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Chapter 7 Compliance and Regulatory Programs

Authors

William W. King, Yasmina A. Paramastri, and Javier GuillÁ©n.

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Introduction

The past several decades have witnessed dramatic changes in the regulatory environment involving the use of animals in research and education. A cursory review of citations using the keywords “animal model or animal models” in PubMed (http://www.ncbi.nlm.nih.gov/pubmed) indicates a steady increase in manuscripts involving the use of animals (Figure 7.1). As research findings enhanced collective knowledge and experimental techniques and goals became more sophisticated, scientists demanded greater control of experimental variables. Concerns about variability inherent to animal models, such as housing environment, disease status, procedure-related pain and distress, nutritional stabilization, and sanitation practices, dictated adaptation of recognized *standards* (Box 7.1). As science continues to globalize, reproducibility and comparability provided by the application of accepted standards become increasingly important.

The use of animals for research and teaching has consistently polarized public opinion, and governments have recognized a need for *regulations* to address the ethical responsibility for acknowledging the needs of the animals used for societal purposes (Schwindaman 1999). Regulations therefore provide a means of reassuring the public that animal use is limited to situations of strict necessity and conforms to their demands for providing species-appropriate daily care, reducing avoidable pain and distress, eliminating unnecessary duplication, and preventing illegal activities, such as animal theft.

Therefore, an animal compliance program is simply an oversight system designed to address two fundamental objectives: conformity to established standards as dictated by scientific rigor and assurance of humane animal treatment as demanded by the public (Box 7.2).

Those with management responsibilities for animal care and use programs play an important role in ensuring regulatory compliance and in serving as a primary conduit of communication between the animal users and regulatory authorities. Thus, it behooves the manager to develop a keen awareness and understanding of regulatory oversight and the responsibilities of various institutional and external entities involved, and a basic understanding of pertinent laws, regulations, principles, guidelines, and policies at local, state, national, and international levels. This is no small feat; regulatory complexities have been compared with Russian matryoshka dolls with seemingly unending layers of intricacy (Bayne and Garnett 2008). Knowing where to seek additional information is often the most crucial step. The goal of this chapter is to introduce concepts concerning animal program compliance, describe the entities that are commonly involved, and provide a brief summary of pertinent sources of guidance.

Typical Compliance Programs

Salient Features

Hierarchy of Guidance

To establish a framework for understanding the components of a compliance program, one must be a student of the published work that serves as guidance, including regulations (i.e., codes, rules, decrees, laws, orders, and statutes) and guidelines (e.g., guides, principles, manuals, handbooks, or other sets of instructions). Figure 7.2 depicts a

hierarchy of such information in order of obligation.

- Arguably, an individual's or society's *ethical principles* provide a foundation upon which all other sources of guidance are based. Because simply abiding by regulations does not equate to being ethical (Pimple 2002), these underlying precepts contribute to what is considered acceptable behavior and conduct.
- *Regulations* represent a government's attempt to express the will of the public they serve. Regulatory application may be limited, not only geographically, but also in scope, species, intended purpose, and source of financial support; however, adherence to regulatory requirements is usually not optional.
- *Guidelines* typically provide additional breadth and detail to the concepts introduced in regulations. Frequently, guidelines are considered recommendations; however, when adopted by regulatory bodies, they may become the equivalent of regulations.
- Peer-reviewed *publications* present a nimble source of guidance based on new knowledge or novel interpretation, and frequently yield additional information for specific circumstances. Their application is generally not compulsory, although program managers have an obligation to remain familiar with current information (ILAR 2011a).
- *Industry standards* are relatively subjective and not easily defined, but add useful direct experience and anecdotal evidence, especially in the absence of other guidance.
- *Institutional policies* afford a valuable means of interpreting and applying guidance to specific circumstances. Once established, institutional policies are often supplemented with *practices* outlined in step-by-step *procedures* (e.g., standard operating procedures [SOPs]).

The relevance of the various forms of guidance can be protean. In fact, determining which *must* be used and which *can* be used presents a formidable challenge to the program manager. Applicability is frequently dictated by location and mission of the institution, species utilized, and funding source for the specific project. For example, a U.S.-based pharmaceutical company in Boston using only mice with private funds may be required to follow municipal, state, and some but not all federal regulations. Because of their wider applicability, this chapter focuses primarily on national regulations and guidelines. This should not be interpreted to be a dismissal of other types of guidance when managing a compliance program.

Regulations cannot address all experimental circumstances and may be silent on some issues impacting animal welfare in a complex research environment. This reality requires that program managers maintain at least a cursory knowledge of the guidance typically applied to other institutions or situations. For example, many institutions choose to voluntarily apply a given federal agency's regulations program-wide to enhance consistency, for example, the Public Health Service Policy on Humane Care and Use of Laboratory Animals (PHS Policy), regardless of the funding source (see description below). Similarly, U.S. regulations lack specific recommendations on primary enclosure space for ferrets and numerous other species; the descriptions presented in the European standards (CoE 1986) may provide a useful baseline. While presenting some obstacles, benefits to global harmonization of standards include the use of data to support federal applications to multiple countries, collaborative scientific efforts, and an increase in international transfer of animal models (e.g., genetically engineered mice), which has both transportation and health status implications (ILAR 2004, 2011b, 2012; GuillÁ©n 2014; see also Chapter 8).

Engineering, Performance, Practice, and Professional Standards

When reviewing regulations and guidelines, one should acknowledge the difference between *engineering*, *performance*, *practice*, and *professional standards* (ILAR 2011a), which reflect some of the themes presented in the hierarchy of guidance. Engineering standards are rigid, firmly established, prescribed criteria that represent minimally expected values or ranges of values for a given circumstance. Applying and assessing compliance with such standards is relatively straightforward because deviation beyond the defined units is generally considered unacceptable. Performance standards are goal oriented and defined by a specified outcome, regardless of the means of achieving that outcome. A benefit of a performance standard is its flexibility; that is, as long as the desired result is clearly defined, the user may determine the path to achieve the goal. Note that an important and often overlooked precondition for employing performance standards is objectively measuring the outcome to ensure intended impact (Klein and Bayne

2007).

Historically, regulations have tended to rely heavily on engineering rather than performance standards, although that trend has shifted in recent years. Regardless, contemporary animal compliance programs should incorporate both. Engineering standards are used when required or to provide a baseline; performance standards may be adopted when engineering standards are unavailable, or when acceptable substitutes are identified and, through careful evaluation, prove to be preferable.

Underlying all sources of guidance is the *professional judgment* of the program manager, veterinarian, and other specially trained personnel used to identify and interpret guidance and its application. When evaluating the suitability of standards, the utilization of generally accepted "practice" or "industry standards" and incorporating the experience of competent and qualified scientists and veterinarians becomes indispensable, especially in the absence of established specifications.

Self-Regulation and Trust

Society expects its members to acknowledge their responsibility to obey established rules of order. Similarly, regulatory agencies presuppose a willingness to comply with established standards. Evidence suggests that promoting a culture of compliance by an organization is more effective in determining personal behavior than the existence of rules and regulations (Brønstad and Berg 2011). Therefore, regulatory authorities expect self-regulation by both the institution and individuals within the program (Box 7.3).

In most countries, regulatory authority to use animals in research and education is granted to the institution, not the individual scientist. Similarly, penalties for noncompliance are addressed to the institution, not the individual responsible for the infraction. Thus, to protect the interests of all animal-using scientists, institutions are compelled to develop a comprehensive system of institutional oversight based on a spirit of self-regulation. In some ways, this is purely practical"“no regulatory body could sustain the resources required to police all activities. On the other hand, the fact that self-regulatory systems function effectively illustrates the research community's acknowledgment of its responsibilities to the public.

Self-regulation can only succeed if all parties deliberately and faithfully engage and respectively acknowledge each other's roles. Therefore, the first obligation to the compliance program is to ensure cooperation among those entities involved. For the principal investigator (PI), the nature of modern science dictates a comfort with self-regulation. The processes of grant application, presentation, and publication based on peer review are inherently self-monitoring (Steneck 2007). However, scientists also face a difficult balance pursuing original discovery within regulatory and financial constraints (Bayne and Garnett 2008). Compliance with animal welfare regulations is particularly challenging if those who are regulated simply view compliance programs as another level of bureaucracy, especially if the rationale behind the regulations appears capricious or counterproductive (Dress 2007).

This underscores the need to promote not only a culture of compliance, but also adoption of scientifically based standards. Science-based regulations provide the best means of counteracting concerns over regulatory burden, a topic that has absorbed increasing bandwidth in recent years (Decker et al. 2007; see also Chapter 10). There is no doubt that regulations have benefitted both animal welfare and research data. However, there remains growing concern over the negative impact of excessive regulation. As stated by Thulin and colleagues (2014), regulations "will not be rescinded, and, if history tells us anything, these requirements are likely to become even more stringent."

Although momentum from some initiatives to rectify conflicting regulations and duplicative reporting requirements has abated (Klein and Bayne 2007), U.S. federal agencies acknowledge the benefits of reducing regulatory burden. For example, the National Institutes of Health's (NIH) Office of Laboratory Animal Welfare (OLAW) maintains memoranda of understanding outlining cooperation between the U.S. Department of Agriculture's (USDA) Animal and Plant Health Inspection Service (APHIS) and Food and Drug Administration (FDA) (OLAW 2012), the National Science Foundation (NSF) (OLAW 2015b), and the Department of Veterans Affairs (VA) (OLAW 2013).

Fortunately, the concepts of performance- and science-based standards are correlative. Performance-based standards incorporate developing knowledge without depending on preestablished engineering standards that may not apply to an institution, species, or circumstance (Klein and Bayne 2007). Unfortunately, an unintended side effect may be the creation of overly intricate mechanisms of oversight extending beyond the intent of regulations (DeHaven 2002). If

motivated by absolute risk aversion, institutions may inadvertently or willingly exaggerate the burden of compliance without fully examining or realizing that there may be a lack of benefit to animal welfare, thereby introducing unfortunate opportunities for alienating those who are regulated (Bayne and Garnett 2008; Haywood and Greene 2008; Thulin et al. 2014).

The escalating financial requirements for research should also be considered (CLS 1988). The use of resources for unnecessary compliance programs may hinder the ability to identify improvements in animal care. Reduction in animal use should be directed by increased availability of better alternatives, not simply because of fiscal constraints. Science-based performance standards, which focus on outcomes, can be an important means of improving research cost-effectiveness (Klein and Bayne 2007).

Institutions must bear these concepts in mind. As long as standards can be seen to directly improve animal welfare and research data, regulatory compliance may be viewed as a professional virtue comparable with scientific integrity (DuBois 2004).

Constituents and Their Interaction

Ensuring appropriate oversight of animal care and use involves numerous institutional entities, including not only the PI, but also the institutional official (IO), Institutional Animal Care and Use Committee (IACUC) or equivalent ethical oversight body (EOB), attending veterinarian (AV), and their respective staffs (Box 7.4). Compliance programs also routinely involve analogous oversight of hazardous agent use, such as biological and radiation safety officers and committees, chemical hygienists, and occupational health professionals and emergency preparedness personnel. The organizational structure of animal compliance programs implies a system of checks and balances, drawing benefits from the unique perspectives and expertise of each component. A crucial characteristic of such arrangements is the effective interaction among the above-mentioned parties. An awareness of and commitment to synergy and a sense of common purpose is paramount (see also Chapter 3).

Role of the Principal Investigator

As previously stated, the primary role of the PI in the regulatory program is to recognize the benefits of viewing the compliance program as a partnership and to remain committed to that relationship. The responsibility for actual study conduct obligates the PI to both the funding agency or sponsor and the public through regulatory agencies via the IACUC or EOB. PIs must also acknowledge animal welfare as an ethical and scientific obligation. Given the complexities involved in devising and executing scientific experimentation and managing a laboratory, a team approach utilizing the abilities and skills of professionals with specific expertise is crucial.

Role of the Institutional Official

Accountability for the animal care and use program rests with the IO (ILAR 2011a). The IO is the primary agent committing the institution to abide by the regulations and enforce institutional policies across departmental and divisional boundaries (Potkay and DeHaven 2000; Brown and Shepherd 2014). To meet this responsibility, the IO must maintain adequate authority to not only ensure adequate financial resources for program needs, but also impart a spirit of cooperation and commitment to humane care and use “from the top down.” Given his or her status in the organization, the IO is rarely directly involved in day-to-day management decisions, but appropriately depends on the self-monitoring of the PI, the professional judgment of the AV, and the oversight of the IACUC or EOB. However, the IO cannot completely relinquish operational duties. Lowman (2008) describes the critical elements of the IO as (1) an ability to understand and predict future programmatic research needs and ensure that the animal care and use program is suited to meet those needs, (2) a commitment to and means of assessing both quality and integrity, (3) dynamic engagement in planning and resource development, and (4) an emphasis on accountability.

Role of the Institutional Animal Care and Use Committee or Ethical Oversight Body

To the IACUC or EOB belongs the primary task of overseeing animal welfare compliance. Pertinent guidance agrees that a “jury of peers” is the best entity to (1) compare the likely beneficial outcomes of a study or exercise with the possible induction of unrelieved pain or distress to animal subjects, that is, potential “harm versus benefit analysis”; (2) assess the oversight, management, and ultimate use of animals in the institution; and (3) investigate and resolve alleged instances of noncompliance. The diverse roles and responsibilities of this important committee have been the

subject of numerous texts, to which the reader is referred (Podolsky and Lucas 1999; ARENA and OLAW 2002; Silverman et al. 2014).

A mainstay of IACUC or EOB responsibility is the review of proposed animal use, often summarized in documents referred to as animal use protocols. Written protocols provide the committee membership, which usually consists of other scientists, veterinarians, administrators, and community representatives, with a detailed description of anticipated animal use. This includes not only animal-related procedures, but also the rationale behind the need for the procedures specified, the species and animal models selected, the number of animals requested, and an assurance of addressing and incorporating the "three Rs" (see description below). Committee endorsement provides the PI with the knowledge that, if conducted in accordance with the IACUC- or EOB-approved protocol, all relevant regulatory requirements are met or exceptions are adequately justified.

The IACUC or EOB generally assists the institution in ensuring that personnel have or obtain appropriate training in the tenets of animal care and use and are proficient in the specific procedures they are expected to perform. There are numerous references available to assist the IACUC or EOB in this task (ILAR 1991; Kennedy 2002; Pritt et al. 2004; Dobrovolny et al. 2007; Greene et al. 2007; Medina et al. 2007; Van Zutphen 2007; Rush and Dyson 2014; see also Chapters 5 and 12).

Inadequate composition and function of the IACUC have been a primary source of citations from regulatory authorities in the United States (Potkay and DeHaven 2000). The IACUC or EOB must remain informed and engaged with the animal care and use program; otherwise, the system of institutional self-regulation is threatened. Comprehensive programmatic oversight demands the IACUC's or EOB's intimate familiarity with the daily operation of the animal care and use facilities. Protocol review must be thorough, requiring adequate detail to fully grasp the potential experiences of animals assigned to each experimental group. That said, while expected project outcomes should be readily apparent, the IACUC or EOB should avoid limiting animal-based projects or experiments to those that appear to directly lead to immediate therapeutic findings. The utility of study results may only be apparent in a distant future when viewed as one component of an overwhelmingly complex process (CLS 1988).

Role of the Attending Veterinarian

While international regulations vary in the emphasis assigned to the institutional entities involved in overseeing veterinary care, that is, the veterinary staff, research personnel, or ethics committees, provision of adequate veterinary care is universally recognized as a fundamental element of an appropriately operating animal care and use program (Zurlo et al. 2009). Veterinary professional organizations worldwide acknowledge the importance of the attending or designated veterinarian (Poirier et al. 2015).

The American College of Laboratory Animal Medicine (ACLAM) maintains a position statement on adequate veterinary care (ACLAM 1996). This document outlines key components of a veterinary care program, including a reliance on the professional judgment of specially trained and qualified veterinarians directing programs of disease detection, surveillance, prevention, diagnosis, treatment, and resolution; handling, restraint, the use of anesthetics and analgesics, and euthanasia; surgical and perioperative care; and overall animal well-being. In its position statement, AAALAC International summarizes the *Guide for the Care and Use of Laboratory Animals* (the *Guide*) (ILAR 2011a; see description below) and its interpretation of the AV's role, which also includes assurance of emergency medical care, integration within the IACUC and protocol review, and involvement in ensuring personnel training and proficiency (AAALAC 2016a). These and many other references confirm the need for the AV to retain adequate authority to oversee or assist in the oversight of the overall animal care and use program and to intervene on the behalf of animals in pain or distress beyond that explicitly approved by the IACUC or EOB.

Role of the Program Manager

In many institutions, the role of the manager closely approximates that of the AV, and in fact, these functions may be provided by the same person. Depending on the size and complexity of the program, however, the attention of the AV may be directed primarily to veterinary medical issues and IACUC or EOB responsibilities. This may require the manager to direct centrally provided animal facility and support services, and thereby implement much of the program of daily animal care approved by the IACUC or EOB. As content experts, program managers may also be asked to serve as voting or *ex officio* members of the IACUC or EOB, or at least provide input on committee decisions. Regardless, because all activities that potentially impact animal health and well-being are the purview of the IACUC

or EOB, a healthy working relationship is advisable.

Team Approach to Compliance

Once again, the importance of collegial cooperation among these constituents cannot be overstated. This is best accomplished by generating a "culture of care," which requires an IO with appropriate authority and involvement, an IACUC or EOB willing and able to share its expectations with the research staff, veterinary staff that are seen as colleagues in the research team, and training programs to ensure uniform distribution of these tenets (Klein and Bayne 2007).

Inherent to any compliance system is a potential for conflicts of interest (COIs). COIs, both real and perceived, must be avoided, as their prevalence will erode public confidence in the oversight structure. That said, some COIs are inevitable. In fact, the composition of the IACUC or EOB presents several opportunities for COIs, for example, instances when the IO, AV, or IACUC chair also serves as a PI. Of course, even the AV's or scientists' service on the IACUC or EOB presents a potential for COIs. Notably in academia, PIs are expected to publish their own results while training and collaborating with other scientists, and even reviewing potential competitors' manuscripts and grant applications (Steneck 2007). Although complete elimination is not feasible (Thulin et al. 2014), continued efforts to address avoidable COIs will bolster public perception of a compliance program. Examples may include preventing IO service on the IACUC or EOB, or the AV serving as IACUC or EOB chair, and IACUC or EOB member recusal from voting on protocols for which he or she has a vested interest.

