

# The Evolution of Animal Welfare and the 3Rs in Brazil, China, and India

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Increasingly, scientific collaborations and contracts cross country borders. The need for assurance that the quality of animal welfare and the caliber of animal research conducted are equivalent among research partners around the globe is of concern to the scientific and laboratory animal medicine communities, the general public, and other key stakeholders. Therefore, global harmonization of animal care and use standards and practices, with the welfare of the animals as a cornerstone, is essential. In the evolving global landscape of enhanced attention to animal welfare, a widely accepted path to achieving this goal is the successful integration of the 3Rs in animal care and use programs. Currently, awareness of the 3Rs, their implementation, and the resulting animal care and use standards and practices vary across countries. This variability has direct effects on the animals used in research and potentially the data generated and may also have secondary effects on the country's ability to be viewed as a global research partner. Here we review the status of implementation of the 3Rs worldwide and focus on 3 countries—Brazil, China and India—with increasing economic influence and an increasing footprint in the biomedical research enterprise.

**Abbreviations:** ARRIVE, Animal Research: Reporting of *In Vivo* Experiments; CALAS, Chinese Association of Laboratory Animal Science; CAPN, Chinese Animal Protection Network; CIOMS, Council for International Organizations of Medical Sciences; CPCSEA, Committee for the Purpose of Control and Supervision of Experiments on Animals; IAEC, Institutional Animal Ethics Committee; ICLAS, International Council for Laboratory Animal Science; MOST, Ministry of Science and Technology; OIE, World Organization for Animal Health.

Although Russell and Burch<sup>50</sup> published their seminal treatise on the 3Rs (replacement, refinement, reduction) in 1959, the acceptance and, more importantly, implementation of these precepts have been gaining global momentum only in recent years. Inclusion of reference to the 3Rs in multinational documents has resulted in these principles gaining traction in laboratory animal science in all parts of the globe. For example, in 2010, the World Organization for Animal Health (OIE) issued standards for the “Use of Animals in Research and Education” in chapter 7.8 of its Terrestrial Animal Health Code.<sup>54</sup> The OIE is recognized as a reference organization by the World Trade Organization and has a total of 178 member countries that span the globe. By serving as members of the OIE, these countries commit to incorporating the OIE standards in their regulatory framework. The chapter in the Terrestrial Animal Health Code pertaining to the use of animals in research, testing, and education stipulates that oversight of the animal program ensures the implementation of the 3Rs, typically by including consideration of the 3Rs during project proposal review. The global effect of requiring inclusion of the 3Rs in the 180 Member Countries' regulatory frameworks is potentially enormous.

Similarly, the “International Guiding Principles for Biomedical Research Involving Animals”<sup>13</sup> issued by the Council for International Organizations of Medical Sciences (CIOMS) and the International Council for Laboratory Animal Science (ICLAS) state (principle III):

“Animals should be used only when necessary and only when their use is scientifically and ethically justified. The principles of the Three Rs—Replacement, Reduction and Refinement—should be incorporated into the design and conduct of scientific and/or educational activities that involve animals. Scientifically sound results and avoidance of unnecessary duplication of animal-based activities are achieved through study and understanding of the scientific literature and proper experimental design. When no alternative methods, such as mathematical models, computer simulation, *in vitro* biologic systems, or other nonanimal (adjunct) approaches, are available to replace the use of live animals, the minimum number of animals should be used to achieve the scientific or educational goals. Cost and convenience must not take precedence over these principles”.

Through its membership, CIOMS is representative of a substantial proportion of the biomedical scientific community. In 2013, the membership of CIOMS included 49 international, national and associate member organizations, representing many of the biomedical disciplines, national academies of sciences, and medical research councils. ICLAS also has an extensive international influence, manifest by its aim to promote and coordinate the development of laboratory animal science throughout the world, especially in developing countries. Therefore, the influence of its Guiding Principles, particularly those elements related to the 3Rs, has similar global scope and effect.

Although many nations, whether explicitly or implicitly, now include 3Rs requirements within the regulations, codes, or guidelines that govern the use of animals in science within their jurisdictions, the implementation of the 3Rs within biomedical science is difficult to judge. One group<sup>33</sup> suggested that the extent of 3Rs implementation is “substantially underestimated” due to the lack of recognition by the investigator or protocol

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review committee that a proposed procedure will result in a reduction, refinement or replacement outcome. The authors<sup>33</sup> refer to these as “invisible 3Rs applications.”

As noted in another article,<sup>4</sup> a number of literature reviews have attempted to assess the implementation of the 3Rs, although results vary. One study<sup>8</sup> looked at 2,800 articles from biomedical journals from 1970, 1980, 1990, and 2000 and found that despite a doubling in the number of articles published annually during that time, the proportion of studies using animals fell by 30%, with a 50% drop in the average number of animals used per published paper. The authors<sup>8</sup> also demonstrated an increase from 21% to 35% in the proportion of studies that used tissue from untreated euthanized animals as compared with live animals. However, another study<sup>40</sup> found no large fluctuations in categories of biomedical experiments based on increasing ethical concern for laboratory animals from all animal-based research published in *Nature Medicine* between 1998 and 2003, although there was a dramatic increase—from 24% in 1998 to over 90% in 2003—in the number of articles including a statement about “the relevant laws and institutional guidelines with which each experiment should comply, and the institutional committees which approved each experiment, as requested by *Nature Medicine*.” This latter result indicates the potential role journals can play in raising awareness of laboratory animal welfare among scientists. However, a study<sup>41</sup> evaluating editorial policies of a random sample of journals publishing original research involving animals found that only 153 of the 288 journals had policies relating to the use of animals, although these varied widely in their detail. This contrasts with one author’s<sup>47</sup> conclusion that of 138 journals listed in MedLine, almost 62% included a requirement for the author to provide assurance that ethical standards were met during the research.

And yet disappointment has been expressed<sup>2</sup> recently regarding the inadequate implementation of the Animal Research: Reporting of *In Vivo* Experiments (ARRIVE) guidelines<sup>25</sup> developed in response to an initiative of the National Centre for the Replacement, Refinement, and Reduction of Animals in Research. The ARRIVE guidelines are intended to improve the level of detail provided in the methods section of the published literature, to include the number and characteristics of the animals use (for example, species or strain, sex, age, weight), randomization or blinding to decrease bias in the study, and well-described statistical methods applied to the data. The goals of implementing the guidelines extend beyond the obvious increased transparency that would be achieved in the use of animals. With more information published regarding the statistical analyses applied and the types of animals used, there is greater opportunity for researchers to refine and possibly streamline their animal use by building on lessons learned in other laboratories. Although more than 300 journals have endorsed the ARRIVE guidelines, some authors<sup>2</sup> have expressed concern, using experimental autoimmune encephalomyelitis in rodents, a model for multiple sclerosis, as their exemplar, that this endorsement has not resulted in actual improvement in the quality of information contained in preclinical research publications.

