and values of a civilized society. One big difference, though, is that the IACUCs reviewing wildlife research have to deal with the fact that virtually every project is unique in its operations. This requires that IACUC members look

[3] This section is based on the presentation by John Bryan II, and the statements are not endorsed or verified by the National Academies of Sciences, Engineering, and Medicine.

at each submission from scratch, given that from project to project species change, climate changes, terrain changes, and seasons change. Seasons, for example, can affect how a particular species metabolizes drugs, its reproductive activity, and its foraging and other behaviors. In addition, there are occupational health issues associated with the research being conducted in the field, where conditions can change dramatically over the course of a study.

For an IACUC with responsibility for oversight of wildlife research, on which Bryan has served, the key considerations for a wildlife performance standard are that they represent a standard or guideline, describe a desired outcome, and most importantly, provide flexibility in achieving that outcome while respecting the discretionary authority residing with the IACUC, the animal care and use procedure managers, and the principal investigators. Bryan noted that no two wildlife IACUCs will come up with the same interpretation of a proposed performance standard, since each IACUC is composed of members with varied experience.

Some wildlife performance standards, he said, are designed de novo, but many are designed using resources and best practice tools employed in the assessment of animal activities. The point of the design process is to achieve the desired outcome of the highest possible standards of animal care in the context of compliance and regardless of circumstance, Bryan explained. The traditional resources an investigator can draw upon when designing a performance standard are the Animal Welfare Act and the *Guide*. The Animal Welfare Act defines a field study as one conducted on free-living wild animals in their natural habitat as long as it does not involve an invasive procedure, have the potential to harm an animal, or materially alter the behavior of an animal under study. If a study does meet the definition of a field study, the Animal Welfare Act says it is exempt from the requirement for review by an IACUC. The *Guide*, meanwhile, states that "it does not purport to be a compendium of all information regarding field biology and methods used in wildlife investigations, but the basic principles of humane care and use apply to animals living under natural conditions. IACUCs engaged in the review of field studies are encouraged to consult with a qualified wildlife biologist."

While these two sources of information do mention wildlife research, they provide little in the way of guidance for those who are conducting wildlife research. Professional organizations, such as the American Fisheries Society, the American Society of Mammologists, and the Ornithological Council, have issued guidance documents that wildlife researchers and IACUCs use to help reach decisions on a proposed performance standard. Most of what goes into developing new

performance standards comes from knowing the ecology of the system being studied, having experience working in the field, and being flexible by developing contingency plans for when nature does something unexpected.

Ecology, said Bryan, is the cornerstone of wildlife project oversight and it cannot be underestimated as a key variable. A system's ecology comprises the environment, climate, season, and species; understanding how they relate to one another is critical for developing a sound performance standard. For example, the best time to study wolves is in winter because the snow makes it possible to track them, so proposing studying wolves in the middle of summer may raise concerns for a wildlife IACUC. Similarly, a project proposing to chemically immobilize and tag grizzly bears in winter will raise flags because bears are hibernating then. So, too, would a project that proposes to dart a bear emerging from hibernation in March in the shoulder, given that after months of hibernation, the only place on a bear with excess fat is the rump. In those cases, a wildlife IACUC would pull out a performance standard and suggest changes to the investigator. A big challenge for wildlife IACUCs, said Bryan, is that since the wildlife field is so large there will be many projects it needs to review for which none of the members have any experience relevant to those projects. What the IACUC has to do then is find an outside expert with the experience needed to make a sound decision. One step Bryan took when he was chair of the U.S. Park Service IACUC was to create an archive of projects the IACUC had reviewed as a resource the committee could use when reviewing a proposal.

Being a wildlife veterinarian, said Bryan, is much more akin to being an ecologist than being a veterinarian who works with small or farm animals because the animal cannot be considered in isolation. Working with predators, for example, requires thinking about territoriality and social structure. Wolves are extremely territorial, and darting a wolf in an area that is too close to a rival pack's territory can be dangerous for both the animal and the biologists. He recounted a principal investigator who came before the IACUC with a project to study mountain goats, but had not considered this research would be conducted at altitude, perhaps as high as 12,000 feet. None of the team members had experience working at altitude.

Flexibility is a key feature for a wildlife IACUC, just as it is for the biologist conducting research. "The flexibility that you build into wildlife IACUC oversight has to be or should be minimally as dynamic as the project itself, while inflexibility in oversight begs catastrophe," stressed Bryan. It is hard to apply strict engineering-type standards to wildlife

research, he said, because of the complexity of the environment within which any wildlife project operates and the number of unknown unknowns present in the system. Wildlife IACUCs, he said, need to have the room to be flexible so they can exercise ingenuity and be responsive to the investigator's needs.

As an example of how a wildlife IACUC puts these concepts into action, Bryan described a project the Park Service IACUC reviewed involving studying desert bighorn sheep. The IACUC immediately identified this project as an extremely challenging one in terms of the environment, the terrain, the climate, the species, the capture technique, and the handling procedures. The IACUC held a full committee review of the project to apply as much expertise as possible to the review. It quickly concluded this project was going to be highly dynamic and require the IACUC to be ready to exercise flexibility and ingenuity given the opportunity for almost radical change in the project at a moment's notice. Nonetheless, the IACUC also accepted this was an important project and it would have to keep in touch with the principal investigator and monitor the study.

In fact, almost from the start the project needed to adapt to conditions in the field. The original capture and handling plan was not working, but because the principal investigator and IACUC had considered this might be a possibility, a backup plan was ready, and IACUC members were prepared to meet and discuss what was going to be a significant change when the principal investigator called in by satellite phone. In real time, the IACUC approved an amendment and filed the paperwork in the project folder and the committee archive, enabling the project to continue without delay. The key, said Bryan, was the IACUC was staffed with wildlife researchers who knew wildlife research can be chaotic, and so when the IACUC created its standard operating procedures for this project it built in flexibility to respond to dynamic change while also achieving compliance and following existing rules. Rigid standards, he said, would have resulted in catastrophe. In closing, Bryan said the definition of performance standards as written in the *Guide* fits well with wildlife IACUC oversight. This definition allows for a skeletal framework of discretionary authority and then the flexibility to carry out and address the needs of the investigators, the IACUC, and the institution that it serves while staying in compliance with the rules and existing standards. Certainly, he said, there are some details of wildlife project oversight that differ from what might be thought of as traditional guidelines, and those are important and need to be emphasized.

THE AGRICULTURAL PERSPECTIVE[4]

While most published performance standards for the care of agricultural species address production parameters, many of these species are used for biomedical research, said Bart Carter. These uses include medical device testing, drug development, surgical training, imaging technique refinement, oncology treatment testing, and human nutritional research. One noteworthy species, said Carter, is the miniature swine, which behaves similarly to commercial swine and is susceptible to all swine diseases, but of a size similar to that of a dog.

Agricultural species used in biomedical research have a few characteristics Carter said are worth noting. For example, they are herd animals and want to be together in groups. Commercial breeds grow rapidly and require large amounts of feed, even when young, and as a result, these animals will grow during the course of a study, something that needs to be considered when creating standards for these animals. Many agricultural species can become aggressive at sexual maturity, and these animals can be large, which not only has ramifications for housing needs but for the safety of animal facility staff and researchers. "If an animal that weighs 250 to 300 pounds objects to something that you want to do, it can push back hard enough that someone may be injured," said Carter. While the size of these animals is often what makes them useful research subjects of imaging or physiology studies, size also can create challenges that have to be addressed.

There are three basic types of housing for agricultural animals in a research setting. The traditional biomedical facility is constructed to be easily sanitized, with sealed surfaces and stainless steel. It provides easy access to resources such as surgical suites, imaging centers, and enrichment items such as toys, but is likely to have limited space with a fixed pen size and limited ability for these large animals to get exercise or to exhibit species-specific behaviors.

An agricultural facility is designed for production agriculture with species-specific handling capabilities and a variety of housing conditions. The environmental conditions can vary from being fully air-conditioned, heated, and ventilated to being little more than a barn. Typically, this type of facility can house animals at a reduced cost compared to a biomedical facility, but it frequently has floors and other surfaces that are not easily sanitized. Most often, they are located remotely from the rest of the

[4] This section is based on the presentation by Bart Carter, and the statements are not endorsed or verified by the National Academies of Sciences, Engineering, and Medicine.

campus and thus animals must be transported for access to imaging and surgical facilities.

The outdoor pen or pasture is the third type of housing, and it offers the advantage of providing plenty of space, exercise opportunities, and the ability for the animals to exhibit herd behavior. The disadvantage of this type of housing is that there is little control of the environment and the animals can be exposed to other wildlife that can transmit parasites and infectious diseases. Observations after surgery, for example, become more difficult and again, it is likely that transportation will be needed to get the animals to imaging and surgical facilities.

Developing an agricultural animal performance standard, said Carter, requires everyone involved in the process – the veterinarians, the IACUC, the husbandry staff, and the research staff – to be familiar with the basic needs of the species of concern. One way for individuals who are less familiar with agricultural species to become informed is to read what is known as the "Ag Guide," the *Guide for the Care and Use of Agricultural Animals in Research and Teaching, 3rd Edition* (Federation of Animal Science Societies, 2010), which AAALAC adopted in 2011 as a primary reference for agricultural species. This peer-reviewed and thoroughly referenced document, developed by the Federation of Animal Science Societies, contains information on both normal and abnormal behavior of agricultural species and on animal well-being. Though this book focuses on production agriculture, it has value for biomedical researchers, said Carter, as it can serve as a source of what is considered appropriate management for an agricultural species when developing a performance standard. It can be particularly valuable, he added, when trying to learn about a given species' normal behaviors.

One challenge in creating a performance standard for agricultural animals is specifying how to maintain herd animals inside a biomedical facility while meeting their enrichment and socialization needs, particularly during the post-procedural care, said Carter. Moving them into a biomedical facility reduces their ability to engage in normal intraspecies behaviors. The reverse situation – moving animals from a biomedical facility to a more traditional farm setting – might seem easier, but these animals may not have been housed in that manner for some time, if ever, so it is important to consider what steps will be necessary to acclimate them to a less structured environment.

An acceptable performance standard for agricultural animals, said Carter, allows the animals to remain dry, be at a comfortable temperature, and remain free of urine and fecal contamination, and it also allows for appropriate data collection by the research staff.

Complicating the development of a new performance standard for agricultural species is the need to accommodate their size, growth rate, and temperament. The health status of individual animals can be important when they are mixed with other animals. Respiratory disease outbreaks, for example, can quickly infect numerous animals, and post-surgical care can be difficult if they are catheterized and need regular monitoring. The scientific goals of the study can also complicate the development of performance standards.

To illustrate what goes into developing a performance standard for agricultural animals used in research, Carter discussed a few examples. The first hypothetical example was of a study involving five 100-pound pigs in a biomedical facility with 25 square-foot pens. The Ag Guide says pigs of that size need 10 square feet apiece, so the question is whether to house them as two sets of two animals and one animal by itself, which meets the space requirement but does not meet the need for herd behavior or socialization. The key here is to determine if placing three pigs in one pen gives them enough room to lay down, stretch out, and remain clean and dry. If so, that might be the time for a performance standard that allows for three animals in a pen to accommodate the socialization needs, rather than the exact space requirement, with an additional feeder to accommodate the third pig.

Carter discussed a different situation when a biomedical facility needs to farrow a sow as the piglets are required for a particular study. Standard agricultural practice would be to put the mother in a farrowing crate for a week before she is due and allow the piglets to be with her until they are weaned at three weeks. That, however, would place her in the farrowing crate for four weeks, so the crate must be of appropriate size to allow her to lay on either side, stand up, and rest without bumping her head on the feeder. During that period, sanitation would be limited to not disturb the piglets. The advantages of this system are many: the sows adjust to the farrowing crate with little training; the odds of the piglets surviving are increased; and it is easy for staff to access the animals. One question that arises, given there will be a farrowing crate in the middle of a biomedical facility, is how to deal with sanitation needs that differ from those of the more traditional biomedical research animals also housed in the facility.

In the farm setting, Carter said often there are agricultural pigs in one area of a large facility and biomedical pigs in another area, raising the question of whether the one group of animals negatively impacts the other if they are being treated differently. This is when the IACUC, veterinarians, researchers, and animal husbandry staff have to work together to answer project-specific questions, such as whether the two

groups can be mixed in the same room or if the presence of the two groups is going to alter sanitation schedules. There will be a need to account for the thermal comfort of the animals, the humidity, and floor space. When creating performance standards relating to husbandry, the conditions must be such that they keep the animals' stress level low.

The answers to these questions are not always straightforward. For example, the thermal comfort zone for cattle is -15°C to 25°C, which is the range in the Ag Guide and in the Animal Welfare Act. For animals adapted to life outside and brought into a facility in winter, however, heat stress can develop at temperatures as low as 10°C, suggesting that a performance standard may be needed for this situation. Staff, said Carter, need to be familiar with the signs of heat stress and are aware of the normal behaviors and normal requirements for that species.

Achieving adequate ventilation is another issue that often arises when dealing with agricultural species. Tunnel ventilation, which uses wind chill to regulate temperature, is common in agricultural facilities, but it is a much different system than the one found in biomedical facilities for which the regulations mandate a set number of air changes per hour. Tunnel ventilation systems, in contrast, have set points for temperature, humidity, and even ammonia levels, and the system adjusts itself to establish what is known to be a comfortable condition for the animals in that facility. In a large building designed for agricultural species, the ventilation rate can be more accurately determined by these complex tunnel systems than one that simply produces the set number of air changes per hour, given ventilation needs change depending on the number of animals in the facility, their age, what they are eating, the amount of waste they produce, how that waste is handled, and the atmospheric conditions outside of the facility.

For poultry, group housing on a solid surface is the preferred system. There are situations, though, where individual egg production collection may be needed, such as when chickens are used in place of rabbits for polyclonal antibody production. Moving laying chickens into and out of pens or cages can be stressful and cause injury, raising the question of whether it is worth moving the animals regularly to clean and sanitize the cage or leave them in the cage for the duration of their egg-laying period and just clean the pans and floor underneath, said Carter. That is a question for the IACUC to address.

The last example he discussed involved the pasture or confined lot in a farm setting. From an animal's perspective, this is where they may like to be as there is plenty of space for them to exhibit normal behavior and for timid animals to get away from aggressive ones. For such a setting,

there should be sufficient dry space available and the ability for the animals to regulate their temperature, such as shade in the summer or having a windbreak in the winter to block prevailing winds. The challenge, said Carter, is to evaluate an area such this. Features to examine, he suggested, would include feeders and waterers; general physical plant maintenance; drainage; waste management; how surgical procedures not related to a study, such as castrations and dehornings, are done; and how medical emergencies at the facility are handled. The discussion arises as to whether these should be performed as normal agricultural management or whether they require special conditions. His advice is that if routine surgical procedures are performed as normal agricultural practices, the methods used should be those that are least likely to cause pain or distress to the animal and should include pain prevention. These techniques should be written in a standard operating procedure reviewed by the attending veterinarian and IACUC. Medical emergencies would be dealt with as sterile surgeries.