Van Sluyters (2008) illustrates productive cooperation between the IO, AV, and IACUC or EOB via a "three-legged stool"; effective programs depend on the appropriate level of pressure and control by each. Figure 7.3 offers an alternate representation that includes the program manager and PI, depicting the realms of concern and influence as spheres. Each entity involved in the compliance program has its own area of expertise and bias; successful programs encourage these constituents toward central, common objectives.

Program Assessment

The increasing quantity and complexity of regulations present opportunities for noncompliance, especially if the rationale behind certain standards has less obvious direct benefits to science and/or animal well-being. Performing studies or procedures not explicitly described and approved by the IACUC or EOB is considered among the most serious of noncompliance. Mechanisms to detect and prevent noncompliance are paramount, but institutions should also regularly assess the interaction between the PI, IACUC or EOB, and other constituents to minimize weaknesses that may lead to noncompliance. Conditions of grant awards include regulatory compliance, which provides another motivation for ongoing evaluation. Considerable financial ramifications are associated with an animal study out of compliance with IACUC or EOB approval, institutional policies, or regulations (Bayne and Garnett 2008). Advisory committees and confidential surveys can gauge the success of IACUC or EOB oversight (Ingham et al. 2000; Van Sluyters 2008). Using methods frequently adopted by continuous quality improvement programs may also engender PI responsiveness by improving both animal health and data integrity, as well as protocol approval time (Nolte et al. 2008). There are several other means of assessing these working relationships, which include regulatory oversight, voluntary accreditation, and periodic evaluation by the IACUC or EOB, which are often mandated by regulations.

Postapproval monitoring (PAM) is a term gaining in popularity for addressing the institutional responsibility in ongoing oversight of study conduct. The duties of the IACUC or EOB include such monitoring, accomplished via periodic rereview of protocols, routine inspections of facilities and laboratories, and regular evaluation of the overall animal care and use program. Special attention to other IACUC or EOB practices, such as *de novo* protocol and amendment review, investigating reports of animal welfare concerns, and assessing unexpected outcomes, augments the IACUC's or EOB's responsibility for continuing review (Plante and James 2008). Results of evaluations by regulatory authorities, and especially by accrediting agencies (e.g., AAALAC International), provide exceptional assessment of program effectiveness. Given their expertise and intimate familiarity with ongoing studies, the program manager and other support personnel provide important sources of "real-time" information.

To enhance or at least verify self-regulation, many programs have found it necessary or advisable to institute additional study conduct monitoring via specially trained personnel (Banks and Norton 2008; Collins 2008; Dale 2008; Lowman 2008). As discussed in Chapters 10 and 15, PAM can take myriad shapes and complexities and should be tailored to the needs of the program. Regardless of mechanisms used, ensuring open lines of communication and

conducting PAM in a collegial manner is crucial to its success. Any PAM must avoid the appearance as a regulatory mandate without value to each individual researcher and demonstrate to all parties involved, including researchers, the IACUC or EOB, veterinarians, program managers, and institutional safety officers, that the PAM is a resource profiting both animal welfare and scientific results (Dale 2008).

Special Considerations for the Program Manager

As previously stated, the program manager must balance several obligations. As depicted in Figure 7.3, the primary duty is daily operational management, often with a focus on cost-effectiveness. Program managers are also frequently recruited for routine animal health and research-related technical procedures. Furthermore, the program manager is charged with implementing many guidance-driven issues, such as environmental enrichment, social housing, monitoring for pain and distress, and reducing husbandry-related research variables, all of which require careful and continuous attention. This frequently involves compiling uniform practices outlined in SOPs, which encourage consistency. Review of SOPs by the IACUC or EOB also provides an efficient and effective means of augmenting committee oversight (DeHaven 2002).

By definition, research involves change. PIs request new species, models, and methods. Novel situations present opportunities for achieving outcomes. Similarly, innovation in addressing pain and distress evolves. Advances in techniques and methods emerge regularly; programs and program managers must remain current and apply enhancements whenever feasible. The judicious manager benefits from interacting with colleagues and sharing “what works and why.” Fortunately, there are a number of comparative medicine and laboratory animal science societies, associations, and other means of communicating with colleagues with which the manager should be familiar. These associations frequently host continuing education events and often play integral roles in developing guidelines, especially in regions without national regulations. AAALAC International maintains a list of advocacy and educational groups that provides a useful resource (AAALAC 2016b).

A hallmark of adopting performance and professional standards is the ability to apply contemporary and creative processes. Utilization of “best practices” is sensible. However, it is important to recognize that simply because something *can* be done does not mean that it *should* be done. Scientists are appropriately wary of change; change must be driven by superior results and approached cautiously so as to not introduce unexpected variables to ongoing studies. In compliance programs, imprudent fixation on best practices can also lead to regulatory “creep,” or imposing a practice that was deemed necessary for one circumstance or facility onto another. Alternative practices should not simply do no harm or have negligible impact, they should demonstrably improve animal welfare.

The spirit of self-regulation also requires a willingness to self-report. Regulatory authorities expect some level of reporting noncompliance and adverse events to the IACUC or EOB and the governmental agency. In the United States, failure to self-report is among the more common sources of noncompliance cited by regulatory agencies (Potkay and DeHaven 2000). A reluctance to report deviations or departures may result in a loss of credibility or worse”“allowing conditions to negatively influence animal well-being or research results. Conversely, a reputation for excessive reporting beyond regulatory requirements risks loss of the collegial relationship required of compliance programs and the flexibility intrinsic to application of performance standards. When serving as an extension of the IACUC or EOB, this requires careful attention to diplomacy for the program manager. Ensuring that all parties maintain attention to their ultimate shared goals, research standardization and regulatory compliance, will assist in determining the most effective response plan to reported concerns.

Introduction to Regulations Impacting Animal-Based Research

The reader is strongly encouraged to review the source documents for regulations and guidelines that impact their program directly. No summary can provide adequate detail for the issues raised and discussed in these documents. The intent of the remainder of the chapter is to provide an introduction to the extant regulations and guidance documents around the globe and to identify common themes. Note that AAALAC International maintains an impressive collection of links to U.S. and international regulations (AAALAC 2016c).

An introduction to regulations and guiding documents would be remiss without a brief discussion of Russell and Burch’s *The Principles of Humane Experimental Technique* (1959). This historic text is divided into two parts. Part One, “The Scope of Humane Technique,” describes concepts of inhumanity and underlying themes of removing inhumanity. Part Two, “The Progress of Humane Technique,” introduced what has since been referred to as the three

Rs: replacement, reduction, and refinement. Numerous works describe and expand the basic maxims of the three Rs (e.g., Goldberg et al. 1996; Guhad 2005; Brønstad and Berg 2011; Curzer et al. 2013) and encourage their implementation in theory (e.g., Van Zutphen and Van Der Valk 2001; Lloyd et al. 2008; Jennings et al. 2010; Slob 2014; Bratcher and Reinhard 2015; Kramer and Font 2015) and in practice (e.g., Agelan et al. 2008; Kim et al. 2012; Michelini et al. 2014; Lilley et al. 2015), or reflect their influence (e.g., Carlsson et al. 2004; Fenwick et al. 2009; Bayne 2011; Törnqvist et al. 2014).

Briefly, *replacement* strategies include the use of tissue culture, microorganisms, and other models in lieu of live animals. Appropriate study design and analysis of sources of variation address the *reduction* in numbers of animals required. *Refinement* may take many paths, but involves consideration of alternatives to potentially painful procedures and other means of minimizing animal distress. The vast majority of, if not all, regulations, guidelines, and other references to animal use in research, teaching, and testing refer to the fundamental concepts of the three Rs, which have been cited as the primary benchmarks for ensuring public confidence and avoiding unnecessary pain and distress (ILAR 2008).

The Americas

There are several excellent summaries of U.S. regulations, including within the previous edition of this text (Gonder 2002; see also Anderson 2002; Cardon et al. 2012; Silk et al. 2013; Bradfield et al. 2014).

United States

Animal Welfare Act and Regulations

Stimulated at least in part by animal welfare organizations and the general public, as exemplified by a cover article in *Life* magazine investigating pet theft (Wayman 1966), the U.S. Congress passed the Laboratory Animal Welfare Act in 1966 (Public Law [P.L.] 89-544), which primarily addressed the acquisition, transportation, and basic veterinary care of dogs, cats, nonhuman primates, rabbits, guinea pigs, and hamsters (LAWA 1966; Loew and Cohen 2002).

The original 1966 act focused on the acquisition of dogs and cats, and required licensing of dealers and registration by research facilities using these two species. The use of these companion species in research remains a polarizing topic (ILAR 2009). The title of the act was pared to the Animal Welfare Act in 1970 (P.L. 91-579), reflecting an expansion of the species covered; this amendment also broadened the entities requiring licensure and introduced a requirement for annual reports summarizing activities and providing assurance of appropriate animal care (AWA 1970). Amendments to the act in 1976 (P.L. 94-279) broadened the oversight of animal transportation (AWA 1976). In 1985, the Food Security Act (P.L. 99-198) included the Improved Standards for Laboratory Animals Act, which compelled oversight of animal research by an IACUC (AWA 1985). The Pet Theft Act of 1990 (AWA 1990) reemphasized the public concerns over the acquisition of companion animals in research (Anderson 2002). Amendments in 2002 and 2008 clarified the species included in the definition of *animal* and fines levied for violations (AWA 2002, 2008; Cardon et al. 2012).

The text of the Animal Welfare Act is primarily a collection of principles that empower the USDA to develop and implement specific standards within regulations. The regulations are established and enforced by the Animal Care section of APHIS; public input is sought by circulating proposed revisions to standards, followed by accepted revisions, in the *Federal Register*. The regulations are subsequently published in the Code of Federal Regulations (CFR), Title 9, “Animals and Animal Product,” Subchapter A, “Animal Welfare,” Parts 1–4. For use in biomedical research and education, the species covered by the USDA regulations are homeothermic vertebrates excepting traditional farm animals used for production research and rats of the genus *Rattus*, mice of the genus *Mus*, and birds bred specifically for research. Other bird species are covered; however, standards for their use have not been established (USDA 2015a).

The Animal Welfare Regulations are published along with the act in a document internally referred to as the “Animal Care Blue Book” (USDA 2015b). The regulations are divided into four parts: (1) definition of terms, (2) regulations, (3) standards, and (4) rules of practice governing proceedings under the Animal Welfare Act. Part 2 contains 9 subparts. Subpart C pertains specifically to research facilities; other subparts that impact or mention research facilities include (E) identification of animals, (F) stolen animals, (G) records, (H) compliance with standards and holding period, and (I) miscellaneous. Part 3 outlines “specifications for the humane handling, care, treatment, and

transportation" in six subparts for (A) dogs and cats, (B) guinea pigs and hamsters, (C) rabbits, (D) nonhuman primates, (E) marine mammals, and (F) other warm-blooded species.

The regulations contain specific requirements for facility registration; IACUC membership and operation, including review of proposed animal use and semiannual program assessment and facility inspections; investigating animal-related concerns; personnel training and qualifications; the role of the AV and adequate veterinary care; recordkeeping; and annual reports. Emphasis includes avoiding unnecessary pain, distress, and duplicative experiments; considering alternatives to procedures likely to cause pain or distress; and special consideration for multiple major survival surgical procedures. The USDA regulations also oblige institutions to develop means by which animal welfare concerns may be reported and investigated, with stipulations for anonymity and freedom from repercussion, also known as "whistle-blower" protection.

Inspectors for the USDA, termed either veterinary medical officers (VMOs) or animal care inspectors (ACIs), are charged with conducting annual inspections of licensees and registrants (USDA 2015a). In 2013, the USDA released the *Animal Welfare Inspection Guide* (AWIG) (USDA 2013), which replaced the earlier *Research Facility Inspection Guide* and the *Consolidated Inspection Guide* (Bennett et al. 2014). The purpose of the 424-page AWIG "is to provide an aid for APHIS Animal Care personnel when inspecting USDA licensed and registered facilities." Information specifically related to the inspection of research facilities is included in the first seven of the eight chapters of the AWIG. Chapter 9 contains 20 Animal Care policies, also published separately as the *Animal Care Policy Manual* (USDA 2015c), which incorporated the former 2011 *Animal Care Resource Guide*. These documents, along with "fact sheets" covering topics such as a summary of the act, methods of conducting compliance inspections, and appealing inspection findings, may be found at the USDA APHIS Animal Welfare website (USDA 2015d). Note that none of these texts are considered regulations, but are intended to "improve the quality and uniformity of inspections, documentation, and enforcement of the Animal Care Program."

Violations identified during USDA inspections are outlined as noncompliant items in publicly available inspection reports; severe or ongoing violations may result in fines to the institution. Several authors outline effective means of managing the USDA inspection process (e.g., Ingham et al. 2004; Cardon et al. 2012). All emphasize the importance of ensuring that institutional representatives are intimately familiar with not only the regulations, but also the additional guidance available and used by VMOs and ACIs when conducting inspections.

Public Health Service Policy

For decades, participation in the NIH intra- or extramural research program required recipients to follow the recommendations of the *Guide* (ILAR 2011a; see description below) and maintain either accreditation by AAALAC International or a system of internal oversight by an institutional committee (ILAR 1978). In 1985, the Health Research Extension Act (P.L. 99-158) authorized the secretary of Health and Human Services to work with the director of the NIH and develop guidelines for the appropriate use of animals in biomedical research (HREA 1985). Incorporating and supplementing the U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training (IRAC Principles) (IRAC 1985), the subsequent PHS Policy (OLAW 2002) was published in 1986 and revised in 2002 and 2015 (NIH 2015) (Box 7.5).

The PHS Policy applies to any use of live vertebrate animals conducted or supported by PHS agencies, including the NIH, FDA, Centers for Disease Control and Prevention (CDC), and Health Resources and Services Administration (HRSA). Through a memorandum of understanding, institutions supported by the NSF must also employ PHS Policy (OLAW 2015b). Implementation of the policy requires negotiation of an "animal welfare assurance" between OLAW and an institution wishing to conduct PHS-supported activities. The assurance details the institutional animal care and use program and methods used to comply with the PHS Policy. Features such as organizational structure, personnel training and qualifications, and occupational health and safety for personnel are included in the description. While not requiring accreditation by AAALAC International, OLAW categorizes institutions based on accreditation status. Special mechanisms are also in place to ensure compliance with PHS Policy at institutions with no animal care and use program and foreign institutions receiving PHS funding.

In addition to the IRAC Principles, the PHS Policy requires compliance with the Animal Welfare Act and other federal regulations, as applicable; the *Guide* (ILAR 2011a); and the *AVMA Guidelines for the Euthanasia of Animals* (AVMA 2013). OLAW requires that non-U.S. institutions receiving PHS support pledge compliance with the Council for

International Organizations of Medical Sciences (CIOMS) and International Council for Laboratory Animal Science (ICLAS) International Guiding Principles for Biomedical Research Involving Animals (CIOMS and ICLAS 2012; see description below).

The PHS Policy outlines the membership requirements and major functions of the IACUC, including semiannual facility inspections, programmatic reviews, and reports to the IO; approval of PHS-conducted or -supported research projects; and review of animal-related concerns; and otherwise advises the IO. Assured institutions are required to submit an annual report, notify OLAW of protocol suspensions and instances of noncompliance with the policy or *Guide*, and periodically renegotiate the assurance. Through OLAW, PHS performs site visits to assured institutions both "for cause" and on a random basis (Potkay and DeHaven 2000). Federal funding may not be used to support noncompliant activities; failure to abide by PHS Policy is considered a breach of contract. Thus, the impact of noncompliance may range from a single project to the entire institution's ability to use or receive PHS awards.

The OLAW website contains links to these references, as well as a considerable amount of guidance, including, at the time of writing, 36 NIH Guide Notices and 13 "Dear Colleague" letters, 84 frequently asked questions (FAQs), 20 articles penned by OLAW staff, 65 published commentaries on protocol review, and 3 letters to editors. Educational resources include archives of 34 webinars and podcasts, a tutorial on the PHS Policy, training videos, and other resources (OLAW 2015a).

Other Regulations

There are numerous other regulations impacting the use of animals in research and/or employees working in vivaria in the United States. For example, the Food, Drug, and Cosmetic Act, originally legislated in 1938 with significant amendments in 1962 and 1976, regulates the development of drugs, biological products, and medical devices for use in humans and animals (FDA 2015a). This act requires that the FDA ensures that research supporting, or intending to support, applications for such products will be conducted in accordance with the good laboratory practice (GLP) standards (21 CFR, Part 58; Anderson 2002; Gonder 2002; FDA 2015c). The FDA also includes provisions termed "the Animal Rule," for limited market approval of drugs completing animal trials but for which human clinical trials are not ethical or feasible (FDA 2015b). Similarly, research supporting, or intending to support, applications to the Environmental Protection Agency (EPA) for new pesticides must also abide by GLP standards (Anderson 2002).

Other regulations affecting the use of animals in research include the Occupational Safety and Health Act, designed to protect the health of personnel; the Controlled Substances Act, regulating the use of opioids and other substances overseen by the Drug Enforcement Administration; the Atomic Energy Act, controlling the use of radioactive materials; the Radiation Control for Health and Safety Act, regulating the use of medical devices emitting radiation; and the Endangered Species Act, monitoring the use of threatened species (Anderson 2002; Gonder 2002).

As previously mentioned, there are agreements between OLAW and the USDA, FDA, NSF, and VA (OLAW 2012, 2013, 2015b) for sharing compliance reports and other information. Note that in addition to distribution within federal agencies, most compliance reports become available to the general public through the Freedom of Information Act (FOIA) (Potkay and DeHaven 2000).

Numerous states and other municipalities also have laws impacting the use of animals in research, including the use of animals in education, acquisition from humane shelters, and direct oversight, including inspection by local authorities. Many laws also have been promulgated to protect animal-using enterprises. The National Association for Biomedical Research website maintains a list of such statutes (NABR 2016).

