ILAR Journal, 2016, Vol. 57, No. 3, 301–311

doi: 10.1093/ilar/ilw018
Article

Laboratory Animal Laws, Regulations, Guidelines and Standards in China Mainland, Japan, and Korea

Bryan E. Ogden, Wanyong Pang (William), Takashi Agui, and Byeong Han Lee

Bryan E. Ogden, DVM, is Director of the SingHealth Experimental Medicine Centre and an adjunct associate professor in the Research Department at Duke-NUS Medical School in Singapore. Wanyong Pang (William), BVM, MS, PhD, is Director of Animal Research and Welfare, DSAR, in Sanofi Research & Development, Sanofi China in Beijing, China. Takashi Agui, DVM, PhD, is a professor in the Laboratory Animal Science and Medicine and Department of Disease Control at Hokkaido University School of Veterinary Medicine in Hokkaido, Japan. Byeong Han Lee, DVM, MS, PhD, is Chief Researcher in the Laboratory Animal Center at Osong Medical Innovation Foundation in Seoul, Korea.

Address correspondence and reprint requests to Dr. Bryan E. Ogden, Singapore Health Services Pte Ltd, SingHealth Experimental Medicine Centre, 20 College Road, The Academia, Level 6, Discovery Tower, Singapore 169856 or email bryan.ogden@singhealth.com.sg.

Abstract

China, Japan, and Korea have spent decades developing and amending laws, regulations, and guidelines to address the humane care and use of laboratory animals. This process began in 1983 in China, 1973 in Japan, and 1991 in Korea and has continued to the present. The governmental oversight of research varies between these countries, ranging from regulations by multiple levels of government in China to self-regulation under multiple government guidelines in Japan. Common to all is incorporation of the internationally recognized principles of the 3Rs: replacement, reduction and refinement. This paper reviews how the framework of laws, regulations, and guidelines evolved in each of these countries, their current status, and the expectation that they will continue to evolve.

Key words: animal research; China; guidelines; Japan; Korea; laboratory animal; laws; regulations

Introduction

The Laws, Regulations, and Guidelines for Animal Research in China Mainland (China), Japan, and South Korea (Korea) will be discussed in this chapter. Each country recognizes modern society's ethical concerns over the use of animals in research and each has developed their own regulatory framework to support the humane care and use of laboratory animals. While there are significant differences in how these have been developed and implemented in each country, they are based on basic ethical principles similar to those promoted in Western countries. Laboratory animal societies in each country have contributed greatly to the evolution of laws, regulations, and guidelines in their respective countries, resulting in continued improvements to the welfare of research animals and ultimately the quality of science.

China Mainland (China)

Laboratory animal science (LAS) and biomedical research utilizing animals have developed tremendously in China in the recent decades. Animal research in China is currently regulated and administratively managed according to national and provincial laws, regulations, guidelines, and standards. In China, the People's Congress is the legislature; therefore, the National

People's Congress and provincial People's Congresses, respectively, approve and issue national and provincial laws. The State Council approves and issues administrative statutes, and the ministries and provincial governments issue national and provincial regulations/bylaws/rules, respectively. The ministries, provincial governments, and industries issue national, provincial, and industrial standards, respectively. Laboratory animal affairs are regulated and administered in an integrated and multi-tiered governmental system (Table 1). In 1983, the Ministry of Health of China issued the very first LAS regulations (Ministry of Health 1983), and in 1988 the Commission of Science and Technology (which had been renamed as Ministry of Science and Technology [MOST]) issued the Regulations for the Administration of Affairs Concerning Experimental Animals, hereafter abbreviated as AdminReg (Ministry of Science and Technology 1988). Most provinces, municipalities, and autonomous regions issued similar regulations to implement and strengthen oversight. Therefore, according to the AdminReg, the regulation and administrative oversight for laboratory animals reside in MOST and in provincial bureaus of science and technology (BOST). The information with respect to laboratory animal regulation and administration system in China; AdminReg; mandatory licensure system; laboratory animal welfare; laboratory animal standards and quality control system; quarantine, infectious disease control, and biosafety; laboratory animal seed centers and breeding centers; genetically modified animals; import, export, and transportation; qualified staff; and voluntary accreditation programs are introduced and briefly discussed as follows.

Laboratory Animal Regulation and Administration System in China

In China, laboratory animals are defined as any animals bred and reared according to relevant standards and intended to be used in experiments or for other scientific purposes (GB14925-2010, Oct 1, 2014). While this definition does not specifically exclude invertebrates, the focus of enforcement in China is mainly vertebrate animals. Laboratory animals must have defined genetic background or clear sources and be subject to control of their health status and the microorganisms and parasites they may carry. MOST is in charge of all relevant activities, including breeding, use, testing, experimentation, and laboratory animal-related products (Fig. 1). In addition, provincial or municipality BOST oversee laboratory animal administration in each province or municipality, usually through an administration office of laboratory animals to implement policies, manage licensures, and oversee related affairs. The other ministries that are involved in animal research (such as the Ministries of Health, Education, and Agriculture) also have relevant guidelines and take responsibility for the care and use of animals in their laboratories. The LAS associations/societies and the national and provincial laboratory animal quality

Table 1 A brief list of laboratory animal regulations, guidelines and standards in China

Type of regulation	Title of regulation	Issued by
AdminReg	Regulations for the Administration of Affairs Concerning Experimental Animals	MOST
Ministerial bylaws/ departmental rules	Laboratory Animal Quality Management	MOST and National Tech Supervision Bureau
	Laboratory Animal License Management Regulations	MOST, etc.
	State Laboratory Animal Seeds Center Management	MOST
	Guidelines on Humane Treatment of Laboratory Animals	
	The Approach to Research Misconduct during the Implementation of National Science and Technology Plans	
Local statute	Regulations for the Administration of Laboratory Animals	Such as People's Congress in Beijing, Hubei, Yunnan, and Heilongjiang
Local bylaws	Local Admin Policies for Lab Animals	Local governments
Standards	Departmental Admin Policies for Laboratory Animals	Central government departments
Tech standards	National Standards (GBs) for Laboratory Animals	AQSIQ
	Local Standards for Laboratory Animal Quality Control and Testing	Local governmental supervision agencies

Table 2 Laws, guidelines, and standards on the care and use of animals in research, testing, and education in Japan

