

## Japanese guidelines and regulations for scientific and ethical animal experimentation

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What risk did animal experimentation in Japan present in terms of laboratory animal welfare? First, the 3R (Replacement, Reduction, Refinement) principle was not legally specified [1]. This resulted in criticism from Western countries ([2] and personal communication). Second, no national guidelines for animal experimentation were established. This caused disparities in appropriateness of animal experimentation among diverse institutions.

### Legal standing of the 3R principle

With the amendment of the Law for the Humane Treatment and Management of Animals, the specifications for the use of animals for scientific purposes have been revised and the 3R principle has been given legal standing (Tab. 1). The amendment came into force on June 1, 2006. The Ministry of the Environment regulates humane treatment of animals under the Law, and “Refinement” is specified in the Standards Relating to the Care and Management of Laboratory Animals and Relief of Pain as shown on the left in Figure 1. “Replacement” and “Reduction” are considered as the items to be discussed when the animal experimental protocol is prepared and are not direct methods to implement well-being of animals.

There was a critical debate on whether it is wise to regulate scientific procedures by legislative measures, and if yes, whether the Law is the most preferable one or not. Eventually, members of the Japanese Diet concluded that bioscience should not be regulated only from the aspect of humane treatment of animals. They thought that appropriate animal experimentation could be better accomplished based on guidelines and not by stringent legislation.

*Table 1 - Amended Law for the Humane Treatment and Management of Animals*

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Article 41. Where an animal is used for the purposes of education, testing, research, manufacturing of biologic products or other scientific purposes, consideration shall be given to proper use of animals such as use of alternative methods not using animals and using as few animals as possible within the limits to fulfill the purposes.

2. When an animal is used for scientific purposes, methods that do not cause pain or distress to the animals should be used within the limits imposed by this use.

3. When an animal is beyond recovery after use for scientific purposes, the person who used the animal for such scientific purposes must immediately dispose of the animal by a method that causes the animal as little pain and distress as possible.

4. The Minister of the Environment may, after consultation with the heads of the administrative agencies concerned, prescribe applicable standards with regard to the methods in Paragraph 2 and the measures in the preceding Paragraph.

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### **Basic guidelines established by regulatory agencies**

Animal experimentation in Japan had been conducted based on the local regulation system at each institution following the administrative guidance of the Ministry of Education since 1987. (The Ministry of Education was reorganized in 2001 as the Ministry of Education, Sports, Science and Technology, MEXT.) The guidance also had some influence on animal experiments conducted by pharmaceutical companies as a reference. However, the guidance, just recommending the formulation of local regulations, was too soft to rectify disparities among academic institutions. Therefore, in 2004, the Science Council of Japan (SCJ) proposed the establishment of national guidelines on animal experimentation with the objective of scientific rationalization of animal experimentation in balance with laboratory animal welfare [3].

In accordance with the proposal, MEXT as well as the Ministry of Health, Labor and Welfare (MHLW) established animal experimentation guidelines “Basic policies on animal experimentation” as quasi-regulations on June 1, 2006, based on the 3R principle as shown on the right in Figure 1. These guidelines focus on scientific rationalization of animal experimentation rather than humane treatment of laboratory animals and simply describe basic policies and institutional responsibilities for conducting animal experiments. The institutional animal care and use committee (IACUC), appointed by the director of the institution, should review the animal experimental protocol prepared by a principal investigator and determine if the protocol complies with the local regulations and the national guidelines of the compe-