The Guide

First published in 1963 as the *Guide for Laboratory Animal Facilities and Care* by the U.S. Public Health Service (Animal Care Panel 1963) and now in its eighth edition, the *Guide* (ILAR 2011a) has become an internationally recognized resource for assisting "institutions in caring for and using animals in ways judged to be scientifically, technically, and humanely appropriate," with recommendations "based on scientific principles and on expert opinion and experience with methods and practices that have proved to be consistent with high quality care." From its inception, the authors of the *Guide* acknowledged the "scientific community's ethical commitment to provide the best possible care for animals used in the service of [hu]man[s] and animals" and highlighted the need for professionally qualified leadership, trained and experienced animal care personnel, and efforts to enhance animal health and well-

being through appropriate facility construction and operation (Animal Care Panel 1963). Subsequent prefaces confirmed the widespread acceptance of the *Guide* by the scientific community and an ongoing commitment to the adoption of high standards. The 1968 *Guide* stated that it intended to extend recently adopted federal legislation by "defining humane care in professional terms and describing the facilities that provide humane care" (ILAR 1968). All editions reconfirm the notion of the shared responsibility between individual scientists and the institution, as well as the concept that nothing should interfere with the conduct of appropriately designed experiments. The latest edition states, "The *Guide* is created by scientists and veterinarians for scientists and veterinarians to uphold the scientific rigor and integrity of biomedical research with laboratory animals as expected by their colleagues and society at large" (ILAR 2011a).

As described previously, PHS Policy requires compliance not only with the IRAC Principles, Animal Welfare Act and Regulations, and other federal regulations, but also with the *Guide* (NIH 2015). The *Guide* is also considered a reference by USDA inspectors (USDA 2013), and is one of the three primary standards used by AAALAC International in evaluating animal care and use programs (AAALAC 2016d). Furthermore, numerous other countries, research sponsors and funding sources, scientific societies, and journal editorial boards require adherence to the recommendations of this text.

The eighth edition of the *Guide* contains five chapters and four appendices. Chapter 1, "Key Concepts," defines *laboratory animal* as "any vertebrate animal (i.e., traditional laboratory animals, agricultural animals, wildlife, and aquatic species) produced for or used in research, testing, or teaching." While the authors state that the *Guide* does not specifically address the use of invertebrates, wildlife used in field studies, or agricultural research or teaching, it "establishes general principles and ethical considerations that are also applicable to these species and situations." This section reconfirms the three Rs and incorporates not only personnel but "policies, procedures, standards, organizational structure, staffing, facilities, and practices put into place" into the institutional animal care and use program.

Chapter 2, "Animal Care and Use Program," outlines the roles and responsibilities of the IO, AV, and IACUC or EOB. It emphasizes the importance of personnel training and education, occupational health and safety, means of investigating and reporting concerns regarding animal welfare, and institutional preparedness for natural disasters and other emergencies.

Recommendations regarding the maintenance of animal housing environments and husbandry practices, such as environmental enrichment, illumination, noise and vibration, and population management, are separated into terrestrial and aquatic animal sections in Chapter 3, "Environment, Housing, and Management." While this section provides some recommended engineering standards that institutions may find useful, the *Guide* repeatedly endorses performance standards, especially for such considerations as available space within the primary enclosure.

Chapter 4, "Veterinary Care," expands on the bulk of the 1963 and subsequent editions of the *Guide* and provides a detailed review of concepts inherent to both individual animal and colony health. The subject matter includes animal procurement and transportation; preventive medicine practices, such as quarantine, acclimation, and health surveillance; and clinical care, including routine and emergency care. The largest section of the chapter is devoted to surgery, outlining recommendations from surgeon training and presurgical planning to postoperative care. This chapter also describes approaches to managing pain and distress via anesthesia, analgesia, and euthanasia.

Recommendations for the construction and maintenance of animal facilities provided the greater part of earlier *Guide* editions and are now included as the final chapter, "Physical Plant." The eighth edition expands discussions on special housing facilities, such as barriers, aquatics, and hazard containment, and special procedural areas for surgery, behavioral observation, imaging, and irradiation.

The Ag Guide

The *Guide for the Care and Use of Agricultural Animals in Agricultural Research and Teaching* (the *Ag Guide*) was first published by the Federation of Animal Science Societies (FASS) in 1988 and revised in 1999. In the latest edition (FASS 2010), the title was changed to *Guide for the Care and Use of Agricultural Animals in Research and Teaching* to reflect a broader application of its recommendations, stating, "Farm animals have certain needs and requirements and these needs and requirements do not necessarily change because of the objectives of the research or teaching activity." The *Ag Guide* endorses the IRAC Principles (1985). The *Ag Guide* is used as a reference for USDA

inspectors (USDA 2013) and is one of the three primary standards used by AAALAC International in its accreditation program (AAALAC 2016d).

The first five chapters of the *Ag Guide* outline key features of institutional animal care and use programs. Chapter 1, "Institutional Policies," describes the roles and responsibilities of the IACUC, and highlights the importance of developing written operating procedures, ensuring biosecurity, and providing attention to personnel qualifications and occupational health. Chapter 2, "Agricultural Animal Health Care," considers veterinary health issues, such as medical care, surgery, restraint, and euthanasia; monitoring for zoonotic diseases and drug residues; and special considerations for genetically modified and cloned animals. Chapters 3 and 4, "Husbandry, Housing, and Biosecurity" and "Environmental Enrichment," respectively, discuss standard practices and environmental management, emphasize biological security and containment, and delineate species-specific recommendations. Chapter 5, "Animal Handling and Transport," provides background information and practical guidance for transporting, moving, and restraining animals to minimize the potential for animal and personnel distress and injury. The remaining six chapters expand the concepts outlined in Chapters 3 through 5 for beef cattle, dairy cattle, horses, poultry, sheep and goats, and swine.

Canada

The *Guiding Principles on the Care of Experimental Animals* was first published in 1961 by the Canadian Federation of Biological Societies (Griffin and Baar 2014). In 1968, the Canadian Council on Animal Care (CCAC) was established with the primary responsibility to create, maintain, and oversee the implementation of high ethical and quality assurance standards for the care and use of experimental animals throughout Canada. The CCAC is a nonprofit, national, peer review organization funded primarily by the Canadian Institutes of Health Research (CIHR) and the Natural Sciences and Engineering Research Council (NSERC), and through participating institutions (CCAC 2016a).

Species under the scope of CCAC oversight include all nonhuman vertebrates and cephalopods. The CCAC establishes recommended practices by its standards program. Policy statements provide basic requirements for animal care and use (CCAC 2016b). The *Guide to the Care and Use of Experimental Animals* (*Guide*) outlines more specific standards and species-specific recommendations (CCAC 1993). Guidelines address specific aspects of program oversight, such as humane endpoints, antibody production, euthanasia, animal procurement, protocol review, personnel training, and use of wildlife, fish, and transgenic, farm, and marine mammals (CCAC 2016c).

A CCAC Certificate of Good Animal Practice (GAP) is earned by institutions that participate in the Assessment and Certification Program (CCAC 2016b,c,d). Using the policy statements, guidelines, and the *Guide*, the Assessment and Certification Committee awards certificates based on reviews conducted by an assessment panel every 3 years.

All Canadian provinces have adopted some legislation regarding the use of animals in research and teaching. For example, in Ontario, animal use is governed by the Animals for Research Act (Griffin and Baar 2014). Although participation in the CCAC certification program is intended to be voluntary, most provinces reference CCAC standards, and several require it. Furthermore, certain sponsors require an institutional certificate as a condition of funding.

Establishing an institutional Animal Care Committee (ACC) is a prerequisite for CCAC eligibility. The ACC is expected to oversee all aspects of animal care and use, including protocol review and approval. ACCs are expected to meet at least twice annually, conduct facility inspections at least annually, and otherwise ensure institutional compliance with veterinary, personnel training, occupational health and safety, and facility maintenance standards.

Latin America

Latin America is an enormous and heterogeneous area with the Spanish language as the main common denominator, except for Brazil, where Portuguese is spoken. Only three countries in Latin America have developed specific laws protecting animals used for research: Brazil, Mexico, and Uruguay. In others, for example, Peru, Venezuela, and Costa Rica, general animal welfare laws contain brief references to research animals. Other countries have no such regulations; the level of care and use in research is left exclusively to institutional and personal commitment.

The Brazilian regulation is known commonly as the "Arouca law" and was issued in 2008 (Brazil 2008). This law mandates the creation of the National Council to Control Animal Experimentation (CONCEA), composed of representatives from several prestigious public institutions and charged with establishing a framework for overseeing

animal care and use. In Mexico, the specific regulation is the Mexican Official Norm for the Production, Care, and Use of Laboratory Animals (NOM-062-ZOO-1999) (Mexico 1999). The law in Uruguay is entitled Use of Animals in Experiments, Teaching and Research Activities Law (No. 18.611) (Uruguay 2009). Similar to Brazil, a National Commission for Animal Experimentation (CNEA) is established to control the use of research animals. These three pieces of legislation mandate a prospective evaluation of all research proposals to be performed by an institutional ethical oversight committee.

In these and other countries lacking specific research animal welfare regulations, professional national and supranational associations and societies play a vital role in developing standards, training personnel, and promoting new legislation. Examples include the Federation of South American Societies for Laboratory Animal Science (FESSACAL) (http://www.fessacal.com/) and the Federation of Hispanic Societies and Associations for Laboratory Animal Science of North America, Central America and Caribbean (FESAHANCCCAL) (http://www.fesahancccal.com/).

Europe

European Union

To understand the regulatory framework in Europe, it is essential to understand the organization of the European countries. The Council of Europe (CoE) comprises most of the European countries (47 of currently 51 independent states), including the 28 European Union (EU) member states. The CoE is intergovernmental, has no legislative powers, seeks voluntary cooperation, and may issue recommendations, agreements, and conventions. One of these conventions is the European Treaty Series 123 (ETS 123) (CoE 1986), which established the foundations for the current research animal protection legal framework across Europe. However, conventions must be voluntarily ratified and signed by CoE members, by which they commit to incorporating them into their national legislation. But as a voluntary process, signature and ratification does not always occur. The current chart of signatures (26) and ratifications (21) is available at http://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/123/signatures.

On the other hand, the supranational EU retains policy-making and legislative powers. The EU issues regulations, requiring direct compliance by member states, and *directives*, which must be transposed into national legislation within a certain time period. The current piece of legislation concerning the protection of animals used for scientific purposes is Directive 2010/63/EU (EP and CEU 2010). This directive has already been adopted by all EU member states, and establishes common requirements for breeders, suppliers, and users in the EU, which must be authorized by, and registered with, the “competent authority” in each member state. However, during the transposition process, member states can implement in a different manner some of the requirements (see example described below). Importantly, although requirements established prior to implementation of the directive may be maintained, member states cannot extend new stipulations beyond those established by the original charge.

Directive 2010/63/EU is based explicitly on the principles of the three Rs (Article 4), and applies to all vertebrates, including independently feeding larval forms and mammalian fetuses from the last third of normal development, as well as live cephalopods. Annex I lists the species that must be purpose bred, which includes traditional laboratory species and others, such as zebrafish. Special attention is paid to the use of nonhuman primates, which is limited to specific purposes (Article 8).

A feasibility study by the European Commission to be finalized before November 10, 2017, will be used to investigate an intent to limit the use of nonhuman primates to the second generation only, that is, the offspring of animals bred in captivity or from self-sustaining colonies. The use of great apes is banned, although a safeguard clause could permit their use in cases of emergency (Article 55).

All procedures must be classified as “nonrecovery,” “mild,” “moderate,” or “severe” on a case-by-case basis using the assignment criteria set out in Annex VIII. The classification of “severe” has implications concerning the reuse of animals (Article 16) and the need to perform a retrospective assessment (Article 39).

Directive requirements for animal care and use (Annex III) are based on ETS 123 Appendix A, guidelines for accommodation and care of animals (CoE 2006). Of particular impact, adoption in the directive transforms recommendations within Appendix A for cage sizes into obligations for EU member states, significantly increasing required minimum cage sizes for many species by comparison with previous standards. Nonetheless, institutions had

to comply with the directive by January 1, 2017.

Other important concepts in the directive include the competence of personnel, who must be adequately educated and trained prior to (1) designing procedures and projects, or performing (2) animal-related procedures, (3) animal care, or (4) euthanasia (Article 22). For the latter three functions, a period of direct supervision to demonstrate competency is required; that is, training itself is not sufficient. In fact, institutions must designate one or several persons responsible for ensuring that staff are trained and supervised until demonstrating competency, and receive continuing education. Note that authority for identifying specific training requirements remains with the member states, and Annex IV lists acceptable methods of performing species-specific euthanasia.

All institutions must also have a designated veterinarian with expertise in laboratory animal medicine charged with advisory duties related to animal treatment and well-being (Article 25). The article allows substitution for the designated veterinarian by a "suitably-qualified expert." This controversial clause was intended to provide flexibility for institutions using only rare species; however, the loophole may be used to justify a lack of an institutional veterinarian. That said, the responsibilities and authority assigned to the designated veterinarian beyond animal medical care are mainly advisory, which includes providing input to the Animal Welfare Body (AWB) (see below) and advice concerning reuse or other nonterminal disposition.

Oversight and ethical review is distributed among several parties, including one or more designated persons bearing the responsibility for overseeing animal care and welfare for the institution. Additionally, institutions must establish an AWB composed of a scientist and the designated responsible individuals for animal care and welfare. The designated veterinarian, or other expert, also provides input to the AWB. Minimum AWB functions include advising on the care and use of animals and implementing the three Rs, assisting in internal operational processes, following the development and outcome of projects, and recommending rehoming schemes (Article 27).

A critical difference compared with oversight systems in other areas of the world is that the project evaluation required for authorization is not assigned to the institutional AWB, but to the "competent authority." This is generally a public entity; however, member states retain some flexibility in identifying others to perform the mandatory project evaluation. This may include designation of the AWB or other institutional ethics committees, or an external body (GuillÁ©n et al. 2015). In any case, project evaluation must be transparent and performed in an impartial manner, and must include, in addition to the customary items (listed in Annex VI), a "harm–benefit analysis," and assessment of the severity classification. Designation of the body responsible for project review exemplifies the flexible implementation and transposition into national legislation from the common framework provided by the directive.

Following evaluation, projects may be authorized for up to 5 years. Final authorization, which generally must not take longer than 40 working days, or 55 in case of great complexity, is granted only at the competent authority level, except in Belgium, where authorization may be granted by the institutional body performing the evaluation. To enhance transparency, nontechnical project summaries produced by the applicant are published anonymously by the competent authorities for general public access.

Competent authorities are required to inspect establishments. Inspections are to be carried out on at least one-third of the user institutions each year in accordance with a risk analysis. However, breeders, suppliers, and users of nonhuman primates must be inspected at least annually.

To facilitate harmonization in the implementation of the directive, the European Commission developed a number of Expert Working Groups (EWGs) that have produced important consensus documents (European Council 2016). These texts, addressing such areas as AWB function, genetically altered animals, inspections and enforcement, nontechnical summaries, project evaluation, and severity assessment, may be adopted by member states and others affected by the directive. Consensus documents involving education and training continue to significantly foster harmonization of practices across member states. Note that ancillary topics such as occupational health and safety and animal transportation are not addressed in Directive 2010/63/EU, but may be presented in other independent pieces of legislation at the EU or national level (GuillÁ©n et al. 2014).

Other European Countries

Many European countries not subjected to the EU Directive have specific legislation. For example, Switzerland has a well-established regulation, including an Animal Welfare Act (FASF 2005) with amendments and ordinances

addressing the care and use of research animals. The act includes both cephalopods and decapods, and abides by the principles adopted by the EU. Project evaluation is performed at the competent authority level, with committees established at the regional (Kanton) level.

Norway also has specific regulations (NMAF 2015) that closely adhere to the EU Directive. Given a relatively high use of fish in research, Norwegian legislation typically expects involvement of a veterinarian, or "fish health specialist" to serve the role of a veterinarian, concepts similar to those in Article 25 of the EU Directive.

Another country that belongs to the CoE but not to the EU, and has neither signed nor ratified ETS 123, is the Russian Federation. Lacking specific legislation, the Russian Laboratory Animal Science Association (Rus-LASA) continues to promote modern animal welfare regulations.

Laboratory animal professionals in Israel have close relationships with European colleagues and participate in European professional organizations, such as the Federation of European Laboratory Animal Science Associations (FELASA) and European Society for Laboratory Animal Veterinarians (ESLAV). Research animal care and use has been legislated in this country since 1994 with the prevention of cruelty to animals law and prevention of cruelty to animals rules (Assembly of Israel 2005; Kalman et al. 2014). The law in Israel is based on a national council appointed by the Minister of Health and the establishment of institutional animal care and use programs overseen by an IACUC appointed by the council. The council can issue rules and guidance; the latest edition of the *Guide* (ILAR 2011a) is used to define the legal framework. As such, animal research oversight closely resembles that in the United States, with the IACUC retaining primary authority and supported by an AV.

Africa

Little can be said on specific legislation on the protection, care, and use of research animals in Africa (Hau 2014). Only general laws concerning animal welfare can be found in some countries, such as Kenya (1983), South Africa (1962), and Tanzania (2008). The most recent, Tanzanian Animal Welfare Act, contains a general reference to the "Five Freedoms" (FAWC 1979) and, more importantly, explicit recognition of the three Rs when addressing animal experimentation. In South Africa, where more laboratory animal research is conducted, there are other less official codes of conduct concerning the care and use of laboratory animals. For example, the South African Medical Research Council published ethical guidelines on the use of animals for research and training (MRC 2004). The South African national standard for the care and use of animals for scientific purposes (SABS 2008) is a voluntary national standard. Minimum standards for research animal facilities are also described within the rules related to the practice of veterinary medicine in this country (DAFF 2015). Personnel who complete training by the British Institute of Animal Technology (IAT), with additional practical training at institutions recognized by the South African Veterinary Council (SAVC), can be registered as laboratory animal technologists.

Given humanitarian needs on the African continent, it is not surprising that laboratory animal legislation has not been prioritized; however, initiatives are underway. Continuing education courses are routinely organized in the Magreb (Tunisia, Algeria). The association ACURET.ORG (2016) is "a multinational, interdisciplinary non-governmental not-for-profit organization, incorporated in Nigeria for the purpose of promoting humane animal care and use for scientific purposes in developing countries, in particular, in Africa" that "values and implements the Principles of the 3Rs as the basis for its promotion."