For any study that requires working with agricultural animals, there is always the option of collecting tissue from a slaughterhouse, said Carter. IACUC protocols and oversight are not required, and neither are performance standards. He noted one scenario in which a researcher needs fresh blood or tissue and no other source is available. "Should they obtain an animal solely for that purpose or can an arrangement be made to collect the sample from a local farmer?" asked Carter, who strongly recommended the latter course of action.

Handling and transporting farm animals is another consideration, one covered in detail in the ILAR publication *Guidelines for the Humane Transportation of Research Animals* (NRC, 2006), said Carter. He noted, too, when developing a performance standard for agricultural animals outside of a traditional biomedical facility, the animals may require vaccinations and deworming, and they may be exposed to infectious diseases.

THE PUBLIC INTEREST PERSPECTIVE[5]

The Animal Welfare Institute, said Kenneth Litwak, was founded in 1951 to take the middle ground between researchers and anti-vivisectionists. The organization is dedicated to reducing animal suffering caused by people by seeking better treatment of animals everywhere, be

[5] This section is based on the presentation by Kenneth Litwak, and the statements are not endorsed or verified by the National Academies of Sciences, Engineering, and Medicine.

it in the laboratory, on farms, in homes, or in the wild, and it is a strong supporter of the Animal Welfare Act. With respect to research animals, the Institute seeks to improve the housing and handling of animals and to encourage the development and implementation of alternatives to animal experimentation. The Animal Welfare Institute produces many publications, including *Comfortable Quarters*, a new edition of which is planned for the summer of 2015. This volume was written by veterinarians, technicians, and scientists in the research field and describes the state of the art for housing for the most common laboratory animal species.

The Institute maintains a refinement and enrichment database it updates quarterly, and it gives out refinement and enrichment grants that aim to identify better ways to handle laboratory animals and enrich their environment. It also sponsors the Laboratory Animal Refinement and Enrichment Forum, an online venue in which over 300 veterinarians, technicians, and scientists discuss methods of refinement and answer questions about performance standards. Three volumes of discussions from this forum have been published, with a fourth coming out shortly.

The history of the Animal Welfare Institute's involvement with performance standards started in 1985 with the Improved Standards for Laboratory Animals Act, which laid out the minimum requirements for canine exercise and promoted the psychological well-being of primates. In the final regulations, USDA allowed facilities to develop a plan to implement those requirements. A lawsuit filed six years later by the Animal Legal Defense Fund and others claimed USDA had yet established a means of determining if institutions were following these plans, if the plans were in compliance with regulations, or if the plans accomplished their stated goals. Another lawsuit filed five years after that by the same plaintiffs charged that there had been an unreasonable delay in promulgating standards to promote the psychological well-being of primates. An initial ruling held that the regulations had not set standards, but that ruling was overturned on appeal in 2000 (Animal Legal Defense Fund, 2000).

The Animal Welfare Institute's chief concern regarding regulation of performance standards is identifying who is responsible for determining if they are appropriate. The least desirable situation from Litwak's perspective is when there is a performance standard but no engineering standard, which is the case with the psychological well-being of non-human primates. The performance standard holds dealers, exhibitors, and research facilities responsible for developing, documenting, and following an appropriate plan for environment enhancement to promote the

psychological well-being of nonhuman primates (CFR 2012). The plan must be in accordance with currently accepted professional standards, and it must require the physical environment be enriched by providing a means of expressing non-injurious species-typical behavior (ibid). The problem with this performance standard is vague language, said Litwak, regarding who defines what a professional standard is. Also vague is how many and what type of enrichment is needed and who defines what enrichment is acceptable. Even more confusing, he said, is understanding what is normal and abnormal. All of this, said Litwak, gets to the crux of the issue for his organization, which is there are multiple interpretations possible, making enforcement difficult to impossible.

Next on the desirability scale is when there are performance and engineering standards but they are not synchronized. In the case of cage space for non-human primates, the engineering standard requires primary enclosures to meet a minimum space requirement, while the performance standard states there has to be sufficient space to make a normal postural adjustment for freedom of movement. As an example of how these two standards conflict, Litwak used the case of a 20-pound Cynomolgus macaque whose typical body size would be 15 to 22 inches and with a tail 16 to 26 inches long. The engineering standard says floor space should be 4.3 square feet, but a monkey of that size would not be able to make a normal postural adjustment in a cage of that size, begging the question of which standard applies, particularly when the definition of a normal postural adjustment is unstated.

The ideal situation from the Animal Welfare Institute's perspective would be the 1999 USDA draft policy on environmental enhancement to promote psychological well-being of non-human primates. This exhaustively written and researched draft policy described typical behavioral needs of primates and included the critical elements that would need to be addressed in an environmental enhancement plan as well as strategies to address those needs. The draft also included a list of relevant literature, talked about the specific needs of the most common primate species, and provided many examples of specific enrichment techniques. Unfortunately, said Litwak, this policy was never enacted.

In closing, Litwak said when considering engineering standards or performance standards, there is always the caveat there can be exemptions when required by a particular research protocol or in the judgment of the attending veterinarian, both with the approval of the IACUC.

From his organization's perspective, though, "performance standards may be acceptable in support of an engineering standard, if properly

synchronized; however, they are not acceptable as alternatives to the engineering standards." The Animal Welfare Institute, he added, does appreciate those individuals in research institutions who are providing more than minimum engineering standards and recognizing that all animals require an enrichment environment.

AN ACCREDITING ORGANIZATION'S PERSPECTIVE[6]

The publication of the 7th edition of the *Guide*, said John Bradfield, was a game-changer for AAALAC International (AAALAC) because it codified the concept of performance-based assessments and standards in the management and operation of research animal facilities and provided flexibility on how to establish and operate Animal Care and Use Programs. This made AAALAC's job more difficult as there is no single right answer for how to promote animal welfare. Bradfield noted that the *Guide* is one of three primary reference AAALAC uses in its assessments - the other two are the Ag Guide and Appendix A of ETS 123 (Council of Europe 2006), which also contain performance-based language.

As an example of how the 8th edition of the *Guide* extended the performance-based approach and in so doing created stumbling blocks for AAALAC, Bradfield cited the following section:

> "Solid-bottom caging, bottles, and sipper tubes usually require sanitation at least once a week. Some types of cages and housing systems may require less frequent cleaning or disinfection; such housing may include large cages with very low animal density and frequent bedding changes, cages containing animals in gnotobiotic conditions with frequent bedding changes, individually ventilated cages, and cages used for special situations."

The 7th edition required facilities to clean and sanitize cages, bottles, and sipper tubes at least once a week, which could be easily assessed. The 8th edition added the proviso about cage types and housing conditions for which cleaning and sanitizing may take place less often, but the phrase "may require less frequent" has no defined time element and that triggered a debate within the AAALAC Council on how to assess this

[6] This section is based on the presentation by John Bradfield, and the statements are not endorsed or verified by the National Academies of Sciences, Engineering, and Medicine.

performance-based standard. Bradfield said the Council developed a performance standard to assess a facility's performance standard, measuring any issues with animal health and wellbeing, and whether cages are cleaned at least once a week. If the cleaning interval was longer than one but less than two weeks, which for ventilated rodent cage racks is a practice standard, the IACUC would need to be aware of the situation and consider what the potential impacts might be on the microenvironment and the animals, but the IACUC review need not be rigorous. However, if the cleaning interval was longer than two weeks, the IACUC needs to conduct a more rigorous evaluation validating the cage microenvironment is satisfactory, preferably including an objective, data-based analysis to show why the practice does not negatively impact animal health and well-being.

This example, said Bradfield, illustrates the mental gymnastics going through the minds of the site visit team for one simple topic in the *Guide*. Looking at the *Guide* from a higher level, it is clear what is expected but virtually silent on how to do it. Bradfield said this was an intentional decision on the part of the *Guide*'s authors to provide the targets and let facilities choose how to best meet those targets.

A second important concept arising from the 8th edition of the *Guide* is that professional judgment plays an important role in how site visits proceed. In AAALAC's case, said Bradfield, it is not the professional judgment of one person, but of a body of people that come to an agreement. As he explained, a good performance standard to the AAALAC Council is precise, detailed, and has a defined goal, and it should spell out the assessment criteria and methods used to determine that the goal is met.

To illustrate the exercise AAALAC expects facilities to go through when establishing a performance standard, Bradfield discussed a hypothetical facility primarily housing rodents. This facility is about to undergo an AAALAC inspection and management is unsure if its sanitation policy meets the standards of the *Guide*. The facility team could start by consulting the *Guide* to determine the appropriate benchmark or goal for the performance standard. In this case the goal is for washing times to reduce or eliminate potential pathogens. From that goal, the facility would develop precise definitions for how to sanitize the cages based on the published literature, staff experience, and input from the manufacturer. This definition could include a preference for using mechanical washers whenever possible as well as a specific protocol for how to wash cages by hand when necessary. Assessment criteria could include husbandry and sanitation logs, visual inspection of the cages,

temperature-sensitive tapes for ensuring that wash water is hot enough, and bioluminescence and microbiological assays with established pass/fail criteria. The methods of evaluation could include standard operating procedures for day-to-day monitoring by facility staff; periodic reviews of microbiological monitoring records to see if pass/fail criteria are met; supervisor checks of cages, logs, and other records; and preventive maintenance of machinery.

Bradfield then briefly addressed the issue of global or program-wide exceptions to the *Guide*. There are times when institutions need to develop or evolve a practice that technically may not meet some criteria in the *Guide*, and when applied across a program AAALAC calls it a global exception or a program-wide exception. These arise from some unique feature or unique need of an institution and they require a site-specific, data-driven analysis of the practice demonstrating the institution is meeting an equivalent standard in the *Guide* in a manner that upholds the well-being of the animals and scientific integrity.

Bradfield concluded his presentation with a real-life story from a site visit to a large institution with many dogs bred in-house primarily for dental research. This institution had a goal of housing the dogs in social groups of compatible animals and adopting them out when the study was finished. The nature of the studies benefitted from having dogs grouped in this particular manner, but the inspection team noticed that pen size was slightly smaller than recommended in the *Guide*. When asked about this, the researchers said they explored two options. The engineering approach would have had them remove one dog from each pen according to *Guide* standards, while the performance-based approach took into account the housing method that worked best for the dogs and the science. The facility team defined their goal, which was that group size and age were important scientific factors in the housing strategy. They also recognized the importance of social housing and compatibility. To develop their assessment criteria, the team did a study in which they compared group-housed dogs according to the *Guide* standards and according to their plan, which was one half of a dog too many. Technicians and staff counted over the course of a year the incidents of stereotypic and aberrant behaviors observed and their impact on the scientific outcomes. At the end of one year, the IACUC, the attending veterinarians, and the investigators analyzed the data and found the performance-based strategy produced a greater number of socially compatible groups, fewer stereotypic behaviors, a higher rate of producing litters, and less variable scientific data while using fewer dogs. As a result of the effort these investigators and facility staff put into

creating this performance standard and meeting the three primary components that AAALAC wants to see (i.e., "professional input, sound judgment and a team approach"), the site visit team determined it was a reasonable performance-based approach to housing.

SUMMARY OF THE AFTERNOON SESSIONS

Paul Locke noted that the presentations represented different approaches to operationalizing performance standards. The first two and the last speaker – Lipman, Vasbinder, and Bradfield – illustrated the evidence-based approach of setting up hypothesis-driven research to show whether a performance standard works. The advantage of this approach is that it mimics how research is done by combining scientific testing, data collection, methodology development, and evaluation in one package.

The next two speakers – Bryan and Carter – were faced with different situations that in many ways are more challenging and where the one-package model could not be applied. These situations, said Locke, require an approach based on collecting evidence and constantly evaluating it with no clear hypothesis to test. While these are unique situations all of these speakers clearly pointed out the goal is to ensure that animal welfare is held to the highest standards and the best science is done with the fewest number of animals.

The last two speakers, Litwak and Bradfield, provided what Locke characterized as interesting views of how the system works or does not work. Locke noted that Bradfield pointed out that performance standards, in many ways, can be opaque, and while a lot of effort is spent explaining performance standards, it may be that the community is not getting everyone to understand how performance standard evaluations are conducted and assessed. The question Locke was left with after hearing these six presentations is whether the community can do a better job of thinking about the concept of performance standards. "The burden really is and should be on the IACUCs and the institutions to make sure the performance standards are measurable and can be evaluated and can be explained," said Locke.

DISCUSSION

David Anderson posed the first question, from an online participant, to Vasbinder, about the requirement that dogs get 15 minutes of exercise daily and whether that requirement changed if the dogs are getting social

exercise in their cage. Vasbinder replied the requirement is 15 minutes of social exercise per dog, but that some dogs cannot tolerate a social exercise environment. For those animals, there is a separate space where they exercise individually with the help of staff. Her preference is for a long exercise space that enables the dogs to truly run.

The second question from the online audience was addressed to the entire panel and asked if modern veterinary skills and the use of appropriate therapeutics need to be incorporated in discussions about performance standards. For example, the questioner asked, should there be a requirement for veterinarians to maintain a current license to practice and prescribe drugs in their working jurisdiction? Bryan, a licensed veterinarian, answered there have been some interesting issues regarding Drug Enforcement Administration licensure over the use of certain drugs in the field, and these have been resolved recently. He also said that when he was a federal veterinary officer the government recognized his Georgia and Colorado licensures as sufficient to practice on federal lands, and he and all of his colleagues who were veterinarians maintained their licensures and met the requirements for continuing education credits.

Robert Dysko from the University of Michigan Medical School asked how often studies validating a performance standard need to be repeated. Vasbinder said programs need reevaluation because there can be differences between practice and perception and that GSK addresses this issue by having outside consultants review its programs. Her program formed an advisory panel to help plan and carry out the evaluations, which it conducts every three to four years. Bradfield said AAALAC's approach is to pose the question, "What is your strategy for periodic reevaluation of any performance standards that are in place?" with no answer in mind except that AAALAC does anticipate some periodicity in evaluations. At his former institution, for example, the IACUC reviewed standards monthly for one particular study involving infectious diseases, but a performance standard that was more innocuous and for which the conditions did not change would require far less frequent reevaluations.

Malak Kotb, from the University of North Dakota, asked if anyone had looked at the effect of sterilizing cages on the gut microbiota of the animals and, if so, whether this had any experimental effects. Bradfield said if there are studies in which the cage environment is critical for establishing the microbiota, there might need to be an institutional or study-specific, precise definition of clean.

Judy MacArthur Clark commented that Bryan and Carter both spoke about how they addressed conflicts between engineering standards and

performance standards, but she wondered if these conflicts represented instances where the engineering standard was wrong. Bradfield said this question captured the angst with which the AAALAC Council deliberates on these issues. He added he would never suggest the solution one institution established as working best for its animals would apply to another institution or scenario. The engineering standard, he added, is a starting point and a critical factor. He noted that AAALAC is clear on the point that limited resources and cage size alone are not acceptable justifications for housing animals too densely while recognizing there can be unique circumstances in which a broader consideration, other than the pure engineering approach, is more appropriate for the animals and the science.

Carter said it is important to remember that the IACUC and veterinary and animal care staff have the opportunity to evaluate a performance standard and weigh in on whether they think it is working. Vasbinder noted there is an opportunity to be creative about the needs of each species by modifying their housing to create more space within a cage to allow the animals to interact with their environment and give them control over whether they are interacting with each other or not. In the case of dogs, for example, a flat roofed dog house the dogs can jump onto or hide within could be one form of added enrichment not requiring more space per cage.