Laws, Guidelines, or Standards	Year
Act on Protection and Management of Animals	1973
Renamed and amended: Act on Humane Treatment and Management of Animals	1999
	2005 (amended)
	2012 (amended)
Standard Relating to the Care and Management of Laboratory Animals and Alleviation of Pain, by Ministry of Environment	2006
Fundamental Guideline for the Conduct of Animal Experimentation in Research Institutions, by Ministry of Education, Culture, Sports, Science and Technology	2006
Fundamental Guideline for the Conduct of Animal Experimentation in Research Institutions under the jurisdiction of Ministry of Health, Labor and Welfare, by Ministry of Health, Labor and Welfare	2006
Fundamental Guideline for the Conduct of Animal Experimentation in Research Institutions under the jurisdiction of Ministry of Agriculture, Forestry and Fisheries, by Ministry of Agriculture, Forestry and Fisheries	2006
Guidelines for Proper Conduct of Animal Experiments, by Science Council of Japan	2006

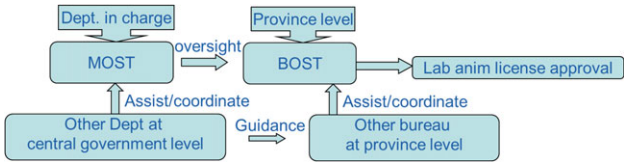

Figure 1 Laboratory animal administration system in China (based upon the AdminReg, 1988). The State Council (i.e., the Central People's Government of P.R. China) has 25 minstries and 17 ministry-level adminstrations/bureaus. The Premier, on behalf of the State Council, is responsible for the National People's Congress and its Standing Committee. There are 31 provinces/municipalities/autonomous regions in mainland China, and each has its local People's Congress and local governments (reporting to the central government and responsible for the corresponding congress). These local governments have relevant bureaus/departments, which report to the local government and functionally report to central governmental ministries.

monitoring centers promote industry self-discipline and laboratory animal quality control (Kong and Qin 2010).

AdminReg

The AdminReg (Order No. 2; Ministry of Science and Technology 1988), as approved by China's State Council and issued by MOST, is the supreme regulation that directly regulates every aspect of laboratory animal care and use. This regulation covers animals that are purpose-bred for use in scientific research and teaching, including the authorized competent government body (i.e., MOST and BOSTs); the classification of laboratory animals based upon their microbiological status (i.e., conventional, clean, specific pathogen free [SPF], and germ free); quarantine and infectious disease control; the provision of suitable housing; feeding and breeding facilities; qualified staff; the use of certified animal breeds and strains; restrictions on the import and export of laboratory animals; safe and reliable transport of animals; quality monitoring and accurate documentation; occupational health and safety; penalties for violation of the regulations, etc. Those who violate the regulation are subject to disciplinary actions such as warning, mandatory modification, or even revocation of license. The relevant central governmental agencies and provincial government bodies may also develop regulations and policies in order to implement this AdminReg, such as the implementation plan issued by the Ministry of Health in 1998. The AdminReg has been under revision recently, and it is expected that laboratory animal welfare and the replacement, reduction and refinement (3Rs) principles will be incorporated into the new regulation.

Mandatory Licensure System

In China, there are two types of licenses, facility license (a breeder or user license, or both) and personal license. All institutions related to breeding, using, selling, and transporting laboratory animals have to apply and receive a license before they can start to run their business in China. In the licensed facilities, the personnel related to care or use of laboratory animals must be trained and pass the examination; the physical facilities are also tested and must meet the national standards.

The Regulation on the Management of Laboratory Animal Licenses (Ministry of Science and Technology 2001) details requirements and processes for license application, review, and approval and for facility inspection and supervision. Licenses are administered by the BOSTs (usually through the administrative office of laboratory animals), which review license holders annually by site visits and reports (Ministry of Science and Technology 2001). In Beijing (Beijing Municipal Bureau of Science and Technology 2005), for instance, the application package (e.g., certificate for laboratory animal use) includes a laboratory animal use certificate application form; an Institutional Animal Care and Use Committee (IACUC) organization chart; standard operating procedures on laboratory animal care and use, and facility operations; a laboratory animal environment testing report issued by a government-certified laboratory or a third party laboratory; a list of certified laboratory animal personnel and their certificate numbers; the vivarium floor plan; the annual health check certificate of laboratory animal personnel and annual professional training schedule; and policies on animal welfare, biosafety, and ethical review. Site evaluation by an expert panel is usually conducted using a checklist, with reference to relevant national standards.

Laboratory Animal Welfare

The China Food and Drug Administration Good Laboratory Practice (GLP) regulations have requirements concerning animal facilities and animal care and use for animals employed in GLP studies (China Food and Drug Administration 2003). The Chinese Veterinary Medicine GLP regulations, which took effect on Dec 9, 2015, mandated the establishment of an institutional animal welfare review body and basic animal husbandry requirements in nonclinical research of veterinary medicines (government bulletin no. 2336, Ministry of Agriculture).

The Guideline on the Humane Treatment of Laboratory Animals is the country's first such guidelines with consideration for laboratory animal welfare (Ministry of Science and Technology 2006). This guideline is applicable to laboratory animal-related institutions and individuals in China. The guideline promotes 3Rs principles and requires each institution to establish an IACUC or ethics committee to oversee their animal care and use program. Five aspects of animal welfare are described, which include general requirements, husbandry, experimentation, transport, and implementation measures. Specifically, the guideline mentions the following: space allowance (to allow natural behaviors) plus environment enrichment; exercise opportunity for large animals such as nonhuman primate (NHP) and canine; promote development and implementation of alternative methods to minimize animal fear and pain; restraining and restraint devices; humane endpoints; humane euthanasia (not in front of other animals); use NHPs only if have to and "retirement" care for NHPs. Implementation measures include administrative licensure system, IACUC approval of protocols before execution, and personnel training.

Some provinces have guidelines on ethics review or IACUC protocol review, such as the Guide of the Beijing Municipalities for the Review of Laboratory Animal Welfare and Ethics (Beijing Administrative Office of Lab Animal 2006). Any activity involved with animal husbandry and animal experimentation shall start only after approval from the committee and is expected to receive routine supervision (i.e., postapproval monitoring). The composition, independence, roles, and responsibilities of an IACUC or ethics committee are described in this guide, and recommendations on general principles for protocol review are also provided. Applicants can request to be present during the review of their protocol for answering questions and can make a proposal for specific member(s) who may violate confidentiality or impartiality of the review to recuse themselves.