Asia

People's Republic of China

Regulation of the People's Republic of China for Administration of Laboratory Animals

The Regulation of the People's Republic of China for Administration of Laboratory Animals was approved in 1988 by the state council under Decree No. 2 Order of the State Science and Technology Commission of the People's Republic of China (SSTC 1988). The regulation consists of 8 chapters and 35 articles. It addresses general requirements for the quarantine and control of infectious disease, personnel training and certification, and the import, export, and use of laboratory animals. The term *laboratory animals* under Chapter I, Article 2 of the regulation is defined as "artificially raised and bred animals with controlled microbes and parasites and definite genetic background and clear sources that are used in scientific research, teaching, production, examinations, and other scientific experiments." This definition

does not further limit the definition of species covered, although sections discussing quarantine specifically address handling procedures for wild-caught species before use as laboratory animals. The regulation is applicable to any institution and individual maintaining, raising, breeding, supplying, or using animals for experimental purposes.

Other Standards, Guidelines, and Local Regulations

The Ministry of Science and Technology (MOST) is the government agency that oversees laboratory animal science development in China, and establishes general requirements and guidelines. Detailed requirements and specific topics on animal care and use are described in National Standards of the People's Republic of China, including Laboratory Animals"‘Requirements of Environment and Housing Facilities (GB 14925–2010) (NSPRC 2010a) and Laboratory Animals"‘Microbiological Standards and Monitoring (GB 14922.2–2010) (NSPRC 2010b). Specific standards for animal facilities are described in Architectural and Technical Codes for Laboratory Animal Facilities (GB 50447–2008) (NSORC 2008) and, more recently, Guidelines of Humane Treatment of Laboratory Animals (MOST 2006).

National regulations require institutions using animals to also comply with local regulations. The Municipal/Provincial Science and Technology Commission oversees the care and use of laboratory animals at the local level (e.g., state or province), which includes conducting an annual inspection. MOST's Management of Laboratory Animal License Systems authorizes the local administration office to issue individual and institutional registrations and licenses to conduct animal-based scientific activities. For example, the Beijing Administrative Office of Laboratory Animals (BOALA) administers the Legal Administration Documents for Laboratory Animals in People's Republic of China and Beijing Municipality, which issues licenses in Beijing (BAOLA 2000). Prerequisites to apply for licensure include records of personnel training, certification, and medical evaluation, and quality assurance monitoring. The license is valid for five calendar years.

MOST requires self-monitoring to be performed by an institutional ethical committee, for example, an IACUC (Bayne and Wang 2014). Detailed requirements for ethical committee function and protocol review are regulated by the local authority. MOST guidelines also address animal transportation, with additional guidelines provided in the local regulation. Permits from the Ministry of Forestry are also required for breeding, transporting, and export of nonhuman primates or nonhuman primate tissues (Bayne and Wang 2014).

Taiwan, Republic of China

Animal Protection Act and Enforcement Rules of Animal Protection

The Animal Protection Act was promulgated in 1998 by the Taiwan's Legislative Yuan and last amended in 2011 (COA 2011). The act, which also covers animal transport in general, consists of 6 chapters and 40 articles; implementation of the act is the authority of the Council of Agriculture (COA), to which institutions must submit annual reports. According to the act, *animal* is defined as "a dog, a cat, [or other] vertebrate that is raised and kept by people, including economic animals, experiment[al] animals, pets, and other animals." The scope of scientific application for experimental animals includes "for the purpose of teaching, experiments, manufacturing biological preparations, experimental products, drug or toxic substance, and organ transplantation." Chapter 2 captures humane aspects of animal use. Chapter 3, Articles 15–18, details the scientific application of animals, including the establishment of a care and use committee or panel to oversee the scientific aspects of animal use. The local competent authority's inspector may inspect facilities to review the implementation of the act.

The Enforcement Rules of Animal Protection were promulgated in 2000 and amended in 2013, and include specifications for the types of institutions conducting animal-based scientific activities (COA 2013).

Guidebook and Other Resources

A Guidebook for the Care and Use of Laboratory Animal (*Guidebook*) published by COA in 2010 addresses husbandry and enrichment, veterinary care, physical plant, breeding, occupational health and safety programs, disaster and emergency planning, and species-specific information (Kurosawa et al. 2014). The standards outlined in the *Guidebook* are used by inspection teams for annual evaluation of facilities selected by the COA.

Training courses for IACUC and program management are offered regularly, sponsored by the Chinese Association for

Laboratory Animal Science (CALAS), Chinese Taipei Society for Laboratory Animal Science (CSLAS), and National Laboratory Animal Center (NLAC) (Chen 2008).

Japan

Law of Humane Treatment and Management of Animals

The Law of Humane Treatment and Management of Animals No. 105 was promulgated in 1973; a 2005 amendment endorses the principles of the three Rs (Kurosawa et al. 2014). The law addresses the proper treatment of animals, such as the responsibilities of the owner and registration and inspection requirements for animal-handling businesses. Although articles under the law pertain to all persons engaged in a business involving animals, the term *animal* is limited to mammals, birds, and reptiles.

Standards Relating to the Care and Management of Experimental Animals

The Standards Relating to the Care and Management of Experimental Animals: Experimental Animal Regulation was published in 1980 (Prime Minister's Office 1980). In 2006, the Ministry of Environment released a revision that included specific guidance for the relief of pain (MEJ 2006). The standards define *experimental animal* as "a mammal or bird reared or kept at a facility (including animal being transported to a facility) for use in experiments." The term *experiment* is defined as an "education purpose, experimental research, or manufacture of biotics or other scientific application." The standards address general considerations for transport, basic care, and the health and safety of animals (Kurosawa et al. 2014).

Other Laws and Resources

Additional guidelines are dependent on the jurisdiction and funding agencies applicable to the institution. For example, the basic policy for the conduct of animal experimentation is pertinent for research under the Ministry of Health, Labor and Welfare (MHLW) and the Fundamental Guidelines for Proper Conduct of Animal Experiments (Fundamental Guidelines) are applicable to organizations conducting animal experiments for the Ministry of Education, Culture, Sports, Science and Technology (MEXT 2006).

According to the Fundamental Guidelines, the term *animal* is defined as a mammalian, avian, or reptilian species, for experimentally related activities conducted in academic research institutions. The Fundamental Guidelines address the responsibility of the research institution and the establishment of institutional regulations and an animal experimental committee. The role and responsibility of the animal experimental committee includes protocol review and approval to ensure concurrence with the law and standards, education, training, and self-inspection.

The Guidelines for Proper Conduct of Animal Experiments were developed by the Science Council of Japan in 2006, and serve as an additional support document for activities under both MEXT and MHLW (SCJ 2006). These guidelines define *animal experiment* as "utilization of animals for education, testing, research, manufacture of biological products or other scientific purposes." The guidelines provide additional details regarding IACUC responsibilities and function; animal health, care, and management; and personnel training and safety. Laboratory animals covered under this guideline includes mammalian, avian, or reptilian species.

Use of genetically modified animals is regulated by the Law Concerning the Conservation and Sustainable Use of Biological Diversity through Regulation on the Use of Living Modified Organism (LCCSU 2007).

South Korea

Animal Protection Law

The Korean Animal Protection Act (APA) was first issued by the Ministry of Agriculture and Forestry (MAF) in 1991, and recently amended under the Ministry of Agriculture, Food, and Rural Affairs (Republic of Korea 2014). A broader definition of *animal* has been reduced in the current law to mean "mammals, birds, reptiles, amphibia, and fish, animals that are prescribed by Presidential Decree after discussion between the head of a relevant central administrative agency and the Minister of Agriculture, Food and Rural Affairs."

The revised law contains 47 articles, including establishment of a central Animal Welfare Committee within the

ministry (Article 5), animal transportation (Article 9), and requirements for registration (Article 12). Chapter III (Articles 23–28) discusses animal experimentation, focusing primarily on minimizing animal pain and suffering; considerations for replacing animal models; qualifications of personnel conducting experiments; and reducing the number of animals used. Article 26 mandates the establishment of an ethics committee, termed the Animal Experimentation Ethics Committee, to ensure ethical treatment, and describes the committee's appointment, composition, and other functions. At least one member of the committee is selected by the ministry.

Laboratory Animal Act

The Laboratory Animal Act (LAA), which is overseen by the Ministry of Food and Drug Safety (MFDS), first issued in 2008 and amended in 2010 (LAA 2010), enhances ethical consideration of laboratory animal use and animal testing. Consisting of seven chapters, the LAA mandates that activities comply with the APA, and specifically applies to testing activities involved in "development, safety control and quality control of foods, functional health foods, medical and pharmaceutical products, non-medical and pharmaceutical products, biomedicines, medical appliances, and cosmetics" and "safety control and quality control of narcotics."

The LAA defines *laboratory animal* as a "vertebrate used or raised for the purpose of animal testing." The term *animal testing* means "testing conducted on laboratory animals, or scientific procedures for scientific purposes, such as education, testing, research and production of biological medicines or such."

Chapter II of the LAA describes education of personnel, consideration of alternatives to animal testing, personnel safety, and the establishment of a Laboratory Animal Management Committee to ensure the ethics, safety, and reliability of animal testing. Other chapters cover animal testing facilities, supply of laboratory animals, safety control, and disclosure of records to the public.

India

Prevention of Cruelty to Animals Act

The Prevention of Cruelty to Animals Act of 1960 (Act 59 of 1960) was the first law to legislate animal welfare in India, and was amended by the Central Act 26 of 1982 (PCAA 1982). The term *animal* is defined in the act as "any living creature other than a human being." Legal provision of experimentation on animals is stipulated in Chapter IV, applying to an "animal for the purpose of advancing new discovery of physiological knowledge for saving or prolong[ing] life, alleviating suffering or combating disease of human beings, animals, or plants." With the aim of preventing unnecessary animal pain or suffering, the act (Chapter IV, Section 15) dictates central oversight of animal experimentation by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). CPCSEA is authorized to supervise and control experimental activity, including conducting inspections (Chapter IV, Section 18).

Breeding of and Experiments on Animal (Control and Supervision) Rules

In 1998, the Indian Parliament, through the Ministry of Social Justice and Empowerment, and later the Ministry of Environment and Forestry, reinforced CPCSEA by enacting the Breeding of and Experiments on Animal (Control and Supervision) Rules, which were later amended in 2001 and 2006 (MSJE 1998, 2001; MEF 2006). The definition of *experimental activity* under the 2001 amendments was expanded to include "use of animals for the acquisition of knowledge of a biological, psychological, ethological, physical or chemical nature; and includes the use of animals in the production of reagents and products such as antigens and antibodies, routine diagnostics, testing activities, and establishment of transgenic stock for the purpose of saving or prolonging life, or alleviating suffering, or for combating any disease whether on human being or animals."

The rules (Section 4) mandate registration of animal facilities conducting breeding and/or experimentation. The registrant is subject to inspection by individuals nominated and authorized by CPCSEA. The requirements include establishment of an ethics committee, known as the Institutional Animal Ethics Committee (IAEC), to review and approve the experimental proposals. The composition of IAEC membership, requirements for records, and qualifications for personnel assuming supervisory responsibilities are described in the rules.

The 2001 revision also required compliance with the Indian National Science Academy (INSA) Guidelines for Care

and Use of Animals in Scientific Research (Guidelines). First published in 1992, the INSA Guidelines describe ethical responsibilities and committee review; housing and environment; breeding, genetics, and transgenic animals; animal husbandry and disease control; personnel training; animal transportation; and veterinary care, including anesthesia and euthanasia (INSA 2000).

Recently, CPCSEA released additional guidelines related to the use of animals for experiments, including the CPCSEA Guidelines for Laboratory Animal Facility (CPCSEA Guidelines) (CPCSEA 2003) and CPCSEA Standard Operating Procedures for Institutional Animal Ethics Committees (CPCSEA SOPs for IAEC) (CPCSEA 2010). The CPCSEA Guidelines contain eight annexures addressing requirements for veterinary care programs, responsibilities of the veterinarian, and anesthesia and euthanasia; personnel training and occupational health and safety; animal restraint, husbandry, and social environment; animal environment control and physical plant; transportation; transgenic animal use; and special procedures for using biological hazards. The CPCSEA SOPs for IAEC were issued in 2010 to ensure quality, consistency, and compliance with the rules and act in the function of the IAEC and its review mechanisms. This comprehensive document stipulates the IAEC objectives, role and function, membership composition, appointment, authority, and requirements for quorum, record keeping, and reporting. Functions of the IAEC include the review and approval of proposed animal use prior to implementation; conducting facility inspections, and submission of reports to CPCSEA. The IAEC is responsible for monitoring research activities and ensuring their compliance with the rules and act.

CPCSEA establishes an official animal experiment proposal form in the “Application for Permission for Animal Experiments (Form B)” and “Checklist for Protocol.” While the IAEC is authorized to approve experimentation involving rodents and rabbits, use of other species requires additional approval by the CPCSEA National Committee, based on a positive recommendation from the IAEC.

IAEC membership includes at least one nonaffiliated member appointed by CPCSEA, also known as the nominee of CPCSEA. All IAEC decisions occur after discussion in a meeting that meets quorum; the presence of the nominee of CPCSEA member is mandatory.

The CPCSEA also provides a “Checklist for Inspection” to assist in conducting facility reviews, and an experimental animal health record describing maintenance of animal receipt, medical and experimental procedures, and rehabilitation efforts. Annual reports to CPCSEA include copies of IAEC minutes and facility inspection reports. Animal procurement, including importation of rodents for research purposes, requires certificates issued by CPCSEA after approval by the IAEC.

The 2006 revision of the rules requires investigators to consider rehabilitation rather than euthanasia for animals used in nonterminal studies, excluding those resulting in an inability to resume natural function or persistent pain, or those involving exposure to hazardous agents posing a risk to humans and other animals. Aftercare and/or rehabilitation is specifically described in the Recommendations of the Sub-Committee on Rehabilitation of Animals after Experimentation Set Up by CPCSEA (CPCSEA 2006).

Thailand

The National Research Council of Thailand (NRCT) has issued regulations applicable for animal care and use for scientific purposes in the *Ethical Principles and Guidelines for the Use of Animals for Scientific Purposes* (*Ethical Guidelines*), the *Fundamental Principles of Designing Animal Care and Use Facilities for Scientific Work* (*Fundamental Principles*), and the *Standards for Institutional Animal Care and Use Committees* (*IACUC Standards*) (NRCT 2006).

The *Ethical Guidelines* reflect revision of the *Ethics for Animal Experimentation* of 1999, which were developed primarily based on the CIOMS International Guiding Principles for Biomedical Research Involving Animals of 1985 (Gettayacamin et al. 2014). The *Ethical Guidelines* define the term *animal* as wildlife or vertebrate laboratory animals. *Laboratory animal* is defined as “animals that are procreated and nurtured in confinement, and are used by human[s] for the benefit of any branch of science and technology,” and is applicable to both animal users and breeders. The document expands the concepts of the three Rs, in five ethical principles: addressing alternatives to animal models, minimizing animal numbers, conserving wildlife, avoiding unnecessary pain and distress, and compliance with animal experimental protocols. General precepts in animal transportation, facilities, husbandry, and health; personnel qualifications; and reliability of equipment are described.

Monitoring implementation of the ethical principles is to be conducted at both the institutional and national level. Institutions using animals in research, testing, the production of biological materials, and teaching must establish an ethics committee to oversee and ensure adherence to the guidelines. Committee responsibilities include establishing SOPs, review and approval of projects involving animal use, monitoring animal use activities, and providing training and continuing education of personnel.

The NRCT appoints the National Committee for Research Animal Development (NCRAD) to monitor and promote the ethical use of animals in scientific activities. In addition, editorial boards of academic journals are advised to request detailed information for research paper submission, including genetic background, justification of animal numbers, animal care, and protocol approval by the institutional ethics committee. In 2009, the NRCT also issued *Fundamental Principles*, which provides recommended standards for facility design, physical plant, animal environment, and personnel safety. *IACUC Standards* addresses IACUC membership and function, and emphasizes IACUC responsibility in accordance with the *Ethical Guidelines* (Gettayacamin et al. 2014).

Singapore

Animals and Birds Act and Animals and Birds (Care and Use of Animals in Scientific Purposes) Rules

The Animals and Birds Act originally enacted under Ordinance 3 of 1965 covered the use of any mammal (other than humans), bird, fish, other living creature, or those categorized under the class of animal, including genetically modified animals (ABA 2002). The Animals and Birds (Care and Use of Animals in Scientific Purposes) Rules, passed by the Ministry for National Development of Singapore, limited the definition of *animal* to “any live vertebrate, including any fish, amphibian, reptile, bird, and mammal [other than] human beings” (AVA 2004).

Prerequisites for transporting, holding, or using animals for scientific purposes include an AV, an appropriately constituted IACUC, a process for approving animal-related projects, and licenses issued by the Agri-Food and Veterinary Authority (AVA). The appointment, membership, and function of the IACUC are stipulated in Rules 7 and 8, and include semiannual review of the animal care and use program, annual inspection of the research facility, investigating reports of noncompliance, and PAM. Rule 11 specifies requirements for the AV and adequate veterinary care, including specifications for training and experience. Licensees submit an annual report to the AVA and are required to immediately report suspected disease outbreaks or unusual mortality levels.

National Advisory Committee for Laboratory Animal Research Guidelines

The AVA also requires compliance with the National Advisory Committee for Laboratory Animal Research (NACLAR) Guidelines on the Care and Use of Animals for Scientific Purposes (NACLAR Guidelines) (NACLAR 2004) for facilities housing or using vertebrates for teaching, field trials, environmental studies, research, diagnostics, product testing, and production of biological products. The NACLAR Guidelines are comprised of (1) the Guiding Principles for the Care and Use of Animals in Scientific Purposes (Guiding Principles), which address humane care and use, including appendices for fish and nonhuman primates, (2) Guidelines for the Institutional Animal Care and Use Committee (IACUC Guidelines); and (3) training guidelines.

The Guiding Principles detail animal housing and management, animal procurement and transportation, veterinary care, and IACUC responsibilities (Chapter 8). An AV licensed by the AVA must be part of the program and has authority to oversee animal care and use.