AAALAC, said Bradfield, takes into consideration the amount of due diligence that an institution puts into developing, testing, and validating its performance standards. In the case of the institution in his example, it had made an intentional decision based on its data about the best way to house its dogs, and the AAALAC Council determined this institution's IACUC had done what an IACUC should do and it had provided a clear explanation of its decision. The wildlife area, said Bryan, is one in which each and every project is judged on its own, and it is the norm with wildlife IACUCs to require investigators to come up with sufficient justification for any variances from existing engineering standards. He also said he did not think engineering standards have a big future in the wildlife area.

Lipman commented on the assumption that the engineering standard is correct, saying he questions whether this is always the case. Steven Niemi pointed out most if not all engineering standards used to be standard practice before they became engineering standards, raising the question of whether there were arbitrary elements in them before they became codified as engineering standards. Whether they are correct or

not, his concern is that the community is creating a higher bar for doing something that differs from these engineering standards.

Niemi then asked Bradfield if AAALAC expects an institution to generate internal data to validate a globally applied change from the *Guide*, and Bradfield said this is what AAALAC expects with one caveat: if an institution can demonstrate that the change it wants to make is identical to that of another institution AAALAC would agree that outside data may indeed apply. However, in AAALAC's experience this seldom occurs.

Given the long time between editions of the *Guide*, said Lipman, it is the intent of the *Guide* committee that as new information becomes available, it could serve as the basis for a new universal performance standard with repeated assessments. Bradfield's example involving dog housing made Vasbinder wonder what would have happened if the IACUC had approved the request to keep litters together without further research based on a 3Rs rationale. Bradfield acknowledged that was an interesting scenario but guessed the AAALAC Council would have found that to be a less compelling case, albeit a valid rationale. What AAALAC Council wants, said Bradfield, is for an IACUC's decision to be fully informed, careful, and thoughtful.

Cathy Liss asked Vasbinder if there was a backup plan in case neither group of dogs was doing well in her study. Vasbinder said if the study had not produced an acceptable outcome, the next step would have been to characterize what good exercise looks like from a behavioral standpoint, a study her team is conducting anyway. Such a study would have given her team a desired outcome that would serve as the vehicle for developing an approach to reach that outcome.

Liss commended the emphasis the panelists placed on social housing, and she asked them to comment on how each of their institution weighs the importance of social housing versus other aspects. Vasbinder said the behaviorists involved with GSK's program put social housing as the highest priority for dogs and primates. Bradfield noted the 8th edition of the *Guide* emphasizes this topic in particular, but it is a complex issue in part because of a lack of knowledge. With rabbits, for example, there is no data on what is an appropriate social grouping, and it took years to understand how to form compatible groups of adult male Rhesus monkeys. Carter said social housing is becoming a higher priority item among investigators and there are fewer situations where animals are housed individually.

5

DETAILED STEPS IN THE DEVELOPMENT AND IMPLEMENTATION OF PERFORMANCE STANDARDS[1]

The workshop's second day began with a presentation by Guy Mulder, Executive Director of Veterinary and Professional Services at CRL and Attending Veterinarian for North American Research Models and Services. Mulder described how CRL, a leading commercial breeder of laboratory animals, develops performance standards. CRL, he said, has developed a standardized process for creating performance standards, including a proposal process and a dedicated form that proceeds step by step, creates consistency, and provides value in the future when reevaluations are conducted. He noted the company started performance approach evaluations in 1997, and when he joined the company a decade ago he was able to go through the company files to review the history of each performance evaluation, which included the data sets the company used to make its decisions at each evaluation along the way.

At CRL, the guiding principle is that if the company deviates from methods outlined in the *Guide*, the resulting conditions for the animals should be equivalent or better. If, however, the changes create conditions that do not meet minimal *Guide* recommendations, then any deleterious changes in animal welfare should be measurable and documented. The challenge, Mulder explained, is to develop the appropriate measurable parameters to enable a valid evaluation of the alternative method.

When the 8th edition of the *Guide* was published, CRL conducted a gap analysis to identify exceptions to the *Guide* and determine where it did and did not comply with *Guide* recommendations. "There are many things that many of us do at our institutions that are historical - we've

[1] This section is based on the presentation by Guy Mulder, and the statements are not endorsed or verified by the National Academies of Sciences, Engineering, and Medicine.

done them for 10, 20, or even 30 years - and the *Guide* suggests we do things otherwise. I think we need to take a moment and evaluate why we are doing it differently and if it is time to change our practices," said Mulder. If the answer to an evaluation shows there is a scientific, operational, or welfare-oriented reason not to adopt the *Guide*'s recommendation, he said, there is then an opportunity to develop and validate a performance standard to address that recommendation in the *Guide*.

Developing a performance standard requires first defining the desired outcomes and goals and conducting a review of the current literature and industry best practices to identify worthwhile performance measures to evaluate the alternative method. The next step is to design, plan, and perform an evaluation, which at CRL includes talking to experts and auditors to gain insights into methods they use at their facilities. This evaluation, which has been reviewed and approved by the IACUC, includes directly comparing the alternative approach to the *Guide* recommendations, something many institutions do not do based on what Mulder has learned through his conversations with experts and auditors. The IACUC then reviews the results of the evaluation and either approves, disapproves, or requires modifications to the alternative approach. Once approved, a post-approval monitoring plan is enacted with an annual review.

The key stakeholders in this process, explained Mulder, include the IACUC, which is involved from the very beginning; the attending veterinarian; the researchers who will be using the animals; any specialists with unique expertise in areas of study design, equipment, or interpretation of the study results; and the vivarium management, including the husbandry personnel, who often have an intimate knowledge and unique insights that he might not have as the veterinarian.

Mulder said that CRL has created a dedicated Request for Exception to ILAR 2011 Guide Recommendations form, which he characterized as a research proposal, complete with hypothesis and proposed statistical analysis. This form requires a description of the specific procedure or practice forming the exception, the species affected, the *Guide* recommendation on the subject, the proposed exception, the rationale for the exception, and the proposed performance measures and methods to investigate the exception. For the cage density guideline exception, this variance request was 18 pages long, and it summarized the relevant literature and included CRL's efforts in the area.

Once the IACUC approves the proposal and the studies are completed, the results are summarized on the form and it goes back to

the IACUC for review and approval. When the variation is approved, there is a final section of the form for the post-approval monitoring program the IACUC must also approve. Examples of variances or exceptions to the *Guide* for which CRL has used a performance approach include cage density for mice and rats, cage change frequency, housing multiple rodent species in the same room, and the frequency of water bottle sanitation. For each of these, Mulder's team developed evaluation criteria unique to the question they were asking.

When the 8th edition of the *Guide* was published, one of the concerns for the company with regard to housing density was the new category of "female plus litter," which did not exist in the 7th edition. Taking a literal application of this recommendation, which was that there be one female plus litter plus a breeding male in one cage, CRL was concerned that the standard cage it uses might not always allow the space allocation described in the *Guide*, Mulder explained. In addition, for many of CRL's mouse strains, the company's practice was to have a second female in the same cage so that the male will breed with two females, creating a communal group in the cage. Such an arrangement would not be appropriate in CRL's cages according to the *Guide*'s density requirements. "To transition away from that breeding scheme would have meant adding a significant number of new cages to our program and building new space simply to achieve the same production, the same output that we were achieving prior to the release of the new *Guide*," said Mulder. The new recommended minimum space requirements challenged the company to ask if there were data showing its existing breeding densities were detrimental to the animals, he added.

The application for variance Mulder's team developed applied only to production facilities housing mice and rats, and it specifically excluded experimentally manipulated animals. Mulder noted that the company has modified cage densities over the years in response to internal evaluations, professional judgment, and changes in the knowledge base, and he expects there will be modifications in the future as well. The rationale for the variance included explicit documentation for why the company believes this variance is necessary. The rationale also included internal data showing that animal welfare is not compromised at current cage densities used by CRL and that existing space allocations meet the definition of adequate space. The variance proposal also noted that the *Guide* states there is a lack of peer-reviewed literature establishing specific space allocations for rodents in breeding setting.

Given the new recommendations in the *Guide*, CRL proposed repeating some of the studies it had previously conducted but with more

measures or indices than it had used in the past. For example, to better assess whether current densities meet a requirement to provide sufficient space for mothers and litters to allow pups to develop to weaning without detrimental effects for mother or litter, the proposed studies needed to assess pup development and maturation as well as the health of the mother. Mulder and five of his colleagues debated which performance measures needed evaluating and ultimately decided that the performance measures should include a range of categories of animal health, behavior, and production indicators and the data should be collected in the standard production setting so as to not add confounders into the evaluation or complicate post-approval monitoring.

The group considered a number of practical issues and decided that the performance measures should not rely on extensive instrumentation, such as telemetry readings for heart rate as a measure of stress, or complex behavioral assessments. It also decided to restrict the evaluations to a representative number of stocks and strains, rather than performing the evaluation for every stock and strain in the company's breeding program, and to a limited number of the company's facilities providing the environments are similar, as they are throughout the company's many North American facilities. The result was a set of measures assessable in an active breeding area and some that needed to be done in a behavioral testing setting.

Mulder and his colleagues then considered what likely measureable events could arise from selecting the alternative housing density and selected the measures they expected would most likely be affected if there were adverse effects. With respect to cage space for a mother with litter or a breeding group, the group adopted reproductive indices, growth, general health, aggression, and lack of stereotypic behaviors as reasonable outcomes. If the performance standard was about cage change frequency, the appropriate measures might involve humidity in the cage, ammonia levels, and other gas production from waste products, Mulder explained.

For reproductive performance, Mulder's team started with a list including the number of pups weaned per female breeder per week, known as the production index; litter size at birth; survival to weaning; sex ratio; weaning weight; inter-litter interval; time to first plug; and time to vaginal opening in female pups. Mulder noted that there is published literature addressing each of these for the stocks and strains CRL commonly uses. For behavioral assessment, the biggest concerns were about space utilization within the cage and aggression or fighting, either maternal aggression towards the pups or aggression between weanlings

and adults. Other concerns included hair loss, stereotypic behavior, and space utilization with the cage. The CRL team developed a scoring system for each parameter, most of which could be measured in the barrier room by standard husbandry technicians who received some additional training from the company's behavioral staff. Assessments of space utilization, however, were performed in a behavioral lab, which Mulder characterized as a quiet room outfitted with video equipment that could simultaneously record 24 hours a day from 48 mouse cages and 32 rat cages, spanning both light and dark cycles and multiple litters of breeding groups. Clinical measures included morbidity and mortality, animals euthanized for cause, body conditioning scoring, and growth curve comparisons from weaning through age 10 weeks.

As an example of the scoring system, Mulder described the behavioral assessment scoring for fighting and aggression (Figure 5-1), barbering (Figure 5-2), and stereotypic behaviors (Figure 5-3). Staff was trained to recognize these behaviors so they could be consistent in how they scored them while performing their normal daily or weekly routines with the animals. Data were collected, collated, and sent to the behavioral staff for evaluation.

Wound Severity Scoring:	
0 = none	No wounding observed
1 = mild	Bruising or slight scratch; barely breaks skin integrity. Smaller than 1cm total area affected. No veterinary care required.
2 = moderate	Definite wound; breaks in skin integrity. 1-1.5cm area affected. Veterinary care may be indicated.
3 = severe	Multiple wounds or severe ulceration or bruising. >1.5cm area affected. Veterinary care definitely required; consider treatment or euthanasia.

FIGURE 5-1 Charles River Laboratory's behavioral assessment scoring for fighting and aggression
SOURCE: Mulder slide 22

0 = full pelage	No hair loss observed (to include vibrissae)
1 = mild	Up to 30% of pelt denuded
2 = moderate	Up to 50% of pelt denuded
3 = severe	Up to 75% of pelt denuded
4 = fully denuded	

FIGURE 5-2 Charles River Laboratory's behavioral assessment scoring for barbering
SOURCE: Mulder slide 22

Behavior	Definition	Duration
Bar Chew	A bout of repeated bites into the metal bars at a particular spot on the cage lid	Count the number of episodes & the duration (frequency, duration, intensity)
Jumping	A bout of either jumping up and down or scratching with the paws along the wall in a corner of the cage	Count the number of episodes & the duration
Pace	A repeated walking pattern that appears without purpose, and is non-circular (see circle/flip)	Count the number of episodes & the duration
Circle/flip/tail carrying	A repeated walking or climbing pattern that appears without purpose. Circling is "two dimensional" and may or may not include carrying the tail in the mouth at the same time. Flipping is a "three dimensional" movement.	Count the number of episodes & the duration.

FIGURE 5-3 Charles River Laboratory's behavioral assessment scoring for stereotypic behaviors
SOURCE: Mulder slide 23 (adapted from Würbel and Stauffacher 1996)

After careful consideration of which stocks and strains, or genotypes, to evaluate the CRL team picked the C57B/6, the most common inbred mouse strain used in research and common background strain for genetically engineered mice; CD-1, or Swiss mouse, the most common outbred mouse; the Sprague-Dawley or CD rat, an outbred strain; and the brown Norway rat, an inbred strain. These strains, said Mulder, reflected

the majority of mice and rats CRL produces as well as the majority of those being utilized in research.

The proposal submitted to the IACUC was put together by a larger team that included veterinarians, a behavioral scientist with significant rodent experience, IACUC members, and production management and husbandry staff. Every team member was going to be involved in the study and so had an opportunity to help plan the study. After the proposal received IACUC approval and the team started collecting data, team members discussed what to do if the data showed there were differences in outcome measures between the groups. A difference, Mulder explained, could identify a problem, or it might reflect the animals are adapting to a new cage without harm to their welfare. For example, housing room temperature for rodents is generally below the thermal neutral zone, but the rodents can adapt if they can huddle together or burrow into bedding or nesting materials.

The experimental design for the cage density evaluation consisted of a Latin square factorial design, with cage type or size, breeding condition, and strain of animal being the three variables. For mice, the breeding conditions consisted of breeding the female and then removing the male so the female is alone with the pups; a matched male and female pair kept together, including when the litter is present; and a trio of two females and one male. For rats, there were two breeding schemes: pair a male and female together for a brief period of time and then remove the male; or a male-female pairing in which the pair is kept together.

The decision about cage size proved to be more complicated than expected. Initially, the plan was to compare the current CRL cage with one meeting the 2011 *Guide* specifications. However, after reviewing the literature and discussing that idea with the behavioral specialist, it seemed doubtful there would be any significant differences between the two groups because the cages were not far apart in size. Instead, the team selected the smallest and the largest cages available on the market to compare with the current CRL cage.

