

Regulatory Issues Surrounding the Use of Companion Animals in Clinical Investigations, Trials, and Studies

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Abstract

Laboratory animal veterinarians sometimes encounter animals with rare conditions and may subsequently become involved in the performance of related animal research outside the laboratory, in homes, in veterinary clinics, or in universities to which owners have donated their animals for study. Similarly, veterinarians may monitor animal companion vaccination studies, performed to optimize preventive health care or minimize physiological variability and research confounders associated with a preventive medicine program for dogs and cats utilized for research procedures. These nontraditional uses of dogs, cats, and other companion animals in research have spurred the establishment of regulations to ensure that the animals benefit from clinical veterinary products and techniques. Included and described are the 2002 Public Health Service Policy, the Animal Welfare Act (AWA), the Federal Food, Drug, and Cosmetic Act, and the regulations of the US Department of Agriculture in response to the AWA. The complexities of clinical research with companion animals outside standard biomedical research facilities are discussed.

Key Words: companion animal research; regulatory affairs; veterinary clinical research; veterinary drugs; veterinary vaccines

Introduction

A career in laboratory animal medicine involves the care and use of a myriad of animal species as well as numerous and diverse types of experimental protocols, personal contacts, and administrative processes. The majority of laboratory animal veterinarians working in research settings do not usually participate actively in the development of new vaccines, drugs, and treatments targeted for the companion animal, nor do they work in traditional companion animal settings such as animal teaching hospitals, veterinary clinics, and subdivisions of pharmaceutical companies devoted to animal health research. Indeed, most of their efforts are directed at the care and use of animals that ultimately serve as research models for the human biomedical research sector.

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It is predictable that as the era of cloning or genetic engineering advances research and treatment paradigms into larger animal species and disease models, these research support veterinarians may well encounter special breeds of dogs or cats that have rare conditions and cause their program of research to conduct interventional treatment regimens on animals outside the laboratory, in homes, in veterinary clinics, or in university research settings to which owned animals have been donated for periods of time. Similarly, vaccination studies are sometimes performed in an effort to optimize preventive health care or minimize physiological variability and research confounders associated with a preventive medicine program for dogs and cats utilized for research procedures. This article provides an overview of regulatory processes associated with these nontraditional uses of dogs and cats in research.

In fiscal year 2000-2001, there were approximately 68 million owned dogs and 73 million owned cats in households within the continental United States. Owners spent yearly averages of \$196.00 per dog and \$104.00 per cat in veterinary-related expenses (APPMA 2000-2001). These large numbers suggest that the clinical research necessary to bring safe and efficacious vaccines, topical insecticides, drugs, and medical or surgical treatments into standard practice is also substantial. Equally large is the current regulatory effort to ensure that animals benefit from such products and techniques and that their owners are sold veterinary medicine and veterinary practices that minimize risk and maximize benefit for their pets.

Laboratory animal veterinarians and animal care personnel receive instruction in Public Health Service (PHS)¹ Policy (PHS 2002), requirements set forth in the Animal Welfare Act (AWA¹) (AWA 1966), and regulations promulgated by the US Department of Agriculture (USDA¹) in response to the AWA. However, biomedical research staff less commonly encounter the complexities of clinical research with companion animals outside the standard biomedical research facility.

¹Abbreviations used in this article: AWA, Animal Welfare Act; CFR, Code of Federal Regulations; CVB, Center for Veterinary Biologics; CVM, Center for Veterinary Medicine; DHHS, US Department of Health and Human Services; EPA, Environmental Protection Agency; FDA, US Food and Drug Administration; FFDC, Federal Food, Drug, and Cosmetic Act; IACUC, institutional animal care and use committee; INAD, investigational new animal drug application; NADA, new animal drug application; ONADE, Office of New Animal Drug Evaluation; PHS, Public Health Service; USDA, US Department of Agriculture.

Differences in Animal Use

The major difference between the use of animals for human benefit and the use of animals for animal benefit is the amount of jurisdictional authority that surrounds each type of study. Companion animal studies are subject to more regulations during the development, testing, and final trials using veterinary procedures and products as well as the close monitoring of their owners' involvement. The regulatory policy surrounding the use of companion animals can be confusing not only to the lay public but also to the laboratory animal specialist because the distinction between what constitutes research, who qualifies as an investigator, and what constitutes clinical discretion is often different from traditional research settings.

