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REGULATORY ISSUES

REGULATORY ISSUES RELATED TO CONTRACEPTIVE DRUG PRODUCTION

Contraceptive products formulated for wildlife, either chemical compounds formulated as pharmaceutical preparations (that is, drugs) or vaccines, require prescriptions by a licensed veterinarian. Worldwide, prescription items are controlled by regulatory agencies at a national level (for example, United States) or supranational level (for example, European Union, EU). These agencies approve the sale of these drugs and vaccines, based on demonstrations of efficacy, safety, and the capability to produce them consistently under good manufacturing practices. In some countries, this approval for sale is called registration. The requirements for approval for sale or registration are not yet globally uniform, but ongoing attempts of harmonization have yielded some progress regarding manufacturing practices. For our readers, regulatory conditions prevailing in North America (United States and Canada) and in the EU are of primary interest.

In the United States, animal drugs and those vaccines influencing physiological processes usually are under the regulatory jurisdiction of the Center for Veterinary Medicine (CVM) of the Food and Drug Administration (FDA), an agency of the Department of Health and Human Services (DHHS) of the federal government. In the United States, vaccines indicated for preventing infectious diseases (biologicals) are regulated by the Animal and Plant Health Inspection Service (APHIS) of the US Department of Agriculture (USDA). Erroneously, the assumption is often made that any vaccine designed to prevent fertility automatically would be handled by APHIS, thus avoiding FDA.

The CVM/FDA and APHIS/USDA have signed a Memorandum of Understanding regarding vaccines, which includes contraceptive vaccines. Sponsors are asked to file applications to both agencies, explaining the product and label claims. The agencies will subsequently interact and decide which will take the regulatory responsibility for the biological product's approval. After the agencies decide which of them will assume responsibility for oversight of the product, the sponsor should request a conference with that agency for review of the intended developmental studies and to agree on the data needed on efficacy, safety, and manufacturing process. These data requirements may differ somewhat between CVM/FDA and APHIS/USDA. An example of such a contraceptive product is an antigonadotropin-releasing hormone (anti-GnRH) vaccine that was recently approved for sale by APHIS/USDA for use in male dogs.

Sponsors for the development of any new contraceptive animal health drug or vaccine intended for approval by CVM/FDA for sale must, as a first step, file an Investigational New Animal Drug Application (INADA) with the CVM (www.fda.gov/cvm/guidance/published.htm). An INADA allows for the interstate shipment of the new drug, which is essential for conducting the required efficacy and safety studies. If the new drug is used in animals that may produce or may become human food (which includes deer, elk, bison, and waterfowl), the product also may be subject to time-consuming and expensive safety and residue studies. All drugs may be evaluated for their potential environmental impact, although this latter requirement can often be waived by requesting an exemption from performing an assessment of environmental impact. Similar steps must be taken with APHIS/USDA.

If this INADA phase is successfully concluded (usually after 3 to 6 years), that is, the drug is efficacious and safe and can be produced to FDA standards, the sponsor can file a NADA (New Animal Drug Application). CVM/FDA has been entitled to charge a user fee for granting a new product approval. A waiver has been granted for products intended only for minor species, which includes wildlife. However, the road to approval still is filled with hurdles that could take several more years.

The regulation of animal health drugs in Canada is the responsibility of the Veterinary Drugs Directorate (VDD), a division of Health Canada's Health Products and Food Branch. The approval process in Canada closely resembles that of the United States. Data on safety, efficacy, and manufacturing generated in the United States are usually accepted, although the VDD often requires that at least one pivotal clinical study be conducted in Canada. In contrast to the situation in the United States, Canada has a pay-as-you-go system in which every step in the approval process generates fees, which are due at the time of submission.

The EU drug approval system is different: sponsors can elect to file for approval either for the entire EU with the Committee for Veterinary Medicinal Products (CVMP) in London, or with 1 of the 18 national regulatory agencies. However, for new chemical ingredients that have never before been used, the compound must pass a safety assessment of the central EU agency (CVMP). Based on data and information the sponsor has to provide and the species in which the drug will be used, the compound will be assigned to lists (Schedules) I to IV, which determines the extent of animal, handler, and consumer safety data required for approval. As outlined earlier, the sponsor can clear further hurdles toward approval from here either nationally (through the regulatory agency in each individual country) or EU wide (through the CVMP). In either approach, the agency's approval will be circulated to all EU member states, which can deny approval individually within 90 days. The kind of data required in the EU is similar to that needed in the United States, but the information has to be presented in a different fashion, and the data are evaluated primarily by experts and committees appointed by the agencies. The experts' recommendations to accept or reject a new drug are usually accepted, but evaluation of a new drug file is costly, irrespective of approval or rejection.