The cage sizes used with the mice were (Figure 5-4):

- 226 cm^2, the smallest cage available
- 305 cm^2, the standard CRL cage
- 432 cm^2, a *Guide*-compliant cage
- 800 cm^2, the largest cage available

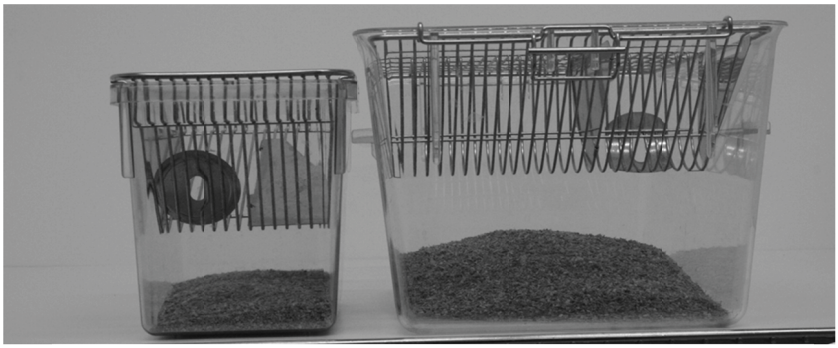

FIGURE 5-4 The smallest and largest mouse cages
SOURCE: Mulder slide 32

For rats, the cage sizes used were (Figure 5-5):

- 580 cm^2, the smallest cage available
- 758 cm^2, the standard CRL cage
- 903 cm^2, a *Guide*-compliant cage
- 1355 cm^2, the largest cage available

FIGURE 5-5 The smallest and largest rat cages
SOURCE: Mulder slide 33

With the final results to be published soon, Mulder presented some preliminary findings, one of which was that cages can be too small. While reproductive performance in mice did not decrease in the smallest cages, which Mulder termed a surprise, CD rats showed a drop in reproductive performance in the smallest cage. There was also excessive soiling in the smallest cage. Mulder said the smallest mouse cage with a female and litter to be weaned was obviously overcrowded and everyone agreed it would never be used in an ongoing breeding program.

There was only one significant difference on the performance indices between the CRL standard cage, the *Guide*-compliant cage, and the largest cage. The one behavioral change observed in adults was something that had not been reported in the literature, and the investigators called it "corner inactivity." This behavior was only seen at specific pup ages, typically two weeks of age and older, and it was seen in all cages, though it was more frequent in smaller cages. It may be, said Mulder, that females may benefit from vertical space that allows them to escape the older pups.

The full results were submitted to the IACUC, which after some discussion approved the continued use of the internal CRL cage densities for breeding of mice and rats. Mulder noted that the study itself took six months to complete, followed by another six months of watching video to obtain scores on the behavior measures. Though the study was perhaps more thorough than it needed to be, he said the data were reassuring. For post-approval monitoring the IACUC will conduct an annual review of key performance indicators for the variance for two consecutive years and then do a *de novo* review at the end of year three with a complete literature review to determine if new or additional studies are warranted. There is also regular ongoing review of production indices that is outside of direct IACUC involvement. This review will involve both management and Mulder or one of his colleagues and will look for differences or drift in the indices that might be an early sign of a developing issue that would then require IACUC involvement.

DISCUSSION

Diane Gaertner asked if the cages were open, static or ventilated, and Mulder replied this study used open cages, which are the standard cages used in production setting barrier rooms. She then asked if the study included monitoring room ammonia or other room parameters, and Mulder replied that those measures were not part of this study, though

room ammonia is monitored on a quarterly basis in all of CRL's barrier rooms.

Norman Peterson from MedImmune asked Mulder for his opinion as to when the published body of knowledge becomes large enough to change the standard of practice. Mulder said he does not entirely agree that there need to be site-specific evaluations for every facility and every institution, and that if there are publications showing generally consistent findings in several different settings, those findings should be generalizable. He added, however, that for cage density, the literature is not all that clear and so for this issue more studies in different settings are still needed before a new practice standard is established. He did note that "perhaps there should be a more common approach to evaluating questions such as housing density so that the results of those studies are more comparable, but at some point we need to be able to say 'this seems reasonable,' and groups such as AAALAC should be ready to agree that individual studies don't need to be performed at every single institution."

Paul Locke asked how another facility might go about generalizing from the publications resulting from the studies Mulder described. The first thing to do, Mulder replied, is to look at the performance measures in the publication and see if they fit the proposed study. One item he noted specifically that might make it difficult to generalize from the CRL study was the use of open top cages in a large production setting, something that other facilities are unlikely to use. He envisioned future studies looking at ventilated housing that could be more generalizable across other ventilated caging systems.

David Kurtz said that he hoped one of the goals of this workshop and for future activity is to encourage those in the community to publish their data and disseminate it, making it possible to judge when a particular performance standard works in multiple different settings. He also suggested that until a new edition of the *Guide* is published or revisions are made to the AWR, data from these performance standard studies could be used to adjust the engineering standards to be more appropriate and realistic. He then asked Mulder if the post-approval monitoring process has identified any strains for which their results on their model strains and species may not apply. Mulder replied that for routine, non-disease models, there have not been any issues identified so far. Disease models, such as for obesity and diabetes, will require a different approach to housing density, cage cleaning, and other parameters, but those studies have not been conducted.

David Anderson posed a question from an online participant, who asked if the presence of engineering standards has inhibited the development of performance standard. In Mulder's opinion, they have because the easiest route is to take the engineering approach rather than developing a justification and rationale for developing a performance standard.

Another question from an online participant asked Mulder about the time and resources required to develop and complete this project. He replied that CRL made a significant investment in both time and resources. The company hired a Ph.D. behaviorist, primarily to assist with designing, performing, and evaluating the study, and it purchased specialized equipment. The study itself took a year for data collection and analysis and another six months to prepare the publications to go out to the peer-reviewed literature. In fact, said Mulder, not many institutions have the internal resources to do this type of extensive study. His hope is that as the literature base grows, subsequent studies could be scaled back to produce smaller data sets that will align to the published studies and can justify site-specific practices.

6

REPORTS FROM THE BREAKOUT SESSIONS[1]

The breakout sessions on the second day of the workshop enabled four working groups to draft a mock performance standard on a topic under the theme of Post Approval Monitoring (PAM) of ongoing research projects using laboratory animals, to better understand the process involved in its development and implementation. All workshop registrants were pre-assigned to a group to ensure diversity in perspectives and each group designated a rapporteur who described the performance standard, followed by the process the group used to develop its standard. Each group was assigned one of the following topics:

- Personnel training in animal handling and procedures
- Workplace safety
- Scientific flexibility, or study drift, in animal use protocols
- Perioperative surgical management

Under each topic, the working groups would address the following:

1. Who are the stakeholders?
2. Why develop this standard?
3. What is the objective and/or desired outcome?
4. What are the criteria for measurements?
5. How should this performance standard be implemented?
6. What would be the method of implementation and its schedule?
7. What are the known and unknown limitations to this performance standard and what is the reporting responsibility?

[1] This section is based on the presentations during the workshop by the rapporteurs of the four ad hoc working groups. Statements attributed to the working groups have not been reviewed and do not necessarily reflect the views of the National Academies of Sciences, Engineering, and Medicine.

PERFORMANCE STANDARD FOR PERSONNEL TRAINING IN ANIMAL HANDLING AND PROCEDURES

Sandra Scherrer, Manager of the Preclinical PET Facility at the Feinstein Institute for Medical Research, began her report with a list of the relevant stakeholders, which included the IACUC, the Institutional Official (IO), the animal care staff, the research staff and the animals themselves. A performance standard for personnel training would ensure consistency in supporting good animal welfare practices across the board, as there is a need to document the abilities of staff and researchers to do good science.

The objectives and desired outcomes for this performance standard are consistency, competency, and proficiency, as well as high-quality training, said Scherrer. Measurement criteria included a post-procedural monitoring program for both animal care and research staff to establish a process for follow-up monitoring of animals after experiments are completed and for ensuring that staff understand that follow-up process.

This group, said Scherrer, wanted to create (a) consistent feedback loops among staff to enable effective communication, verification of competency and thorough documentation of training in a shareable format; (b) a prospective review of undesirable outcomes to prevent their occurrence; (c) an assessment plan to track personnel compliance; and (d) a plan for reassessment and retraining to correct deficits.

The working group, said Scherrer, proposed a system of self-review and self-reporting as a means of documenting training and competency. A didactic review, as part of a pre-training assessment would be conducted to identify individual needs. A mechanism for documenting the quality of the trainers' training ability would help assess their improvement or decline over time, although progress/failure reports are not the best metric of a good training program.

The centerpiece of this performance standard, said Scherrer, would include a training program for trainers ("train-the-trainers"), a hands-on training program for staff and assessment of competency levels within trainee group.

The schedule and method of implementing this performance standard would depend on whether a program is big enough to have its own trainers or training coordinators and whether those people would need to be trained themselves. According to the working group, smaller facilities may not need to create their own training program, but larger institutions would need to estimate their resource needs before instituting this performance standard. A training program would be

composed of structured modules and both didactic and hands-on components that incorporate active learning.

Potential limitations include the need for significant resources in advance and for a team effort. Challenges may also arise from the dichotomy of research versus animal staff and the need to bridge cultural differences.

Developing the Performance Standard for Personnel Training in Animal Handling and Procedures

Bruce Kennedy, Compliance Associate at California State Polytechnic University, Pomona, explained that the group thought a culture of training, not just what was being taught, was important and that this message needed to come from the institution's leadership. The working group recognized the minimum expectations for training in both the *Guide* and the AWR but thought that relevant language in these documents was not well-defined.

The group created a method to contribute ideas and share expectations, for example, to include evidence of what learning management was. The group voiced concern, said Kennedy, about competency and measures of ability to complete an activity or task after being trained, which led to the view that there needed to be competent trainers, competent trainees, and programs to train trainers.

The group also discussed rubrics and what it meant to have good surgical models or good cage changing processes for evaluating the competency of an individual once he or she has been trained. There was some discussion, Kennedy said, about outcomes and issues related to poorly trained individuals. The group also discussed ways to reinforce positive behavior and outcomes that reflected specific tasks pertaining to the care and use of laboratory animals.

The discussion kept returning, said Kennedy, to the question of assessing the adequacy of training while the group acknowledged that training is a lifelong endeavor requiring regular oversight. Inspections, accreditations, and semiannual reviews were stated as possible oversight mechanisms. The group also recognized training as a challenge for everyone involved in the care and use of animals. To avoid drift over time, the working group pointed to a need for concrete training programs adaptable to changing regulations, changing research projects, and changing institutional characteristics.

PERFORMANCE STANDARD FOR WORKPLACE SAFETY

Robert Dysko, Clinical Professor at the University of Michigan Medical School, presented the workplace safety performance standard, which would affect the IACUC, the IO, the animal care staff, the research staff, and the occupational and environmental health committees. A workplace safety performance standard would lead to regular review as part of the semi-annual review of an entire Animal Care Program. Desired outcomes would primarily include an increase in the percentage of staff enrolled in an occupational safety program; an assurance of training; and documentation of competency. Secondary outcomes would involve the establishment of minimum and acceptable levels of workplace injury and the identification and management of hazards at the laboratory site.

Measurement criteria, said Dysko, would be (a) adherence to occupational and environmental health standards and (b) tracking of incidents and exposures. The working group thought it would be important to provide a basic set of questions to be used by post-approval monitors to evaluate what was taking place in the laboratory without being led point by point through the approved protocol. Other criteria would include assessing staff's knowledge of the occupational safety program; the consequences of not following the program's rules; and a visual evaluation of the animal laboratory space.

The assessment plan would include timely reports of occupational safety-related incidents to the appropriate institutional committee, the IACUC, and the IO via the semi-annual report process. The report would include information gathered from all involved program components, such as environmental health, occupational safety, and the animal care program.

The action plan, explained Dysko, would include efforts to follow up on any reported incidents with retraining, lockout from the facility, or other actions to ensure the laboratory was compliant with all workplace safety codes. Assessment could be tiered to increase post-approval monitoring visits to areas in which there was an increased safety risk or elevated levels of non-compliance. The working group, said Dysko, thought it was important to identify individual stakeholders to be involved in the resolution and remediation process.

Regarding scheduling and the method of implementation, the working group suggested monthly and semi-annual notification of incidents and issues, Dysko said. The group noted that big changes at an institution, such as one company acquiring another, adding a new species

to an animal facility, or significant staff turnover might require additional training to address occupational safety and workplace safety compliance.

One important limitation was the (lack of) strength of an institution's occupational and environmental health programs, said Dysko, while others included accuracy of reporting issues and exposures, and financial and institutional support.

Developing the Performance Standard on Workplace Safety

Dysko noted that the diversity of the group's members played an important role in the discussions, especially during the brainstorming phase, so it would be worth bringing in people from outside an institution to provide different perspectives. As an example, Dysko noted that workshop speaker John Bryan, a member of the group, explained that aerial darting of wildlife from a helicopter was one of the easiest protocols to evaluate for occupational safety, something nobody else in the working group could grasp since helicopters are not common in most institutional protocols.

This working group, said Dysko, noted the following challenges:

- Accounting for the many ways in which institutions set up their workplace and environmental monitoring and enforcement programs
- Establishing protocols to enable the IACUC to monitor occupational safety concerns, normally the purview of other institutional entities
- Changing institutional culture regarding the importance of occupational safety and compliance.

PERFORMANCE STANDARD FOR SCIENTIFIC FLEXIBILITY OR STUDY DRIFT IN ANIMAL USE PROTOCOLS

Kent Lloyd, Professor and Head of the Mouse Biology program at the University of California, Davis, and Judy MacArthur Clark served as the rapporteurs for this working group. Lloyd noted that the word "drift" does not appear anywhere in the *Guide*, while the word "flexibility" appears only five times and never in the context of scientific research or progress. Thus, he said, it was first necessary to define terms, and the working group decided that while drift is a natural occurrence of science, it can cross over into non-compliance of an IACUC-approved protocol. From that starting point, Lloyd explained, the working group focused on protecting and promoting animal welfare while reducing administrative burden.

MacArthur Clark explained that drift occurs due to a tendency for investigators to go outside the terms of the IACUC-approved protocol because the approved authorizations are so tightly constructed. As a result, investigators either have to apply for approval of an amendment or they continue along, knowingly violating the approved protocol and reporting the deviation in the regular post-approval report. One way to resolve this problem would be to introduce more flexibility into the protocols, as long as animal welfare is not compromised. The resulting performance standard would be more flexible, allowing science to evolve while avoiding unnecessary bureaucracy and protecting animal welfare. The working group noted that culture change, in addition to a performance standard, would be necessary in both the IACUC and the investigators to truly realize the benefits of flexibility.

The desired outcome of this performance standard is to have appropriately authorized and reviewed research protocols with the IACUC recognizing the need for flexibility but also inflexibly protecting animal welfare. For example, said MacArthur Clark, if a study called for four blood draws over the course of an experiment, but might occasionally require six, the IACUC might decide there is a significant burden in the welfare of the animal from six blood draws and so it would not authorize the additional draws. However, if the IACUC takes the view that six blood draws would not be any more detrimental to the animal that four, it might authorize them with the proviso that the investigators should do the minimum number whenever possible because that would be less intrusive to the animal. An important component of this performance standard, then, would be to train the IACUC to think about flexibility in a new way and to train investigators to request realistic and reasonable flexibility in their protocols.