Another major difference between human and animal research is the vastly greater number of federal authorities that regulate the use of drugs, vaccines, flea and tick products, and new veterinary procedures in animal research. In the final phases of human health investigations, nearly all clinical trials are ultimately regulated by the Department of Health and Human Services (DHHS¹). Human vaccines, biologics, drugs, and devices are regulated under rules enacted in response to the Federal Food, Drug, and Cosmetic Act (FFDCA¹) (FFDCA 2001) under the Food and Drug Administration (FDA¹). Human Subjects research may also be dually regulated by FDA's parent department, DHHS, through the Office of Human Research Protections.

Animal clinical research, vaccine and drug testing, and the regulation and monitoring of clinical trials may be subject both to regulation from various federal government departments and to institutional-specific policies that may address issues not completely covered by federal rules. The subject of the complex regulations related to laboratory animals is described in a previous issue of *ILAR Journal* (VandeBerg et al. 1999). In short, animal research of any kind is regulated by rules promulgated by the USDA in response to the AWA. These rules establish minimal criteria for humane care and use, and they must be bolstered by strong institutional policies when there are no other rules.

Research at facilities directly or indirectly funded by the DHHS is also subject to rules enacted by US PHS Policy (PHS 2002). Research involving vaccine testing is additionally regulated by rules established by the USDA under the Virus-Serum-Toxin Act (USDA 1913, as amended in 1985). Through the Code of Federal Regulations 21, the FDA articulates regulatory policy regarding drugs, devices, feeds, and feed additives. Flea and tick products are regulated by the Environmental Protection Agency (EPA¹) in accordance with the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA 1996).

Other products are occasionally regulated under multiple acts of the Federal Trade Commission or the Consumer Product Safety Commission. Vaccine research is predominantly confined to preapproval registration of products based on testing inside the research facility.

A recent increase in feline vaccine-associated sarcomas

has catapulted consent for vaccination procedures to the forefront of feline medicine issues (AAFP 1998). However, the trials that go to clinics for testing in client-owned pets are still largely limited either to new clinical treatments and test therapies or to new drugs or new vaccines. These areas are discussed below.

Commonality of Regulatory Intent

Common regulatory roots between research involving animals to derive drugs, devices, procedures, teaching, and testing for human benefit and those developed for animal benefit can be examined in the following publications: (1) the *US Government Principles for the Utilization and Care of Vertebrate Animals Used in Teaching, Research, and Training* (IRAC 1985), and (2) the *Guide for the Care and Use of Laboratory Animals* (NRC 1996). The latter document serves as a foundation for PHS principles, which define the boundaries and other important characteristics of clinical research eligible for federal funding. The following principles are common to the laboratory animal industry and the drug development industry:

- Principle II: Overall relevance of the study to human or animal health
- Principle III: Appropriate species, quality, and number to obtain relevant results
- Principles IV-VI: Appropriate care and housing; and minimization of pain and distress, utilizing measures up to and including humane euthanasia
- Principles VIII and IX: Properly trained and experienced investigators; discretion regarding humane outcome should rest not only with investigators but also with review groups and boards

Testing New Techniques and Veterinary Methods

Advances in companion animal care typically are the result of cutting edge veterinary research at major teaching hospitals. In these cases, the level of the investigators' training and the availability and cost of support staff are typically much higher than in investigative settings or local animal hospitals. Additionally, compared with research laboratories, standard minimal criteria for humane care as described in the AWA and PHS Policy are usually exceeded at veterinary teaching hospitals due to more uniformly experienced personnel who are highly skilled in animal medicine and surgery. Because owners are generally quite desperate to solve problems, concerns arise over client vulnerability. Universities must always devise additional procedures that protect the veterinary/client relationship, shield the pets from unnecessary pain or distress, and safeguard the pet owner from consumer fraud. Such cases almost always involve additional input from ethics panels and board-

certified specialists. To accomplish this high standard, institutional care committees in veterinary teaching hospitals must fine-tune their existing national policies and guidelines to adapt to regulations.