The final draft of Laboratory Animals—Codes of Welfare and Ethics, the potential first ever National Standard on Laboratory Animal Welfare in China, had been submitted to the National Technical Committee on LAS, Standardization Administration of China for review. It is expected that the standard will be approved for implementation in 2016. The National Standard will regulate the welfare and ethical review and administration, with respect to the production, transportation as well as the utilization of the laboratory animals, including the technical requirements for the ethics review body, the principles of ethical review, personnel qualification, facilities, responsibilities of the veterinarians, resources, technical procedures, animal care and use, occupational health and safety, transportation, recommended ethical review processes and criteria, and records and documentation. The codes are applicable to the review as well as the quality management of the laboratory animal welfare and ethics (W. Pang, Sanofi China, personal communication, 2015).

The Ministry of Agriculture (MOA) has assigned the Chinese Veterinary Medical Association to draft welfare requirements of laboratory animals, a standard that is applicable to the animals used in agricultural research. The main references for this standard are OIE Terrestrial Animal Health Code and EU Directive 2010/63. The standard is under final review at MOA (W. Pang, Sanofi China, personal communication, 2015). This standard, as a minimum recommendation on laboratory animal welfare, could be applicable to all veterinarians no matter what industry sector they are working in, since the veterinarians are regulated in China by the MOA.

Laboratory Animal Standards and Quality Control System

All animal experiments must use qualified and certified laboratory animals, according to the AdminReg. In 1994, The State Technology Supervision Administration issued 47 National Standards for Laboratory Animals that were revised in 2001, reflecting the global advancement in LAS, while the number of national standards increased to 83. The Standardization Administration of China established a National Technical Committee on LAS in 2005, and about 100 standards had been set up for laboratory animal quality control covering microbiology (68, including virology, bacteriology, and parasitology, and sampling and testing methodologies), genetic quality control of mammalian laboratory animals (3), feed (12, including testing methodologies), facilities and environment (2, including facilities and building techniques), and SPF chickens (10, including microbial control and testing methodologies). These national standards are mandatory recommendations and are referred to wherever appropriate with regard to laboratory animals, such as when the China FDA is certifying GLP labs. These standards are mostly engineering standards, leaving very limited flexibility for a performance standards approach.

The other governmental bodies, such as the MOA and Commission of Health and Family Planning, have their own laboratory animal quality standards. In addition, some of the more developed municipalities and provinces, such as Beijing (laboratory fish and minipig standards, technical requirements for laboratory animal environment and facility), Shanghai (laboratory minipig standards), Guangdong (laboratory animal microbiologic testing, laboratory animal diet standards, and macaques care standard), Jiangsu (caging standards, laboratory pig standard), and Yunnan (tree shrew standards) developed and implemented their own standards (Quality Standards 2015).

A national laboratory animal quality control network was established according to the relevant regulations (Beijing Administrative Office of Lab Animal 2006) on the management of laboratory animal quality control (Ministry of Science and Technology 1997). About 6 national and 26 local laboratory animal quality-monitoring centers were established, with oversight from MOST and relevant BOSTs. The tasks of these centers are to explore research on testing methodologies, train technical staff, and improve the quality of such monitoring.

Quarantine, Infectious Disease Control, and Biosafety

All laboratory animals are subject to isolation and quarantine for infectious disease control before their entry into destination buildings or laboratories. The relevant vaccination programs and infectious disease control policies (People's Congress of China 2008; Ministry of Agriculture 2002; State Council 2005) should be followed according to laws on animal disease prevention and control, etc. The biosafety regulation for laboratories involving microbiologic pathogens (State Council 2004; State Administration of Environmental Protection 2006; National Standards Committee 2008) should be followed, as appropriate. The regulation on medical waste disposal (State Council 2003a) is probably the only such regulation relatively applicable to wastes generated in laboratory animal production and research.

Laboratory Animal Seed Centers and Breeding Centers

Laboratory animal seed resources in China are maintained and managed according to the Regulation on the Management of Laboratory Animal Quality (Ministry of Science and Technology 1997). Through these laboratory seed centers (covering rodents, genetically modified mice, rabbits, miniature pigs, beagle dogs, SPF chickens, NHPs, and aquatic and special animals), MOST administers and regulates the importation, maintenance, and exportation of laboratory animals (Ministry of Science and Technology 1998, 1999).

Genetically Modified Animals

Regulation on the Administration of Genetic Engineering Safety (MOST 1993) and Safety Administration Implementation Regulation on Agricultural Biological Genetic Engineering (Ministry of Agriculture 1996), and the Regulation on the Import and Export of Transgenic Products (AQSIQ 2004) should be complied with in order to prevent genetic contamination of humans, the environment, and the ecosystem. These regulations define biosafety levels and evaluation, application, safety control methods, and penalties.

Import, Export, and Transportation of Laboratory Animals

Institutions that plan to import breeding animals from overseas as laboratory animal seed stock must register in the designated laboratory animal seed centers administered by MOST (Ministry of Science and Technology 1999). Units that plan to export laboratory animals must make an application to the relevant BOST before exportation.

The quarantine of imported and exported laboratory animals is covered by the Entry and Exit Animal and Plant Quarantine Law and regulations (People's Congress of China 1992;

State Council 1996), Wild Animal Protection Law (People's Congress of China 2004), Convention on International Trade in Endangered Species of Wild Fauna and Flora (the office of which is affiliated with the General Administration of Forestry in China), and Quarantine and Health Requirements for SPF Animals to be Imported into China (AQSIQ; trial, W. Pang, Sanofi China, personal communication, 2015), and quarantine and health requirements for SPF animal genetic material to be imported into China (AQSIQ, trial, W. Pang, Sanofi China, personal communication, 2015).

The transportation of animals should comply with the AdminReg, Guideline on the Humane Treatment of Laboratory Animals (Ministry of Science and Technology 2006), and relevant International Air Transport Association requirements. An animal health certificate/quarantine certificate is needed from a local, competent veterinary authority for cross-province animal transport in China and international transport (Civil Aviation Administration of China 1996; Ministry of Agriculture 2010; People's Congress of China 2008). It is important to note that for cross-province purchase and transport of NHP, an application must be submitted to and an approval be granted from the local competent forestry authority (General Administration of Forestry 1998; People's Congress of China 2004).