Regarding measurement criteria, MacArthur Clark said one approach would be to measure how many trivial amendments are granted with little consideration or debate by the IACUC. If this occurs frequently, it would indicate a problem with the initially authorized proposal. If the IACUC does not have to deliberate about an amendment it probably did not need to be an amendment in the first place and should have been put into the original proposal, the working group noted. Another measure would be to examine the number of essentially technical non-compliances that occur without endangering animal welfare. An example of a technical breach would be if a proposal called for collecting blood from an anesthetized animal via cardiac puncture but the investigators found it was easier to draw blood from the abdominal aorta. This change would make no difference to the animal but would be a breach in the protocol

nonetheless because that was not what was detailed in the proposal. Another measurement criterion, MacArthur Clark added, would be the number of interventions by the attending veterinarians.

The working group, MacArthur Clark reported, thought a survey, including nonscientific staff, would be an appropriate way of gathering information on how well the performance standard is being accepted and how well it is working. The working group further suggested that before implementing this performance standard, the IACUC would need to explain to the institution the rationale for this new approach and how it will continue to protect the welfare of animals used. Part of this launch program might include a pre-survey to understand the views of the larger community and collect feedback on the new standard, while training at the institutional level will be an important piece of the implementation.

An important limitation for this performance standard, said MacArthur Clark, would be if researchers start taking flexibility to mean the liberty to make changes to a protocol whenever they want. The working group noted investigators may start preparing excessively complex protocols covering every possible variation and the IACUC will need to push back on that type of proposal.

Post-approval monitoring and ongoing review, said MacArthur Clark, could be accomplished through repeated surveys that focus on numbers of non-compliances and similar measures. These surveys could also solicit more qualitative views on how well the performance standard is helping researchers deliver their science, making it easier for an animal care technician to protect the welfare of the animals, helping veterinarians feel that they are having an impact, and enabling IACUC members to feel they are spending their time doing something important instead of wasting time processing trivial amendments.

Developing the Performance Standard for Scientific Flexibility or Study Drift in Animal Use Protocols

Similarly to the other working groups, Lloyd noted the importance of having individuals with diverse experiences contributing to the discussions. MacArthur Clark recounted that the working group saw post-approval monitoring as an opportunity not so much to check whether or not people had complied with their protocol, but rather an opportunity for learning. An IACUC can identify the lessons about flexibility from one study and apply them to other protocols. She reiterated that the group had difficulty working through what the performance standard should be because it may conflict with the engineering standard nature of a protocol. Thinking about performance, she added, provides opportunities

for communication both within the research group and with others in an institution about how responsible animal research is conducted.

One clear message from the group's discussion, said MacArthur Clark, was there cannot be gray areas in terms of compliance with an IACUC-approved research protocol, for that creates a slippery slope of determining what amount of non-compliance is allowed. Thus it is important to maintain a black and white view of what a protocol permits and what it does not. This approach still allows the IACUC to determine that there were no welfare consequences of noncompliance. However, it is still important to send the message to the investigators that they failed to comply with the protocol. Deciding on this hardline approach, said MacArthur Clark, was important for the group before it could agree on the need to allow more flexibility within a protocol so investigators can be compliant when making sensible decisions about alternatives.

PERFORMANCE STANDARD FOR PERIOPERATIVE SURGICAL MANAGEMENT

Randall Nelson, Associate Vice Chancellor for Research and Professor of Anatomy and Neurobiology at the University of Tennessee Health Science Center, served as rapporteur for this working group, which thought there were several reasons for developing a performance standard for perioperative surgical management. The main reason is the lack of specificity in the *Guide* and the AWR with regard to key elements of perioperative management. As a result, he said, there is a need to provide the necessary details to ensure consistency and to provide a mechanism for protocol flexibility when addressing unexpected outcomes. These outcomes may or may not affect the animal but they probably affect the science, thus the working group thought it important to respond to both of those situations. The stakeholders for this performance standard would include the IACUC, the IO, the animal care staff, the research staff, and the animals.

The working group, said Nelson, identified three objectives for this performance standard: (a) ensure animals are handled appropriately to minimize pain and distress; (b) set consistent standards for investigator performance that reduce outcome variability and achieve planned protocol outcomes; and (c) assess the competency of the staff to ensure consistent and competent execution of the research plan as approved by the IACUC. This last objective would require education to ensure that staff have the appropriate skills to conduct a study.

Criteria to be measured, said Nelson, include personnel assessments designed to understand what staff members are doing as well as what their needs are to do their job correctly; species-specific concerns; equipment and space concerns; observational intervals and intensity; how well trained the monitors are in assessing these criteria; and a review of the experimental design by those doing the experiment and those monitoring the researchers. The working group also thought that since protocols should incorporate flexibility, it would be important to measure adherence to the ranges and options stated explicitly in the protocols. It would also be important to ensure that protocols are written broadly enough to account for known possible adverse outcomes and provide mechanisms to deal with them. By accomplishing the latter, the result is protocols that are not rate limiting but flexible enough to account for the possible adverse outcomes. Another important criterion to measure would be preoperative animal health to ensure the animal is in a reasonable condition for surgery and appropriately acclimated. In addition, the planned use and execution of analgesia and anesthesia should be assessed, Nelson stated.

In terms of implementation, Nelson reported that the working group thought monitoring surgical outcomes would identify problems and determine the procedures needing modification to ensure both animal welfare and good science. The working group suggested using a checklist to verify adherence to approved procedures and protocols, and one was supplied to the working group by an online participant listening to this working group's discussions (Figure 6-1). Such a checklist could help the investigators know what the IACUC had approved and reduce the possibility of intentional or unintentional deviation from IACUC-approved activities. An audit process could be developed to include both planning and outcomes.

In terms of implementing this performance standard, Nelson said the working group wanted to make sure there was a way for checking appropriate post-operative conditions, such as during recovery, and to make sure that whoever was responsible for monitoring these animals did so at regular intervals to ensure minimization of pain and distress. The working group also wanted to ensure that investigators would be involved with this monitoring.

In thinking about limitations, Nelson said, there is an opportunity to do a trend analysis across an entire program to determine outcome patterns that may need to be addressed. The working group noted that post-approval monitoring, especially when it comes to perioperative management, can be extremely important in raising standards and

minimizing pain and distress, and it should involve not just those working in the laboratory, but also animal care staff, IACUC members, and members of the compliance office. In the case of protocol deviations that warrant reporting, there should be well-defined procedures for disseminating information internally and for reporting it externally.

Post Approval Monitoring (PAM) Program
Laboratory Checklist

☑	
☑	**Protocol and Personnel**
	Does the lab staff have easy access (paper or electronic) to the most recent version of the complete protocol?
	Have the laboratory personnel read the protocol?
	Have the people performing the study been trained to perform protocol specific procedures?
☑	**Study procedures**
	Does the protocol number on the animal's cage card match the protocol number of the study?
	Are the procedures performed consistent with those in the approved protocol?
	Are laboratory personnel wearing appropriate PPE or other attire appropriate for species and procedures?
☑	**Laboratory/Safety**
	Are drugs, suture material and other items within the noted package expiration dates or stored in separate area?
	Are controlled substances stored appropriately and are inventory records kept?
	Are expired controlled substances marked accordingly and stored so that they will not be used mistakenly?
	Do the laboratory personnel know how to dispose of expired and unwanted controllec substances appropriately?
	Do lab personnel know to report any animal bites or work-related injuries or illnesses to their supervisor?
	Do lab personnel know that they can go to Employee Health or Emergency Room (after hours) for treatment?
	Are sharps containers available, filled only to level listed on the container?
	Are needles are only recapped by safe recapping devices and not by hand?
	Is an SOP posted if a needle recapping device is used?
	Are all gas cylinders properly secured to a wall or a stable cart or dolly with chains or straps?
	Are there logs for guillotine inspection and maintenance?
☑	**Anesthesia**
	Are the methods of anesthesia in compliance with the protocol?
	Are the anesthetized animals monitored according to the protocol?
	Do vaporizers have a current date sticker indicating when it was serviced or certified?
	If inhalant anesthetics are used, are they scavenged appropriately?
	Are animals monitored continuously while waking from anesthesia?
	Are animals fully recovered before returning to the vivarium?
☑	**Surgery**
	Is surgery performed in a location that has been approved by IACUC?
	Are there separate areas for animal preparation, surgery and recovery?
	Are the areas clean and free of clutter?
	Is the method of animal preparation appropriate and in accordance with the approved protocol?
	Is survival surgery performed using sterile instruments, sterile gloves, proper PPE and aseptic technique?
	Is an appropriate heat source used to keep the animal warm throughout the procedure and recovery?
☑	**Euthanasia**
	Does the method of euthanasia correspond with what is written in the protocol?
	Is death assured by performing the appropriate physical method of euthanasia listed in the protocol?
	Are appropriate procedures followed for the disposition of the carcass?
	Breeding Colonies
	Records of mating, birth, genotyping and weaning kept up to date?
	Are animals separated into appropriate cages in a timely manner?
	Is the annual breeding report submitted to ARC on time - October?
	Is genotyping performed according to IACUC policy?

FIGURE 6-1 Post-approval monitoring program checklist
SOURCE: Working Group 4 slide

Nelson concluded the report from this working group with a message sent by one of the online participants, who wrote: "The goals of post-approval monitoring are to ensure that the protocol is being carried out as the IACUC understood and approved it. The protocol itself must be the framework for the evaluation using the checklist as a tool. In addition, the monitor can also ensure the approved protocol procedures (in this case perioperative) also adhere to the AWR, the PHS Policy, and the *Guide*."

Developing the Performance Standard for Perioperative Surgical Management

Nelson explained that this group first identified the relevant text in the *Guide* and AWR on perioperative surgical management and then the topics missing from these documents. This information was used to construct a framework. The group also wrestled with performance measures versus checklists. The participants, said Nelson, chose to look beyond what was not in the *Guide* and in the regulations, and instead used convention, best practice, and professional judgment to develop a performance standard.

DISCUSSION

Joseph Newsome, Clinical Director of the Division of Laboratory Animal Resources and Associate Professor of Pathology at the University of Pittsburgh, said one theme he picked up on that he had not heard before was the need for well-trained moderators and leaders who can work through the process to develop performance standards. Kennedy said this emphasizes the need to establish an institutional culture that makes those resources available and expects them to be used. MacArthur Clark remarked that while people with process mapping skills could be useful and accelerate the progress that an IACUC can make, a good committee can do good work without a professional facilitator. There is much to be gained, she stated, from letting discussion range over many ideas and not always stay focused on the task at hand.

Steven Niemi said the discussions from the first day of the workshop and from the working group activities highlight how hard it is to develop performance standards and how thoughtful and thorough people have to be to create good ones. Commenting on Newsome's idea, Niemi recommended against relying on outside experts and said this is an activity that an institution needs to undertake itself, drawing on the expertise and years of experience that reside internally.

Donna Mathews Jarrell asked if any of the groups could elaborate on how difficult it was to determine which metrics would be needed to reflect desired outcomes. Dysko said that the workplace safety group had an easier time identifying metrics for post-approval monitoring, but a harder time thinking about what the IACUC or IO would need to see to know the post-approval monitoring process was working. Lloyd said the scientific flexibility working group was able to identify metrics once it agreed on the reason performance standards were needed, which is to protect and promote animal welfare while reducing administrative and bureaucratic burden. The training group, said Kennedy, easily identified metrics for quantifiable components of a protocol, but not metrics that could assess skill. Scherrer added that for training assessment the group agreed the size and scope of the facility or institution played a big role in determining the type of useable metrics. A smaller facility, for example, can more readily monitor training. As a final comment, MacArthur Clark said her group soon realized that depending on hard numbers was not going to provide all the needed metrics and that the qualitative information from surveys combined with quantitative data was the best approach.

COMPARING AND CONTRASTING THE WORKING GROUPS' PERFORMANCE STANDARD DEVELOPMENT PROCESS

As a final piece of the working group exercise, Mary Ann Vasbinder was tasked by the workshop organizing committee to compare and contrast the process the four teams went through to develop a performance standard. She found it fascinating and even amazing that the groups could develop a set of performance standards that are inclusive and flexible and that stress the importance of professional judgment. She also noted the importance of a project management process starting with creating a team, setting out a business plan, engaging key stakeholders, and getting buy-in from the institution.

It was clear, she said, that diversity in creating performance standards is valuable because of the perspectives and range of knowledge that different voices bring to the process. The importance of engaging all key stakeholders was another point that each of the working groups made.

Communication and leadership were two other key features identified as essential for the success in creating and implementing a performance standard. Vasbinder said one huge benefit from creating a performance standard is that by engaging key stakeholders, the process starts changing culture within an organization. Instead of simply checking

boxes, the process requires thoughtful discussion and communication among the stakeholders, she said. Strong leadership committing to the time and effort needed to develop good performance standards also creates a culture that encourages engagement and communication.

With respect to the planning phase, the groups identified desired outcomes by involving each member of the groups. When it comes to executing performance standards, Vasbinder added, pilot studies can help, but the best approach may be to roll out the performance standard and see what happens.

There was a significant amount of discussion within the four working groups about what to measure, how to monitor the effects of a performance standard, and how challenging it can be to create appropriate and practical measurements. The working groups noted the importance of developing both quantitative and qualitative measures and the ease of measuring failure but the importance of measuring positive outcomes as well. Though the latter is admittedly more difficult, it is important to reward success and provide positive reinforcement. There was a good discussion, Vasbinder said, about absolutes and gray areas and the need to establish limits, which is also a part of monitoring the success of these programs.

The groups pointed out the pivotal role of the IACUC in providing leadership and direction for developing and applying performance standards. Not only does the IACUC have to approve performance standards, but it is the collective body that gives an institution the weight to administer and monitor them properly. Vasbinder said she was also struck by the integrative ideas for performance standards that were brought to the table. She reiterated the opportunity to change culture and the ways in which such a change can engage people and get them to participate more fully in the process of developing and implementing performance standards. As a final point, Vasbinder said the working group stated the most important outcome of any performance standard is the welfare of the animals.

Vasbinder then asked other workshop participants for their comments. Dysko said that he will take back to his institution the need to capture diversity in the teams convened to develop performance standards. Too often, he said, these teams are focused narrowly on a presupposed solution.

Malak Kotb said one of the helpful lessons she learned was to build some flexibility into the performance standard and to not shy away from trying to convince IACUC members of such need, so investigators can comply without holding back the science or creating artificial results.

Vasbinder then asked the panel of rapporteurs if they had ideas on how to encourage IACUC members, IO's, and others, including veterinarians, to embrace the idea of flexibility. Dysko said flexibility starts with those creating protocols, adding that too often researchers are their own worst enemies when they add too much detail to a proposal.

Reflecting on his own institution, Dysko said what needs to happen is for the veterinarians and IACUC members who review proposals to determine those areas that could benefit from flexibility, convey that information back to the investigators, and get them to take some of the specifics out of their proposals. The challenge, he added, will be getting all of the reviewers to agree to this approach. Nelson wondered if the problem of limited flexibility rests with proposals being written without getting input from the people who see and care for these animals daily.

Kennedy asked Dysko if his IACUC had any facility managers or animal care technicians as voting members, as they may be the ones most likely to suggest where flexibility would be beneficial. Dysko responded there are not, but they do come to the IACUC meetings and are encouraged to participate in the discussion. Scherrer said the IACUC at her institution does not have anybody at her level as a member, which she and her animal care colleagues are trying to change. Input from the animal care and laboratory staff, said Scherrer, is missing in many proposals.