One report<sup>4</sup> also notes that a number of surveys of scientists have indicated areas of difficulty in the further implementation of the 3Rs. In a Canadian survey,<sup>19</sup> participants felt that they were already practicing reduction in numbers to the minimum necessary, but many still indicated a reluctance to use pain relief in case it compromised scientific outcomes. Two Netherlands studies<sup>29,53</sup> indicated that scientists had problems with effective searching for 3Rs alternatives and had limited knowledge of

specialized databases. A British study<sup>38</sup> found that scientists had a positive attitude toward the 3Rs but that relatively few had developed 3Rs techniques or applied for 3Rs funding. Whether these data reflect an under-reporting of 3Rs techniques being used or a lack of understanding about the 3Rs, there is room for greater understanding and implementation within the animal research community.

Global progress in this regard is made possible, in part, by institutions participating in the accreditation program conducted by AAALAC International. AAALAC uses various standards in its on-site assessments of animal care and use programs that note the importance of applying the 3Rs to the use of animals in science. Specifically, AAALAC has adopted chapter 7.8 of the OIE’s Terrestrial Animal Health Code<sup>54</sup> as a Reference Resource (<http://www.aaalac.org/accreditation/resources.cfm>). In addition, AAALAC requires conformance with 3 primary standards in its global assessments: the *Guide for the Care and Use of Laboratory Animals*,<sup>24</sup> the *Guide for the Care and Use of Agricultural Animals in Research and Teaching*,<sup>17</sup> and the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (ETS 123).<sup>14</sup> The *Guide*<sup>24</sup> encourages researchers apply the 3Rs when developing experiments using animals. Both ETS 123 and the European Union’s counterpart, Directive 2010/63/EU, implicitly address application of the 3Rs.<sup>19</sup> Therefore, as AAALAC conducts its on-site assessments of animal care and use programs, consideration is given to the institution’s implementation of the 3Rs principles.

To illustrate the point that the 3Rs are increasingly being accepted around the world as fundamental to a quality animal care and use program, we profile here 3 countries—Brazil, China and India—because they are developing or newly industrialized countries and are distinguished by their large, fast-growing economies (which include biomedical research as an economic engine) and significant influence on regional and global affairs. Several indicators of the embedding of the 3Rs into oversight and use of animals in science are compared across these countries.

## Public Awareness of the 3Rs

**Brazil.** In the past 2 decades, Brazil has made substantial progress in multiple aspects of the conduct and oversight of scientific research. Government programs, such as the creation of a unified platform of scientific curricula (Plataforma Lattes, <http://lattes.cnpq.br/>) and the “Science Without Frontiers” scholarships (which send promising young scientists to complete part of their studies in world-renowned universities, <http://www.cienciasemfronteiras.gov.br/web/csf-eng/faq>) are evidence that science has become a priority of the Brazilian public sector. Private companies also are investing in local talent. It can be said that science, and all of its resulting benefits such as healthcare and economics, has been ‘discovered’ in Brazil.

There is a long-standing history of valuing scientific research in Brazil, but recently a broader acknowledgment of this industry has resulted in building an expanded framework for the conduct of research on the successful efforts of high-level scientists active in the field. However, as in other Latin American countries, there is little to no acknowledgment by the *general public* of those scientists’ achievements. The Brazilian media does not devote much time or interest to scientific news and, when it does, it usually focuses on ‘outside news’—that is, it merely reports discoveries and advancements made in Europe, Asia, and the United States.

Therefore, it comes as no surprise that, in Brazil, the lay public is largely unaware of the 3Rs, and their application by the local scientific community. For example, in October 2013, activists

broke into the Instituto Royal in São Roque to “free dogs used in scientific research,” claiming the animals were subjected to unnecessary pain and suffering. Later investigations showed that the Institute complied with the Brazilian law regarding animal experiments (Law 11794/08) and other international regulations, thus following the 3Rs. However, the aftermath of the news coverage made it painfully clear that the general public had no idea of the importance of animal experiments and how animal welfare is taken into consideration by Brazilian animal researchers. After the event, the local scientific community felt the need to provide the public with more detailed information on how research with animals is conducted in Brazil—that is, in a respectful and ethical way—and to inform the public regarding the concept of the 3Rs and, mainly, how these principles are put into practice in Brazil. To address this concern, the main Brazilian governmental organization responsible for the promotion of scientific and technological research, Conselho Nacional de Desenvolvimento Científico e Tecnológico, provided financial support to the program [eticanapesquisa.org.br](http://eticanapesquisa.org.br). Informational material was developed and distributed in elementary and high schools, and laboratory animal scientists gave lectures to these students. Television programs and newspapers highlighted and interviewed people who work with laboratory animals.

**China.** Several factors may play a role in the evolution of the regulatory framework for, and attention paid to, laboratory animal welfare in China. The Chinese culture has long-standing traditions of Confucianism, Taoism, and Buddhism that variably speak to a relationship between human beings and nonhuman animals and advocate concern for living things.<sup>34</sup> Some philosophies consider humans to be superior to other animals and view animals as a source of food, labor, and utility. In such a perspective, a person treats an animal with kindness not because of their inherent value but as a reflection of one’s own refinement as a human being. Other schools of thought, particularly those that emphasize reincarnation, place value on animals as a component of the human–animal continuum. However, in addition to religious influences and societal mores—customs, teachings, and so forth—can affect commonly held opinions regarding the appropriate care and use of animals.<sup>3</sup> Recently, the Chinese government has called for the establishment of a harmonized society. Therefore, promoting animal welfare is in accord with governmental aims and, of course, is good for society and people.

Since 1978, China has adopted reforms and become open to outside policy, leading to increased international academic exchange and collaborations. In 1989, a group of prominent American veterinarians held a week-long training course organized by the Chinese Ministry of Agriculture in the School of Veterinary Medicine in what was then the Beijing Agricultural University. This inaugural and pivotal training by Western veterinarians covered basic laboratory animal medicine, and the concept of animal welfare was introduced. Today, funding agencies from Western countries usually require Chinese counterparts for most academic collaborations to assist with animal welfare assurance, which promotes the improvement of animal welfare in China. Chinese scientists now annually publish the second-largest number of scientific papers, and most Chinese scientists have come to realize that this increasing research output—as measured by high-quality publications in *Cell*, *Nature*, *Science*—requires good animal welfare. In addition, researchers who have trained overseas and return to China bring with them a wealth of information and technical skills, thus promoting the quality of animal care and use in China. Furthermore, the increasing number of international symposia hosted in China promotes sharing animal

welfare knowledge and information with a highly receptive audience. Another significant influence is the presence of many multinational pharmaceutical companies as well as contract research organizations that have business operations in China. These multinational companies and organizations have a positive influence on animal welfare in China, including a tangible evolution of the acceptance of the 3Rs.