Qualified Staff

Laboratory animal institutions must have qualified managers, veterinarians, scientific staff, and technicians. They must have regular medical checks, receive training and obtain a personal license before caring and handling animals, and must care for the animals in a humane manner (Ministry of Science and Technology 1988). The person has to attend the training (as per the curriculum recommended by BOSTs) and pass the examination in order to be granted a personal license, which is valid for 5 years. The license can be renewed after receiving continuous training and passing a recertification exam.

Veterinary licensing in China started in 2009. Eligible candidates have to take and pass the Chinese veterinary licensing examination in order to be licensed to practice veterinary medicine in China (Ministry of Agriculture 2008).

The Chinese Association for Laboratory Animal Science proposed a national standard on qualifications of staffing in the LAS field, covering the different levels of eligibilities and certifications of laboratory animal veterinarians and animal technicians. The final draft was submitted to the National Technical Committee on Laboratory Animal Science of the Standardization Administration for review. However, the Chinese government has initiated a reforming plan (to streamline and reduce governmental administrative management) that will impact whether this will be approved and issued as a mandatory national standard per se. It will likely be published as a society or industry standard. It is not clear currently whether and how foreign credentials, qualifications, and certifications, such as the ACLAM board certification, US vet license, laboratory animal technician certifications from AALAS, etc., would be recognized in China.

Behaviors such as abuse or teasing of laboratory animals are strictly prohibited and subject to punitive measures (Ministry of Science and Technology 2006). Institutions must have plans for continuous training of staff according to their job requirements to ensure that they have the current knowledge to perform their duties.

Voluntary Accreditation Programs

In 2006, AAALAC International accredited its very first animal care and use program in China. As of early 2016, there were approximately 60 AAALAC-accredited units in China. Those units refer to and follow the Guide (ILAR 2011) recommendations.

Certification and accreditation in China are governed by the Certification and Accreditation Regulation of China (State Council 2003b). There is a national standard entitled "Laboratory Animal Institutions: General Requirements For Quality and Competence" (Standardization Administration of China 2014), which was proposed and administered by Technical Committee 261 of the Standardization Administration of China. The standard became effective in October 2014. By referring to internationally recognized management tools and scientific achievements, this standard aims to guide the laboratory animal institutions to realize scientific and humane treatment and reduce or avoid use of animals through management of the processes involved in the full cycle of animal breeding and use. In addition, this standard aims to assure the quality of laboratory animals and animal experiments; guarantee the occupational health of their staff, safety, and environment friendliness; and promote the development of scientific undertakings. The China National Accreditation Service for Conformity Assessment has initiated a trial accreditation program using this standard as the reference, though such accreditation is not mandatory. This voluntary accreditation program is similar to the Good Animal Practice program of the Canadian Council on Animal Care.

In conclusion, there are laws, statues, regulations, standards, and guidelines that cover almost every aspect of LAS in China, including mandatory licensing and quality control, laboratory animal welfare, occupational health and safety, staff qualifications, and biosafety. In short, the Chinese LAS laws/regulations/standards/guidelines are a combination of performance and engineering standards, with a heavier focus or emphasis on engineering standards.

Japan

In Japan there is one main law to regulate the use of animals in research, testing, and education and several ministry guidelines to provide administrative guidance (Table 2). In addition, there are numerous voluntary guidelines provided by various organizations. The main law is the "Act on Humane Treatment and Management of Animals," which mandates a self-regulation system for animal experimentation. The emphasis in Japan is on promoting animal welfare practices compatible with scientific needs without strictly stipulating them by law. Rather, Japan relies on self-regulation within each animal facility with administrative guidance and voluntary guidelines to encourage flexible animal research (Kagiyama and Nomura 2004; Nomura 1995; Shoji 2007). The history and evolution of the law and guidelines are summarized below.

Act on Protection and Management of Animals

The law, established in 1973, was originally named the "Act on Protection and Management of Animals". Before establishing this law, Japan was receiving criticism from foreign, developed countries, because there was no legislation or guidelines relating to animal protection, including the use of animals in research, testing, and education. The 1973 the law covered mammals, birds, and reptiles owned by people, but did not cover amphibians and fish. This law described mostly companion animals and

contained only one article, Article 11, describing measures when using animals for scientific purposes. In Article 11, the principal measures were equivalent to "refinement," one of the 3Rs, with no reference to the other two Rs, replacement and reduction.

Act on Humane Treatment and Management of Animals

In 1999, the original law was amended and the name changed to the "Act on Humane Treatment and Management of Animals" (Law No. 105, revised 2000). Most noteworthy in this amendment was the preamble in which animals were reconsidered as living beings, distinguishing them from human property. This greatly increased the punishment, such as the amount of fines for the cruelty to animals. In addition, because many articles concerning companion animals were added, Article 11, "Measures When Using Animals for Scientific Means," was changed to Article 24.

The next amendment occurred in 2005 (Law No. 105, revised 2005). In this version, Article 24 was changed to Article 41, because many more articles concerning companion animals were added before this article. Further, Article 41 was amended to include the 3Rs concepts. The amount of fines for violating the law were further increased, and penal servitude was added in this amendment.

The last amendment occurred in 2012 to become the present law. In this amendment, Article 41 was not changed at all, despite strong requests from groups involved in the movement against animal experimentation to make the law more strict. However, fines and penal servitude for violations did become more strict, in part to appease these groups. Despite multiple amendments, the registration of laboratory animal facilities, training of personnel, and regulatory inspections are still not required by Japanese law.

Standards Relating to the Care and Management of Laboratory Animals and the Alleviation of Pain

To ensure appropriate regulation of the use of animals in research, testing, and education, the "Standards Relating to the Care and Management of Laboratory Animals and Alleviation of Pain" (the standard) was issued from the Ministry of Environment in 2006 (Ministry of Environment 2006). This standard contains five articles. Article 1 states that "the use of animals is indispensible for the development of medical and life sciences." Article 2 defines laboratory animals as mammals, birds, and reptiles housed in a facility to be used for scientific means. It is noted that amphibians and fish are not included as laboratory animals in Japan. In other words, the use of amphibians and fish in research, testing, and education is not regulated by any law or guidelines. Although Articles 3 and 4 in the standard state some principal measures for care and use of laboratory animals, details are not provided.

Fundamental Guidelines for the Conduct of Animal Experimentation in Research Institutions

In 2006, less than 2 months after the standard was issued by the Ministry of Environment, three other guidelines were independently issued on the same day from the ministries with different jurisdictions as follows: (1) the Ministry of Education, Culture, Sports, Science and Technology, covering animal research at universities (Ministry of Education, Culture, Sports, Science and Technology 2006); (2) the Ministry of Health, Labor and Welfare, covering animal research at government facilities, pharmaceutical companies, and contract research organizations (Kagiyama, Ikeda, and Nomura 2006); and (3) the Ministry of Agriculture, Forestry and Fisheries, covering animal production facilities.