Additional functions of the IACUC are described in the IACUC Guidelines. Oversight function at the institutional level is maintained by the IACUC. Their responsibilities include protocol review and approval of proposed animal activities, semiannual program review, annual inspection of animal housing and procedure areas, and annual reporting to AVA ensuring compliance with and describing IACUC-approved exemptions to the Guiding Principles.

The training guidelines outline recommendations for all personnel involved in the animal care and use program, including researchers, animal facility personnel, and IACUC members. IACUC members are required to attend the Responsible Care and Use of Laboratory Animals Course within 12 months of appointment. Occupational health and safety is also addressed, and must comply with biosafety standards issued by the Ministry of Health and the Ministry of Manpower.

Other Guidelines

Supported by the Genetic Modification Advisory Committee (GMAC) guidelines, the GMAC is responsible for overseeing the transportation and use of genetically modified organisms (GMOs) (GMAC 2013).

Malaysia

As of this writing, the proposed Malaysian Code of Practice for the Care and Use of Animals for Scientific Purposes has been developed by the Laboratory Animal Science Association of Malaysia (LASAM) and adopted by many research institutions and the National Bioethics Council (Gettayacamin et al. 2014; LASAM 2016).

The term *animal* under the proposed code is applied to any member of the animal kingdom and includes "any mammal (other than [hu]man), bird, reptile, amphibian, fish, mollusk, arthropod, and other vertebrate or invertebrate, whether alive or dead, and the egg, young or immature from thereof." The scope envelops all aspects of animal care and use in scientific activities, "in medicine, biology, agriculture, veterinary or other animal science, industry and teaching," and in "research, teaching, field trials, product testing, diagnosis, the production of biological products and environmental studies."

The proposed code endorses the three Rs and stipulates an institutional ethics committee. It describes the investigator responsibilities; animal housing, transportation, and veterinary care; and personnel qualification and training; and outlines principles and recommended engineering standards for animal space and environmental control. Section 2 provides a comprehensive description of IACUC appointment, responsibility, membership, proposal review processes, monitoring, and reporting functions.

Indonesia

Animal Welfare Law

The Law of Republic Indonesia No. 6, issued in 1967, specifies animal welfare in Article 22 (LRI 1967). The law was replaced in 2009 by the Law of the Republic Indonesia No. 18, which includes sections devoted to veterinary public health and animal welfare (Chapter VI), and veterinary authority in laboratory animal and comparative medicine (Chapter VII, Article 74). The term *animal* under this law (Chapter VI, Part 2, Article 66) includes both vertebrates and invertebrates. It governs the housing, care, handling and restraint, transportation, use, euthanasia, and humane treatment of animals (LRI 2009).

Regulation and Guidelines for Care and Use of Animals for Scientific Purposes

Principles of the ethical treatment of animals in comparative medicine are described in the government of the Republic of Indonesia Regulation No. 95 (GRIR 2012). Detailed guidelines for laboratory animal care and use in biomedical research supported by the Ministry of Health were developed by the Health Research Ethics Committee, and consist of (1) National Guidelines on Health Research Ethics (HREC 2011a) and (2) *Teaching Guide Book for Ethics on Health Research* (*Teaching Guide Book*) (HREC 2011b). The guidelines and *Teaching Guide Book* address the three Rs and the "Five Freedom Principles" (hunger and thirst; discomfort; pain, injury, and disease; fear and distress; and expression of natural behaviors) (FAWC 1979), and other aspects of an animal care and use program.

The guidelines describe appointment and oversight responsibilities of a veterinarian, competency and training for personnel involved in animal care and use, behavior and environmental management, and occupational health and safety. Mandated oversight by the Health Research Ethics Committee is limited to governmental institutions under the Ministry of Health; however, most other academic and private research institutions have voluntarily established ethics committees in accordance with the guidelines.

Philippines

Animal Welfare Act

The Animal Welfare Act (Republic Act No. 8485) was enacted by Congress in 1998 (AWA 1998) and amended in 2013 (AWA 2013). Animal experimentation is briefly addressed under Section 6.

Rules and Regulation on the Conduct of Scientific Procedures Using Animals

Following the act, the Department of Agriculture Administrative Order No. 40 (AO No. 40) Series of 1999 requires the registration of institutions using animals for research and scientific procedures, excluding animal clinical tests for evaluating veterinary products. A formal animal care and use program overseen by an IACUC is required to obtain authorization. Additionally, the Rules and Regulations on the Conduct of Scientific Procedures Using Animals govern the use of animals for scientific purposes (RPDA 1999).

The rules define *animal* as "any live vertebrate (domestic or wild) that is used or intended for use in scientific purpose[s]." Pertinent activities include biomedical research, teaching and instruction, product testing, and the production of antisera or other biologicals. The rules describe requirements for authorization, and detail appropriate euthanasia procedures for commonly used species and agents. Annexes include specific guidance for the IACUC, including composition, obligations, protocol review, and inspection processes (Annex A); the application for authorization (Annex B); and a description of the animal care and use program (Annex C), which includes veterinary medical care, husbandry, physical environment, personnel qualification, and physical plant; and a standardized animal care and use statement/protocol review form.

Other Regulations and Guidelines

The Code of Practice for the Care and Use of Laboratory Animals (COP) developed by the Philippine Association of Laboratory Animal Science (PALAS), is applicable to animals used in biomedical research, teaching, testing, and the production of biological products. It references and affirms both the CIOMS International Guiding Principles for Biomedical Research Involving Animals (CIOMS and ICLAS 2012) and the *Guide* (ILAR 2011a). The COP is endorsed by local regulatory agencies and includes standards for husbandry, occupational health and safety, training, and the ethics committee; transportation, housing, and environmental enrichment; and veterinarian responsibilities, veterinary care, and euthanasia methods (Gettayacamin et al. 2014). Authorization for use of animals is granted by the director of the Bureau of Animal Industry (BAI) under the Department of Agriculture, and presumes adherence to PALAS COP and ethics committee approval (Gettayacamin et al. 2014).

Cambodia

Chapter 7.1 of the OIE *Terrestrial Animal Health Code* (OIE 2015) is generally adopted by government and academic research institutions in Cambodia. Permits to export nonhuman primates are authorized by the Ministry of Agriculture, Forestry and Fisheries (MAFF), and enforced by the Forestry Administration (FA) and the Department of Animal Health and Production (DAHP). Regular inspections of nonhuman primate breeding and holding facilities are conducted by the veterinary authority of FA and DAHP (Gettayacamin et al. 2014).

Australasia

Australia

Australian Code for the Care and Use of Animals for Scientific Purposes

The *Australian Code for the Care and Use of Animals for Scientific Purposes* (the *Code*) was first developed in 1969 to promote the ethical, humane, and responsible care and use of research animals. The most recent revision of the *Code*, the eighth edition, was released in 2013 (ARC 2013). Although the *Code* serves as guidance, adherence to the *Code* is mandated for institutions receiving funding from the National Health and Medical Research Council (NHMRC) (Schofield et al. 2014). The *Code* applies to all scientific activities involving animals, defined as "all activit[ies] conducted with the aim [of] acquiring, developing, or demonstrating knowledge or techniques in all area[s] of science." This includes the use of animals for teaching, field studies, the generation of animal lines with undefined genetic impact on animal well-being, disease diagnosis, biological agent production, and product testing, noting that the latter is precluded from NHMRC funding (NHMRC 2016). The definition of *animal* according to the *Code* includes "any live nonhuman vertebrate (that is fish, amphibians, reptiles, birds, mammals, encompassing domestic animals, purpose-bred animals, livestock, wildlife), and cephalopods." Some territories and states may include other species under local legislation.

Awareness of and compliance with the *Code* and acceptance of specified responsibilities is required of institutions, including the Animal Ethics Committee (AEC) and all personnel involved in any aspect of the animal care and use program. The *Code* applies throughout the involvement of the animal in the scientific activities, from acquisition,

transport, and breeding until the ultimate disposition, and requires that all involved in the care and use of animals maintain compliance with other relevant and applicable commonwealth, state, and territory legislations. The *Code* is comprised of six sections: (1) governing principles, (2) responsibilities, (3) animal well-being, (4) care and use of animals for the achievement of educational outcome in science, (5) complaints and noncompliance, and (6) independent external review of the operation of institutions.

Section 2 of the *Code* stipulates the responsibilities of the institution, investigators, animal care personnel, and AEC, which is given primary responsibility for ensuring that all animal care and use activities are conducted in accordance with the *Code*. The AEC must review applications for proposed animal care and management, monitor animal care and use activities, take appropriate action regarding unexpected adverse events and noncompliance, and establish institutional guidelines for animal care and use. The *Code* specifies activity monitoring methods, such as inspection of animals, animal housing areas, and procedures, and review of records and reports. The AEC is expected to determine the frequency and timing of inspections in which the nonaffiliated member should participate. This section also outlines institutional responsibilities regarding occupational health and safety related to the animal care and use program.

Animal importation, discussed in Section 3, requires authorization by the Australian Department of Agriculture, Fisheries and Forestry, and Quarantine Inspection Service. Air transportation of genetically modified and exotic animals is subject to commonwealth, state, and territory regulation as well. Although the *Code* does not enumerate training, qualifications, or experience requirements for veterinary expertise, the availability of veterinarians to advise and oversee the veterinary care program is specifically outlined.

Section 4 of the *Code* describes standards for primary enclosures, husbandry, environmental control and maintenance, and emergency action plans. Additional standards for housing, including environmental enrichment, are generally specified by state and territory animal welfare legislation.

The *Code* mandates an independent external review to be conducted at least every 4 years. Details on the coordination, membership requirements, and duties of the review panel are specified in Section 6 of the *Code* (ARC 2013).

NHMRC Guidelines

Other guidelines have been developed by the NHMRC to supplement the *Code*. Like the *Code*, these documents are mandatory for institutions receiving funding from the NHMRC.

The Guidelines to Promote the Well-Being of Animals Used for Scientific Purposes: The Assessment and Alleviation of Pain and Stress in Research Animals (NHMRC 2008a) provides background material, basic strategies, and fact sheets to advance the well-being of animals use for scientific purposes. Parts of this document also discuss appropriate means of euthanasia, anesthesia, and analgesia, and use of anxiolytics. An additional reference frequently cited for euthanasia is *Euthanasia of Animals Used for Scientific Purposes* by the Australian and New Zealand Council for the Care of Animals in Research and Teaching (ANZCCART 2001).

Other relevant references developed by NHMRC include *A Guide to the Care and Use of Australian Native Mammals in Research and Teaching* (NHMRC 2014), Policy on the Use of Non-Human Primates for Scientific Purposes (NHMRC 2003), Guidelines for the Generation, Breeding, Care and Use of Genetically Modified and Cloned Animals for Scientific Purposes (NHMRC 2007), Guidelines on the Use of Animals for Training Interventional Medical Practitioners and Demonstrating New Medical Equipment and Techniques (NHMRC 2009a), Guidelines for Monoclonal Antibody Production (NHMRC 2008a), and Guidelines on the Care of Dogs Used for Scientific Purposes (NHMRC 2009b).

Local Legislation

While compliance with the *Code* is only required for institutions receiving funding from NHMRC, animal welfare regulations impacting the use of animals in research exist for states and territories, which adhere to its principles and guidelines. For example, the New South Wales Animal Research Review Panel Guidelines encompass several aspects of animal care and use, such as species-specific care and housing standards, acquisition of dogs and cats, use of feral animals in research, and production of monoclonal antibodies. Institutions in Victoria are referred to the Code of Practice for Housing and Care of Laboratory Mice, Rats, Guinea Pigs, and Rabbits and the Code of Practice for the Use of Animals from Municipal Pounds in Scientific Procedures (Schofield et al. 2014).

Ethical review and oversight functions by an AEC, as outlined in the *Code*, are required by all states and territories. Facility licensing and registration is also required in all states and territories for institutions that use, breed, supply, or hold certain species for scientific purposes. An annual report of compliance with the *Code* is required.

Training and education for animal users, care staff, and AEC members are described in both the *Code* and regional legislation. Resources for AEC members are specifically available from the ANZCCART and animal welfare units in certain states, such as Queensland, New South Wales, and Victoria. Training for new or inexperienced personnel working with nonhuman primates must be arranged in consultation with NHMRC National Nonhuman Primate Breeding Colonies.

Other Guidelines

GMOs, including laboratory animals, are regulated under the Commonwealth of Australia Gene Technology Act of 2000, which addresses licensing, certification, accreditation, advisory and ethics committees, and inspections (GTA 2014); Gene Technology Regulations 2001, which include standards for containment and monitoring activities (GTR 2001); and the Guidelines for the Transport, Storage and Disposal of GMOs (DHA 2011).

New Zealand

Animal Welfare Act

New Zealand's Animal Welfare Act was promulgated in 1999 (Public Act No. 142) and has been amended several times, most recently in 2015 (NZAWA 1999, 2015). The term *animal* under the act is defined as "any live member of the animal kingdom," that is, a mammal, bird, reptile, amphibian, or fish; octopus, squid, crab, lobster, or crayfish; any other member as specified by the governor general, by order in council; and any mammalian fetus, or avian or reptilian prehatched young that is in the last half of its period of gestation or development. Use in research includes any work involving the manipulation of animals in investigative, experimental, diagnostic, toxicity, or potency testing; in producing antisera or other biological products; and in teaching. The act specifically prohibits the use of animals in any research, testing, or teaching for the purpose of developing, making, or testing cosmetics, or an ingredient that is intended exclusively for use in cosmetics.

Part 6 of the act, entitled "Use of Animals in Research, Testing, and Teaching," dictates that any person wishing to use animals in research is required to both have a project approval from the IAEC and maintain an approved code of ethical conduct (CEC) document. The CEC is authorized by the director general of the Ministry of Agriculture and Forestry (MAF), based on the recommendation from the National Animal Ethics Advisory Committee (NAEAC), and is issued for up to 5 years (NZAWA 1999). The CEC holder is generally the chief executive officer of an institution. To assist applicants, the NAEAC released the *Guide to the Preparation of Codes of Ethical Conduct* (NAEAC 2012). The AEC functions on behalf of the CEC holder, reviewing applications for project approval and monitoring compliance with the conditions of the project and with CEC. Part 6 also details the AEC membership composition and reporting of noncompliance. The act specifies restrictions to and classification of surgical procedures, including conditions applied when personnel other than veterinarians perform surgical procedures.

Good Practice Guide for the Use of Animals in Research, Testing, and Teaching

The most recent edition of the *Good Practice Guide for the Use of Animals in Research, Testing, and Teaching* (*Practice Guide*) was published by the NAEAC in 2010 (NAEAC 2010). The *Practice Guide*, which is intended to expand and supplement the act, applies to all aspects of the care and use of animals in scientific activities in medicine, biology, agriculture, veterinary and other animal science, industry, and education. The *Practice Guide* describes standards for animal acquisition and transportation; environmental enrichment and facility management, including special considerations for farm animals; recommendations for personnel qualifications, training, and staffing levels; hazard communication; and the responsibilities of investigators and instructors using animals.

Other Guidelines and Standards

The *Practice Guide* provides general guidance and principles related to animal euthanasia; detailed guidelines are published in *Euthanasia of Animals Used for Scientific Purposes* (ANZCCART 2001). Similarly, expanded information regarding animal transport is described in International Air Transport Association (IATA) regulations and

"Transport of Animals within New Zealand" by the National Animal Welfare Advisory Committee (2011).

Genetically modified animal use is overseen by the Hazardous Substances and New Organism Act of 1996 and the Biosecurity Act of 1993. Requirements for facility construction, operation, and semiannual internal review, and periodic MAF audits are specified in MAF Biosecurity Authority Standard 154.03.03: Containment Facilities for Vertebrate Laboratory Animals (MAF 2002). Authorization from the Ministry of Primary Industries is required to transfer genetically modified animals (Schofield et al. 2014).

Multinational Guidance

AAALAC International

The American Association for the Accreditation of Laboratory Animal Care (AAALAC) was conceived by the Animal Care Panel, which became the American Association for Laboratory Animal Science (AALAS) as a means of supporting high-quality science by ensuring humane animal care and use, and thereby assuring the general public that research was conducted appropriately (AAALAC 2016e). The organization was incorporated in 1965 as a not-for-profit association conducting voluntary reviews of animal care and use programs. In 1996, the name was changed to the Association for the Assessment and Accreditation of Laboratory Animal Care International (AAALAC International), to reflect a rapidly growing interest in the benefits of accreditation worldwide. Most recently, the association discontinued defining the acronym to avoid overinterpretation of the term *laboratory* and uses "AAALAC International" as its official title (AAALAC 2016e). The AAALAC International mission statement reads, "AAALAC International is a voluntary accrediting organization that enhances the quality of research, teaching, and testing by promoting humane, responsible animal care and use. It provides advice and independent assessments to participating institutions and accredits those that meet or exceed applicable standards" (AAALAC 2016f).

Governing the organization is a Board of Directors appointed by delegates from more than 60 member organizations that share AAALAC's core values. The board appoints internationally recognized experts in laboratory animal medicine, science, and use as members of the Council on Accreditation, who conduct triennial reviews leading to a determination of accreditation status. These reviews include on-site evaluation of institutions for initial or continuing accreditation, using three primary standards: the *Guide*, the *Ag Guide*, and ETS 123. Augmenting these standards are numerous reference resources acknowledged by the council (AAALAC 2016g), eight position statements summarizing the council's interpretation of high-impact issues (AAALAC 2016h), and at the time of this writing, 58 frequently asked questions (AAALAC 2016i).

Accreditation is discussed in more detail in Chapter 9. While not a regulatory organization, accreditation provides an extraordinarily valuable means of program assessment.

Terrestrial Animal Health Code

Another organization seeking to advance common animal welfare principles is the World Organization for Animal Health (OIE). Headquartered in Paris, the OIE is recognized by the World Trade Organization, represents 180 member countries, and is "the intergovernmental organization responsible for improving animal health worldwide" (OIE 2016). Among its contributions are research animal welfare standards described in the *Terrestrial Animal Health Code* (OIE 2015), which specifically endorses the three Rs and a system of oversight by independent institutional, regional, or national ethical review entities (see also Chapter 8).