Generally speaking, the Chinese people support animal research; but it goes without saying that China is not immune to attention from animal rights or protection organizations.<sup>31</sup> For example, PETA Asia–Pacific calls for a stop to animal experimentation on its website (<http://www.petaasiapacific.com/issues-nottoexperiment.asp>). The Chinese Animal Protection Network (CAPN) addresses many animal issues, including what they refer to as “academic research of animal ethics” and an “awareness campaign of lab animal protection,” and in 2008, CAPN organized the first World Lab Animal Day in China. This nonprofit organization is the first Chinese network for animal protection.<sup>11</sup> As an organization founded by native Chinese people, these are some of the most dedicated Chinese activists. CAPN is well known for its pioneering role in the rapid development of the modern animal rights movement in China in recent years. It has led some important trends of the movement, including converting from emotion-based to science-based animal protection among the animal protection communities. Since the launch of its first project, the Chinese Companion Animal Protection Network, the organization has continued to expand. By April 2008, there were 48 member groups, 2 branches, and more than 10,000 individual supporters who espoused CAPN’s values: “using technology, research, education, artistry, and creativity to make the world a better place for all sentient beings.” CAPN is an animal rights group with a science-based philosophy of animal rights. Its proponents oppose violence in the animal rights movement and see animal rights as a dynamic concept; they believe the rights of animals are different because their needs are different. But through the introduction of a World Animal Rights Day in China and developing a network of Chinese animal protection groups, public awareness of animal welfare has increased in China.<sup>31</sup>

**India.** Ethical concern about the use of animals in research is gaining traction in India because of the strict guidelines stipulated by the regulatory authority the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA, <http://envfor.nic.in/division/committee-purpose-control-and-supervision-experiments-animals-cpcsea>). However, in India, the general public is mostly unaware of the 3Rs as a fundamental set of principles for the use of animals in research, testing, and teaching. Even though the Animal Welfare Act was introduced in 1960, progress has been slow with regard to engaging stakeholders (scientists, the public, and so forth) in adopting the 3Rs. As early as the 1960s, India enacted the Prevention of Cruelty to Animals Act, which addresses the prevention of cruelty to animals in a general manner ([https://docs.google.com/document/d/1221OXj5\\_VSt\\_dUbdTJeiHn-8M2f0xrg866RIKJGLcwpo/edit?pli=1](https://docs.google.com/document/d/1221OXj5_VSt_dUbdTJeiHn-8M2f0xrg866RIKJGLcwpo/edit?pli=1)). The concept of the 3Rs is only recently slowly attaining recognition among Indian scientists who use animals in their research.

## Awareness of the 3Rs in the Scientific and Veterinary Communities

**Brazil.** Scientists in Brazil have become increasingly aware of the 3Rs, mainly since 2000, due to international collaborations in which adherence to the 3Rs was expected<sup>20</sup> and with the imple-



mentation of an ethics committee on the use of animals (a CEUA or 'Ethical Committee') in almost every university. Scientists must submit their proposed project to an Ethical Committee for review and approval before starting their studies. The researcher also must confirm that the number of animals used will be reduced to the minimum necessary for a statistically meaningful result. Finally, the researcher must affirm that the animals will not experience unnecessary pain or suffering, including identifying humane endpoints in the protocol. In this way, the scientists who work with animals must be conscious of the 3Rs and apply them in their day-to-day work. It should be noted that the Ethical Committees conduct inspections to see whether the 3Rs are, in fact, being followed during the studies (Law 11794/08 in its Decree 6899/09 Chapter IV, Article 44, item VI, [http://www.planalto.gov.br/ccivil\\_03/\\_Ato2007-2010/2009/Decreto/D6899.htm](http://www.planalto.gov.br/ccivil_03/_Ato2007-2010/2009/Decreto/D6899.htm)). Whenever needed (generally once or twice a year), a short course and lectures are given to all animal users, with the 3Rs serving as the starting point of these courses and lectures. Indeed, scientists have adjured their colleagues to carefully consider alternatives (replacement models) in some areas of research.<sup>38</sup>

Conversely, only a small number of veterinarians are aware of the 3Rs—primarily those who take part in research at or work for universities. But now, under Law 11794/08, Annex number 6 (DOU 11/07/2012, Section 1, p. 13, <http://www.jusbrasil.com.br/diarios/DOU/2012/07/11/Secao-1>), which states that the veterinarian is responsible for the medical care of laboratory animals, this gap in awareness will change, and a larger number of veterinarians will know the concept of the 3Rs and will have a significant role in ensuring their implementation.

**China.** In late 1970s and early 1980s, when China's diplomatic relationship with the United States became more open, the 2 countries initiated cultural and educational exchanges, and an official communication was sent from the US Department of Agriculture to the Chinese Ministry of Agriculture offering to help train Chinese veterinarians in comparative medicine. Unfortunately, the offer was premature, given that personnel in the Ministry of Agriculture did not know what comparative medicine or laboratory animal science was. Subsequently, the letter was forwarded to Dr Ruishan Liu, a prominent veterinarian and now considered a pioneer in modern Chinese laboratory animal science. Dr Liu went to the University of Maryland in Baltimore as a visiting scholar to study laboratory animal medicine. When he returned to China, he lectured on animal welfare, the 3Rs, and animal rights activities in a conference in Shanghai in late 1980s; however, the audience was not receptive to these ideas. It must be recalled that in the late 1970s and early 1980s, the Chinese people were still short of materials, animal protein was still scarce, and working with laboratory animals was considered a menial job. At that time, often denounced or disgraced staff were punished by being assigned to work in animal farms or facilities. Laboratory animal science was not even considered strongly as a scientific discipline, the concept of animal welfare (let alone the 3Rs concept in animal research)—unknown to almost all Chinese scientists—was thought of as a luxury.

However, a sea change has taken place in development of laboratory animal science in China. Due to the recent government policies for reform and openness to external collaborations, laws and regulations regarding animal welfare and the 3Rs are being promulgated. All institutions are required to establish an IACUC to oversee animal research (Article 4, "Examination Guideline for the Welfare and Ethics of Laboratory Animals").<sup>6</sup> When a protocol is submitted, animal welfare and the 3Rs are elements of IACUC discussion. Topics covered include a justification for the animal model selection, redundancy of the studies, use of analgesics

and anesthetics, humane endpoints, and methods of euthanasia. Laboratory animal veterinarians are particularly aware of animal welfare and the 3Rs. Currently, the broader veterinary and scientific communities in China are very well aware of the 3Rs and animal welfare, although there is uneven implementation of these principles in different regions of the country.

