



## Laws Governing the Use of Animals in Medical Research

### How are Research Animals Protected?

Biomedical research, teaching, and testing are the subject of and are controlled by an extensive system of laws and regulations that provide for the use, care, and welfare of laboratory animals, that govern and insure the integrity of research, and the require the inspection of research facilities and the inspection of research protocols. This extensive federal oversight includes two significant laws, the Animal Welfare Act (AWA) and the Health Research Extension Act, a large collection of policies and regulations from the federal agencies involved in the U.S. research effort (EPA, NSF, DoD, etc.), and additional laws that govern other facets of research, drug development, and drug testing, such as the federal Food, Drug, and Cosmetic Act and the Controlled Substances Act, as overseen by the FDA. In addition, facilities and researchers may also be licensed and inspected by their state and/or international organizations, depending on the research and teaching they conduct, the species involved, and regional laws.

### Federal Laws and Regulations

Under federal law and many international treaties and agreements, it is illegal to experiment on humans, and human clinical trials must be predicated on animal studies. According to the Nuremberg Code, drawn up after World War II, any experiments on humans ". . . should be designed and based on the results of animal experimentation." (The Nazis outlawed all animal experimentation, but allowed experiments on prisoners in concentration camps). The Declaration of Helsinki, adopted in 1964 by the 18th World Medical Assembly and revised in 1975, also states that medical research on human subjects "should be based on adequately performed laboratory and animal experimentation." Under the Food and Drug Administration, permission to conduct clinical (human) trials will only be granted after the review and approval of an Investigational New Drug application (IND). This extensive process must demonstrate safety and effectiveness in animal models for FDA review, and approval. No new drug may be marketed in the United States without final approval by the FDA.

The federal AWA is the key law governing research with animals. The AWA was first passed in 1966 and has been amended several times since (1970, 1976, 1985, and 1990). It mandates that all research facilities (with some exceptions discussed below) register with the U.S. Department of Agriculture (USDA). The Animal and Plant Health Inspection Service (APHIS) within the USDA is responsible for administering and enforcing the AWA. This process includes requirements for reporting animals used, for making at least one unannounced, detailed, inspection a year, and for inspecting the practices of their IACUCs, and investigating complaints and violations of the AWA. Research facilities are required by the Animal Welfare Act (AWA) (7 USC 2131 *et seq.*) to have an attending veterinarian to provide for the health care and oversight of animal welfare. The regulations implementing the AWA (9 CFR Ch. 1) go on to specify the requirements of appropriate housing, feeding, handling, sanitation, ventilation, lighting, enrichment, and sheltering of all animals used in research. The AWA also requires that scientific proposals to use animals in research must be prepared and detailed, and that these proposals must be reviewed and *approved* by a federally-mandated committee whose membership includes, at a minimum, an experienced scientist, a veterinarian, and an individual who is not affiliated with the institution (such as a local veterinarian, minister, or employee of the local Society for the Prevention of Cruelty for Animals) before any research can begin. Membership on this committee must also include a veterinarian with specific experience in laboratory animal care. These federally-mandated committees, called Institutional Animal Care and Use Committees (IACUCs), must review, approve or disapprove protocols, and then monitor and inspect every research study to help ensure that animals are not subject to unnecessary pain and distress.

Review committees are charged with keeping abreast of, and requiring research scientists to use, state-of-the-art methodology and protocol-design to prevent pain in laboratory animals, and the exploration and implementation of alternatives to animal use when possible. Guidelines for and specifications detailing the care and treatment of research animals, as enforced by the USDA, is the *Guide for the Care and Use of Laboratory Animals*, which is currently in its 8<sup>th</sup> edition.