Lloyd noted he is fortunate that his staff includes trained veterinarians who have served on an IACUC and having their input on proposals as part of a team effort is invaluable. Nelson added this type of team approach should be continued after the proposal is approved, perhaps starting with briefing everyone involved in a project on what was approved and how to carry out the specifics of the proposal.

Kurtz said that he had advocated for and firmly believes that the most important people in an animal care and use program are the husbandry staff members, because nobody knows the animals better on a day-to-day basis than they do. It is important, he said, to not only engage them but to get their advice when writing proposals and making plans to enact performance standards. Norman Peterson said he believes part of the problem with proposals lies with investigators who do not understand they are allowed to write amendments with the proper justification and that IACUCs will consider those amendments. Carol Clarke responded she used to be an IACUC coordinator and her institutions held pre-review meetings with investigators to discuss those kinds of issues. What was missing from that process was a team approach in which the reviewers worked with the investigators to improve their proposals before formal submission to the IACUC. Kennedy added that combining a pre-review

meeting with a pre-launch meeting would be a great idea, particularly if it better engaged the animal care staff.

Kotb asked if it would be possible for the roundtable to generate scenarios and examples to teach investigators how to include flexibility in their proposals. Kennedy said the Collaborative Institutional Training Initiative group at the University of Miami has put together an animal care and use course that includes those kinds of case studies. Nelson, who helped write some of these case studies, explained they provide detailed explanations of the many choices investigators can make and the ramifications of those choices. Nelson said there is a need to educate IACUC members and the animal care staff, as well as investigators, about what is acceptable flexibility because they do not know how much flexibility is appropriate and allowable.

7

SHARING ACCEPTABLE PERFORMANCE STANDARDS[1]

According to Steven Niemi, Roundtable member and Liaison to the American College of Laboratory Animal Medicine and Director of the Office of Animal Resources for the Harvard University Faculty of Arts and Sciences, this workshop represented the first serious and in-depth discussion of performance standards among the research community. He began his talk by focusing on funds that are available for the U.S. biomedical discovery enterprise. The pharmaceutical industry's contribution to research and development expenditures, while substantial, began flat-lining just prior to the last economic downturn and has not yet begun to rise again (Figure 7-1). At the same time, NIH funding in constant dollars has fallen by 6.2 percent since fiscal year 2000. Together, these numbers translate into fewer investigators getting funded (Figure 7-2).

[1] This section is based on the presentation by Steven Niemi, and the statements are not endorsed or verified by the National Academies of Sciences, Engineering, and Medicine.

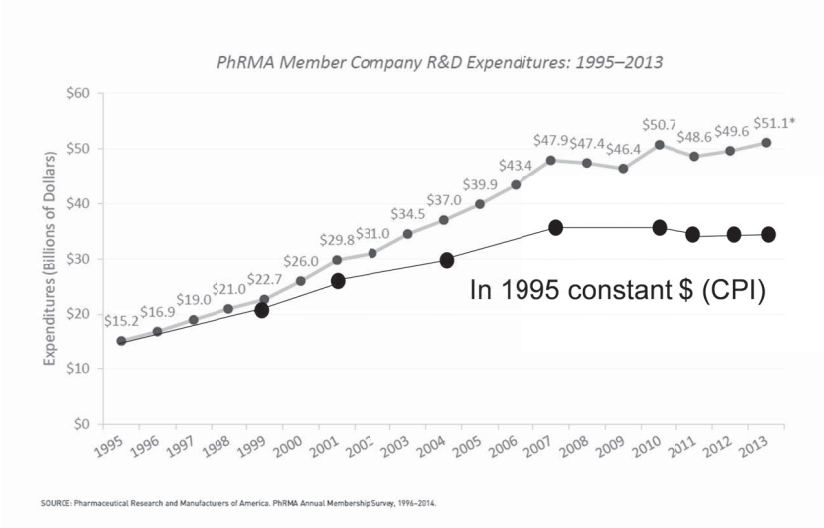

FIGURE 7-1 Expenditures on research and development by the pharmaceutical industry in real and 1995 constant dollars
SOURCE: Niemi slide 5

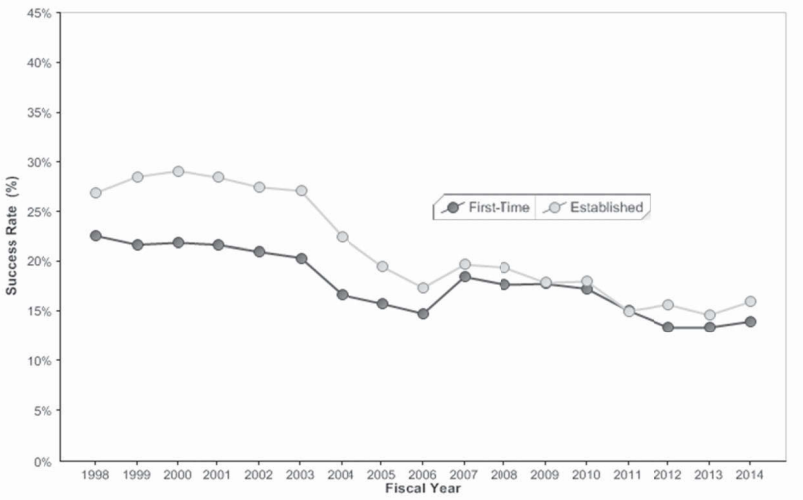

FIGURE 7-2 Success rates, by career stage of investigator, for securing NIH RO-1 equivalent grants
SOURCE: Niemi slide 7

In the last fiscal year, NIH awarded about $26 billion in extramural grants, including RO1, RO1-equivalent and large, collaborative research program grants. There were 14,404 awards, with an average of $1.8 million per year per award. Niemi estimated that 1.67 percent of an institution's life science research budget is devoted to animal care. He further estimated that about $430 million was invested by NIH in animal care expenses, including husbandry, veterinary medicine, management, and training for staff, the next generation of animal care providers, and investigators. Up to 30 percent of that, he calculated, is unnecessarily spent trying to meet engineering standards, so a conservative estimate of 20 percent waste would translate into $86 million dollars that could be spent funding 48 additional average-size awards.

Even more distressing, said Niemi, are the generational changes underway. In 1980, investigators under 35 years of age were far more likely than investigators age 66 or older to receive NIH funding. Today, the opposite is true (Figure 7-3), and he expressed his concern about the graying of academic science (Figure 7-4). In another what-if exercise, he calculated that the $86 million wasted on meeting engineering standards could support 215 additional new investigator awards at an average $250,000 per year above the current level of 144. These financial considerations, Niemi explained, lead him to label this problem of wasted resources as vitally important.

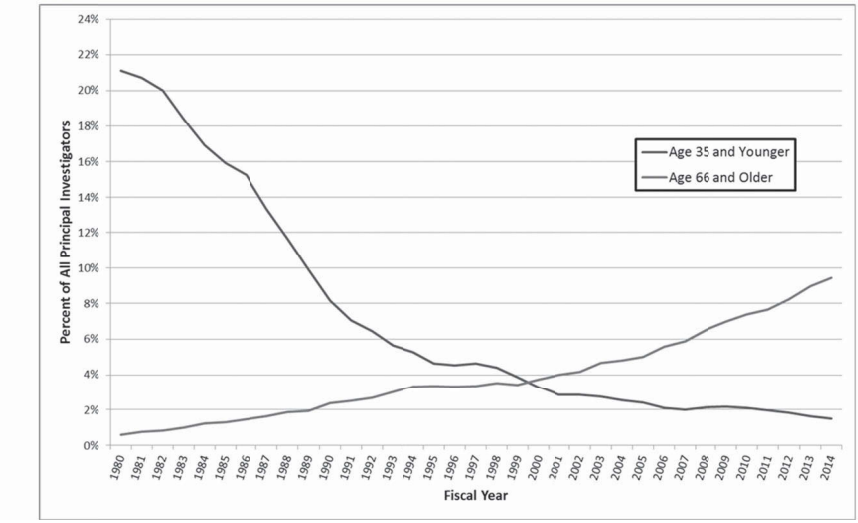

FIGURE 7-3 Percentage of NIH R01 Equivalent Principal Investigators of All Degrees, Age 35 and Younger vs. Age 66 and Older, Fiscal Year 1990 – 2014
SOURCE: Niemi slide 9

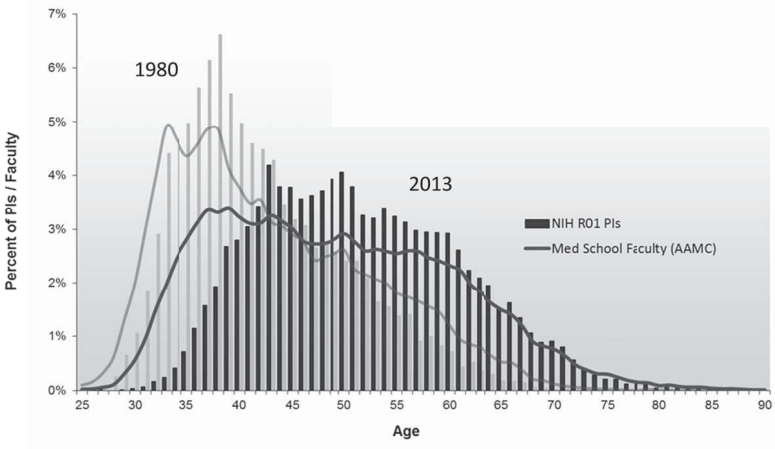

FIGURE 7-4 The graying of academic science from 1980 to 2013
SOURCE: Niemi slide 10

Performance standards can be valued, he said, in terms of liberating funds for academic science and for shareholders in the for-profit sector. Savings could also result from compliance relief, which, Niemi explained, was discussed in a paper published in the *FASEB Journal* in May 2014 (Thulin et al., 2014) and was one of the foci of the 2015 Public Responsibility in Medicine and Research (PRIM&R) IACUC conference. Niemi said the discussions at this conference highlighted the idea that more regulation is not always better regulation.

The challenge is how to scale back over-regulation. He presented four questions to be used in any program:

1. Are we doing things right?
2. If so, what would be even better, faster, easier, more humane, cheaper, safer, and less prone to mistakes even if animal welfare remains unchanged?
3. Are we doing the right things?
4. If not, what would be even better, including faster, easier, more humane, cheaper, safer, and less prone to mistakes even if animal welfare remains unchanged.

Niemi said that when he meets with the animal care staff or supervisors, he often asks them to point out things that do not make sense to them. These discussions have empowered staff to be vigilant about ways to improve operations and the welfare of the animals. For example, before Niemi arrived at Harvard, typically animal technicians took three 30-second air showers a day, which equaled about $1,500 in labor costs annually. While this may not seem a large amount, it would be enough for two to three people to attend a national meeting or three to four technicians to attend a regional or local one. Harvard has now stopped using these air showers.

Another example concerned the use of full personal protective equipment (PPE), including head cover, face mask, gloves, Tyvek jumpsuit, and shoe covers. Given that Harvard's animal facilities use ventilated cages, laminar flow, purified air, and hoods for animal work, Niemi copied procedures established at the University of Michigan and the University of Houston that require only personnel working with rodents or handling animal-contaminated products to wear gloves and a paper gown. A paper published last year in the *Journal of the American Association of Laboratory Animal Science* by researchers from Columbia University (Baker et al., 2014) showed that eliminating full PPE had no negative impact on the virus-naïve status of animals as long as personnel used gloves, gowns, and proper technique. The authors calculated that these

procedures, which are based on experiences with micro-isolator cages accumulated over 25 years, would result in savings of $150,000.

Research conducted by Donna Matthews Jarrell and her colleagues at Massachusetts General Hospital and presented at the 2009 American Association of Laboratory Animal Science annual meeting showed possible savings from changing cage-cleaning cycles based on research data. Investigators viewed a series of photographs depicting a variety of caging situations and voted on when a cage appeared to need bedding change. Jarrell and her colleagues also measured ammonia levels and assessed animal welfare. Based on the data collected approximately 30 percent of cages did not need changing at the scheduled times. For the facility Niemi was managing at the time, which had 27,000 mouse cages, 85 percent of which are ventilated and 15 percent of which are not, such a reduction would translate into saving over 8,000 hours of labor, require over 242,000 fewer changes, and disturb the mice less often.

Niemi explained his facility had piloted spot changing immediately prior to an AAALAC site visit, but the study was not completed before the AAALAC review. He noted current standard practice at most institutions is to spot change before two weeks based on decisions made by animal care technicians, but he does not believe this policy is based on rigorous scientific criteria. Genentech, said Niemi, has instituted a system of scheduling changes not by calendar but by occupancy rate, and he has been told this change reduced inefficiency by 37 percent.

Other options for reducing waste in animal care, which may not have risen to the level of a performance standard, include:

- Sterilize the incoming bedding rather than the rodent barrier cages and racks.
- Allow 20 percent relative humidity in rodent barrier rooms during frigid weather because humidity within the animals' primary enclosure remains at the engineering standard of 30 percent.
- Maintain non-human primate rooms at six or more air changes per hour compared to the standard engineering level of 10 to 15 air changes per hour.
- Use routine care for animals not receiving toxic substances or that are receiving drugs at such low levels that metabolite levels secreted into bedding will be too low to be toxic.
- Allow human cell line xenografts to be handled in Animal Biosafety Level 1 facilities instead of Level 2 as long as the cell lines can be tested for and are free from common pathogens of concern.

For compliance with veterinary medicine issues, Niemi presented the following list established at his facility:

- Replace sentinel rodents with polymerase chain reaction swabs of inanimate surfaces such as the exhaust plena of ventilated racks. While this procedure is not more cost-efficient, it reduces numbers of animals used.
- Eliminate annual reviews of non-USDA, non-Department of Defense research protocols.

Turning to the assigned topic of his talk – how to share and promote performance standards – Niemi first discussed his thoughts on the process to enable the dissemination of a performance standard, which should be based on standards that are evidence-based, accompanied by many examples of local adoption deposited in one or more public repositories and have been approved by an IACUC. For performance standards to displace engineering standards, a repository for performance standards populated almost immediately by at least 500 examples is crucial. Such a repository, Niemi suggested, should be hosted on a reliable and secure server, be accessible and searchable via a user-friendly website, and list entries by specific categories, such as species, date of entry, and institution. Entries should be linked to pertinent sections of the *Guide* or the Animal Welfare Act, and perhaps even EU, UK, and Japanese regulations and should indicate the name of the USDA inspector who allowed the modification. He was unsure if access to the repository should be restricted. Just as important, he said, would be to invite contributions or suggestions from the public.

Niemi stated that someone or some organization would have to manage the repository and act as a primary filter to keep useless data from publication. There should also be a second, in-depth review provided by a panel of expert peers – including members of the animal welfare community. The community, he said, would ultimately decide on the utility of a given performance standard. The repository should also invite commentary and discussion that would go through the same primary and secondary filters, perhaps along the lines of a Wikipedia model. One possible outcome is that the repository could serve as the mechanism for making the *Guide* a living document. The animal care community has talked about this possibility given it was 14 years between the release of the 7th and 8th editions of the *Guide.*

In Niemi's opinion, an obvious host for the repository would be the ILAR roundtable. Operation costs could be supported by dues, subscriptions, donations, and grants. If the roundtable chooses not to

support this idea, any one of a number of other non-governmental organizations could be enlisted to host it.