Although these three guidelines were issued separately, the contents were almost the same (Kurosawa 2007). They described more details on the care of laboratory animals than the standard; however, these details did not provide sufficient guidance on how researchers should conduct animal experimentation.

Guidelines for Proper Conduct of Animal Experiments

On the same day these guidelines were issued by the three ministries, the "Guidelines for Conduct of Animal Experiments" was issued by the Science Council of Japan (Science Council of Japan 2006). Because this set of guideline describes very detailed issues on the care and use of laboratory animals for experimentation, it is called the "unified and detailed guideline." This set of guidelines seems to be equivalent to the ILAR Guide, because most issues described in the ILAR Guide are covered by this guideline. However, there are still discrepancies between the ILAR Guide and the Japanese guidelines

Major Discrepancies between the ILAR Guide and Guidelines of the Science Council of Japan

The major discrepancies between the ILAR Guide and the Unified and Detailed Guidelines of the Science Council of Japan are summarized in Table 3. First of all, composition of the IACUC is significantly different, and the role of the IACUC in final approval of protocols also differs. In Japanese guidelines, a veterinarian and public member are not required. Also, the role of the IACUC is to review animal use protocols and make recommendations for approval to the CEO or director of the institution, but the final protocol approval is done by the director of the institution. As mentioned above, amphibians and fish are not included as laboratory animals, so researchers can use these animals in research without an approved protocol. Housing environments, including caging space, temperature, and relative humidity as well as environmental enrichment and social or individual housing, can be freely determined by researchers and a manager of the animal facility. Although several issues concerning welfare of laboratory animals, such as being free of diseases and injuries, alleviating pain with anesthesia and analgesia, establishing humane endpoint, etc. are described in the Japanese guidelines, veterinary care by an attending veterinarian is not described. This means that a veterinarian is not required for the use of laboratory animals in Japan, which may be very surprising to readers in other developed countries.

Voluntary Guidance, Accreditation, and Additional Laws

While Japanese law does not require an attending veterinarian at each facility, veterinarians and others with LAS expertise are actively involved in promoting humane, ethical animal care and use in Japan through organizations and societies providing voluntary guidance, standards, and publications (Omoe 2006). The Japanese Association for Laboratory Animal Science, the Japanese College of Laboratory Animal Medicine, and the Japanese Center for the Validation of Alternative Methods and the Japanese Society for Alternatives to Animal Experiments are included, among numerous others. Some additional laws

Table 3 Major discrepancies between ILAR Guide and Guideline of Science Council of Japan

	ILAR Guide	Guideline of Science Council of Japan
Composition of IACUC	• Veterinarian certified by ACLAM, ECLAM, JCLAM, or KCLAM or with training and experience in LAS and medicine • Researcher using animals • Nonscientist • Public member	• Researcher using animals • Specialist for laboratory animals • Others (person with experience or an academic background)
Definition of laboratory animals	• Vertebrates	• Mammals, birds, and reptiles
Housing/ environment	• Engineering recommendations for caging space, temperature, humidity, illumination, air changing rate, noise, etc. • Environmental enrichment and social housing	• No engineering recommendations • Animals should be housed as expressing species-specific behavior; however, no description of environmental enrichment and social housing
Veterinary care	• Veterinary care is an essential part of an animal care and use program • Attending veterinarian is responsible for the veterinary care	• Veterinary care is not described • Veterinarian is not required for the use of laboratory animals

and guidelines affecting animal research deal with genetically modified animals, import and export of animals, and GLP.

The importance of independent evaluation and accreditation of laboratory animal care and use has gained increased attention in Japan. In 2005 the first Japanese facility was accredited by AAALAC International and as of early 2016 there were more than 20 AAALAC-accredited facilities in Japan. The Center for Accreditation of Laboratory Animal Care and Use in Japan Health Science Foundation (Japan Health Sciences Foundation 2008) and the Japanese Association of Laboratory Animal Facilities of National University Corporations (Kojima 2009) have both established accreditation programs for Japanese animal research facilities. It is expected that Japanese animal care and use will continue to evolve towards harmonization with international standards.

Korea

Animal experiments are regulated under two main laws in Korea, which are the Animal Protection Act (APA) established by the Ministry of Agriculture Food and Rural Affairs (MAFRA), and the Laboratory Animal Act (LAA) established by the Ministry of Food and Drug Safety (MFDS). Penalties for violations can include fines and/or penal servitude.

Historical Perspective of Laws for Animal Research in Korea

The first animal welfare law, MAFRA's APA, was enacted in 1991 (Animal Protection Act 1991). However, at that time this law was primarily focused on preventing abuses of companion animals. There was only one provision dealing with research, which simply stipulated pain reduction and humane euthanasia conditions for laboratory animals. It did not include specific information related to animal experiments and enforcement of the law. Because of this, it was ineffective, lacking adequate direction and legal force. Beginning in 2003 there was an emergence in Korea of greater interest in the welfare of animals used in research. This may have been in part due to the publicity surrounding animal cloning work conducted at the Seoul National University and the introduction of the Bioethics and Biosafety Act (BSA 2005). By 2005, some universities and research institutes had voluntarily started to establish and operate IACUCs. An amendment to the APA was made in 2006 and promulgated in 2007, following a consensus process involving animal welfare groups and animal researchers. This amendment, for the first time, included establishment and composition of animal experimentation ethics committees or IACUCs and the related enforcement ordinances and regulations, giving actual legal force. Meanwhile in 2006, two legislators proposed the enactment of laws specific to animal experiments and finally in 2008, following several public hearings and meetings, the LAA of the MFDS was promulgated (Laboratory Animal Act 2008). This law was enacted to increase confidence in the ethics of animal experiments and a proper management of laboratory animals and animal facilities, including establishment of an Animal Experimentation Operating Committee, which could be referred to as an IACUC. But the amended APA and the LAA each required establishment of IACUCs with different roles and membership requirements. Therefore, many facilities that had existing IACUCs, in compliance with the APA took on the uncomfortable burden of setting up and operating a second IACUC to satisfy the LAA. To resolve this inconvenience, in 2011 the MFDS and the Animal and Plant Quarantine Agency (QIA), an affiliated organization of MAFRA, collaborated to prepare the IACUC Standard Operating Guidelines regarding the installation and proper operation of the integrated IACUC. Mutual recognition was negotiated and recently completed to allow a single IACUC to meet the requirements of both Ministries, with enforcement beginning February 2016. In 2015, the Guidelines for Reviewing Animal Study Protocols (vol. 1, rodents) were developed by the QIA and the Korean College of Laboratory Animal Medicine (KCLAM) for use by each local IACUC when reviewing rodent protocols. These guidelines were designed to encourage the welfare of animals used in biomedical research and enhance researchers' ethical awareness on the respect for life. Prior to this, Korea's animal research facilities were voluntarily using the pain level classifications of foreign countries such as the United States, Japan, and others. The need for enactment of a standard system for