**India.** More than 1700 institutes and organizations that use animals in biomedical research in India are registered with the CPCSEA. The scientists who conduct animal-based research and laboratory animal veterinarians who support them in these institutes and organizations are familiar with the concept of the 3Rs. Continued efforts of the CPCSEA through periodic workshops (for example, the Certificate Course in Laboratory Animal Science, designed to meet standards of the Federation for Laboratory Animal Science Associations) and stringent guidelines sustain and promote awareness among animal users in India.

## Incorporation of the 3Rs into Law or Prevailing Guidelines

**Brazil.** In Brazil, animal welfare is encompassed in the Constitution (Article 225) and the Federal Decree on Anti-Cruelty (1934). The Brazilian Environmental Crimes Law (Law 9.605, 1998) supplements the Constitution to include cruelty crimes against animals. Article 32 of the Environmental Crimes Law specifically addresses experiments with animals.<sup>5</sup> This Article encourages the use of alternatives and requires the use of anesthesia and analgesia for painful procedures. Indeed, Article 32 sets forth penalties (imprisonment, fines) for "whoever performs a painful or cruel experiment on a live animal for scientific or teaching purposes, when alternative resources are available."<sup>32</sup> In 2008, a Brazilian federal law was approved (Law 11794/08, also known as the Arouca Law, [http://www.planalto.gov.br/ccivil\\_03/\\_Ato2007-2010/2009/Decreto/D6899.htm](http://www.planalto.gov.br/ccivil_03/_Ato2007-2010/2009/Decreto/D6899.htm)) that addressed aspects of the 3Rs. This law created Brazil's National Council for the Control of Animal Experimentation, an advisory, deliberative, and appellate body responsible for monitoring and evaluating the introduction of alternatives to replace the use of animals in education and research.<sup>20,49</sup>

Specifically, the following concepts are addressed:

Chapter IV, Article 14, Section 3: use of alternatives instead of animals in teaching procedures;

Chapter IV, Article 14, Section 4: use the minimal possible number of animals to achieve conclusive results and procedures should avoid causing suffering to animals;

Chapter IV, Article 14, Section 5: If an experiment may cause pain and distress, sedatives, analgesia or anesthesia must be used; and

Chapter IV, Article 14, Section 9: other procedures may be conducted on an animal undergoing a teaching activity or "traumatic" procedure so long as the adjunctive procedures occur during the same anesthetic period and the animal is euthanized before recovering consciousness.

Concern has been expressed that the 2008 law, which took 13 y to be adopted, does not explicitly reference the 3Rs nor give direction for their implementation,<sup>20</sup> and the law emphasizes refinement more than replacement or reduction, although all 3 Rs are a component of the law.<sup>15</sup> Other authors<sup>51</sup> have noted that Law 11794 does not include the previous legal requirement that animal experiments "must demonstrate the relevance of their results for the progress of science and show that alternative, equally effective method do not exist."

A Brazilian *Guide* is currently being written; the first chapter addresses laboratory animal welfare, and the 3Rs serve as the

cornerstone of this discussion. Until the new *Guide* is published, internationally recognized guidelines are accepted, such as the *Guide*<sup>24</sup> and the Australian *Code for the Care and Use of Animals for Scientific Purposes* (2013, <http://www.nhmrc.gov.au/guidelines/publications/ea28>), which very clearly reference application of the 3Rs. In addition, the CIOMS/ICLAS *International Guiding Principles for Biomedical Research Involving Animals* (<http://www.cioms.ch/index.php/12-newsflash/227-cioms-and-iclas-release-the-new-international-guiding-principles-for-biomedical-research-involving-animals>) have been largely adopted, and they are placed on the front page of almost every Ethical Committee's website.

**China.** In September 2009, China's first comprehensive look at a national animal welfare law, the Animal Protection Law of the People's Republic of China, was prepared by legal scholars and animal welfare advocates, with input from overseas specialists and consultants (<http://www.actasia.org/uploads/file/Feedback%20on%20draft%20APlegislation.pdf>). The proposed draft addresses, among other matters, animal abuse and neglect, responsibilities of animal owners, livestock breeding, and the ethical responsibility for caring for animals. The proposed law makes animal abuse, neglect, and broadcasting any messages about animal abuse criminal acts punishable under criminal law. The draft law covers various types of animals including wildlife, marine animals, companion animals, farm animals, and laboratory animals. Because the scope is so broad, consensus has been difficult to reach. However, a laboratory-animal-specific protection law may be passed, given the momentum surrounding such a law. In 2012, a grant was given to a group of prominent laboratory animal scientists and veterinarians by the Ministry of Science and Technology (MOST) to establish a Chinese laboratory animal care and use accreditation process according to relevant regulations and national standard;<sup>9</sup> it is designed to emulate the accreditation program promulgated by AAALAC International or the Canadian Council on Animal Care. For both the proposed law and the proposed national accreditation system, the 3Rs provide an overarching approach to research animal use.

The Chinese Association of Laboratory Animal Science (CALAS) recently established a committee to develop Chinese standards for laboratory animal welfare and ethics (CALAS Animal Welfare Committee, <http://www.calas.org.cn/html/news/xsdt/20131018/2040.html>). It bodes well for the quality of Chinese research that the OIE's Chapter 7.8 of the *Terrestrial Animal Health Code*<sup>54</sup> was encouraged to be used as the framework for these standards, given that China is a member of the OIE, and this document predicates the care and use of research animals on the 3Rs. Chinese colleagues are very keen to pursue this, evidenced by the cohosting of a two day seminar with the United Kingdom Home Office for invited experts from China (government, academia, and industry) and overseas in Beijing in March 2014. The aims were 3-fold: to finalize and endorse the standards which the committee had in late draft form; to initiate a dialogue on harmonizing pharmaceutical safety testing guidelines and develop a forward plan; and to explore a strategy for China to cease unnecessary animal testing of cosmetics. This seminar was considered to be the first phase of a 2-stage project that would address the last 2 aims in greater detail over a period of 2 to 3 y. This effort aligns with a UK Coalition Agreement to promote the 3Rs across research through a science-led approach (see "Working to Reduce the Use of Animals in Scientific Research," <http://www.understandinganimalresearch.org.uk/resources/document-library>). The Coalition's delivery plan includes an international program that seeks greater global harmonization of regulatory testing requirements, with a focus on China.