Consent Form

The principle of informed consent is common to the use of companion animals both in drug testing and in university experimental, procedural, and testing validation. In contrast to the institutional animal care and use committee (IACUC¹) review process for a biomedical research animal, clinical studies can proceed with a companion animal only if the owner is willing. Key aspects in the prevention of consumer fraud during the consent process are relevant facts about just how new the procedure or drug in question really is and the chances that the animal in question might not benefit from such a new procedure. Likewise, if there is a high rate of side effects in foundation research with the drug, vaccine, or procedures, that probability should be discussed and defined with the owners before administration.

In September 1999, informed consent issues rose to the forefront of popular press with the case of Jessie Gelsing (Washington Post 1999). Since then, abuses of the consent process have been the subject of intense public scrutiny. Pet owners have become aware of their need to be informed about risks and benefits of experimental drugs and procedures. Press reports have resulted in the re-examination of what constitutes a fully informed owner or patient (AAFP 1998; Homes-Rovner 2002; Lantos 1993; Silverman 1996). The level of reading skill and comprehension has been especially problematic in addition to how investigators and clinical research committees define lay language (Davis 1998). Procedures for obtaining informed consent before conducting animal clinical studies stem from those developed for human clinical research within the 1976 Belmont Report (NCPHS 1976). In achieving an ethical and humane objective, clinical studies programs within animal hospitals have also tried to emulate these policies. The owner consent form is based on the Belmont Report principle of "beneficence." The underlying premise is that hospital staff and practitioners should treat animals and their owners in an ethical manner, not only respecting their owners' decisions and protecting the animal patient from harm but also making efforts to secure animal wellness. As stated in the report, beneficence is more than a charitable act; it is an obligation. The report further describes objectives of beneficent actions, which do not harm and which maximize possible benefits and minimize possible harms.

Clinical Studies Involving Drugs

The regulation of clinical studies involving companion animals is very comprehensive due to the FDA mission of ensuring the utmost safety and efficacy of new animal

drugs. The final phases of drug testing, when clinical trials are initiated, include extensive legal discussions between pharmaceutical companies (sponsors) and the responsible administrative center, the FDA's Center for Veterinary Medicine (CVM¹). Oversight of clinical research activities involving drug development in dogs and cats also differs in facility, clinical conduct, veterinarian-to-investigator relationships, and reporting of results from studies involving early pharmaceutical development conducted in common laboratory animal species within laboratories or medical schools. Basic research in pharmaceutical development is an activity performed in the following sequence: (1) using *in vitro* or small mammal models, (2) using dogs or cats held as research subjects by research facilities, and (3) performing single or multiple center clinical trials outside biomedical research structures.

However, before clinical drug trials can be conducted in companion animals outside the laboratory, this preliminary work must be summarized for CVM to establish whether there is a rational basis to allow further development of the drug. Toward this goal, the CVM's Office of New Animal Drug Approval (ONADE¹) is responsible for reviewing investigational new animal drug applications (INADs¹) and new animal drug applications (NADAs¹) stemming from INADs. The INAD usually documents the discovery phases of the drug, the drug manufacturing or drug components, the intended use, the results of any laboratory animal studies, and the results of early pilot studies (e.g., *in vitro*, teratogenic, toxicological, environmental assessment and human exposure, bioavailability, and pharmacokinetic). The INAD includes the portions of the preliminary work for clinical studies with which the laboratory animal veterinarians are most familiar. Data submitted by the pharmaceutical company (sponsor) to ONADE are then evaluated by the company or sponsor and the FDA reviewers for safety and efficacy. Only sufficient data permit the design of target animal safety and efficacy work (Vaughn 1998).

The FDA's mission also necessitates the study of early detection of adverse drug effects. Humane concerns of the FDA are not blatantly stated, but they appear basically inescapable in the guidelines for very frequent and specific periods of observation with corresponding data collection. These procedures are exceptionally detailed and, if followed by investigators, necessitate prompt detection and relief of pain and distress because they must enable FDA reviewers to determine the earliest possible time of adverse drug effects. Guidelines suggest that study animals be examined twice daily 7 days per week; examinations may include, for example, collection of clinical pathological and histopathological data as well as a timely necropsy (FDA 1997, 2001).

The final phases of new animal drug evaluation involve more investigator controls than are commonly seen in the laboratory setting. Compared with the IACUC requirement that an investigator must have adequate training and oversight to accomplish the research humanely, guidelines from CVM have more comprehensively defined what constitutes investigator adequacy and veterinary oversight. The inves-

tigators should be veterinarians or their designates, and they should provide complete details about their research. In contrast to the laboratory setting, the final evaluation of the safety and efficacy of the drugs or techniques are the responsibility of the animals' owners, who have volunteered the animals for participation in the clinical trials outside the confines of biomedical research facilities, sometimes in academic teaching institutions, private veterinary hospitals, or the home. Here, the veterinary role has shifted from one of oversight to one of investigation, which entails additional controls.