DISCUSSION

Joseph Newsome asked if NIH could be a source of funding. Niemi replied that his preference would be to seek support from other sources first. Clarke and Jarrell seconded

Niemi's suggestion of the roundtable driving the creation of a repository, and Clarke hoped the repository would contain examples of performance standards that did not work. MacArthur Clark urged that the repository be international in nature as the issues addressed in the United States are the same she and her colleagues face in Europe and other parts of the world. Having the repository as an international initiative would also create more opportunities for international collaborations, MacArthur Clark added, and she cautioned against having a regulator such as NIH managing it. She also voiced support for ILAR taking a leading role in creating and managing the repository. Niemi said he hoped that in time, the repository would be translated into other languages so it could be used globally. Peterson suggested that the repository be augmented by a feature to post questions and engage in discussion, as well as to link it to the CompMed listserv to notify the community when a new performance standard is entered into the repository.

Regarding the idea of reducing the use of PPE, Clarke suggested that National Institute of Environmental Health and Safety and the Environmental Protection Agency, which are similarly interested in lower levels of PPE in biological facilities, could be a source of funding for studies in this area. Dysko then noted that, although Niemi used his facility as an example of an institution that had reduced the use of PPE, he has received comments that staff are not protected from allergies because they no longer wear face masks. As a result, an additional performance standard evaluating the human safety aspect of reduced PPE use may be necessary. Niemi responded that at Harvard, this change was approved by the biosafety office, the environmental health and safety office, and the occupational health physician.

Neil Lipman pointed to a European study showing that rodent allergens accumulate in human hair and can be traced to a person's home and bedding (Krop et al., 2007). He said this finding suggests the need to be careful about reducing PPE use and eliminating air showers and changing stations.

Kennedy asked if technology exists for measuring ammonia levels and if it could be used to establish an engineering standard for cage-changing frequency. Niemi replied it is difficult to measure ammonia reliably and even more difficult to set a threshold below which ammonia levels are safe and above which they are deleterious. At his facility, the standard procedure is to observe every animal at least once daily without disturbing them. Niemi envisions a day where smart cages will monitor animals for activity and send out an alarm when activity does not fall within some predetermined range.

Jarrell reemphasized the importance of talking with the people who are directly working with the animals and asking them where they see opportunities for improvement, including reallocating time to activities that benefit the welfare of the animals. Her staff, for example, did not like disturbing animals in clean cages and were excited to participate in the spot cleaning study. The biggest challenge in instituting spot cleaning is the need to also move to a seven-day-a-week workforce to ensure spot changing is consistent, therefore some facilities in her institution are pursuing this idea.

8

REFLECTIONS ON THE WORKSHOP

Workshop organizing committee co-chair David Kurtz highlighted a few points he thought were important. He appreciated the comments of the regulators who stressed the need to focus on the fundamentals in the regulations and to take advantage of the opportunity to build flexibility into performance standards. He also valued the emphasis many of the speakers and working groups placed on engaging a diverse group of end-users and stakeholders when developing performance standards. He applauded, too, that CRL was publishing its data so the community can examine the results and decide whether they are valid for other facilities.

Kurtz recognized the seriousness with which the working groups treated their tasks. He noted that there were many common themes emerged from the groups regardless of the topic, particularly the importance of keeping animal welfare paramount. Another important theme was using the regulations as an initial framework and to first understand what is and is not contained within the regulations as a starting point for addressing important questions. Brainstorming proved to be valuable for developing performance standards that were not one-size-fits-all solutions but that could accommodate flexibility and enable good science. At the same time, said Kurtz, every institution has its own unique culture and collection of personnel, and a performance standard must match those institutional characteristics. He added while he supports the development of a repository, institutions will have to realize they will not be able to take a deposited performance standard and use it as is in their facilities.

Developing a performance standard is a learning opportunity, said Kurtz. He recounted Mary Ann Vasbinder's comments that performance standards can evolve as they are being developed and tested and this should not be a source of frustration but of learning. Performance standards are living, breathing documents, Kurtz said, requiring constant monitoring and assessment. It is unclear where performance standards will go in the future, but that is not a reason to maintain the status quo, and he stressed the importance of publishing performance standard research. Performance standards, he said in closing, represent the mechanism the community can use to move forward better ways of doing things without having to wait for the next revision of the *Guide* or to move the *Guide* toward being a living, breathing document.

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APPENDIX A

WORKSHOP AGENDA

Monday, April 20

7:30 - 8:30am	**Registration**
8:30	**Opening Remarks** Lynn Anderson, Covance Laboratories - *ILAR Roundtable Co-Chair* Lida Anestidou, National Academies of Sciences, Engineering, and Medicine - *Director, ILAR Roundtable*
9:00	**Overview of Performance Standards for the Humane Care and Use of Laboratory Animals** Patricia Turner, Ontario Veterinary College, University of Guelph, Canada *Planning Committee Co-Chair*
10:00	**Coffee Break**
10:20	**Development, Implementation and Assessment of Performance Standards: Regulatory Perspectives** **Office of Laboratory Animal Welfare at the National Institutes of Health** - Susan Brust Silk - *ILAR Roundtable Member* **United States Department of Agriculture** - Carol Clarke - *ILAR Roundtable Member* **Canadian Council on Animal Care** - Gilly Griffin **Perspective from Europe/UK** - Judy MacArthur Clark, UK Home Office, Animals in Science Regulation Unit
11:40	**Question & Answer Session - Speakers' Roundtable** Patricia Turner, Susan Silk, Carol Clarke, Gilly Griffin, Judy MacArthur Clark
12:00 - 1:00pm	**Lunch** (will not be provided. A cafeteria is located on the third floor of the NAS Keck Center.)

1:00	**Development, Implementation and Assessment of Performance Standards: End-User Perspectives I** **U.S. Academic** - Neil Lipman, Memorial Sloan Kettering Cancer Center / Weill Cornell Medical College **Industry (biotechnology/pharmaceuticals)** - Mary Ann Vasbinder, GlaxoSmithKline - *Planning Committee Member* **Wildlife -** John Bryan II, University of Georgia College of Veterinary Medicine
2:30	**Coffee Break**
2:45	**Development, Implementation and Assessment of Performance Standards: End-User Perspectives II** **Agricultural** - Bart Carter, University of Texas Southwestern Medical Center **Public Interest** - Kenneth Litwak, Animal Welfare Institute **AAALAC International** - John Bradfield
4:15	**Summary of the Afternoon Session** Paul Locke, Johns Hopkins University - *Liaison to ILAR Council*
4:45	**Q&A Session: Speaker's Roundtable** Neil Lipman, Mary Ann Vasbinder, John Bryan II, Bart Carter, Kenneth Litwak, John Bradfield, Paul Locke
5:15	**Day 1 Wrap-up and Planning for Day 2** David Kurtz, National Institute of Environmental Health Sciences – *Planning Committee Co-Chair*

Tuesday, April 21

8:30am **Registration**

8:45 **Welcome and Focus of the Day**
Patricia Turner

9:00 **Detailed Steps in the Development and Implementation of Performance Standards**
Guy Mulder, Charles River Laboratories - *Planning Committee Member*

10:00 **Introduction to Breakout Sessions**
Donna Matthews Jarrell, Massachusetts General Hospital – *Planning Committee Member*

10:15 **Coffee Break**

10:30 **Breakout Sessions**

Group 1: Personnel Training in Animal Handling and Procedures (red stickers)
Keck 100
Facilitators: Mary Ann Vasbinder and David Anderson

Group 2: Workplace Safety (blue stickers)
Keck 104
Facilitators: Donna Matthews Jarrell and David Kurtz

Group 3: Scientific Flexibility in Animal Use Protocols (Study Drift) (yellow stickers)
Keck 106
Facilitators: Andrew Grady and Patricia Turner

Group 4: Perioperative Surgical Management (green stickers)
Keck 201
Facilitators: Guy Mulder and Randall Nelson

12:00 **Lunch** (will not be provided. There is a cafeteria located on the third floor of the NAS Keck Center.)

1:00	**Presentations of Performance Standards**
2:00	**Presentations of Process in Developing Performance Standards**
3:00	**Coffee Break**
3:15	**Compare and contrast the performance standard development process by the different groups** Facilitator: Mary Ann Vasbinder
3:45	**Sharing of Acceptable Performance Standards** Steven Niemi, Harvard University – *ILAR Roundtable* Co-Chair
4:30	**Workshop Summary and Meeting Closing** David Kurtz and Lynn Anderson

APPENDIX B

BIOGRAPHICAL SKETCHES OF WORKSHOP SPEAKERS AND ORGANIZING COMMITTEE MEMBERS[1]

David M. Anderson has directed a significant portion of his career towards biomedical research, specifically through development and implementation of animal models to address complex issues of human health and biology. Dr. Anderson's current responsibilities as Executive Director for Health Science Administration provide opportunities for leadership across a variety of University research and operational activities. The Office of Health Science Administration provides administrative oversight and financial supervision for three interdisciplinary research Centers as well as departments with responsibility for environmental health and safety, facilities and academic support, risk management, animal use in research and education, student and staff health care, and strategic communications. In addition, Health Science Administration provides support for interdisciplinary initiatives involving the six health sciences schools: Dentistry, Medicine, Nursing, Pharmacy, Public Health, and Social Work. Dr. Anderson serves to integrate teaching, research, and operational support with an emphasis on efficiency and continuous process improvement. Health Science Administration units play a critical role in maintaining the University's current and future status as one of the preeminent education and research institutions in the world.

John Bradfield is the Senior Director for AAALAC International. He has served as Director of the Division of Laboratory Animal Medicine and Attending Veterinarian at UNC Chapel Hill, and also as Chair for the Department of Comparative Medicine at East Carolina University. He has had many years of experience on animal care and use committees and currently serves on the Board of Directors of the North Carolina Academy of Laboratory Animal Medicine.

John A. Bryan II is a public service assistant and wildlife veterinarian focusing on issues involving exotic invasive species and wildlife disease at the Southeastern Cooperative Wildlife Disease Study (SCWDS). Dr. Bryan is a native Georgian who received his undergraduate education from

[1] Names appear in alphabetical order

Emory University, and his professional and graduate degrees from the University of Georgia. Following graduation from veterinary school, Dr. Bryan received postdoctoral training at SCWDS in the diagnosis, pathology, and epidemiology of wildlife disease. From 2009 to 2015, Dr. Bryan served as served as chair and attending veterinarian of the National Park Service (NPS) Institutional Animal Care and Use Committee, Veterinary Diagnostic Service Coordinator, and as a Field Wildlife Veterinarian in the Biological Resource Management Division of NPS. In 2015, Dr. Bryan returned to SCWDS as a Public Service Assistant and Wildlife Veterinarian focusing on issues involving exotic invasive species and wildlife disease.

Bart Carter is a veterinarian with 25 years of experience working with a variety of agricultural animals in both private practice and research settings. He grew up in a small farming community in rural Missouri and attended the University of Missouri as an undergraduate student of Animal Sciences and graduated from the College of Veterinary Medicine in 1990. Dr. Carter worked in a private veterinary practice for 9 years as a large animal practitioner in Kentucky and Missouri. He then left private practice to return to the University of Missouri to complete a residency in Comparative Medicine. As part of his training, he received a Master's of Science degree working with cloned and genetically modified pigs. After completing his residency, Dr. Carter continued at the University of Missouri serving as the Assistant Director of the Office of Animal Resources and later, moved to Kansas State University where he was the Attending Veterinarian and Director of the Animal Research Facilities. In 2008, he moved to his current position, as the Director of Animal Resources and Attending Veterinarian for the University of Texas Southwestern Medical Center. He served as an AAALAC International ad hoc consultant for several years and is currently a member of the AAALAC International Council on Accreditation. He has been a consulting veterinarian to several Universities and biotech companies who utilize agricultural animals in research.

Judy MacArthur Clark has worked for over 35 years in animal welfare and research in a variety of academic and commercial roles. For over 20 years she has consulted on ethical policy development and improving public understanding of science. She is a veterinarian and has been President of the UK Royal College of Veterinary Surgeons. She has chaired and served as a member of many high level national and international advisory committees on topics such as xenotransplantation, farm animal welfare,

research regulation and bioethics. In 2004, her achievements were recognised in her appointment by the Queen as Commander of the British Empire. In 2007 she joined the UK Home Office as Chief Inspector and is now Head of the Animals in Science Regulation Unit. She actively works on research regulation and policy development in the UK, Europe and the USA.

Carol Clarke received her Bachelor's degree in the Natural Sciences from Johns Hopkins University and her DVM degree from the Tuskegee School of Veterinary Medicine. After receiving her DVM, she practiced small animal medicine in New York City for 13 years before entering the laboratory animal medicine training program at SmithKline Beecham Pharmaceuticals located in King of Prussia, PA. Upon completion of the program, she entered the National Institutes of Health in 1998 as the primate facility veterinarian for the Veterinary Resources Program. In 2001, she accepted a position with the Comparative Medicine Branch of the National Institute of Allergy and Infectious Diseases (NIAID) at NIH and became a Diplomate of the American College of Laboratory Animal Medicine in 2005. During her 10 years with NIAID, she served as IACUC coordinator, Vice Chair of the Rodent Gnotobiotic Committee, and Chief of Shared and Central Facility Operations. In addition, she prepared all USDA, OLAW, and AAALAC annual reports. Dr. Clarke accepted a position with the USDA in 2011, and currently serves as the Research Program Manager at APHIS Headquarters located in Riverdale, MD. Her duties include serving as a laboratory animal subject matter expert, participating in inspections, collaborating with other federal agencies, and representing Animal Care at various meetings.

Janet C. Garber received her DVM degree from Iowa State University and her Ph.D. from the University of Wisconsin. Her experiences have included infectious disease research, primate medicine and research, GLP device and materials evaluation, and transplantation immunology. She most recently was Vice President, Safety Assessment at Baxter Healthcare Corporation and is now a consultant with Garber Consulting, LLC, focusing on research facility management. Dr. Garber is currently an ad hoc consultant for AAALAC International and previously served as Chair of the AAALAC Council. She recently chaired the ILAR Committee to Update the Guide for the Care and Use of Laboratory Animals.

Andrew W. Grady serves as the Director of the Laboratory Animal Facilities and Attending Veterinarian for the University Medical Center. Dr.

Grady received his veterinary medical degree from Mississippi State University (1986) and specialty training in laboratory animal medicine from the University of Missouri (1991). Additionally, he completed an Aquatic Medicine residency in 1987. Diplomate status with the American College of Laboratory Animal Medicine was achieved in 1992. He has directed the Medical Center's LAF organization since 1993. Dr. Grady serves as a Council Member for AAALAC International. Continuing education includes attendance at national meetings, electronic/computer information sources, institution-sponsored training seminars and reading laboratory animal journals.

Gilly Griffin is the Director of Standards at the Canadian Council on Animal Care, where she has worked for the past 19 years. She trained as a physiologist in the UK and has a background in both biomedical and agricultural research, the common link being the study of insulin and related hormones. Dr. Griffin has also spent many years working to further the concept of the Three Rs: as a research scientist; as managing editor of ATLA, the peer-review journal published by the UK-based Fund for the Replacement of Animals in Medical Experiments; and as Executive Director of the Canadian Centre for Alternatives to Animals in Research. She now heads the Standards sector of the CCAC, where she continues to develop guidelines, champion the principles of the Three Rs, and foster national and international collaborations to improve the ethical use of animals in science.

