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Research Compliance Professional's Handbook, Third Edition
5 The Regulation of Research Using Animals

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Overview

The area of animal research presents a myriad of regulatory and ethical issues. Currently, clinical trials in animals are required as a condition to approval of new drugs by the U.S. Food and Drug Administration (FDA),[2] and thus, animal research plays an important role in pharmaceutical innovation. Accordingly, research compliance officers should be familiar with the regulatory requirements governing animal research. This chapter will provide an overview of the regulatory structure that governs animal research and includes a discussion of the following topics:

- Primary principles, laws and regulatory agencies governing animal research
- Major players in animal research programs and their roles and responsibilities
- Additional compliance considerations unique to animal research

Within each of these areas, focus areas for effective compliance programs are identified.

Primary Principles, Laws and Regulatory Agencies Governing Animal Research

The overarching set of ethical principles that govern animal research conducted or regulated by the federal government is the U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research and Training (the "Principles.")[3] The principles set forth the premises that should be followed in designing and conducting animal research, and they form the basis of all other laws regulating animal research.

The principles are based on the "3 Rs" of animal research: **R**educe the number of animals used in research; **R**efine experiments to minimize pain and discomfort to animals; and **R**eplace animal experiments with alternatives when feasible. Research compliance programs should ensure that personnel who staff animal care and use programs are familiar with the principles' main tenets:

- Avoid using animals needlessly. Design and perform research procedures in a way that ensures the research is relevant to advancing human/animal health or important knowledge.
- Use an appropriate animal species and the minimum number of animals necessary to obtain valid research results.
- Research should be designed to prevent or minimize discomfort, pain, and distress in animals. If a procedure would hurt a human, it should be assumed to hurt an animal, unless specific knowledge to the contrary has been established.
- Research that causes more than momentary or slight pain or distress in an animal should incorporate the use of anesthetics, analgesics or tranquilizers ("AAT Drugs").

- Animals that suffer severe or chronic pain or distress that cannot be relieved should be euthanized.
- Research animals must have appropriate living conditions and receive care that is directed by a qualified veterinarian.
- Research must be conducted by qualified investigators who are trained in the use of research animals.
- Animal research must be conducted in accordance with all applicable federal regulations, and any exceptions to the regulations must be pre-approved by an Institutional Animal Care and Use Committee (IACUC).

The principles' influence is readily apparent in the two main sets of federal laws that govern animal research in the United States: (a) the Public Health Service Policy on Humane Care and Use of Laboratory Animals,[4] and (b) the Animal Welfare Act[5] and its implementing Animal Welfare Regulations,[6] referred to collectively as the "AWA." Each of these laws is discussed more fully below. As with any area in which multiple laws and regulations apply, the strictest of the applicable laws or regulations should always be followed.

Public Health Service Policy and the Office of Laboratory Animal Welfare

The Public Health Service Policy on Humane Care and Use of Laboratory Animals ("PHS Policy") applies to live, vertebrate animals of all types (whether warm or cold blooded) that are used in research, research training or experimentation that is supported by funding from the United States Public Health Service (PHS) or one of its components (*e.g.*, National Institutes of Health [NIH], FDA, Centers for Disease Control and Prevention, etc.). The PHS Policy covers PHS-funded activities that take place both inside or outside of the United States, and it applies to both traditional lab-based research and field work in the animals' natural setting.

The PHS Policy is administered and enforced by the federal Office for Laboratory Animal Welfare (OLAW). The PHS Policy requires that individuals who receive PHS-funding for animal research be affiliated with an institution that assumes responsibility for complying with the PHS Policy. The PHS Policy requires that the institution comply with the Guide for the Care and Use of Laboratory Animals (the "Guide")[7] and that euthanasia methods conform to the American Veterinary Medical Association Guidelines for the Euthanasia of Animals.[8] Additionally, the PHS Policy requires inclusion of the following information in PHS grant applications for animal research: rationale for use of animals; appropriateness of species to be used; number of animals to be used; description of proposed use; description of methods used to minimize pain and discomfort; and euthanasia methods.

Prior to the receipt of any PHS funds for animal research, and every four years thereafter, institutions must file an Animal Welfare Assurance ("assurance") with OLAW.[9] The assurance mandates, among other things, that institutions adhere to the following requirements:

- Compliance with the Principles, AWA, PHS Policy and the Guide.
- Establishment of an institutional animal care and use program with appropriate lines of responsibility and participation by qualified veterinarians.
- Establishment of an IACUC.
- Maintenance of specific assurance, IACUC and animal care and use program records.

The assurance document must provide an accurate description of the research institution's animal care and use

program, and the research compliance officer should be very familiar with the assurance's contents. If the institution makes any changes to its animal care and use program that affect the assurance, an amended assurance must be filed with OLAW at the time of the change.