The AWA also requires institutions to report the number of animals used in research and the number of animals that experience not only pain, but also distress, along with an explanation of why the research had to be performed in this manner. A veterinarian must also be consulted for such research. For additional information about the Animal Welfare Act and its regulations for biomedical research institutions the following websites are very useful. <http://www.nal.usda.gov/awic/legislat/usdaleg1.htm> and <http://www.nal.usda.gov/awic/legislat/regsqa.htm>

### **The Public Health Service Policy on Humane Care and Use of Laboratory Animals**

While the AWA covers the majority of research animals, it does not cover rats, mice, or birds. The Public Health Service Policy, however, specifically regulates the care and use of *all* vertebrate animals used in research, testing, and education, giving rodents and birds the same protections given other AWA species. The Health Research Extension Act (Public Law 99-158) of 1985 made Public Health Service (PHS) Policy the law, requiring all medical research funded through the National Institutes of Health (NIH) to conform to the PHS Policy. The NIH, which funds more than half of all medical research in the U.S, also conducts unannounced visits to ensure compliance with their regulations.

The Office for Laboratory Animal Welfare (OLAW) is the entity at PHS responsible for administration of PHS Policy as authorized by the Health Research Extension Act. PHS Policy consists of:

- A primary document, PHS Policy for Humane Care and Use of Laboratory Animals, which incorporates the U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training as a framework for the conduct of animal research;
- A second document, the *Guide for the Care and Use of Laboratory Animals* (known simply as the *Guide*), addresses institutional policies and responsibilities related to animal program operations including animal husbandry, the housing and caging environment, veterinary care, and many aspects of the physical plant (surfaces, heating, ventilation, and air conditioning).

Research facilities that receive such funding are required to file an Assurance with the Office of Laboratory Animal Welfare (OLAW) of the National Institutes of Health (NIH) before carrying out any activities involving live vertebrate animals. This Assurance is a legal commitment that the facility will comply with the PHS Policy and the *Guide* and includes extensive descriptions of the institution's facilities, personnel, policies, equipment, etc., and in particular a description of its program of veterinary care. All vertebrate species are covered. An approved Assurance is a prerequisite for the award of federal research funding. Non-compliance with the Assurance may result in disqualification of the facility to receive federal research funds, and even withdrawal of funds already approved. There is also a possibility of prosecution under the Federal False Claims Act.

Under these agencies, like the AWA, each research facility must have an animal care and use committee (IACUC) that reviews every research project to ensure that animals are treated responsibly and humanely, and that oversee and evaluate all aspects of the institution's animal care and use program. The *Guide* also offers expert advice and the latest scientific research on how to care for various species of animals to meet scientific, technical, and humane standards, and provides guidelines for designing and operating an animal care program that fulfills the requirements of the AWA and the PHS Policy. Other federal funding agencies also require scientists to use the *Guide for the Care and Use of Laboratory Animals* to determine appropriate standards for animal care.

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

These nine principals are the foundation for humane care and use of laboratory animals in this country. These principles were developed by the Interagency Research Animal Committee and adopted in 1985 by the Office of Science and Technology Policy.

### **U.S. Department of Defense (DoD)**

Intramural and extramural animal research supported by the U.S. Department of Defense (DoD) is governed by the Animal Welfare Act, applicable regulations of the Animal and Plant Health Inspection Service (APHIS), the Guide for the Care and Use of Laboratory Animals and the U.S. Government Principles for Animal Use (1985). DoD also has implemented animal research policies particular to the department and its extramural grantees in DoD Directive 3216.1, "Use of Laboratory Animals in DoD Programs" and the 1995 policy memorandum entitled "Department of Defense (DoD) Policy for Compliance with Federal Regulations and DoD Directives for the Care and Use of Laboratory Animals in DoD-Sponsored Programs". The 1995 DoD Directive increases and clarifies requirements for IACUC membership and directs all DoD animal facilities to apply for AAALAC accreditation. Service regulations implementing the Directive were revised and implemented in 2005. The Policy Memorandum outlines training requirements for IACUC members, implements standard formats for animal use protocols and IACUC inspection checklists, and implements a standard reporting requirement for all animal research to support DoD's publicly accessible Biomedical Research Database.