The local administrative office of laboratory animals inspects each institution annually according to relevant national standards (referred to as "GB" standards (note, there is no direct English translation for this acronym)). If the quality of laboratory animals or facilities for an institute does not meet the national standard, a period of time is given to correct findings. During the annual inspection, the personal or facility license could be revoked if an institution breaches national standards. However, to date, the inspection mostly focuses on quality of the staff and facility; animal welfare, the 3Rs, and environmental enrichment are not mandatory elements of the program, although they are encouraged. Parameters for animal welfare during inspections have yet to be established in accordance with a new GB for laboratory animal institutions, "General Requirements for Quality and Competence."

Animal welfare and the 3Rs are evolving with the development of laboratory animal science in China. The concept of animal welfare was first implied in the Statute on Administration of Lab Animals promulgated by the State Council in 1988 ([http://www.google.com/url?sa=t&rct=j&q=&esrc=s&frm=1&source=web&cd=3&ved=0CCgQJfAC&url=http%3A%2F%2Fww2.lasec.cuhk.edu.hk%2FGuidelines%2FCollection%2520of%2520Laws%2C%2520Regulations%2520and%2520Policies%2520on%2520Laboratory%2520Animals.pdf&ei=D0zNU96SCkkyASVkoHABA&usq=AFQjCNGtO8xT5w5Inb1B8t\\_zn7Hu\\_lbPjQ](http://www.google.com/url?sa=t&rct=j&q=&esrc=s&frm=1&source=web&cd=3&ved=0CCgQJfAC&url=http%3A%2F%2Fww2.lasec.cuhk.edu.hk%2FGuidelines%2FCollection%2520of%2520Laws%2C%2520Regulations%2520and%2520Policies%2520on%2520Laboratory%2520Animals.pdf&ei=D0zNU96SCkkyASVkoHABA&usq=AFQjCNGtO8xT5w5Inb1B8t_zn7Hu_lbPjQ)). The first use of language referring to animal welfare and the 3Rs occurred in MOST documents in 1997.<sup>27</sup> In May 2003, the Beijing Municipal Legal Affairs Office announced that it had drafted legislation on animal welfare. The news engendered a heated debate, so the draft was withdrawn from consideration later that year. At that time, the overriding opinion was that it was impractical and premature to implement animal welfare legislation. However, a chapter on animal welfare was added to the Regulations on the Management of Experimental Animals, which was promulgated in 2004. Although the chapter is brief, it represents the first time that animal welfare is to be regulated in China. Therefore, this chapter is perceived to be a significant step toward the legislation of animal welfare.<sup>36</sup> The chapter concerning animal welfare clearly defines the status of laboratory animals. There are standards to follow when dealing with experimental animal welfare, and the chapter emphasizes the need to reduce the number of animals used in experiments, to improve the animals' environment, and to alleviate animal pain. In this way, Beijing has taken the lead in establishing animal welfare and the principles of the 3Rs in research animals in China.

The Guideline on Humane Treatment of Laboratory Animals promulgated by MOST in 2006 is considered another milestone for research animals in China.<sup>37</sup> It is the country's first broad animal welfare regulation. The guidelines require each institution to establish an IACUC to oversee and evaluate all aspects of its animal care and use program. Other requirements include that effective measures should be taken to protect laboratory animals from injury, hunger or thirst, discomfort, fear, disease, and pain; each institution must ensure that research animals receive good husbandry and veterinary care in a clean, comfortable environment; animals must have access to palatable food and water of sufficient quantity and quality to maintain health; and they must be able to display natural behaviors. Furthermore, the facility and environment must adequately provide for the animals' behavioral and physiologic needs. Pain and distress for animals in research are a particular focus of the guidelines, which call for adherence to the 3Rs during every stage of the animal experiment. After the experiment has been completed, the animals must be euthanized according to established

humane endpoints, the first appearance of such criteria in China's policies. To date, the concept of laboratory animal welfare and the 3Rs has been well accepted by scientific community.

**India.** The Government of India considered harmonization of the ethical use of animals during experimentation a necessity. Therefore, a sound and cohesive regulatory framework for the use of animals in research was formulated by the Government of India with the help of members from the scientific community, animal welfare groups, and veterinarians. Experimentation on animals in India is regulated by the CPCSEA, a statutory body under the Prevention of Cruelty to Animals Act, 1960. The persons and institutes engaged in scientific experiments on animals must act in conformity with the provisions of the Prevention of Cruelty to Animals Act and the Breeding of and Experiments on Animals (Control and Supervision) Rules, 1998 (<http://envfor.nic.in/legis/awbi/awbi10.html>). These provisions are enforced by an independent committee, CPCSEA, the Ministry of Environment and Forests, and the Government of India (<http://envfor.nic.in/division/committee-purpose-control-and-supervision-experiments-animals-cpcsea>).

CPCSEA is constituted under Section 15 of the Prevention of Cruelty to Animals Act. The main mandate of the Committee is to ensure that animals are not subjected to unnecessary pain or suffering before, during, or after the performance of experiments on them. CPCSEA functions within the ambit of the Act and the Rules for Breeding of and Experiments on Animals (Control and Supervision), 1998 (amended in February 2001). The CPCSEA has formulated guidelines for experimentation on animals, with animal welfare as its utmost concern. The main aim of these guidelines is to ensure humane and ethical treatment of animals as legitimate scientific research on animals is performed. The goal is to promote the humane care of animals used in biomedical research and to provide information that will enhance animal wellbeing, the quality of biomedical research, and the advancement of scientific knowledge that is relevant to humans or animals. The approval of animal facilities by CPCSEA is mandatory for premises where experiments are to be conducted (Rule 5 of the Breeding of and Experiments on Animals [Control and Supervision], 1998). Most of the animals used for experimentation are under the purview of CPCSEA. Specifically, any animal in the evolutionary scale or phylogenetic scale higher than invertebrates in terms of level of sentience—such as rats, mice, birds, and farm animals—is subject to regulation. The relative sentience of different species of animals is considered to be as follows: invertebrates (for example, cockroaches) < birds < rodents < canines and felines < bovines and equines < primates (for example, rhesus monkey) < more evolved primates (for example, chimpanzee).