In the companion animal clinical drug study, for example, investigators operate largely within federal regulations (sections 511 and 512 of the FFDCA and further defined in Title 21 Code of Federal Regulations [CFR¹]) (CFR 2002) with oversight from individuals or organizations called clinical trials monitors. The FFDCA does not duplicate any portion of the Animal Welfare Act. Rather, the regulations in CFR Title 21 require compliance with all existing federal regulations in the AWA. Some similarities exist between the Acts. For example, CFR 21 describes requirements for submitting NADAs. Clinical studies must be carried out according to certain criteria described in the FFDCA §512 and further under §514.117 of CFR 21 *Ad-equate and Well-Controlled Studies*. Subparts (a) and (b) require the sponsor to (1) describe key investigators and subordinate personnel, with their qualifications, training, and functions; (2) describe the facilities in which they will work; (3) clearly state the rationale and purpose of the study; and (4) describe the standards of conduct to which the institution will hold such personnel.

CVM has also published guidelines in documents 58 and 85. Guidance 58, *Good Target Animal Study Practices* (FDA 1997), imposes additional, very detailed requirements on the investigative study. In addition to the legal requirements (of the AWA, possibly of the PHS, and possibly of the institution), there are requirements regarding the storage, distribution, and disposal of any investigational drug. Guidance Document 85 (FDA 2001) comprehensively describes key professional contacts, conduct, and record-keeping that will be involved in studies. For example, investigators must be masked to treatment identities; animals owned by individuals other than the investigator must be maintained according to the study protocol; investigators must promptly report to the sponsor any adverse drug experience associated with the use of the investigational new animal drug; and investigators must permit a monitor and FDA representative to inspect the facilities used by the investigator for the study and, for the purposes of verifying the validity of the data collected for the sponsor, to inspect and copy records made or kept by the investigator as part of or pertaining to the studies. Records must be much more detailed than is typically the case in protocols subject only to USDA or PHS Policy. Investigators must maintain records to the extent that all contacts with the monitor or other representatives of the sponsor, FDA, and their designees may be contacted. Records must therefore include dates and

times of meetings, purpose of meetings, affiliation of individuals involved, and a summary of contact findings.

Monitors

Monitors of clinical trials are required during the investigational and new animal drug approval process. Some veterinary teaching hospitals in which nonpharmacological therapies are tested also establish internal monitoring committees; however, the composition and responsibilities of these members are less detailed and less uniform compared with FDA/CVM Policy. For example, the University of Florida's consent form defines two types of clinical studies. Type 1 studies may involve the following: (1) comparison of a new therapeutic or diagnostic procedure with an accepted procedure or placebo treatment, (2) required collection of additional tissues or fluids during the course of standard treatment, or (3) collection of tissues from a client's animal after it has been euthanized. Such studies generally provide the committee and owners with a rationale or hypothesis, justification for the use of their animals, description of the experimental methods, and anticipated results. The owner must review this information and sign a consent form. Such studies differ from Type 2 studies in which additional blood or fluid samples may be required from what is already considered standard practice. In addition, the size and volume of the fluid collected are usually standard amounts. The samples or tissues are identified anonymously (UFVTH 2002).

Policy 58 of the CVM policy and procedures (FDA 1997) provides a detailed description of suitable monitors and required documentation during the phases of a study. Monitors must be qualified to oversee the study protocol and to implement quality assurance measures so that the study is consistent with the objectives. Monitors must be unbiased, must personally contact each investigator, must make frequent trips to the study site to ensure appropriate functioning of the study, and must continually record visits, actions, and correspondence with the investigative staff and sponsor. All study documentation and record keeping must comply with the detailed requirements.