classification of pain levels for all species to reflect national circumstances, while conforming to international standards, has been raised and more guidelines will be developed. In 2016, the Guidelines for Reviewing Animal Study Protocols (vol. 2, rabbits, dogs, and pigs) will be produced and distributed (B.H. Lee, Osong Medical Innovation Foundation, personal communication, 2015). Such guidelines are expected to help principal investigators as they design studies and help IACUCs as they review and approve animal study protocols.

APA Administered by MAFRA

The current APA consists of 7 chapters, 47 articles, and 128 clauses. From among these, 1 chapter, 6 articles, and 21 clauses are for animal studies. The contents of each of the articles on animal studies are as follows: Principles for Animal Experimentation; Prohibition, etc. of Animal Experimentation; Establishment, etc. of Animal Experimentation Ethics Committee; Functions, etc. of Ethics Committee; Formation of Ethics Committee; Instruction in, and Supervision over, Formation, etc. of Ethics Committee. The principles behind the APA are characterized by two main points: first is to consider the welfare of laboratory animals and the second is to establish the IACUC to monitor animal welfare. These are considered key because the well-being of the animals becomes the foundation for ensuring the reliability of laboratory animal research. The APA specifies that the IACUC consist of 3 to 15 members, including a laboratory animal veterinarian and a person with animal protection training and experience who is recommended by a nongovernmental organization selected by presidential decree. The IACUC is appointed by the CEO. This IACUC is primarily concerned with protocol review and oversight but does not specifically oversee the management of the animal care and use program or facilities.

LAA Administered by MFDS

The LAA consists of 7 chapters, 33 articles, and 47 clauses. The contents of the main articles are as follows: Duties of Operator of Animal Testing Facilities; Establishment of Laboratory Animal Management Committee; Registration of Animal Testing Facilities; Use of Laboratory Animals; Designation of Excellent Animal Testing Facilities; Guidance and Supervision on Animal Testing Facilities; Registration of Supplier of Laboratory Animals; Matters to be Observed by Supplier of Laboratory Animals; Matters concerning Importation of Laboratory Animals; Designation of Excellent Laboratory Animal Production Facilities; Guidance and Supervision on Supplier of Laboratory Animals; Education; Prevention of Disasters; Reporting on Use of Biological Harmful Substances; and Waste Matter, such as Carcass. The main target of the LAA is laboratory animals used in experiments and management of animal facilities. The LAA specifies that the IACUC be composed of 10 members, including a veterinarian and a laboratory animal scientist, to be appointed by the animal facility manager. The main objective of IACUCs under the LAA can also be described as scientific management and safety of the laboratory animals.

IACUC Standard Operating Guidelines by Both Ministries (MAFRA and MFDS)

The separate IACUC standard operating guidelines under the APA from MAFRA and under the LAA from MFDS for operating IACUCs were provided to improve the consistency of IACUC evaluation of animal study protocols and management of animal facilities, etc., and to provide accurate knowledge of animal experiments to guide IACUC members. In addition, the LAA includes the self-regulation requirements under standard operating procedures for the IACUCs of animal research institutions.

Prior to the launch of the LAA, some big institutions had already set up two separate IACUCs, one to review animal welfare and the other to review management of their animal facilities. However, most small- and medium-sized facilities had only one IACUC, primarily to review protocols, and were concerned about setting up two separate IACUCs. They wanted one IACUC to combine together the APA and LAA requirements. Until mutual recognition legislation is passed, the QIA and MFDS have finally accepted tentatively these facilities' single IACUC as long as they cover the standard operating guidelines required by both the APA and the LAA. Since 2013, there has been an effort underway to revise the APA and it is now being referred to as the Animal Welfare Act (Han and Gwi 2013).

Guidelines for Reviewing Animal Study Protocols by QIA and KCLAM

The Guidelines for Reviewing Animal Study Protocols is 38 pages long and includes classification of pain levels according to animal suffering, humane endpoints in rodents, methods for euthanasia of rodents, and other criteria for reviewing protocols. In the guidelines, the criteria on the pain classification in laboratory animals is as follows: Pain Classification A (Category A) is an experiment using dead organisms, or training or research in plants, bacteria, protozoa, or invertebrates; Pain Classification B (Category B) is training or research that does not cause distress in vertebrates; Pain Classification C (Category C) is training or research that causes only mild pain or distress for only a short period of time to vertebrates; Pain Classification D (Category D) is training or research that causes moderate to severe pain or distress to vertebrates; Pain Classification E (Category E) is training or research that is accompanied by excruciating pain or distress to vertebrates. The humane endpoints in rodents are composed of animal observation frequency and point, animal observation scoring, responsibilities of animal observation and observer's training, IACUC's role for selection of humane endpoints, guidelines according to research topics, etc. Euthanasia methods in rodents are described as the acceptable, acceptable with condition, and unacceptable methods.

Additional Influences on Animal Research

Additional influences on animal research in Korea include laws on genetically modified organisms, GLP guidelines, cosmetic testing laws, certified training by the government, education and technician certification provided by KALAS, a government certification scheme to designate excellent animal research facilities, an assessment and accreditation program by the Korean Association for Laboratory Animals, and promotion of alternatives by both the Korean Society for Alternatives to Animal Experimentation and the Korean National information Center for the 3Rs. In addition, AAALAC International accredited the first facility in Korea in 1998 and as of early 2016, there were 18 AAALAC accredited facilities in Korea. It is expected that efforts will continue to improve the quality of animal care and use in Korea.