### **The U.S. Environmental Protection Agency (EPA)**

The U.S. Environmental Protection Agency (EPA) enforces "Good Laboratory Practice" (GLP) regulations that apply to all studies related to approvals of new pesticides or industrial chemicals "to ensure the quality and integrity of test data submitted to the Agency under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Toxic Substances Control Act (TSCA)." The GLPs address all areas of laboratory operations, including provisions specifying standard operating procedures for the housing, feeding, handling and care of animals. The EPA compliance monitoring program inspects facilities, audits data and prepares detailed inspection reports. Noncompliance with GLPs can result in the federal agency's refusal to consider a study in support of an application; disqualification of the testing facility; or, in extreme cases, recommendation for criminal prosecution.

### **The Food and Drug Administration (FDA)**

The FDA enforces the Food, Drug, and Cosmetics Act an act that requires non-clinical (animal) safety and efficacy testing and reporting for human and animal drugs, medical devices/electronic medical products, diagnostic products, food additives and colors, and cosmetics. The FDA regulates all human-trials (clinical trails) of new drugs and devices, and requires extensive documentation in the form of an Investigational New Drug Application (IND) before allowing any clinical trials to begin. Part of the IND is evidence of safety and efficacy of the proposed product from pre-clinical (animal trails). Along with the EPA, the FDA sets Standards for Good Laboratory Practices (GLPs) and Good Manufacturing Practices (GMPs). GLP studies are required by the FDA for food and color additives, animal food additives, human and animal drugs, medical devices, and biological products.

### **USDA-NIH-FDA 2006 Memorandum of Understanding**

An MOU signed March 2006 between The Animal and Plant Health Inspection Service of the USDA and The Food and Drug Administration U.S. Department of Health and Human Services and The National Institutes of Health of the U.S. Department of Health and Human Services Concerning Laboratory Animal Welfare sets a framework for reciprocal cooperation that assists the listed agencies in promoting proper laboratory animal care and welfare. Implementation of this agreement is intended to maintain and enhance agency effectiveness while avoiding duplication of efforts to achieve required standards for the care and use of laboratory animals.

### **State Laws and Regulations**

Research facilities that are registered with the USDA and/or hold a PHS Assurance are not required to register with the State of California, signifying the intent of the state to defer to federal regulatory authority in this area. Facilities within California that are not PHS Assured (they receive no funding from the NIH), and/or do not have species regulated under the AWA, however, must register with the State of California, Department of Public Health.

<https://www.cdph.ca.gov/Programs/OSPHLD/LCS/Pages/LaboratoryAnimalUseApprovalProgram.aspx>

In some cases, facilities must also obtain an additional permit from the Department of Fish and Wildlife and/or the Fish and Game Commission to conduct and house certain research species – species deemed “restricted” in California. See *California Code of Regulations*, TITLE 17, Div. 1, Chpt. 2 § 950 to 1021, and/or *California Code of Regulations*, Title 14, Div. 1, Sub 3. Chpt. 3. §671. The basis for the care and use of laboratory animals and regulation for facilities registered with the State of California is the the national *Guide for the Care and Use of Laboratory*

*Animals.* For those outside of California, please contact CBRA for the specific state regulations as they pertain to research.

### **Voluntary Monitoring and Self-Regulating**

In addition to state and federal regulation, most research facilities seek voluntary accreditation by the Association for the Assessment and Accreditation of Laboratory Animal Care International (AAALAC), a private, nonprofit organization that promotes the humane treatment of animals in science through a voluntary accreditation program administered by veterinarians specializing in laboratory animal medicine, among other experts. Accreditation is entirely voluntary. It is a complex process requiring months or years. Every aspect of an institution's facilities, policies, procedures, and personnel is examined in detail. One of the critical aspects to be considered is the program of veterinary care. Although AAALAC accreditation is voluntary, its benefits are so significant that accreditation is mandatory for all practical purposes in many situations. Some federal agencies, for example, require AAALAC accreditation of a research institution, in order to even apply for grants.