International Guiding Principles for Biomedical Research Involving Animals

Two additional associations with similar interests include the CIOMS (2016) and the ICLAS (2016). In 2012, these organizations published the International Guiding Principles for Biomedical Research Involving Animals (CIOMS and ICLAS 2012). This document shares many of the same principles as the OIE *Terrestrial Animal Health Code*, such as an affirmation and application of the three Rs in ethical reviews of proposed animal use, including minimizing opportunities for pain and distress and incorporation of humane endpoints, and the importance of personnel competency and provision of veterinary care (see also Chapter 8).

Summary

Although it is tempting to justify practices "because the regulations require it," managers are urged to view

compliance as a by-product of the partnership between and pursuit of common goals by the PI, IO, AV, and IACUC or EOB, and thereby serve as a *tool for validating* their efforts (see also Chapter 10). Applying accepted standards to animal care and use encourages consistency and minimizes the potential for animal pain and distress, thereby meeting both scientific and ethical obligations. Oversight, including that provided by external reviewers, such as regulators and accrediting bodies, and the outcome of their scrutiny should be used to foster and confirm the existence of a well-managed program with those two symbiotic objectives.

References

AAALAC International. 2016a. The attending veterinarian and veterinary care. http://www.aaalac.org/accreditation/positionstatements.cfm#vetcare (accessed February 11, 2016).

AAALAC International. 2016b. Advocacy and education. http://www.aaalac.org/resources/links.cfm#advocate (accessed February 11, 2016).

AAALAC International. 2016c. International regulations and resources. http://www.aaalac.org/resources/internationalregs.cfm (accessed February 12, 2016).

AAALAC International. 2016d. About AAALAC. http://www.aaalac.org/about/guidelines.cfm (accessed February 12, 2016).

AAALAC International. 2016e. About AAALAC, history. http://www.aaalac.org/about/history.cfm (accessed February 11, 2016).

AAALAC International. 2016f. AAALAC international mission statement. http://www.aaalac.org/about/mission.cfm (accessed February 11, 2016).

AAALAC International. 2016g. AAALAC's reference resources. http://www.aaalac.org/accreditation/resources.cfm (accessed February 11, 2016).

AAALAC International. 2016h. Position statements. http://www.aaalac.org/accreditation/positionstatements.cfm (accessed February 11, 2016).

AAALAC International. 2016i. Frequently asked questions. http://www.aaalac.org/accreditation/faq_landing.cfm (accessed February 11, 2016).

ABA (Animals and Birds Act). 2002. The statutes of the Republic of Singapore. http://statutes.agc.gov.sg/aol/download/0/0/pdf/binaryFile/pdfFile.pdf?CompId:b39eb414-ccf3-415e-8b4d-541340b82590 (accessed February 13, 2016).

ACLAM (American College of Laboratory Animal Medicine). 1996. Adequate veterinary care. https://www.aclam.org/education-and-training/position-statements-and-reports (accessed January 20, 2016).

ACURET.ORG. 2016. https://www.linkedin.com/in/acuret-org-5a4215b2 (accessed February 15, 2016).

Agelan, A., A.S.Braverman, G.E.Dean, and M.R.Ruggieri. 2008. Refinement in the management of the denervated canine urinary bladder using an abdominal vesicostomy. ILAR J49(4): E8–E14. [PMC free article: PMC3277083] [PubMed: 18506057]

Anderson, L.2002. Laws, regulations, and policies affecting the use of laboratory animals. In Laboratory Animal Medicine, ed. J.G.Fox, L.C.Anderson, F.M.Loew, and F.W.Quimby, 19–33. 2nd ed., American College of Laboratory Animal Medicine Series. San Diego: Academic Press/Elsevier Science.

Animal Care Panel. 1963. Guide for Laboratory Animal Facilities and Care. Washington, DC: U.S. Government Printing Office.

ANZCCART (Australian and New Zealand Council for the Care of Animals in Research and Teaching). 2001. Euthanasia of Animals Used for Scientific Purposes. 2nd ed. https://www.adelaide.edu.au/ANZCCART/publications/Euthanasia.pdf (accessed February 13, 2016).

ARC (Australian Research Council), National Health and Medical Research Council, Australian Government. 2013. Australian Code for the Care and Use of Animals for Scientific Purposes. 8th ed. https://www.nhmrc.gov

.au/_files_nhmrc/publications/attachments/ea28_code_care_use_animals_131209.pdf (accessed February 13, 2016).

ARENA and OLAW (Applied Research Ethics National Association and the Office of Laboratory Animal Welfare). 2002. Institutional Care and Use Guidebook. 2nd ed. Bethesda, MD: Office of Laboratory Animal Welfare. [PubMed: 12271329]

Assembly of Israel. 2005. Prevention of cruelty to animals laws (experiments on animals; 5754–1994) and the prevention of cruelty to animals rules (experiments on animals; 5761–2001). www.weizmann.ac.il/vet/Law.htm (accessed February 13, 2016).

AVA (Agri-Food and Veterinary Authority of Singapore). 2004. Animals and birds (care and use of animals for scientific purposes) rules. http://www.ava.gov.sg/docs/default-source/legislation/animals-and-birds-act/19web_ab_careanduseofanimalsforscientificpurposesr.pdf (accessed February 13, 2016).

AVMA (American Veterinary Medical Association), Panel on Euthanasia. 2013. AVMA Guidelines for the Euthanasia of Animals. 2013 ed. https://www.avma.org/KB/Policies/Documents/euthanasia.pdf (accessed February 13, 2016).

AWA (Animal Welfare Act). 1970. P.L. 91-579, United States. Approved December24, 1970.

AWA (Animal Welfare Act). 1976. Amendments. P.L. 94-279, United States. Approved April22, 1976.

AWA (Animal Welfare Act). 1985. Food Security Act. P.L. 99-198, United States. Approved December23, 1985.

AWA (Animal Welfare Act). 1990. Food, Agriculture, Conservation, and Trade Act. P.L. 101-624, United States. Approved November28, 1990.

AWA (Animal Welfare Act). 1998. Republic Act No. 8485, Republic of Philippines. http://www.paws.org.ph/uploads/2/1/2/7/21275318/:ra8485_animal_welfare_act.pdf (accessed February 13, 2016).

AWA (Animal Welfare Act). 2002. Farm Security and Rural Investment Act. P.L. 107-171, United States. Approved May13, 2002.

AWA (Animal Welfare Act). 2008. Food, Conservation, and Energy Act. P.L. 110-246, United States. Approved June18, 2008.

AWA (Animal Welfare Act). 2013. Amendment. Republic Act No. 10631, Republic of Philippines. http://www.gov.ph/2013/10/03/republic-act-no-10631/ (accessed February 13, 2016).

Banks, R.E., and J.N.Norton. 2008. A sample postapproval monitoring program in academia. ILAR J19(4): 402–418. [PubMed: 18849594]

BAOLA (Beijing Administrative Office of Laboratory Animals). 2000. Legal administration documents for laboratory animalS in People's Republic of China and Beijing municipality. English translation. http://www.aaalac.org/intlRefs/IntRegs/China/P.R.%20China/Legal%20Administration%20Documents%20for%20Lab%20Animals.PDF (accessed February 8, 2016).

Bayne, K.2011. The IACUC's impact on advancing best practices and the three R's. ILAR J52(Suppl): 436–439.

Bayne, K., and N.Garnett. 2008. Mitigating risk, facilitating research. ILAR J49(4): 369–371. [PubMed: 18849589]

Bayne, K., and J.Wang. 2014. Oversight of animal research in China. In Laboratory Animals: Regulations and Recommendations for Global Collaborative Research, ed. J.GuillÁ©n, 244–266. San Diego: Academic Press/Elsevier.

Bennett, B.T., A.D.Cardon, and M.R.Bailey. 2014. USDA Animal Welfare Inspection Guide. Lab Anim (NY)43(6): 191. [PubMed: 24844998]

Bradfield, J.F., B.T.Bennett, and C.S.Gillett. 2014. Oversight of research animal welfare in the United States. In Laboratory Animals: Regulations and Recommendations for Global Collaborative Research, ed. J.GuillÁ©n, 5–59. San Diego: Academic Press/Elsevier.

Bratcher, N.A., and G.R.Reinhard. 2015. Creative implementation of the 3Rs principles within industry programs: Beyond regulations and guidelines. J Am Assoc Lab Anim Sci54(2): 133–138. [PMC free article: PMC4382616] [PubMed: 25836958]

Brazil (Presidência da República, Casa Civil, Subchefia para Assuntos Jurídicos Brazil). 2008. Lei No. 11.794 de 8 de Outubro, 2008 (Arouca law). http://www.planalto.gov.br/ccivil_03/_ato2007-2010/2008/lei/l11794.htm (accessed February 11, 2016).

Brønstad, A., and A.G.Berg. 2011. The role of organizational culture in compliance with the principles of the 3Rs. Lab Anim40(1): 22–26. [PubMed: 21173772]

Brown, M., and M.J.Shepherd. 2014. Reporting lines of the IACUC. In The IACUC Handbook, ed. J.Silverman, M.A.Suckow, and S.Murthy, 39–43. 3rd ed. Boca Raton, FL: CRC Press.

Cardon, A.D., M.R.Bailey, and B.T.Bennett. 2012. The Animal Welfare Act: From enactment to enforcement. J Am Assoc Lab Anim Sci51(3): 301–305. [PMC free article: PMC3358977] [PubMed: 22776186]

Carlsson, H.E., J.Hageline, and J.Hau. 2004. Implementation of the ”three Rs’ in biomedical research. Vet Rec154(15): 467–470. [PubMed: 15143737]

CCAC (Canadian Council on Animal Care). 1993. Guide to the Care and Use of Experimental Animals. Vol. 1, 2nd ed. Ottawa. http://www.ccac.ca/Documents/Standards/Guidelines/Experimental_Animals_Vol1.pdf (accessed February 8, 2016).

CCAC (Canadian Council on Animal Care). 2016a. About the CCAC. http://www.ccac.ca/en_/about (accessed February 8, 2016).

CCAC (Canadian Council on Animal Care). 2016b. Policy statements. http://www.ccac.ca/en_/standards/policies (accessed February 8, 2016).

CCAC (Canadian Council on Animal Care). 2016c. Guidelines. http://www.ccac.ca/en_/standards/guidelines (accessed February 8, 2016).

CCAC (Canadian Council on Animal Care). 2016d. CCAC certification. \http://www.ccac.ca/en_/assessment/certification (accessed February 8, 2016).

Chen, H.H.2008. The past to present animal use and current animal protection law in Taiwan. Japanese Society for Alternative in Animal Experiments. AATEX J14: 743–748.

CIOMS (Council for International Organizations of Medical Sciences). 2016. About us. http://www.cioms.ch/index.php/2012-06-07-19-16-08/about-us (accessed February 2016).

CIOMS and ICLAS (Council for International Organizations for Medical Sciences and International Council for Laboratory Animal Science). 2012. International guiding principles for biomedical research involving animals. http://iclas.org/wp-content/uploads/2012/10/CIOMS-ICLAS-Principles-Final.pdf (accessed February 15, 2016).

CLS (Commission on Life Sciences), Committee on the Use of Laboratory Animals in Biomedical and Behavioral Research, National Research Council. 1988. Use of Laboratory Animals in Biomedical and Behavioral Research. Washington, DC: National Academies Press. [PubMed: 25032311]

COA (Council of Agriculture), Executive Yuan Republic of China (R.O.C. Taiwan). 2011. Taiwan Animal Protection Act. http://law.coa.gov.tw/GLRSnewsout/EngLawContent.aspx?Type=E&id=120 (accessed March 28, 2017).

COA (Council of Agriculture), Executive Yuan Republic of China (R.O.C. Taiwan). 2013. Enforcement rules of animal protection. http://law.coa.gov.tw/GLRSnewsout/EngLawContent.aspx?Type=E&id=151 (accessed March 28, 2017).

CoE (Council of Europe). 1986. European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes. European Treaty Series 123. Strasbourg, France: CoE.

CoE (Council of Europe). 2006. Appendix A of the European Convention for the Protection of Vertebrate

Animals Used for Experimental and Other Scientific Purposes (ETS No. 123). Guidelines for accommodation and care of animals (Article 5 of the convention). Approved by the multilateral consultation. Strasbourg, France: CoE.

Collins, J.G.2008. Post approval monitoring and the Institutional Animal Care and Use Committee (IACUC). ILAR J49(4): 388–392. [PubMed: 18849592]

CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals). 2006. Recommendations of the Sub-Committee on Rehabilitation of Animals after Experimentation Set Up by CPCSEA. http://hhcro.org/down/Rehabilitation%20of%20animals%20Guidelines.pdf (accessed February 13, 2016).

CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals). 2003. CPCSEA guidelines for laboratory animal facility. Indian J Pharmacol35: 257–274.

CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals). 2010. Standard operating procedures for Institutional Animal Ethics Committees (IAEC). http://cpcsea.nic.in/WriteReadData/userfiles/file/SOP_CPCSEA_inner_page.pdf (accessed February 13, 2016).

Curzer, H.J., M.C.Wallace, G.Perry, P.J.Muhlberger, and D.Perry. 2013. The ethics of wildlife research: A nine R theory. ILAR J54(1): 52–57. [PubMed: 23904532]

Dale, W.E.2008. Postapproval monitoring and the role of the compliance office. ILAR J49(4): 393–401. [PubMed: 18849593]

Decker, R.S., L.Wimsatt, A.G.Trice, and J.A.Konstan. 2007. A profile of federal-grant administrative burden among federal demonstration partnership faculty. A report of the Faculty Standing Committee of the Federal Demonstration Partnership. http://sites.nationalacademies.org/cs/groups/pgasite/documents/webpage/pga_054586.pdf (accessed January 22, 2016).

DeHaven, W.R.2002. Best practices for Animal Care Committees and animal use oversight. ILAR J43(Suppl): S59–S62. [PubMed: 12388853]

DAFF (Department of Agriculture, Forestry, and Fisheries). 2015. Commencement of the Veterinary and Para-Veterinary Professions Amendment Act (Act Number 15 of 2012). Government Gazette29380, November9, 2015.

DHA (Department of Health and Ageing), Office of the Gene and Technology Regulator. 2011. Guidelines for the transport, storage and disposal of GMOs. http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/tsd-guidelines-toc/$FILE/tsd-guidelines.pdf (accessed February 13, 2016).

Dobrovolny, J., J.Stevens, and L.V.Medina. 2007. Training in the laboratory animal science community: Strategies to support adult learning. ILAR J48(2): 75–89. [PubMed: 17420529]

Dress, N.K.2007. The realities of conducting laboratory animal research. Psychological Science Agenda. http://www.apa.org/science/about/psa/2007/01/dess.aspx (accessed January 8, 2016).

DuBois, J.M.2004. Is compliance a professional virtue of researchers?Reflections on promoting the responsible conduct of research. Ethics Behav14(4): 383–395. [PubMed: 16625734]

EP andCEU (European Parliament and the Council of the European Union). 2010. Directive 2010/63/EU of the European Parliament and of the council of 22 September 2010 on the protection of animals used for scientific purposes. Off J Eur Union 2010: L276/33–79.

European Council. 2016. Consensus documents. http://ec.europa.eu/environment/chemicals/lab_animals/interpretation_en.htm (accessed June 23, 2016).

FASF (Federal Assembly of the Swiss Federation). 2005. Animal Welfare Act.

FASS (Federation of Animal Science Societies). 2010. Guide for the Care and Use of Agricultural Animals in Research and Teaching. 3rd ed. Champaign, IL: FASS.

FAWC (Farm Animal Welfare Council). 1979. Five freedoms. http://webarchive.nationalarchives.gov.uk/20121007104210/http:/www.fawc.org.uk/freedoms.htm (accessed February 15, 2016).

FDA (Food and Drug Administration). 2015a. Federal Food, Drug, and Cosmetic Act. Title 21, Chapter 9. http://www.fda.gov/RegulatoryInformation/Legislation/default.htm (accessed December 16, 2015).

FDA (Food and Drug Administration). 2015b. Product development under the animal rule: Guidance for industry. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm399217.pdf (accessed December 16, 2015).

FDA (Food and Drug Administration). 2015c. Good laboratory practice for nonclinical laboratory studies. http://www.ecfr.gov/cgi-bin/text-idx?SID=ea9665b648fb85cd46b99bbd0e5337ff&mc=true&node=pt21.1.58&rgn=div5 (accessed December 16, 2015).

Fenwick, N., G.Griffin, and C.Gauthier. 2009. The welfare of animals used in science: How the “three Rs” ethic guides improvements. Can Vet J50(5): 523–530. [PMC free article: PMC2671878] [PubMed: 19436640]

Gettayacamin, M., R.Grant, I.Winoto, D.Sajuthi, Y.Paramastri, J.Khoo, P.Chatikavanij, J.Villano, and A.R.Mutalib. 2014. Laws, regulations, guidelines, and principles pertaining to laboratory animals in South East Asia. In Laboratory Animals: Regulations and Recommendations for Global Collaborative Research, ed. J.GuillÁ©n, 296–332. San Diego: Academic Press/Elsevier.

GMAC (Genetic Monitoring Advisory Committee). 2013. Singapore biosafety guidelines for research on genetically modified organisms (GMOs)http://www.gmac.gov.sg/pdf/Research/Singapore%20Biosafety%20Guidelines%20for%20GMO%20Research_Jan%202013.pdf (accessed February 13, 2016).

Goldberg, A.M., J.Zurlo, and D.Rudacille. 1996. The three Rs and biomedical research. Science272: 1403. [PubMed: 8633221]

Gonder, J.C.2002. Regulatory compliance. In Management of Laboratory Animal Care and Use Programs, ed. M.A.Suckow, F.A.Douglas, and R.H.Weichbrod, 163–185. Boca Raton, FL: CRC Press.

Greene, M.E., M.E.Pitts, and M.L.James2007. Training strategies for Institutional Animal Care and Use Committee (IACUC) members and the institutional official (IO). ILAR J48(2): 131–142. [PubMed: 17420534]

Griffin, G., and M.Baar. 2014. Canada’s oversight of animal use in science. In Laboratory Animals: Regulations and Recommendations for Global Collaborative Research, ed. J.GuillÁ©n, 61–93. San Diego: Academic Press/Elsevier.