Donna Matthews Jarrell has managed laboratory animal programs in government, industry, and academia throughout her 24 years in animal program management. She has led programs with operating budgets ranging from $2M - $15M. Donna joined Massachusetts General Hospital (MGH) as the Associate Director, Center for Comparative Medicine (CCM) in late 2002 and was promoted to Director, CCM and the Attending Veterinarian for MGH in January 2013. Over 1/3 of the $700 million plus research budget at MGH involves animal models with research performed by more than 300 Principal Investigators and over 3,000 research staff. The CCM is responsible for providing all laboratory animal and veterinary care in support of these research endeavors. On any given day, there are approximately 100,000 rodents and other species of research animals housed in MGH research facilities. As the Director, she leads a department of ~150 staff, including a senior leadership team, veterinarians, program and facility managers, veterinary technicians, animal care staff and administrative staff. Dr. Jarrell received both her undergraduate and

veterinary degrees from North Carolina State University. She became board certified in the veterinary specialty of Laboratory Animal Medicine in 1996. Donna began her veterinary career working for the National Institutes of Health in Bethesda, Maryland. She served over 10 years as a Commissioned Officer in the Public Health Service, rising to the rank of Lt. Commander. After leaving the government, Dr. Jarrell moved to Massachusetts and served as the Attending Veterinarian and Director of Veterinary Services at a Massachusetts contract research organization and then at Millennium Pharmaceuticals, Inc. in Cambridge. She joined MGH in 2002. One of her greatest accomplishments experienced during her MGH tenure is in leadership and operations management. She introduced the Toyota Production System/Lean Management as the department's operations strategy in 2004 after first learning about it at the Harvard Business School. In 2006 she earned an Executive Education Certificate from The General Managers Program at the HBS. In addition to her duties at the MGH, she has served as an Adjunct Associate Professor at the North Carolina State University College of Veterinary Medicine and at the State University of New York-Delhi where she taught an on-line course in lab operations management. Dr. Jarrell has made numerous presentations at the regional, national and international levels on the topic of TPS/Lean Management in the research & development arena.

David M. Kurtz *(Organizing Committee Co-Chair)* received his veterinary medical degree from the University of Tennessee in 1989. He completed a residency in Laboratory Animal Medicine at the University of Alabama – Birmingham (UAB) in 1993 and obtained a PhD in Molecular and Cellular Pathology in 1998. His doctoral research focused on the molecular aspects of inborn errors of lipid metabolism. Dr. Kurtz performed a post-doctoral fellowship in the Cardiology Division at Washington University School of Medicine in St. Louis (WUSTL) focusing on the regulation of metabolic gene expression by nuclear hormone receptors. At WUSTL, Dr. Kurtz also served as a clinical laboratory animal veterinarian in the Division of Comparative Medicine. He became research faculty at WUSTL in 2000 with research funding from the National Center for Research Resources (NCRR) under a Special Emphasis Research Career Award (SERCA – K01) and the WUSTL Diabetes Research Training – Program Project. From 2003 to 2011, Dr. Kurtz served as the Attending Veterinarian at the U.S. Environmental Protection Agency -National Health and Environmental Effects Research Laboratory in Research Triangle Park, North Carolina and became board certified by the American College of Laboratory Animal Medicine (ACLAM) in 2005. Between 2005 and 2011, Dr. Kurtz also served

as the Attending Veterinarian for The Hamner Institutes of Health Sciences and Integrated Laboratory Systems, Inc. both located in Research Triangle Park, NC. Since 2011, Dr. Kurtz has served as a Staff Scientist in the Comparative Medicine Branch (CMB) of the National Institute of Environmental Health Sciences (NIEHS) and currently is the Head of the Quality Assurance Laboratory.

Neil S. Lipman is Executive Director of the Center of Comparative Medicine and Pathology, serving the Memorial Sloan-Kettering Cancer Center (MSKCC) and the Weill Medical College of Cornell University and is Professor of Veterinary Medicine in Pathology and Laboratory Medicine at Weill Cornell as well as a Laboratory Member at the Sloan-Kettering Institute at MSKCC. Dr. Lipman, a graduate of the University of Pennsylvania's School of Veterinary Medicine, completed postdoctoral training in Comparative Medicine at the Massachusetts Institute of Technology (MIT). He is a Diplomate of the American College of Laboratory Animal Medicine with over 25 years of experience in laboratory animal medicine and science. He has held professional and faculty appointments at MIT, Brown University, Tufts University and the University of Chicago. Dr. Lipman has expertise in vivarium design, engineering, and operations, having designed over 1.5 million gross square feet of vivarium space in the US and overseas. He served on the committee for the update of the Guide for the Care and Use of Laboratory Animals 8th Edition. His research interests are principally translational and include development and analysis of new technologies, the characterization and development of animal models, understanding the etiopathogenesis of endocrine disorders affecting laboratory animal species, and development and analysis of novel therapeutic strategies. Throughout his career, Dr. Lipman has been extensively involved in the postgraduate training of laboratory animal specialists.

Kenneth Litwak is the Laboratory Animal Advisor for the Animal Welfare Institute (AWI), based in Washington, D.C. Prior to joining AWI, Dr. Litwak spent nearly 20 years in academia, as an assistant professor at the University of Pittsburgh and University of Louisville, then as the attending veterinarian at the Cleveland Clinic. He received his DVM from Kansas State University and his Ph.D. from Wake Forest University. He has authored or co-authored over 40 publications.

Paul Locke is an environmental health scientist and attorney, an Associate Professor at the Johns Hopkins University Bloomberg School of Public

Health in the Department of Environmental Health Sciences, and Distinguished Visiting Professor of Animal Law and Science at Lewis and Clark Law School in Portland, Oregon. He holds an MPH from Yale University School of Medicine, a DrPH from the Johns Hopkins University Bloomberg School of Public Health and a JD degree from Vanderbilt University School of Law. Dr. Locke is admitted to practice law in the State of New York and the District of Columbia, and before the Southern District Court of New York and the United States Supreme Court. Dr. Locke's research and practice focus on how decision-makers use environmental health science and toxicology in regulation and policy-making and how environmental health sciences influence the policymaking process. His areas of study include radiation policy, as well as the law of humane science and policy, with an emphasis on how in-vitro and non-mammalian toxicology data can be incorporated into regulatory decision making under US and international laws. He also studies the impact of the legal system on the development of non-mammalian toxicology and alternatives to animals in testing. Dr. Locke directs the School's Doctor of Public Health program in Environmental Health Sciences and is a faculty member of the Center for Alternatives to Animal Testing and the Center for Law and the Public's Health. He has published papers in peer-reviewed journals and law reviews, including the New York University Journal of Environmental Law, The Environmental Law Reporter, ALTEX and the Journal of Toxicology and Environmental Health. Dr. Locke has received several awards, including the Yale School of Public Health Alumni Service Award, and the American Public Health Association Environment Section Distinguished Service Award. He has served on eight National Academy of Sciences (NAS) study committees, including the committee that updated the Guide for the Care and Use of Laboratory Animals. He is a member of the Institute for Laboratory Animal Research (ILAR) Council.

Guy B. Mulder is the Executive Director of Veterinary and Professional Services at Charles River Laboratories and he serves as the Attending Veterinarian for North American Research Models and Services. His responsibilities include regulatory, technical, and clinical oversight of commercial rodent and rabbit production and surgical services. Dr. Mulder is active in numerous professional organizations including American Association for Laboratory Animal Science, American College of Laboratory Animal Medicine, American Society of Laboratory Animal Practitioners, Laboratory Animal Breeders Association, and he serves as an ad hoc site visitor with AAALAC International. Prior to joining Charles River Laboratories, Dr. Mulder was Director and Attending Veterinarian

for University Laboratory Animal Resources at the University of California, Irvine. Before entering the field of laboratory animal medicine, Dr. Mulder practiced small animal medicine in Seattle, Washington. Dr. Mulder is a Diplomate of the American College of Laboratory Animal Medicine. He completed postdoctoral training and received his Master of Science degree in Comparative Medicine from the University of Washington, his DVM degree from Washington State University, and his Bachelor of Science degree from Willamette University.

Randall J. Nelson received a BS in Psychology from Duke University in 1975 and completed his doctoral degree in Anatomy from Vanderbilt University in 1979. Following a postdoctoral fellowship at the University of California at San Francisco, he was a Staff Fellow at the National Institutes of Health, first in the Laboratory of Neurophysiology, and finally in the Laboratory of Neuropsychology, both at NIMH. Dr. Nelson came to The University of Tennessee Health Science Center (UTHSC) in 1984 and is currently Professor of Anatomy and Neurobiology, Associate Vice Chancellor for Research, and Director of the Anatomical Bequest Program. Dr. Nelson served on the UTHSC IACUC for 12 years (three as Chair) before becoming the Director of the Office of Research Compliance ten years ago. He is currently the Institutional Official for Animal Care and Use, an Alternate Responsible Official for Select Agents and is the Human Protections Administrator. He has served as a member of several NIH study sections and was continuously funded for 29 years during which he conducted research into the control of hand movement. Dr. Nelson has been a council member of the Institute for Laboratory Animal Research (ILAR). He served on the ILAR Journal Board, and the committees that developed the ILAR reports on Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research and the Scientific and Humane Issues in the Use of Random Source Dogs and Cats in Research. He was named a National Associate of the National Research Council (NRC) for his pro bono publico work on NRC's behalf. He was a member of the Committee on Animal Research of the Society for Neuroscience and was an ad hoc consultant and is now a specialist for AAALAC. He is a member of the Board of Trustees of SCAW and currently serves as Board President and Interim Executive Director. Dr. Nelson has written several animal research-related modules for the CITI Program and serves on its Program Advisory Committee which functions as one of its governance boards. Dr. Nelson serves his community through active participation as a leader in the Boy Scouts of America. He is an Assistant Scoutmaster,

Council Vice President for Program, Order of the Arrow Chapter Advisor and recently served as a Wood Badge Course Director.

Steven Niemi is Director, Office of Animal Resources for Harvard University's Faculty of Arts and Sciences. With over 35 years of experience in biomedical research and commercial biotechnology, he has held senior management positions in contract drug and device development, gene therapy and genomics start-ups, and laboratory animal care and assurance. Dr. Niemi is a Diplomate and past President of the American College of Laboratory Animal Medicine as well as Chair of the Board of Directors, Massachusetts Society for Medical Research. He also co-chaired the NRC/ILAR Committee on Animal Models for Assessing Countermeasures to Bioterrorism Agents, and chaired the National Institute of Environmental Health Sciences/National Toxicology Program's Scientific Advisory Committee on Alternative Toxicological Methods. In addition, he has served on the boards of the Biotechnology Industry Organization's Food and Agriculture Governing Body, ILAR, Illinois Biotechnology Industry Organization, Massachusetts Biotechnology Council, National Association for Biomedical Research, Public Responsibility in Research & Medicine, and the Scientists Center for Animal Welfare, plus numerous national task forces addressing medical product development and lab animal welfare. Dr. Niemi earned an AB in biology from Harvard College, a DVM from Washington State University, and then received a US Public Health Service National Research Service Award while a Postdoctoral Fellow in the Division of Comparative Medicine at the Massachusetts Institute of Technology. He later completed the Program for Management Development at the Harvard Business School.

Susan Brust Silk is the Director of the Division of Policy and Education in the NIH Office of Laboratory Animal Welfare (OLAW) where she oversees the interpretation of Public Health Service Policy on Humane Care and Use of Laboratory Animals regarding the use of animals in research, testing and training at PHS-Assured institutions. She develops and directs educational programs in the ethical and humane care and use of laboratory animals including the OLAW Online webinar programs and the OLAW web resources. Before joining OLAW, Ms. Silk worked at the NIH National Cancer Institute (NCI), Office of the Director as the Senior Scientific Speechwriter and Special Communication Project Developer. She served the NCI Intramural Program as Senior Animal Policy Advisor and Director of the Office of Mice Advice. Ms. Silk has conducted research

on murine plasmacytomagenesis at NIH NCI and the Karolinska Institute. She directed transgenic mouse core laboratories at both NIH and the Johns Hopkins University School of Medicine. Ms. Silk has an MS in Immunology/Genetics from the University of Maryland, a BFA in Design and Fine Art from the Maryland Institute, College of Art.

Patricia V. Turner *(Organizing Committee Co-Chair)* is a Professor in the Department of Pathobiology and Program Leader of Graduate Studies in Laboratory Animal Science at the University of Guelph. She also manages the campus laboratory animal diagnostic pathology core and provides consultative laboratory animal pathology services. Her research interests include infectious diseases of laboratory animals, the influence of environment on rodent affective state, and anesthesia, analgesia, and euthanasia of laboratory animals. She holds a BSc in Biochemistry from McMaster University, an MSc in Pharmacology from Dalhousie University, a DVM from the Ontario Veterinary College, and a DVSc in Comparative Pathology from the University of Guelph. Following post-doctoral work at McGill University, she worked as Director of Animal Care Services and Assistant Professor of Pathology at Queen's University. She later worked for Warner-Lambert and Pfizer as a toxicology team representative in preclinical safety testing. Turner teaches laboratory animal medicine and pathology, animal welfare, and toxicologic pathology at the University of Guelph and is a Diplomate of the American College of Laboratory Animal Medicine, the American Board of Toxicology, and the European College of Animal Welfare and Behavioural Medicine. She is currently President of the International Association of Colleges of Laboratory Animal Medicine, a Councilor for the World Veterinary Association, and a Council Member for the Association for Assessment and Accreditation of Laboratory Animal Care, International.

Mary Ann Vasbinder received her DVM from the University of Florida in 1995. She attended a residency training program at North Carolina State University from 1995-1997 and became ACLAM board certified in 2001. She served as the Attending Veterinarian at GlaxoSmithKline (GSK), with the Research Triangle Park program from 2006-2010. Mary Ann led a team to establish performance standards for dog care and housing programs for global GSK in 2008. She is now a member of the Office of Animal Welfare, Ethics and Strategy and serves as the Head of Corporate 3Rs Responsibility and Training Strategy. Her professional interests lie in animal housing, global animal care and use programs, environmental enrichment and training programs.

APPENDIX C

STATEMENT OF TASK

An ad hoc committee will plan and conduct a public workshop to examine critical issues pertaining to the concept of performance standards for laboratory animal use. The Guide for the Care and Use of Laboratory Animals (NRC 2011, p 6) defines a performance standard as "a standard or guideline that, while describing a desired outcome, provides flexibility in achieving this outcome by granting discretion to those responsible for managing the animal care and use program, the researcher, and the IACUC [Institutional Animal Care and Use Committee]. The performance approach requires professional input, sound judgment, and a team approach to achieve specific goals." Invited speakers will address the challenges of defining, developing, implementing, assessing and validating performance standards to ensure "optimal practices, management, and operations" (ibid, p 7). The ad hoc committee will develop the workshop agenda, select and invite speakers and discussants, and moderate the discussions. An individually authored summary of the presentations and discussions at the workshop will be prepared by a designated rapporteur in accordance with institutional guidelines.