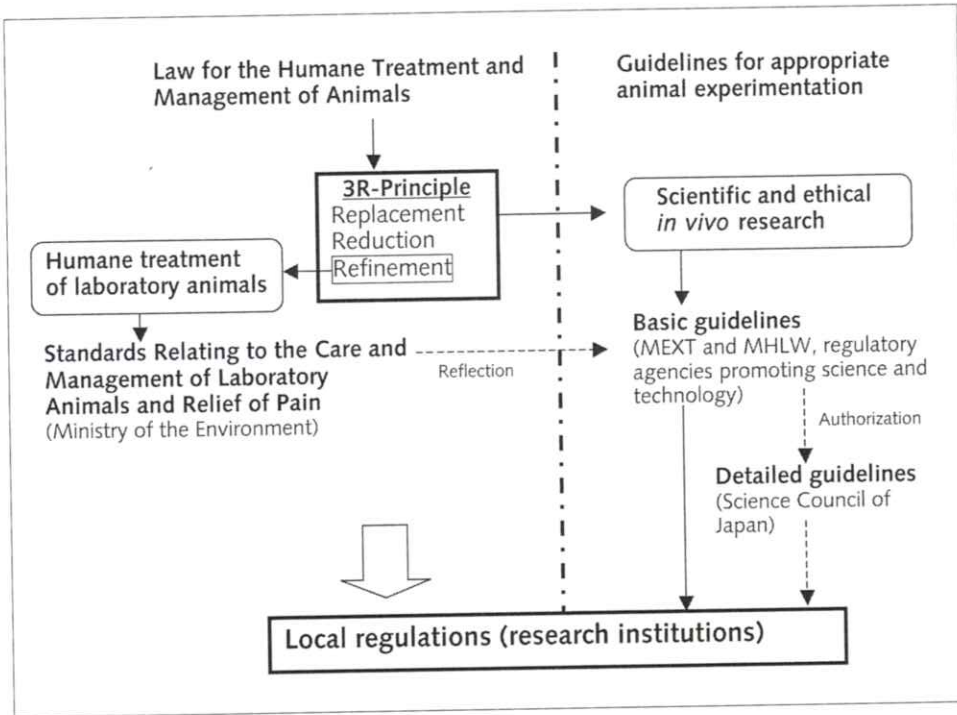


Figure 1  
 Framework for implementing appropriate animal experiments

tent authority. The IACUC reports the results of the review to the director and the director decides whether or not to approve the protocol. The director is also responsible for training and informing investigators and animal technicians about related regulations and policies. The guidelines established by the MHLW give more consideration to information protection than those of MEXT, so that the policies can be applied by profit-making organizations. The Ministry of Agriculture, Forestry and Fisheries also established basic guidelines on animal experimentation and notified the research institutions under its control on June 1, 2006 .

### Detailed guidelines formulated by the SCJ

The two regulatory authorities, MEXT and MHLW, requested the SCJ to formulate more detailed guidelines so that they can serve as a vital reference when institutions establish their local regulations in accordance with respective basic guidelines. Thus, the detailed guidelines "Guidelines for the proper conduct of animal experimen-



tion” were published by SCJ on June 1, 2006 in parallel with the two basic guidelines. The detailed guidelines cover both aspects of scientific rationality of *in vivo* research and humane treatment of animals involved, referring to not only MEXT and MHLW basic guidelines, but also the Standards Relating to the Care and Management of Laboratory Animals and Relief of Pain of the Ministry of the Environment. In this respect, the detailed guidelines resemble the ILAR Guide for the Care and Use of Laboratory Animals in the United States. However, the detailed guidelines do not contain any numerical specifications, based on the concept of “performance approach” that the required conditions should be investigated from the scientific standpoint and set voluntarily.

When drafting an experimental protocol, the items to be considered are listed in the detailed guidelines. They include animal rooms, procedure rooms, necessary equipment, restraint of animals, restrictions on supply of food and drinking water, surgical procedures, anesthesia and postoperative care, humane endpoints, euthanasia, occupational health and safety, and record keeping. The principal investigator should estimate the degree of pain in the animals used, and include in the protocol the methods of alleviating the pain, to the extent that they do not restrict the objective of the research.

### **Deliberation on local self-regulation of animal experiments**

One of the major elements to ensure enforced self-regulation is clearly the education and training of personnel. The detailed guidelines contain items such as related laws, regional ordinances, policies and regulations; experimental procedures and handling of animals; health, care and management of animals; hygienic procedures and safety assurance; and utilization of facilities, as examples of a syllabus. Wet-hand education directly connected with the experimental procedures used is also essential for scientific and humane animal experimentation, and should be given by senior investigators with sufficient knowledge, experience and skills.

As proposed by SCJ, the final step in adequate self-regulation should be validation by an outside organization. It also improves the social transparency of animal experimentation, a weak point in self-regulation. The verification method should be a peer-review system by specialists with scientific knowledge. In Japan, a cross check will start among academic institutions, whereas pharmaceutical companies seem to prefer internationally recognized system(s) with strict confidentiality. Finally, we would like to refer to penalties. The penalties prescribed in the Law can be applied to persons who kill, injure or mistreat laboratory animals without any scientific rationale and thought concerning the animals.

## References

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- 3 The 7th Division, Science Council of Japan. Report concerning the promotion of public understanding of animal experimentation (Proposal), July 15, 2004