Table 4 Comparison of laws, guidelines, and standards between China, Japan, and Korea

	China	Japan	Korea
License/registration for animal research facility	Required	Not required	Required
IACUC	Required	Recommended in guidelines, but not required by law	Required
IACUC membership	Vet and a person representing an animal protection organization	Vet and public member not required by law	Vet and one person with animal protection expertise
Role of IACUC in protocol review	Review and approve	Review and recommend approval by CEO	Review and approve
Attending veterinarian	Required	Recommended in guidelines, but not required by law	Required
Animals covered	Any animal, but focus on vertebrates	Vertebrates, excluding amphibians and fish	All vertebrates
Reporting to government	Annual	None, self-regulation	Annual
Government inspections	Annual	None, self-regulation	Guidance and supervision by MFDS
Penalties for noncompliance	Disciplinary action up to and including revoke of license	Fines and/or penal servitude	Fines and/or penal servitude
Alternatives/3Rs	Not currently included in regulations, but included in guidelines	Included	Included
College of Lab Animal Medicine Specialty Board	None	JCLAM	KCLAM

Conclusions

Significant improvements have been made in the laboratory animal research laws, regulations, and guidelines in China, Japan, and Korea. All three countries have moved closer to harmonization with international standards promoted by Western countries, though not uniformly or at the same pace. Some key differences between the laws, guidelines, and standards in these countries have been listed in Table 4. Comparisons in Tables 3 and 4, notably, show potential shortcomings in the authority granted the attending veterinarian, role of the IACUC, range of species covered, environmental enrichment, and social housing. In general, AAALAC-accredited laboratory animal facilities in China, Japan, and Korea operate in closer harmony with international standards than those not AAALAC accredited. The first author has visited many research facilities in these countries and has noted a need for better training of laboratory animal veterinarians, particularly in China, and a need to grant greater authority to attending veterinarians in all three countries.

Professional LAS and/or medicine organizations in each of these countries continue to promote improvements in existing laws and guidelines aimed toward harmonization with international standards. This process has been encouraged by major Western pharmaceutical companies expanding their businesses into the region, particularly in China. Given the ongoing commitment to supporting animal research in all three countries and international efforts to improve animal welfare, it is likely that the laws regulations and guidelines will continue to evolve.

References

Animal Protection Act. 1991. Ministry of Agriculture Food and Rural Affairs (revised 2008). Available online (http://www.koreananimals.org/animals/apl/2007apl.htm#a13), accessed on March 7, 2016.

AQSIQ. 2004. Regulation on the Import and Export of Transgenic Products, No. 62, Entry and Exit Inspection and Quarantine Administration of Genetically Modified Organisms. Available online (http://www.aqsiq.gov.cn/xxgkml/jlgg/zjl/20032004/200610/t20061027_12236.htm), accessed on October 18, 2016.

Beijing Administrative Office of Lab Animal. 2006. Guide of the Beijing Municipalities for the review of laboratory animal welfare and ethics. Available online (http://www.nicpbp.org.cn/sydw/CL0251/1377.html), accessed on December 7, 2015.

Beijing Municipal Bureau of Science and Technology. 2005. Beijing Municipal Regulation on the Management of Laboratory Animal Licenses. Available online (http://www.lascn.net/Item/11982.aspx), accessed on December 7, 2015.

Civil Aviation Administration of China. 1996. Rules on domestic transportation of goods. Available online (http://www.caac.gov.cn/B1/B6/200612/t20061219_872.html), accessed on December 7, 2015.

China Food and Drug Administration. 2003. Good laboratory practice. Available online (http://www.sda.gov.cn/WS01/CL0053/24472.html), accessed on December 7, 2015.

General Administration of Forestry. 1998. Transportation regulation of live wild animals. Available online (http://www.forestry.gov.cn/portal/lykj/s/1716/content-183745.html), accessed on December 7, 2015.

Han SH, Gwi HL. 2014. Laboratory animal welfare and the three Rs in Korea. Altern Lab Anim 41:45–47.

Japan Health Sciences Foundation. 2008. Center for Accreditation of Laboratory Animal Care and Use. Available online (http://www.jhsf.or.jp/English/active.html), accessed on March 7, 2016.

Kagiyama N, Ikeda T, Nomura T. 2006. Japanese Guidelines and Regulations for Scientific and Ethical Animal Experimentation. In: Stevenson CS, Marshall LA, Morgan DW, eds. *In Vivo Models of Inflammation*, Vol 1. Basel, Switzerland: Birkhauser Verlag. p 187–191.

Kagiyama N., Nomura T. 2004. Japanese Regulations on Animal Experiments. In: ILAR, National Research Council (ed): *Development of Science-Based Guidelines for Laboratory Animal Care. The November 2003 International Workshop*, National Academy Press, Washington D.C., p 50–56.

Kojima H. 2009. Japanese Views in the 3Rs in the 21st Century. (slide presentation). Available online (http://www.bfr.bund.de/cms7/sixcms/media.php/312/kojima_presentation.pdf), accessed on March 7, 2016.

Kong Q, Qin C. 2010. Analysis of current laboratory animal science policies and administration in China. *ILAR J* 51:e1–e10.

Kurosawa TM. 2007. Japanese Regulation of Laboratory Animal Care with 3Rs. AATEX 14, Special Issue, Proc. 6th World Congress on Alternatives and Animal Use in the Life Sciences, Tokyo, Japan. p 317–321.

Laboratory Animal Act. 2008. Ministry of Food and Drug Safety (amended 2010 and 2012).

Law No. 105. 1973. Law Concerning the Protection and Control of Animals.

Law No. 105. 1973. Ministry of Environment. Act on Welfare and Management of Animals. Available online (http://www.cas.go.jp/jp/seisaku/hourei/data/AWMA_2.pdf), accessed May 7, 2016.

Law No. 105. revised 2005. Law for the Humane Treatment and Management of Animals. Available online (http://www.scj.go.jp/ja/info/kohyo/pdf/kohyo-20-k16-2e.pdf), accessed October 19, 2016.

Ministry of Education, Culture, Sports, Science and Technology. 2006. Fundamental Guidelines for Proper Conduct of Animal Experiments and Related Activities in Academic Research Institutions. Available online (http://www.mext.go.jp/b_menu/hakusho/nc/06060904.htm (in Japanese)), accessed on March 7, 2016.

Ministry of Agriculture. 1996. Safety Administration Implementation Regulation on Agricultural Biological Genetic Engineering. Available online (http://faolex.fao.org/docs/texts/chn19141.doc" \t "display" chn19141.doc), accessed on October 19, 2016.