Vaccine Development

The USDA is responsible for the preapproval, licensing, and policy development for companion animal vaccines. The Virus-Serum-Toxin Act of 1913 was amended in 1985 in response to public concern regarding companion animal vaccines, and later associated adverse events (e.g., feline vaccine-induced fibrosarcomas) prompted greater scrutiny of vaccine procedures (AAFP 2000). The Center for Veterinary Biologics, which is part of the USDA's Animal and Plant Health Inspection Service, Veterinary Services, is responsible for the safety and efficacy of marketed US animal vaccines. The Center establishes licensing, testing, and permit requirements and procedures; provides licenses for pro-

duction facilities and biological products; provides permits for importation of products; and reviews production method, labels, and supporting data involved in the licensing and permit process.

In terms of premarket clinical trials, most vaccine studies take place within the confines of the research organization. Study protocols follow the AWA and subsequent requirements. Because clinical trials are not always performed using privately owned animals, postmarketing surveillance is very important when new vaccines become available. Anecdotal search services frequently provide the best glimpse of safety and efficacy during early vaccine use (Veterinary Information Network 2002). Public concern and a growing body of evidence about vaccine reactions prompted a 2002 working group to examine risk/benefit and public accountability for responsible vaccination use and to recommend strengthened postmarketing surveillance of vaccine reactions (Gaskell et al. 2002).

Postmarketing Surveillance

The postmarketing period of use for common companion animal drugs, vaccines, and new medical treatments is the most useful, yet least well described, monitoring process for animal clinical studies. Most laboratory animal veterinarians will attest that there is no perfect animal study design. Indeed, if it were possible to design a perfect study, little reason would exist for the use of pilots. Just as the IACUC may frequently prescribe pilot protocol review mechanisms to describe risk/benefit of new studies fully, sensible veterinarians and pet owners ask questions about risk/benefit during the first few years of marketed use. During the critical time from clinical study to everyday use, the experimental group of animals suddenly changes from a small study group to the numbers discussed in the Introduction of this article.

Good clinical studies also utilize the benefit of strong postmarketing surveillance in an effort to seek true indices of the safety and efficacy of new products and techniques. Fortunately, new surgical and medical techniques usually must meet the scrutiny and selectivity of academic experts. This requirement and the fulfillment of the high standards shared by peer reviewers preceding publication of new medical techniques serve as ultimate safeguards for their eventual use in veterinary practice. Veterinarians' and pet owners' time and resourcefulness are required to read the pertinent literature on an ongoing basis.

Finding the sources of valuable postmarketing information on drugs and vaccines is often difficult because veterinary medicine programs rarely build these resources into the veterinary teaching program. Each federal agency makes this information available; however, some data are more readily accessed than others. Examples of readily available postmarketing information are provided below.

Adverse drug reactions. The FDA adverse drug reaction database is an enormously useful tool for finding in-

formation about common clinical signs associated with drug reactions. The tables are available to the public (<http://www.fda.gov/cvm/index/ade/adetoc.htm>).

Vaccine reactions. Vaccine reactions are monitored by the USDA Center for Veterinary Biologics through their vaccinovigilance monitoring system (Animal Immunobiologic Vigilance, USDA/CVM 510 South 17th Street, Suite 104, Ames, IA 50010) or, alternatively, through the United States Pharmacopeia (Tel: 800-487-7776) (<http://www.usp.org>).

Conclusions

The use of companion animals in nontraditional settings such as animal hospitals, homes, and veterinary teaching hospitals involves channels of approval for clinical studies, drug development, vaccine testing, peer review, and personal malpractice safeguards. Rules and guidelines during review of these procedures have evolved from very complex and thoughtful processes to regulatory systems that still require improvement. It is hoped that future directions will harmonize efforts among the FDA, EPA, and USDA policies and procedures, the ongoing policy development by the American Veterinary Medical Association in areas related to informed consent, and a growing awareness of the possibilities that exist to provide the consumer with genetically engineered pets. This latter arena is exceptionally difficult to address and will require extensive humane, moral, and ethical deliberation.

Veterinarians in laboratory animal medicine are uniquely trained to collaborate with individuals in nontraditional settings because many of these processes are inherently part of their routine. Such outside administration, particularly with respect to vaccines, is presently in its infancy and can be viewed similarly to pilot programs within research settings. Because many companion animal owners now have access to the internet and cable television involving countless animal special productions, these individuals are more informed about the legal processes surrounding the use of their animals as well as their consumer rights. As a result, it is hoped that more cross-communication, uniformity of administrative monitoring, and postprocedural surveillance will occur within the veterinary profession both in and outside the laboratory animal settings.

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