GRIR (Government of the Republic of Indonesia). 2012. Regulation No. 95. Veterinary Public Health and Animal Welfare.

GTA (Gene Technology Act). 2014. Australian government. https://www.comlaw.gov.au/Details/C2014C00587 (accessed February 13, 2016).

GTR (Gene Technology Regulation). 2001. Australian government. https://www.comlaw.gov.au/Details/F2011C00732 (accessed February 13, 2016).

Guhad, F.2005. Introduction to the 3Rs (refinement, reduction, and replacement). Contemp Top Lab Anim Sci44(2): 58–59. [PubMed: 15812977]

GuillÁ©n, J., ed. 2014. Laboratory Animals, Regulations and Recommendations for Global Collaborative Research. San Diego: Academic Press/Elsevier.

GuillÁ©n, J., J.B.Prins, D.Smith, and A.-D.Degryse. 2014. The European framework on research animal welfare regulations and guidelines. In Laboratory Animals, Regulations and Recommendations for Global Collaborative Research, ed. J.GuillÁ©n, 117–188. San Diego: Academic Press/Elsevier.

GuillÁ©n, J., S.Robinson, T.Decelle, C.Exner, and M.Fentener van Vlissingen. 2015. Approaches to animal research project evaluation in Europe after implementation of Directive 2010/63/EU. Lab Anim44(1): 23–31. [PubMed: 25526056]

Hau, A.R., F.A.Guhad, M.E.Cooper, I.O.Farah, O.Souilem, and J.Hau. 2014. Animal experimentation in Africa: Legislation and guidelines. In Laboratory Animals, Regulations and Recommendations for Global Collaborative Research, ed. JavierGuillÁ©n, 117–188. San Diego: Academic Press/Elsevier.

Haywood, J.R., and M.Greene. 2008. Avoiding an overzealous approach: A perspective on regulatory burden. ILAR J49(4): 426–434. [PubMed: 18849596]

HREA (Health Research Extension Act). 1985. P.L. 99-158. Approved November20, 1985.

HREC (Health Research Ethics Committee). 2011a. National guidelines on health research ethics. Ministry of Health, Republic of Indonesia.

HREC (Health Research Ethics Committee). 2011b. Teaching Guide Book for Ethics on Health Research. Ministry of Health, Republic of Indonesia.

ICLAS (International Council for Laboratory Animal Science). 2016. Mission. http://iclas.org/about-iclas (accessed February 15, 2016).

ILAR (Institute for Laboratory Animal Research), National Research Council. 1965. Guide for Laboratory Animal Facilities and Care. Washington, DC: U.S. Government Printing Office.

ILAR (Institute for Laboratory Animal Research), National Research Council. 1968. Guide for Laboratory Animal Facilities and Care. Washington, DC: U.S. Government Printing Office.

ILAR (Institute for Laboratory Animal Research), National Research Council. 1978. Guide for the Care and Use of Laboratory Animals. Washington, DC: U.S. Government Printing Office. [PubMed: 25121211]

ILAR (Institute for Laboratory Animal Research), National Research Council. 1991. Education and Training in the Care and Use of Laboratory Animals: A Guide for Developing Institutional Programs. Washington, DC: National Academy Press. [PubMed: 25144011]

ILAR (Institute for Laboratory Animal Research), National Research Council. 2004. The Development of Science-Based Guidelines for Laboratory Animal Care: Proceedings of the November 2003 International Workshop. Washington, DC: National Academies Press. [PubMed: 20669462]

ILAR (Institute for Laboratory Animal Research), National Research Council. 2008. Recognition and Alleviation of Distress in Laboratory Animals. Washington, DC: National Academies Press. [PubMed: 20669418]

ILAR (Institute for Laboratory Animal Research), National Research Council. 2009. Scientific and Humane Issues in the Use of Random Source Dogs and Cats in Research. Washington, DC: National Academies Press. [PubMed: 20662127]

ILAR (Institute for Laboratory Animal Research), National Research Council. 2011a. Guide for the Care and Use of Laboratory Animals. 8th ed. Washington, DC: National Academies Press. [PubMed: 25121211]

ILAR (Institute for Laboratory Animal Research), National Research Council. 2011b. Animal Research in a Global Environment: Meeting the Challenges: Proceedings of the November 2008 International Workshop. Washington, DC: National Academies Press. [PubMed: 22514813]

ILAR (Institute for Laboratory Animal Research), National Research Council. 2012. International Animal Research Regulations: Impact on Neuroscience Research: Workshop Summary. Washington, DC: National Academies Press. [PubMed: 22934322]

Ingham, K.M., K.Field, and J.Mackta. 2004. Managing inspections: Guidance to biomedical research facilities. Contemp Top Lab Anim Sci43: 60. [PubMed: 15181913]

Ingham, K.M., J.A.Goldberg, H.J.Klein, R.G.Johnson, and M.D.Kastello. 2000. A novel approach for assessing the quality and effectiveness of IACUC oversight in investigator compliance. Contemp Top Lab Anim Sci39(1): 28–31. [PubMed: 11178312]

INSA (Indian National Science Academy). 2000. Guidelines for care and use of animals in scientific research.

https://www.scribd.com/document/216973822/INSA-Guidelines-for-Care-and-Use-of-Animals-for-Research (accessed March 28, 2017).

IRAC (Interagency Research Animal Committee). 1985. U.S. government principles for the utilization and care of vertebrate animals used in testing, research, and training. Federal Register50: 97. https://grants.nih.gov/grants/olaw/references/phspol.htm (accessed February 12, 2016). [PubMed: 11655791]

Jennings, M., D.B.Morton, E.Charton, J.Cooper, C.Hendriksen, S.Martin, M.C.Pearceet al.2010. Application of the three Rs to challenge assays used in vaccine testing: Tenth report of the BVAAWF/FRAME/RSPCA/UFAW Joint Working Group on Refinement. Biologicals38(6): 684–695. [PubMed: 20724180]

Kalman, R., A.Harmelin, E.Ziv, and Y.Fischer. 2014. Israeli legislation and regulation on the use of animals in biological and medical research. In Laboratory Animals, Regulations and Recommendations for Global Collaborative Research, ed. J.GuillÁ©n, 189–204. San Diego: Academic Press/Elsevier.

Kennedy, B.W.2002. Management of education and training programs. In Management of Laboratory Animal Care and Use Programs, ed. M.A.Suckow, F.A.Douglas, and R.H.Weichbrod, 15–77. Boca Raton, FL: CRC Press.

Kenya. 1983. Prevention of Cruelty to Animals Act.

Kim, S.H., S.B.Kim, G.H.Yang, and C.H.Rhee. 2012. Mouse compound muscle action potential assay: An alternative method to conduct the LD50 botulinum toxin type A potency test. Toxicon60(3): 341–347. [PubMed: 22613167]

Klein, H.J., and K.A.Bayne. 2007. Establishing a culture of care, conscience, and responsibility: Addressing the improvement of scientific discovery and animal welfare through science-based performance standard. ILAR J48(1): 3–11. [PubMed: 17170491]

Kramer, M., and E.Font. 2015. Reducing sample size in experiments with animals: Historical controls and related strategies. Biol Rev Camb Philos Soc92(1): 431–445. [PubMed: 26565143]

Kurosawa, T.M., J.H.Park, and C.C.Hong. 2014. Laws, regulations, guidelines and principles pertaining to laboratory animals in Far East Asia. In Laboratory Animals: Regulations and Recommendations for Global Collaborative Research, ed. J.GuillÁ©n, 268–294. San Diego: Academic Press/Elsevier.

LAA (Laboratory Animal Act), Republic of South Korea. 2010. http://www.mfds.go.kr/eng/eng/index.do?nMenuCode=16&searchKeyCode=131&page=1&mode=view&boardSeq=67031 (accessed February 10, 2016).

LASAM (Laboratory Animal Science Association of Malaysia). 2016. Proposed Malaysian code of practice for the care and use of animals for scientific purposes. http://www.lasam.org.my/sites/default/files/resources/document/Code%20of%20Practice.%20-%20Proposed%20for%20Malaysia.pdf (accessed February 10, 2016).

LAWA (Laboratory Animal Welfare Act). 1966. P.L. 89-544, United States. Approved August24, 1966.

LCCSU (Law Concerning the Conservation and Sustainable Use of Biological Diversity through Regulation on the Use of Living Modified Organism). 2007. English translation. https://www.env.go.jp/en/laws/nature/law_ccsubdrlmo.pdf (accessed February 10, 2016).

Lilley, E., R.Armstrong, N.Clark, P.Gray, P.Hawkins, K.Mason, N.López-Salesansky, A.K.Stark, S.K.Jackson, C.Thiemermann, and M.Nandi. 2015. Refinement of animal models of sepsis and septic shock. Shock43(4): 304–316. [PubMed: 25565638]

Lloyd, M.H., B.W.Foden, and S.E.Wolfensohn. 2008. Refinement: Promoting the three Rs in practice. Lab Anim42(3): 284–293. [PubMed: 18625583]

Loew, F.M., and B.J.Cohen. 2002. Laboratory animal medicine: Historical perspectives. In Laboratory Animal Medicine, ed. J.G.Fox, L.C.Anderson, F.M.Loew, and F.W.Quimby, 1–17. 2nd ed., American College of Laboratory Animal Medicine Series. San Diego: Academic Press/Elsevier Science.

Lowman, R.P.2008. The institutional official and postapproval monitoring: The view from 10,000 feet. ILAR

J49(4): 379–387. [PubMed: 18849591]

LRI (Law of Republic Indonesia) No. 6. 1967. Article 22.

LRI (Law of Republic Indonesia) No. 18. 2009. Chapters VI–VII.

MAF (Ministry of Agriculture and Forestry), New Zealand. 2002. Containment facilities for vertebrate laboratory animals. Biosecurity Authority Standard 154.03.03. https://www.mpi.govt.nz/ (accessed February 13, 2016).

Medina, L.V., K.Hrapkiewicz, M.Tear, and L.C.Anderson. 2007. Fundamental training for individuals involved in the care and use of laboratory animals: A review and update of the 1991 NRC core training module. ILAR J48(2): 96–108. [PubMed: 17420531]

MEF (Ministry of Environment and Forests). 2006. Breeding of and experiments on animals (control and supervision) rules. http://envfor.nic.in/legis/awbi/so1818(e).pdf (accessed February 10, 2016).

MEJ (Ministry of Environment of Japan). 2006. Standards relating to the care and management of laboratory animals and relief of pain. Notice No. 88.

Merriam-Webster. 2016. https://www.merriam-webster.com/ (accessed February 13, 2016).

Mexico (Secretaría de Agricultura, Ganadería, Desarrollo Rural, Pesca y Alimentación). 1999. Especificaciones TÁ©cnicas para la Producción, Cuidado y Uso de Animales de Laboratorio. Diario Oficial de la Federación 22 de agosto de 2001 Mexico. NOM-062-ZOO-1999. http://www.fmvz.unam.mx/fmvz/principal/archivos/062ZOO.PDF (accessed February 8, 2016).

MEXT (Ministry of Education, Culture, Sport, Science and Technology of Japan). 2006. Fundamental guidelines for proper conduct of animal experiment. English translation. http://www.clar.med.tohoku.ac.jp/data/kitei/10th/hoi1-10th-E-monkashou.pdf (accessed February 10, 2016).

Michelini, E., L.Cevenini, M.M.Calabretta, D.Calabria, and A.Roda. 2014. Exploiting in vitro and in vivo bioluminescence for the implementation of the three Rs principle (replacement, reduction, and refinement) in drug discovery. Anal Bioanal Chem406(23): 5531–5539. [PubMed: 24908412]

MOST (Ministry of Science and Technology), People’s Republic of China. 2006. Guidelines of humane treatment of laboratory animals.

MRC (Medical Research Council), South Africa. 2004. Guidelines on ethics for medical research: Use of animals in research and training. http://www.kznhealth.gov.za/research/ethics3.pdf (accessed February 15, 2016).

MSJE (Ministry of Social Justice and Empowerment), Indian Parliament. 1998. Breeding of and experiments on animals (control and supervision) rules. http://envfor.nic.in/legis/awbi/awbi10.html (accessed February 10, 2016).

MSJE (Ministry of Social Justice and Empowerment), Indian Parliament. 2001. Breeding of and experiments on animal (control and supervision) rules. http://envfor.nic.in/legis/awbi/awbi11.html (accessed February 10, 2015).

NABR (National Association for Biomedical Research). 2016. State government. http://www.nabranimallaw.org/research-animal-protection/state-government/ (accessed February 12, 2016).

NACLAR (National Advisory Committee for Laboratory Animal Research), Singapore. 2004. The guidelines on the care and use of animals for scientific purposes. http://www.ava.gov.sg/docs/default-source/tools-and-resources/resources-for-businesses/Attach3_AnimalsforScientificPurposes.PDF (accessed February 10, 2016).

NAEAC (National Animal Ethics Advisory Committee), Ministry of Agriculture and Forestry, New Zealand. 2010. Good Practice Guide for the Use of Animals in Research, Testing, and Teaching. http://www.mpi.govt.nz/protection-and-response/animal-welfare/animals-in-research-testing-teaching/resources/ (accessed February 13, 2016).

NAEAC (National Animal Ethics Advisory Committee), Ministry of Agriculture and Forestry, New Zealand.

2012. Guide to the Preparation of Codes of Ethical Conduct. http://www.mpi.govt.nz/protection-and-response/animal-welfare/animals-in-research-testing-teaching/resources/ (accessed February 13, 2016).

NAS (National Academy of Sciences). 1995. On Being a Scientist. http://www.nap.edu/readingroom/books/obas/preface.html (accessed February 13, 2016).

NAWAC (National Animal Welfare Advisory Committee). 2011. Transport of animals within New Zealand by transportation. https://www.mpi.govt.nz/protection-and-response/animal-welfare/codes-of-welfare/ (accessed February 13, 2016).

NHMRC (National Health and Medical Research Council). 2003. Policy on the use of non-human primates for scientific purposes. https://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/ea14.pdf (accessed February 13, 2016).

NHMRC (National Health and Medical Research Council). 2007. Guidelines for the generation, breeding, care and use of genetically modified and cloned animals for scientific purposes. http://www.nhmrc.gov.au/guidelines-publications/ea17 (accessed February 13, 2016).

NHMRC (National Health and Medical Research Council). 2008a. Guidelines to promote the well-being of animals used for scientific purposes: The assessment and alleviation of pain and stress in research animals. https://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/ea18.pdf (accessed February 13, 2016).

NHMRC (National Health and Medical Research Council). 2008b. Guidelines for monoclonal antibody production. http://www.nhmrc.gov.au/guidelines-publications/ea19 (accessed February 13, 2016).

NHMRC (National Health and Medical Research Council). 2009a. Guidelines on the use of animals for training interventional medical practitioners and demonstrating new medical equipment and techniques. http://www.nhmrc.gov.au/guidelines-publications/ea26 (accessed February 13, 2016).

NHMRC (National Health and Medical Research Council). 2009b. NHMRC guidelines on the care of dogs used for scientific purposes. http://www.nhmrc.gov.au/guidelines-publications/ea25 (accessed February 13, 2016).

NHMRC (National Health and Medical Research Council). 2014. A Guide to the Care and Use of Australian Native Mammals in Research and Teaching. https://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/ea29_guide_aus_native_mammals_141003.pdf (accessed June 23, 2016).

NHMRC (National Health and Medical Research Council). 2016. Use of animals in the testing of cosmetics. http://www.nhmrc.gov.au/health-ethics/animal-research-ethics/use-animals-testing-cosmetics (accessed February 10, 2016).

NIH (National Institutes of Health). 2015. Public Health Service policy on humane care and use of laboratory animals. http://grants.nih.gov/grants/OLAW/references/phspol.htm (accessed December 15, 2015).

NMAF (Norwegian Ministry of Agriculture and Food). 2015. Regulation on the use of animals in research.

Nolte, K.B., D.M.Stewart, K.C.O'Hair, W.L.Gannon, M.S.Briggs, M.Barron, J.Pointer, and R.S.Larson. 2008. Speaking the right language: The scientific method as a framework for a continuous quality improvement program within academic medical research compliance units. Acad Med83(10): 941–948. [PubMed: 18820524]

NRCT (National Research Council of Thailand). 2006. Ethical Principles and Guidelines for the Use of Animals for Scientific Purposes. https://www.aaalac.org/resources/Ethical_Principles_and_Guidelines_for_the_Use_of_Animals_for_Scientific_purposes.pdf (accessed February 13, 2016).

NSPRC (National Standards of the People's Republic of China). 2008. Architectural and technical codes for laboratory animal facilities (GB 50447–2008).

NSPRC (National Standards of the People's Republic of China). 2010a. Laboratory animals""Requirements of environment and housing facilities (GB 14925–2010).

NSPRC (National Standards of the People's Republic of China). 2010b. Laboratory animals""Microbiological standards and monitoring (GB 14922.2–2010).

NZAWA (New Zealand Animal Welfare Act). 1999. http://www.legislation.govt.nz/act/public/1999/0142/latest/whole.html#DLM49664 (accessed February 13, 2016).

NZAWA (New Zealand Animal Welfare Act). 2015. Amendment (No. 2). http://www.legislation.govt.nz/act/public/2015/0049/latest/DLM5174807.html (accessed February 13, 2016).

OIE (World Organization for Animal Health). 2015. Terrestrial Animal Health Code. http://www.oie.int/international-standard-setting/terrestrial-code/ (accessed February 15, 2016).

OIE (World Organization for Animal Health). 2016. About us. http://www.oie.int/en/about-us/ (accessed February 15, 2016).

OLAW (Office of Laboratory Animal Welfare). 2012. Memorandum of understanding among the Animal and Plant Health Inspection Service, U.S. Department of Agriculture and the Food and Drug Administration, U.S. Department of Health and Human Services, and the National Institutes of Health, U.S. Department of Health and Human Services, concerning laboratory animal welfare. APHIS Agreement No. 11-6100-0027-MU. MOU No. 225-06-4000. http://grants.nih.gov/grants/olaw/references/finalmou.htm (accessed February 12, 2016).