Ministry of Agriculture. 2002. National Administrative Standard on Surveillance System of Animal Diseases. Available online (http://www.lascn.com/Item/45.aspx), accessed on December 7, 2015.

Ministry of Agriculture. 2008. Decree No. 18 of 2008 the Ministry of Agriculture laying down the Administrative Measures for Practicing Veterinarians Available online (http://faolex.fao.org/cgi-bin/faolex.exe?rec_id=155148&database=faolex&search_type=link&table=result&lang=eng&format_name=@ERALL), accessed on October 19, 2018.

Ministry of Agriculture. 2010. Administrative Regulation on Animal Quarantine. Available online (http://www.gov.cn/zwgk/2010-01/28/content_1521668.htm). Accessed on December 7, 2015.

Ministry of Environment. 2006. Ministry of Environment. Standards Relating to the Care and Management of Laboratory Animals and Alleviation of Pain. Available online (http://www.env.go.jp/sitemap.html (in Japanese)), accessed on March 7, 2016.

Ministry of Health. 1983. Regulation on the Management of Medical Laboratory Animals. Available online (http://www.law-lib.com/lawhtm/1983/2739.htm), accessed on December 7, 2015.

Ministry of Science and Technology. 1988. Regulations for the Administration of Affairs Concerning Experimental Animals. Available online (http://www.gov.cn/gongbao/content/2011/content_1860757.htm), accessed on December 7, 2015.

Ministry of Science and Technology. 1993. Safety Administration Regulation on Genetic Engineering. Available online (http://www.faolex.fao.org/docs/texts/chn19138.doc), accessed on October 18, 2016.

Ministry of Science and Technology. 1997. Administrative Regulation on the Management of Laboratory Animal Quality. Available online (http://www.most.gov.cn/zcfg/kjfg/t20021217_7768.htm), accessed on December 7, 2015.

Ministry of Science and Technology. 1998. Detailed procedures on national rodent seed centers to import and supply rodent breeders. Available online (http://www.chinalawedu.com/news/1200/22016/22030/22435/22444/2006/3/fe963281156122360028550-0.htm), accessed on December 7, 2015.

Ministry of Science and Technology. 1998. Regulation on Managing National Laboratory Animal Seed Centers. Available online (http://www.110.com/fagui/law_93980.html), accessed on December 7, 2015.

Ministry of Science and Technology. 2001. Regulation on the Management of Laboratory Animal Licenses. Available online (http://www.most.gov.cn/fggw/dffggw/dffgah/200703/t20070320_53901.htm), accessed on December 7, 2015.

Ministry of Science and Technology. 2006. Administrative Regulation on the Management of Laboratory Animal Quality Control. Available online (http://www.law-lib.com/law/law_view.asp?id=105243), accessed on December 7, 2015.

Ministry of Science and Technology. 2006. Guideline on the Humane Treatment of Laboratory Animals. Available online (http://www.most.gov.cn/fggw/zfwj/zfwj2006/200609/t20060930_54389.htm), accessed on December 7, 2015.

Ministry of Science and Technology. 1999. Guideline on handling Issues Related to Laboratory Animal Seed in License Issuance. Available online http://www.chinalawedu.com/falvfagui/fg22016/49092.shtml), accessed on December 7, 2015.

Nomura T. 1995. Laboratory animal care policies and regulations; emerging issues. Japan. *ILAR J* 37(2): 60–61.

National Standards Committee. 2008. General requirements for biosafety labs (GB19489—2008). Available online (http://www.labagd.com/Item/14696.aspx), accessed on December 7, 2015.

Omoe H. 2006. Recent trends in animal experimentation in Japan: On the revision and implementation of the Law for the Humane Treatment and Management of Animals. Quarterly Review. Available online (http://data.nistep.go.jp/dspace/bitstream/11035/2728/1/NISTEP-STT021E-13.pdf), accessed on March 7, 2016.

People's Congress of China. 2004. Wild animal Protection Law. Available online (http://www.forestry.gov.cn/main/24/content-204777.html), accessed on December 7, 2015.

People's Congress of China. 1992 (amended in 2009). Entry and Exit Animal and Plant Quarantine Law. Available online (http://www.foodmate.net/law/jiben/1710.html), accessed on December 7, 2015.

People's Congress of China. 2008. Law on Animal Disease Prevention and Control. Available online (http://www.gov.cn/ziliao/flfg/2007-08/31/content_732590.htm), accessed on December 7, 2015.

Standardization Administration of China. 2014. GB/T 27416-2014 Laboratory Animal Institutions—General Requirements for Quality and Competence. Available online (http://www.worldstdindex.com/soft4/3634246.htm), accessed October 19, 2016.

State Administration of Environmental Protection. 2006. Environmental biosafety in labs involving microbiologic pathogens. Available online (http://www.zhb.gov.cn/gkml/zj/jl/200910/t20091022_171837.htm), accessed on December 7, 2015.

Science Council of Japan 2006. Guidelines for Proper Conduct of Animal Experiments. Available online (http://www.scj.go.jp/ja/info/kohyo/pdf/kohyo-20-k16-2e.pdf), accessed on March 7, 2016.

Shoji K. 2007. Japanese concept and government policy on animal welfare and animal experiments. AATEX 14, Special Issue, Proc. 6th World Congress on Alternatives and Animal Use in the Life Sciences. Tokyo, Japan. p 179–181.

State Council. 1996. Regulation on implementing Entry and Exit Animal and Plant Quarantine Law. Available online (http://www.gov.cn/ziliao/flfg/2005-08/06/content_21042.htm), accessed on December 7, 2015.

State Council. 2003a. Regulations on the Administration of Medical Wastes, Order of the State Council of the People's Republic of China No.380. Available online (http://tradeinservices.mofcom.gov.cn/en/b/2003-06-16/25776.shtml), accessed on October 19, 2016.

State Council. 2003b. Regulations of the People's Republic of China on Certification and Accreditation, Order of the State Council of the People's Republic of China No. 390. Available online (http://www.asianlii.org/cn/legis/cen/laws/rotprococaa658/), accessed on October 19, 2016.

State Council. 2004. The Biosafety regulation for labs involving microbiologic pathogens. Available online (http://www.gov.cn/zwgk/2005-05/23/content_256.htm), accessed on December 7, 2015.

State Council. 2005. National Emergency Plan for Important Emerging Animal Diseases. Available online (http://www.lascn.com/Item/9099.aspx), accessed on December 7, 2015.