The assurance must include a description of all of the institution's facilities in which animals and used or housed, and include the species and number of animals that are used. The assurance requires designation of an institutional official who has top-level authority within the organization for oversight of the animal care and use program. A description of the program's specific lines of authority and approval also is required. The assurance must describe the membership of the IACUC and its procedures, including those for reporting and reviewing concerns about the care and use of animals at the institution. Finally, the assurance must describe the training required for animal users and caretakers, as well as the occupational health program in place for all persons who work with animals at the institution. Research compliance officers should ensure that appropriate institutional health and safety officials are involved in the development and implementation of the occupational health program to ensure compliance with any workers compensation and/or state or federal occupational health and safety requirements.

In addition to filing the assurance, each research institution also must file an annual report with OLAW. This annual report must describe any changes in the animal care and use program, including any change in an institution's accreditation status if accredited by AAALAC (see accreditation discussion below). The report also must include an assurance that all IACUC inspections and program evaluations have been conducted, as well as any minority view voiced by an IACUC member who disagreed with the IACUC's conclusions regarding facility or program reviews.

The Guide for the Care and Use of Laboratory Animals

As noted above, the PHS Policy and Assurance require that institutions performing PHS-funded animal research follow the requirements of the Guide for the Care and Use of Laboratory Animals, or the "Guide." The Guide sets forth very detailed standards for the administration and operation of animal care and use programs, including IACUC operations; engineering standards for animal environment, housing and management; veterinary care; physical plant; and emergency and disaster planning. Research compliance programs should undertake a detailed review of the Guide and determine its specific application to their institutions' facilities and programs. Working with the IACUC, the compliance officer should develop appropriate checklists to ensure that Guide requirements are being addressed.

Animal Welfare Act and the U.S. Department of Agriculture

The Animal Welfare Act and its implementing regulations (referred to collectively as the "AWA") governs live or dead warm-blooded animals that are intended for use in research, teaching, testing, experimentation, exhibition or as pets. The AWA is enforced by the U.S Department of Agriculture (USDA) through its Animal and Plant Health Inspection Service (APHIS). The AWA applies to research using all species of live or dead warm-blooded animals ("covered species") with a very important exception: research with mice, rats and birds is not covered.

Under the AWA, organizations or individuals must register with the USDA as "research facilities" if they plan to use a covered species in research and the research is federally-funded, or the animals were purchased in commerce. A new registration must be filed with the USDA every three years, and each registration or renewal requires the facility to certify that it is in full compliance with the AWA. Research compliance officers should be aware that their facilities additionally will need to apply to the USDA for an animal dealer's license if they also sell or trade some of their research animals to other research facilities.

Each registered research facility will be annually inspected by a USDA inspector. The inspector generally arrives at the facility unannounced and visually inspects all facilities in which covered species are used, housed or transported. In addition, the USDA inspector will review program records, as well as records maintained by the IACUC. Deficiencies noted during inspections must be corrected within the timeframe specified by the USDA, and serious or uncorrected deficiencies may result in citations and fines.

In addition to registration, each research facility must file an annual report that the USDA posts on its website. The annual report lists the number and type of each covered species held by the research facility, along with the USDA pain and distress class to which the animal has been assigned. The pain and distress classes are as follows:

Class B: The animal is being held but has not yet been used for research.

Class C: The animal is used in research that does not involve any pain or distress and does not use any analgesics, anesthetics or tranquilizers (collectively referred to as "AAT Drugs")

Class D: The animal is used in research that causes pain and/or distress but AAT Drugs are used.

Class E: The animal is used in research that causes pain and/or distress and AAT Drugs are not used because their use would have an adverse impact on the research. For animal used in Class E research, the annual report must include a description of the procedures that the animals undergo and the scientific justification for withholding AAT Drugs.

The annual report is a very important document because it is posted on the USDA website to permit public scrutiny of the number of animals being held in various pain and distress classes, with particular attention being paid to animals used in Class E research. Research compliance officers should work closely with their animal care and use programs to ensure that there are solid processes in place for maintaining accurate animal counts and that rigorous scientific justification is required for any animals being used in Class E research.

Other Pertinent Laws and Regulations

Although the PHS Policy, Guide and the AWA form the backbone of animal research regulation in the United States, other federal laws and state and local laws also must be considered. For example, if the research involves capturing animals in their natural setting, state or local laws may require that certain capture permits be obtained. Similarly, if the research requires the collection and/or transport of certain animal specimens, U.S. Fish and Wildlife regulations may apply and/or certain USDA permits may need to be obtained. Attention also must be paid to the species of animals involved, in order to determine if there are any species-specific regulatory research requirements or prohibitions. For instance, research involving species of animals protected by the U.S. Endangered Species Act, the Convention on International Trade in Endangered Species of Wild Flora and Fauna (CITES), or other similar laws may require special permits, or in some cases, be prohibited altogether. Accordingly, in all cases involving the collection, transport or use of wild animals or animal specimens, the research compliance officer should consult with counsel's office for assistance in identifying all applicable legal and regulatory requirements.