Every establishment constituted and operated in accordance with the procedures specified by the CPCSEA is required to constitute an Institutional Animal Ethics Committee (IAEC) in accordance with Rule 13 of the Breeding of and Experiments on Animals (Control and Supervision), 1998. The IAEC, after granting permission for conducting experiments on animals, will evaluate the projects for their validity and examine the effective implementation of the 3Rs. Rule 9 (bb) of the Breeding of and Experiments on Animals (Control and Supervision) Rules (1998) suggests that the species that is lowest on the phylogenetic scale and that gives scientifically valid results should be first considered for any experimental procedure, and the experiment should be designed using the minimum number of animals to yield statistically valid results at a 95% degree of confidence. In addition, replacement alternatives not involving experiments on animals should be given due and full

consideration and “sound justification must be provided in case alternatives, though available, are not used.” Similarly, Rule 9 (cc) of Breeding of and Experiments on Animals (Control and Supervision) Rules (1998) deals extensively with the welfare of animals during experimentation. The CPCSEA has developed a standard operating procedure for IAEC to assist them in appropriately discharging their duties.<sup>12</sup>

The aftercare and rehabilitation (a fourth R) of some species of animals (currently, nonhuman primates and dogs) after use in scientific experiments is mandatory, and investigators are designated as having this responsibility according to Rule 9 (cc) of the Breeding of and Experiments on Animals (Control and Supervision), 1998. Rehabilitation of an animal after experimentation extends until such time that the animal is able to resume a normal existence, and investigators discharge their duty by providing a lump-sum amount as costs for rehabilitation and care of such animal to cover its entire statistically expected life span. A list of qualified nongovernmental organizations with rehabilitation experience is planned to assist in this process.<sup>42</sup> Several criteria have been identified that would exclude an animal from a rehabilitation program (for example, untreatable infectious disease, chronic ill health, abnormal behavior, and so forth). Under the auspices of the CPCSEA, hundreds of animals have been “rehabilitated and homed.”<sup>43</sup>

## Implementing the 3Rs in the Conduct of Research

**Brazil.** According to Brazilian law, the methods by which the investigator addresses the 3Rs in the proposed study must be described in the protocol form. In fact, the first sentence in every protocol using animals requires the affirmation that “animals will only be used if there is no alternative, and ... the number must be reduced to a minimum to give a statistically meaningful result and that they will not submit the animals to pain or suffering” (Rivera, personal observation). The principal investigator must document consideration of non-animal alternatives or a species lower on the phylogenetic scale. In addition, the Ethical Committee advises the researcher to consult with a statistician and to determine whether data are available in the literature that may help reduce the number of animals used. The principal investigator and other project personnel must provide the Ethical Committee with their curricula vitae and describe their roles in the project. In this manner, the Ethical Committee can assess the competence of each member of the project.

The concept of providing enrichment as a method of refining the research proposal is relatively new but is now well emphasized, as is social housing for social species of animals. Ethical Committees ask scientists to include a description of the kind of enrichment they will use and may provide the researcher with some guidance in this regard. In addition, refinement of the protocol by the inclusion of well-defined humane endpoints is now required.

Under Brazilian Law, Chapter V, Article 21, “the inspection of all activities regulated by this Law is under the responsibility of the Ministry of Agriculture, Ministry of Education, Ministry of the Environment, and Ministry of Science.” In addition, the Council for the Control of Animal Experimentation (in its Resolution no. 1, July 9th, 2010, Chapter II, Article 6, item VIII) requires that “Ethical Committees ... establish programs and realize annual inspections in order to guarantee the functioning of the facilities and that they are adequate under the norms and patterns defined by these Committees.” Additional assurance



that the 3Rs are being considered appropriately is obtained during these facility inspections.

Discussion of the 3Rs was a key topic as early as the 8th Brazilian Congress on Laboratory Animal Science (2002) and has remained a central theme of each Brazilian Congress on Laboratory Animal Science thereafter. In 2005, the Instituto Nacional de Controle e Qualidade Sanitária organized the Brazilian Meeting on Alternative Methods to Animal Use for Regulatory Purposes, where problems related to financial support for research in the alternatives area and problems in validating assays were discussed.<sup>44</sup> That was the first time that the need of establishing a Brazilian center for validating alternative methods was declared during the discussion of mechanisms of the validation process.

In 2008, Presgrave<sup>45</sup> called for the formation of a Brazilian organization that would facilitate and coordinate the development and validation of alternative methods in a manner comparable to the European Centre for the Validation of Alternative Methods (ECVAM), the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) in the United States, and the Japanese Center for the Validation of Alternative Methods (JaCVAM). He noted that, although recently approved Brazilian legislation called for considering alternatives to animal use, product safety also needed to be assured, yet there was no system to bridge these 2 goals. A Brazilian center would not only benefit in-country efforts but would be a resource to broader Latin America. Such a center would serve as a focal point of information, discussions, and training for the Brazilian scientific community.<sup>16</sup> In 2012, the Brazilian Society of Alternative Methods was formed. In September 2013, a cooperation agreement was signed that officially located the Brazilian Center for Validation of Alternative Methods within FIOCRUZ (Oswaldo Cruz Foundation) and ANVISA (Brazilian Food and Drug Administration). Shortly thereafter, the Ministry of Science, Technology and Innovation established (Ordinance No. 491) a Brazilian National Network of Alternative Methods to be coordinated by located the Brazilian Center for Validation of Alternative Methods (for validation) and INMETRO (Brazilian accreditation body for the accreditation of laboratories).

**China.** In accordance with Chinese laws and regulation, the 3Rs are required to be considered when developing and reviewing an animal study protocol. During the course of an animal study, 3Rs principles must be practiced in every step of the experiment. He<sup>23</sup> has summarized much of the progress made in developing alternatives for quality control of biologic products. More recently, Qi and colleagues<sup>46</sup> described the current status of the use of environmental enrichment as a refinement for research animals. Since 1999, the Chinese government has supported animal replacement studies.<sup>7,55,56</sup> Examples include the malignant transformation of human bronchial epithelial cells as an alternative in long-term carcinogenicity tests; research on tumor drug tolerant gene clips as a laboratory animal substitute; and the use of swordtail fish (*Xiphophorus helleri*) as a recognized research animal by the State Evaluation Committee of Fisheries Stock (Gs01003-2003), the first strain of fish approved and used in the field of quality testing in China (for example, see Liang and colleagues<sup>30</sup>). In addition, the *Limulus* amoebocyte lysate (LAL) test has been accepted as an alternative method to the rabbit pyrogen test, thereby reducing the number of rabbits used in this test.<sup>22</sup> To align with the practices of the Organization for Economic Cooperation and Development, the Chinese government is considering legislation to cease the use of animals for cosmetic testing.