OLAW (Office of Laboratory Animal Welfare). 2013. Memorandum of understanding between the Office of Laboratory Animal Welfare, National Institutes of Health, U.S. Department of Health and Human Services, and the Office of Research Oversight and the Office of Research and Development, Veterans Health Administration, U.S. Department of Veterans Affairs, concerning laboratory animal welfare. http://grants.nih.gov/grants/olaw/references/mou_olaw.htm (accessed February 12, 2016).

OLAW (Office of Laboratory Animal Welfare). 2015a. Guidance. http://grants.nih.gov/grants/olaw/olaw.htm (accessed 15 December 2015).

OLAW (Office of Laboratory Animal Welfare). 2015b. Memorandum of understanding between NIH and NSF. http://grants.nih.gov/grants/olaw/references/mou_nsf.htm (accessed June 22, 2016).

OLAW (Office of Laboratory Animal Welfare), National Institutes of Health. 2002. Public Health Service policy on humane care and use of laboratory animals. Bethesda, MD: OLAW.

PCAA (Prevention of Cruelty to Animals Act). 1982. Ministry of Environment and Forest. Government of India. http://envfor.nic.in/legis/awbi/awbi01.html (accessed February 10, 2016).

Pimple, K.D.2002. Six domains of research ethics: A heuristic framework for the responsible conduct of research. Sci Eng Ethics8: 191–205. [PubMed: 12092490]

Plante, A., and M.L.James. 2008. Program oversight enhancements (POE): The big PAM. ILAR J49(4): 419–425. [PubMed: 18849595]

Prime Minister’s Office. 1980. Standards relating to the care and management of experimental animals: Experimental Animal Regulation. Notification No. 6. English translation. http://www.alive-net.net/english/en-law/viv-kijun.html (accessed February 10, 2016).

Podolsky, M.L., and V.S.Lucas, eds. 1999. The Care and Feeding of an IACUC: The Organization and Management of an Institutional Animal Care and Use Committee. Boca Raton, FL: CRC Press.

Poirier, G.M., C.Bergmann, D.G.Denais-Lalieve, I.A.Dontas, N.Dudoignon, H.Ehall, J.M.Fentener van Vlissingenet al.2015. ESLAV/ECLAM/LAVA/EVERI recommendations for the roles, responsibilities and training of the laboratory animal veterinarian and the designated veterinarian under Directive 2010/63/EU. Lab Anim49(2): 89–99. [PubMed: 25416607]

Potkay, S., and W.R.DeHaven. 2000. OLAW and APHIS: Common areas of noncompliance. Lab Anim (NY)29(5): 32–37. [PubMed: 11381215]

Pritt, S., P.Samalonis, L.Bindley, and A.Schade. 2004. Creating a comprehensive training documentation program. Lab Anim (NY)33(4): 38–41. [PubMed: 15141262]

Republic of Korea, Ministry of Agriculture, Food, and Rural Affairs. 2014. Animal Protection Act. http://elaw.klri.re.kr/eng_service/lawView.do?hseq=32052&lang=ENG (assessed February 14, 2016).

RPDA (Republic of Philippines Department of Agriculture). 1999. Rules and regulations on the conduct of scientific procedures using animals. http://www.paws.org.ph/uploads/2/1/2/7/21275318/awa_ao40-rules_and_regulations_on_the_conduct_of_scientific_procedures_using_animals.pdf (accessed February 13, 2016).

Rush, H.G., and M.C.Dyson. 2014. Personnel training. In The IACUC Handbook, ed. J.Silverman, M.A.Suckow, and S.Murthy, 483–502. Boca Raton, FL: CRC Press.

Russell, W.M.S., and R.L.Burch. 1959. The Principles of Humane Experimental Technique. London: Methuen and Co.

SABSStandards Division. 2008. South African national standard. The care and use of animals for scientific purposes.

Schofield, J., D.Noonan, Y.Chen, and P.Penson. 2014. Laboratory animal regulations and recommendations for global collaborative research: Australia and New Zealand. In Laboratory Animals: Regulations and Recommendations for Global Collaborative Research, ed. J.GuillÁ©n, 333–376. San Diego: Academic Press/Elsevier.

Schwindaman, D.F.1999. The history of the Animal Welfare Act. In 50 Years of Laboratory Animal Science, ed. C.W.McPherson and S.F.Mattingly, 147–151. Memphis, TN: American Association for Laboratory Animal Science.

SCJ (Science Council of Japan). 2006. Guidelines for proper conduct of animal experiments. English translation. http://www.scj.go.jp/ja/info/kohyo/pdf/kohyo-20-k16-2e.pdf (accessed February 10, 2016).

Silk, S.B., L.L.Hampton, and P.A.Brown. 2013. What investigators need to know about the use of animals. ILAR J54(3): 324–328. [PubMed: 24615446]

Silverman, J., M.A.Suckow, and S.Murthy, eds. 2014. The IACUC Handbook. 3rd ed. Boca Raton, FL: CRC Press.

Slob, W.2014. Benchmark dose and the three Rs: Getting more information from the same number of animals. Crit Rev Toxicol44(7): 557–567. [PubMed: 25000332]

South Africa. 1962. Animal Protection Act.

SSTC (State Science and Technology Commission of the People's Republic of China). 1988. Regulation of the People's Republic of China for Administration of Laboratory Animals. English translation. http://www.aaalac.org/intlRefs/IntRegs/China/P.R.%20China/Legal%20Administration%20Documents%20for%20Lab%20Animals.PDF (accessed February 8, 2016).

Steneck, N.H.2007. Introduction to the Responsible Conduct of Research. Washington, DC: Office of Research Integrity, Department of Health and Human Services.

Tanzania. 2008. Animal Welfare Act, Part V.

Thulin, J.D., J.F.Bradfield, V.K.Bergdall, L.A.Conour, A.W.Grady, D.L.Hickman, J.N.Norton, and J.M.Wallace. 2014. The cost of self-imposed regulatory burden in animal research. FASEB J28: 3297–3300. [PubMed: 24784580]

Törnqvist, E., A.Annas, B.Granath, E.Jalkesten, I.Cotgreave, and M.Öberg. 2014. Strategic focus on 3R principles reveals major reductions in the use of animals in pharmaceutical toxicity testing. PLoS One9(7): e101638. [PMC free article: PMC4108312] [PubMed: 25054864]

Uruguay (Senado y Cámara de Representantes de la República Oriental del Uruguay). 2009. Utilización de Animales en Actividades de Experimentación, Docencia e Investigación Científica. Ley No. 18.611. http://www.cic.hc.edu.uy/images/stories/ley_18.611-_investigacin_con_animales.pdf (accessed March 28, 2017).

USDA (U.S. Department of Agriculture). 2013. Animal Welfare Inspection Guide. https://www.aphis.usda.gov/animal_welfare/downloads/Animal-Care-Inspection-Guide.pdf (assessed March 24, 2017).

USDA (U.S. Department of Agriculture). 2015a. Animal Welfare Act. https://www.aphis.usda.gov/aphis

/ourfocus/animalwelfare/sa_awa/ct_awa_program_information (accessed December 13, 2015).

USDA (U.S. Department of Agriculture). 2015b. Animal Welfare Act and Animal Welfare Regulations. https://www.aphis.usda.gov/animal_welfare/downloads/Animal%20Care%20Blue%20Book%20-%202013%20-%20FINAL.pdf (accessed December 13, 2015).

USDA (U.S. Department of Agriculture). 2015c. Animal Care Policy Manual. https://www.aphis.usda.gov/animal_welfare/downloads/Animal%20Care%20Policy%20Manual.pdf (assessed December 13, 2015).

USDA (U.S. Department of Agriculture). 2015d. Publications, forms and guidance documents. https://www.aphis.usda.gov/aphis/ourfocus/animalwelfare/sa_publications/ct_publications_and_guidance_documents (accessed December 13, 2015).

Van Sluyters, R.C.2008. A guide to risk assessment in animal care and use program: The metaphor of the 3-legged stool. ILAR J49(4): 372–378. [PubMed: 18849590]

Van Zutphen, B.2007. Education and training for the care and use of laboratory animals: On overview of current practices. ILAR J48(2): 72–74. [PubMed: 17420528]

Van Zutphen, L.F.M., and J.B.F.Van der Valk. 2001. Development on the implementation of the three Rs in research and education. Toxicol In Vitro15: 591–595. [PubMed: 11566596]

Wayman, S.1966. Concentration camps for dogs. Life60(5): 22–29.

Zurlo, J., K.Bayne, and J.M.Clark. 2009. Adequate veterinary care for animals in research: A comparison of guidelines from around the world. ILAR J50(1): 85–88. [PubMed: 19106455]

Figures

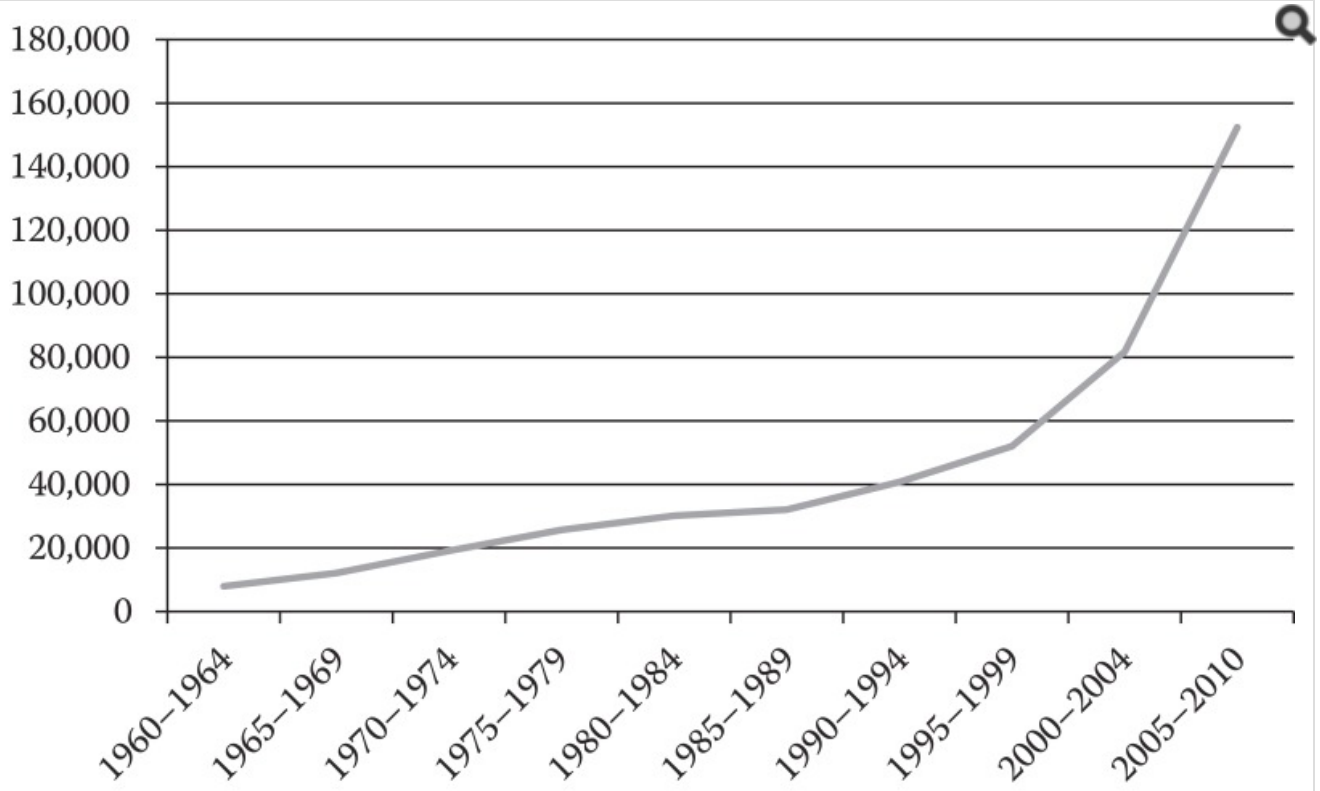

Figure 7.1

Citations involving the keywords “animal model or animal models” in PubMed.

Figure 7.2

Hierarchy of guidance used in compliance programs.

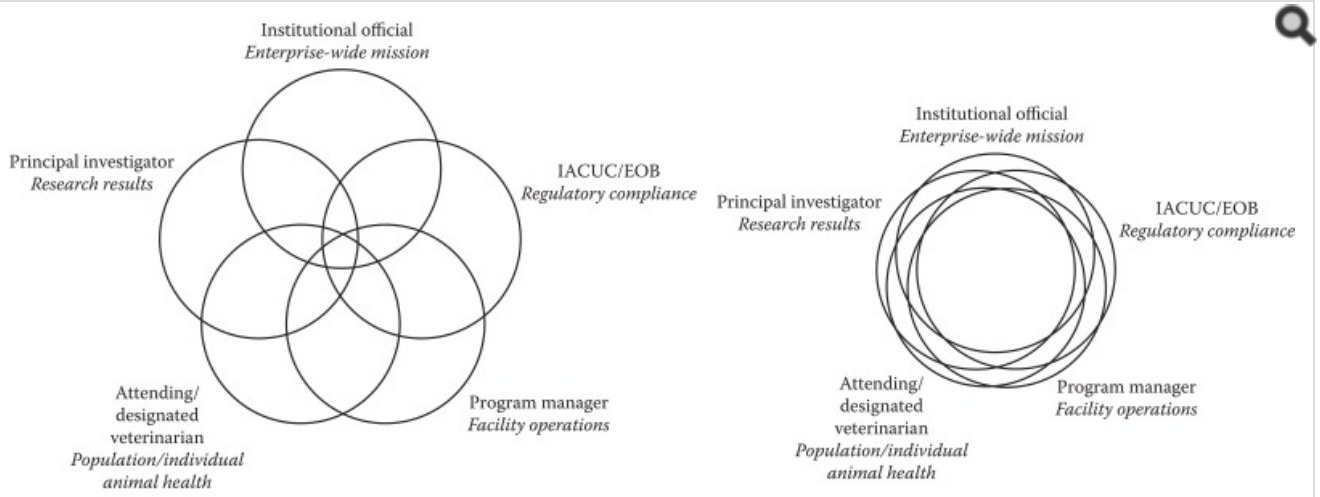

Figure 7.3

Realms of concern for the constituents of an animal research compliance program. The left figure illustrates a small amount of success in achieving a central goal when each constituent places excessive attention on its own bias. The right figure demonstrates greater cooperation and thereby a greater chance for success.

Boxes

Box 7.1

Standard: A level of quality, achievement, etc., that is considered acceptable or desirable.

Standardization: To change (things) so that they are similar and consistent and agree with rules about what is proper and acceptable.

Source: Merriam-Webster, 2016, https://www.merriam-webster.com.

Box 7.2

Because much of the funding for biomedical research originates from federal sources, scientists are accountable to the public and the public's wishes. (Steneck 2007)

Oversight is part of the social contract between scientists and funding agencies that is implicit with the privilege of performing research, working with research subjects, and using public facilities and funds. (Haywood and Greene 2008)

Box 7.3

The scientific research enterprise, like other human activities, is built on a foundation of trust. Scientists trust that the results reported by others are valid. Society trusts that the results of research reflect an honest attempt by scientists to describe the world accurately and without bias. The level of trust that has characterized science and its relationship with society has contributed to a period of unparalleled scientific productivity. But this trust will endure only if the scientific community devotes itself to exemplifying and transmitting the values associated with ethical scientific conduct. (NAS 1995)

Box 7.4

There is growing recognition that the care of laboratory animals is an institutional responsibility as well as the responsibility of individual investigators. The animal care programs of most large institutions are based increasingly on this partnership of responsibility; the recommendations in the *Guide* assume it. (ILAR 1965)

Box 7.5 U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training

The development of knowledge necessary for the improvement of the health and well-being of humans as well as other animals requires *in vivo* experimentation with a wide variety of animal species. Whenever U.S. Government agencies develop requirements for testing, research, or training procedures involving the use of vertebrate animals, the following principles shall be considered; and whenever these agencies actually perform or sponsor such procedures, the responsible Institutional Official shall ensure that these principles are adhered to:

I. The transportation, care, and use of animals should be in accordance with the Animal Welfare Act (7 U.S.C. 2131 et seq.) and other applicable Federal laws, guidelines, and policies.[1]

II. Procedures involving animals should be designed and performed with due consideration of their relevance to human or animal health, the advancement of knowledge, or the good of society.

III. The animals selected for a procedure should be of an appropriate species and quality and the minimum number required to obtain valid results. Methods such as mathematical models, computer simulation, and *in vitro* biological systems should be considered.

IV. Proper use of animals, including the avoidance or minimization of discomfort, distress, and pain when consistent with sound scientific practices, is imperative. Unless the contrary is established, investigators should consider that procedures that cause pain or distress in human beings may cause pain or distress in other animals.

V. Procedures with animals that may cause more than momentary or slight pain or distress should be performed with appropriate sedation, analgesia, or anesthesia. Surgical or other painful procedures should not be performed on unanesthetized animals paralyzed by chemical agents.

VI. Animals that would otherwise suffer severe or chronic pain or distress that cannot be relieved should be painlessly killed at the end of the procedure or, if appropriate, during the procedure.

VII. The living conditions of animals should be appropriate for their species and contribute to their health and comfort. Normally, the housing, feeding, and care of all animals used for biomedical purposes must be directed by a veterinarian or other scientist trained and experienced in the proper care, handling, and use of the species being maintained or studied. In any case, veterinary care shall be provided as indicated.

VIII. Investigators and other personnel shall be appropriately qualified and experienced for conducting procedures on living animals. Adequate arrangements shall be made for their in-service training, including the proper and humane care and use of laboratory animals.

IX. Where exceptions are required in relation to the provisions of these Principles, the decisions should not rest with the investigators directly concerned but should be made, with due regard to Principle II, by an appropriate review group such as an institutional animal care and use committee. Such exceptions should not be made solely for the purposes of teaching or demonstration.[2]

1 For guidance throughout these principles, the reader is referred to the *Guide for the Care and Use of Laboratory Animals*, prepared by the Institute of Laboratory Animal Resources, National Academy of Sciences.

2 Published in the *Federal Register*, May 20, 1985, vol. 50, no. 97, by the Office of Science and Technology Policy (FR Doc. 85-12059).

Source: Interagency Research Animal Committee, *Federal Register*, 50, 97, 1985. https://grants.nih.gov/grants/olaw/references/phspol.htm.

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