The reduction of the number of animals proposed for study is strongly encouraged by government regulation agencies and is strongly promoted in the scientific community. Since 1990, state

and provincial MOST have funded the establishment of animal test information databases with the goal of sharing research results and reducing the number of animals used. The CALAS information network (<http://www.lascn.net/>) is one example of these databases. When research is funded through this mechanism, sharing of the data is required. The government has long-term and very ambitious objectives for laboratory animal science development, and the protection of laboratory animals and implementation of 3Rs practices is part of this plan.<sup>10</sup>

The selection of the most appropriate animal model, experimental design, statistical analysis method and means to provide species-specific ethologic needs, pain recognition and treatment, anesthesia and euthanasia are all essential to conduct successful and humane experimentation with animals. In China, training is required to become qualified for animal experimentation according to the MOST guideline regarding the Humane Treatment of Laboratory Animals.<sup>37</sup> The guideline and recent national standard for laboratory animal care and use sets minimal standards for housing and care, as well as for the training of personnel handling animals and supervision of experiments. The training provided generally is established by the provincial government. In Beijing, the Beijing Administration Office of Laboratory Animals (BAOLA) is responsible for providing and assessing supervisory staff training. For personnel to work with animals, they must obtain a "Position Qualification Certificate of Laboratory Animal Practitioners in Beijing."<sup>6</sup>

Generally speaking, the 3Rs are strongly advocated and promoted in the animal research community in China. The IACUC protocol is required to include the 3Rs in the animal study plan, with input from well-trained scientists and statisticians to the study design and data analysis. The 3Rs also are included in annual animal facility inspections and animal program reviews. Implementation of the 3Rs in animal research has not been achieved consistently throughout China, although these principles are very well implemented in some areas, such as Beijing and Shanghai. To address this inconsistency, CALAS has established an animal welfare subcommittee to develop a detailed 3Rs and animal welfare guideline. Rigorous implementation of the 3Rs in China is anticipated soon.

**India.** To oversee the effective implementation of these guidelines at the institutional level and to approve the project proposals for animal experimentation, CPCSEA appoints a representative to every registered institute or organization. The CPCSEA-appointed representative serves as a link between the institute or organization and CPCSEA. The primary responsibility of this representative is to oversee the welfare of the animals housed or used for experiments or breeding. The CPCSEA nominee has a key role in the interpretation, oversight, and evaluation of institutional animal care programs.

The CPCSEA nominee checks whether any cruelty has occurred during or after experimentation and whether the appropriate number or minimal number of animals has been used. The representative is familiar with CPCSEA guidelines, the concept of the 3Rs, other animal welfare issues, animal experimentation procedures, husbandry conditions, humane animal care, handling procedures, and other requirements as published in the CPCSEA guidelines. In addition, the CPCSEA nominee is familiar with alternatives and reduction and refinement procedures available in biomedical research studies or programs. The CPCSEA nominee and the IAEC jointly monitor the effective implementation of the 3Rs in the animal research.

The CPCSEA nominee and IAEC members ensure that IAEC meeting notices and associated paperwork reach principal investigators well in advance. This practice provides for de-

tailed study of the animal research protocol; when clarification is required, the CPCSEA representative contacts the institute to provide more information or clarification on the concerned project proposal. The nominee and IAEC members review the research proposal to determine whether the project is worthwhile, whether the design of the project is appropriate so that the aim can be achieved, whether the aim could be achieved by using alternate subjects, and whether the likely benefits of the project are sufficiently substantial in relation to the anticipated animal suffering. The research protocol contains information regarding the funding source, experimental design with number of animals, scientific background of the study with relevant bibliography, qualification and competence of staff members, type of anesthesia and analgesia used in the experiment, surgery details, postoperative care details, justification for surgery, and details of euthanasia. The use of any hazardous or infectious materials in animals should be appropriately justified. The investigator must declare that alternatives to animals and the use of lower species on the phylogenetic scale were given due consideration before proposing the species listed in the protocol.

According to the CPCSEA guidelines, the representative should inspect the animal facility at least once in a calendar year and submit the report in the prescribed form to CPCSEA office within a month from the date of inspection. During the inspection, the nominee evaluates the veterinary care of animals, health status of animals, animal procurement, quarantine and stabilization, temperature, humidity, ventilation, lighting, caging or housing system, sheltered or outdoor housing, food, bedding, water, waste disposal, recordkeeping, anesthesia, euthanasia and details of rehabilitation facilities. In addition, the IAEC conducts periodic postapproval monitoring of animal experimentation. These 2 mechanisms help to ensure sustainable implementation of the 3Rs.

### Training in the 3Rs

**Brazil.** In general, training of personnel is provided by the Ethical Committees of the institutions and by the Brazilian Laboratory Animal Science Association (SBCAL/COBEA). Many universities require completion of a course on laboratory animal science before the researcher can begin an experiment using animals. In this training, ethical considerations and the 3Rs are mandatory elements of the curriculum.

The 3Rs are always a theme included in congresses, symposia, meetings of the various colleges such as the Biology College, Veterinary, Medicine and others. In addition, the webpages of Ethical Committees contain links to or suggestions for different sites to assist in the identification of alternatives, refinements, and so forth. Furthermore, books containing 3Rs-specific content are increasingly available and used as reference texts by students.<sup>1,18,28,48</sup>

**China.** Since 1978, China has been working toward conforming with international standards regarding ethics in animal research. Seminars are frequently held to exchange knowledge and institution-specific experience in the implementation of the 3Rs, including topics such as telemetry and animal welfare (<http://www.la-res.cn/la-res/website/index.jsp>). Prominent foreign scholars in animal welfare often are invited to present at these animal welfare and 3Rs conferences (for example, <http://www.baola.org/ContentDetail/tongz.aspx?CategoryId=3&contentId=1191>). In 2003, the first Symposium on Welfare and Resource Diversity of Laboratory Animal was convened in Beijing. Since then, a Beijing international symposium on animal welfare is held regularly and attracts participants from around the world. During the 6th International Forum on Laboratory

Animal Science and Technology in Beijing in 2013, prominent laboratory animal scientists and veterinarians from different institutions shared their knowledge and experience regarding animal welfare and 3Rs.

Other resources also are available to provide training in the 3Rs. Textbooks regarding laboratory animal welfare and farm animal welfare have been compiled and are taught in colleges.<sup>22</sup> More than 20 prominent laboratory animal science journals are circulated and serve to introduce and exchange best-practice information for animal welfare and the 3Rs in the scientific community.<sup>22</sup> Laboratory animal welfare subcommittees are established in many provinces and municipal cities, such as Beijing and Shanghai, and many websites are dedicated to providing updated animal welfare practice and 3Rs information (for example, <http://www.lascn.net/>).

In 2001, MOST issued the Regulation on the Management of the Laboratory Animal License System,<sup>35</sup> which is considered to be another milestone in Chinese laboratory animal research oversight. Under this regulation, a person who works with laboratory animals must receive training and a license from the local administrative office of laboratory animals. Implementation of the 3Rs is required by the MOST guideline for the humane treatment of laboratory animals<sup>37</sup> and is included in the most recent draft of national standards for laboratory animal care and use.<sup>9</sup> To obtain an animal use license, a person needs to attend five days of government-provided training courses and take a daylong test that includes, among other topics, animal welfare and the 3Rs.

**India.** The Indian Council of Medical Research established the Laboratory Animal Information Service at the Indian Cancer Research Centre (now called the Advanced Centre for Treatment, Education and Research in Cancer). This facility performed the first-ever survey of the conditions of animal facilities in the country and started regular courses at the junior level for animal handling and experimentation (for background on the survey, see <http://www.inteqsolutions.com/ninindia.org/nclas.htm>). This facility was transferred to the National Institute of Nutrition–Hyderabad and renamed as the National Centre for Laboratory Animal Sciences in 1976. The Centre provides training for the junior and senior level animal facility personnel, although a dearth of trained manpower at the junior and senior levels remains at many facilities. Laboratory animal science is an emerging field in India and consequently had not been included in the curricula of graduate courses in the country, be they veterinary, medical, pharmaceutical, or in any bioscience. However, due to the unprecedented growth in the use of laboratory animals in the last decade, several veterinary schools have begun to include laboratory animal medicine and management in the veterinary education syllabus. In addition, in recent years training programs based on courses held by the Federation for Laboratory Animal Science Associations have been organized in India.

The Government of India established the National Institute of Animal Welfare in Ballabgarh (Haryana) to promote awareness and disseminate information about animal welfare to the public and to impart education in this discipline in a professional manner. The Institute has been conceptualized as an apex body in the field of animal welfare, and its broad mandate covers the need to improve animal welfare through research, education, and public outreach. More than 2500 organizations are registered with the Animal Welfare Board of India as being involved in the field of animal welfare. It is envisaged that the Institute will provide training and education on diverse subjects in animal welfare, including animal management, behavior, and ethics (<http://www.niawf.org/>).



envfor.nic.in/division/national-institute-animal-welfare-niaw). Indian scientists from various backgrounds and branches of science have joined together and started a network for promoting alternatives and welfare in animal experimentation ([www.fiapo.org/scnetwork.php](http://www.fiapo.org/scnetwork.php)). Several animal welfare organizations are promoting the use of alternatives in animal experimentation, including the Federation of Indian Animal Protection organizations (<http://www.fiapo.org/experimentation.php>).

## Evolution of the Awareness and Implementation of the 3Rs

**Brazil.** An early objective of training in the 3Rs was to change personal mindsets and institutional culture with regard to what constitutes quality science and how that quality is inextricably linked to animal welfare. Great progress has been made in achieving this goal, although not every scientist has embraced the principles of the 3Rs, the majority has. Although this journey to full implementation is long, and considerable work remains, the 3Rs have become embedded in the Brazilian scientific culture.

One of the most important outcomes in Brazil regarding the implementation of the 3Rs has been its effect on education. The Law 11794/08 states that live animals should not be used in teaching if alternatives exist. As a result, teachers have begun to seek and to use alternatives instead of animals, enthusiastically accepting the concept of the 3Rs. The majority of university physiology and pharmacology classes use alternatives and, although the precise number is unknown, the number of animals used in education in Brazil has decreased dramatically. In addition, those educators who still use animals in their classes (for example, those in veterinary schools) are very aware of the need to avoid causing pain or suffering in the animals used. The far-reaching benefits of this understanding are obvious, because this approach serves as the example for the next generation of educators and scientists, who will use animals in a more humane way, having the 3Rs as a guide.

**China.** The first known appearance of laboratory animals in China dates back 1918, when Dr. Changqing Qi bred mice for experiments. Thereafter many murine strains were brought to China from India, Japan, the United Kingdom, and the United States. When the Communist Party assumed power in 1949, many more inbred murine strains were developed.<sup>52</sup> Modern laboratory animal science in China has undergone rapid development since the early 1980s, with the government's policy of reform and openness. In the 1980s, Dr. Ruishan Liu and his colleagues established CALAS. The first national laboratory animal science conference took place in 1982; the Ministry of Health issued the first laboratory animal research regulations in 1983; and the Statute on the Administration of Laboratory Animal Use was promulgated by Decree Number 2 of the State Council in November 1988. Meanwhile, the State Council entrusted MOST to oversee the animals in research.<sup>26</sup> Thereafter, local provincial departments of science and technology assumed similar statutes to strengthen oversight. Through these measures, institutions that use animals in research, teaching, or testing are subject to both ministerial and provincial laws and regulations. Over time, many animal research regulations, policies, and national standards have been issued. Meanwhile, scientific organizations, such as CALAS and local societies for laboratory animal science, play a role in facilitating administration, policymaking, and promoting knowledge exchange for animal welfare in China.

Since 1994, the China State Bureau of Technical Supervision has issued over 100 national standards (GB) that address

quality control for laboratory animal microbiology, genetics, diet, animal facilities, and individual animal species such as SPF chickens and nonhuman primates.<sup>6</sup> The upcoming implementation of GB for laboratory animal institutions—"General Requirements for Quality and Competence"—contains detailed requirements for an institutional animal care and use program such as institutional policies, employee occupational health and safety, the animal facility, animal husbandry, veterinary care, special facilities, and animal welfare, and so forth. The content of this new GB is approximately 95% similar to the 8th edition of the *Guide*,<sup>24</sup> including references to the 3Rs, indicating that China aims to align with international practices and standards in laboratory animal research.

**India.** The CPCSEA has incorporated the 3Rs as a foundation for formulating guidelines and for evaluating animal research protocols (Breeding of and Experiments on animals [Control and Supervision] Rules 1998). Accordingly, investigators must justify the selection of the animal model and the number of animals required, with appropriate experimental design, in the research protocol. In addition, investigators should describe in the protocol the qualifications and competency of the personnel who will carry out the experiment. It is mandatory to declare that no other alternatives are available before animal experimentation. IAEC members critically evaluate research protocols for effective implementation of 3Rs prior to proposal approval. CPCSEA representatives inspect animal facilities once each year and report to CPCSEA regarding their compliance. Typically scientists in India are trained by their respective institutes and encouraged to attend the periodic training programs conducted by CPCSEA and other universities. In addition, CPCSEA trains IAEC members, and all CPCSEA nominees must attend the training program conducted by the National Institute of Animal Welfare. Ever since the implementation of CPCSEA guidelines and due to the continued efforts of CPCSEA, awareness among Indian scientists is steadily increasing, and most of the scientists who are using animals in biomedical research in India are aware of the guidelines and the 3Rs.

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