A sponsor's decision to take these roads to the approval of a new drug is based on feasibility: does the anticipated return justify the investment in time, money, and manpower? In the case of contraceptive drugs and vaccines for wildlife or zoo animals, the answer is clearly negative. The United States provides a somewhat abbreviated route under the general umbrella of "minor species" (Center for Veterinary Medicine 1999). However, in the EU the law does not allow "orphan drug status," that is, the recognition that for economical reasons an abbreviated, inexpensive approval process is needed.

A different avenue to new or existing contraceptive drugs or vaccines, approved for use in humans or domestic animals, has been recently opened in the United States via a procedure called extra-label drug use. This path allows veterinarians to prescribe such drugs for other species, provided that such usage is not specifically prohibited (Center for Veterinary Medicine 1994), is safe, and does not create tissue residues in animal products destined for human consumption. Another avenue to help ensure availability of old or new drugs for wildlife and zoo animals is the emergence of compounding pharmacies, which, based on prescriptions, may provide such drugs in dosage forms more suitable for the treatment of non-domestic animals.

Recently, CVM made it known that research involving unapproved drugs in non-food-producing animals may proceed without notification of the agency, if this drug will not be the subject of a future NADA. Precautions regarding safety

and the avoidance of food residues are required, and detailed records of drug shipments and drug effects are desirable.

Sponsors interested in the use of an approved animal health drug in zoo animals or wildlife species for which it has not been specifically approved can obtain an INADA from CVM for the intended drug use. Presently, melengestrol acetate (MGA), both in implant form and as a feed additive for zoo animals, is available under this umbrella. Individual investigators may obtain an INADA for the same purpose from CVM.

In Canada and in the EU, national regulatory agencies can be petitioned to import drugs available elsewhere but not yet in their country. Conditions of use and precautions taken must be outlined in detail, and a user fee might be required.

CONTRACEPTION AND ANIMAL WELFARE

In the United States, animals being used in research are covered under the Animal Welfare Act, which requires that research be conducted under protocols approved by an Institutional Animal Care and Use Committee (IACUC). Guidelines can be found in publications such as those of the National Research Council (1996), the National Institutes of Health for the Public Health Service (1996), and the Federation of Animal Science Societies (1999). Testing of new contraceptive methods in many cases requires IACUC review and approval.

In Europe, a number of countries have recently passed revisions of animal welfare laws, which explicitly ban surgical procedures in all animals unless they are medically indicated. Technically, this includes contraceptive procedures such as ovariectomy, ovariohysterectomy, castration, vasectomy, and penile deviation. Governments had to be petitioned to allow spaying and neutering in pets with the argument that these procedures have prophylactic medical value. In carnivores, ovariectomy can forestall the occurrence of uterine pathology and mammary tumors in female carnivores. Castration can lessen the chances of prostate hypertrophy and tumors and ameliorate aggression in male dogs. In male cats, castration can also prevent house soiling (spraying of urine), which is sometimes a cause for euthanasia.

Castration in pigs is under attack in Europe; the traditional cutting of week-old male piglets might be banned soon. Male calves are no longer castrated in Europe. Surgical removal of gonads in any animal might become outlawed eventually. Hence, chemical (pharmaceutical) and biological, that is, vaccine-based, contraception, to which this book is dedicated, may come to play a more important role in management of domestic animals as well as wildlife.

CAPTIVE WILDLIFE

The issue of local regulations for contraceptive use in zoos is less complicated than for free-ranging wildlife, for many obvious reasons. The ownership of the animals rests with the zoos and not with state or federal entities, except the few that are in US Fish and Wildlife Service or National Park Service endangered species recovery programs (for example, black-footed ferret, *Mustela nigripes*; red wolf, *Canis rufus*; Mexican wolf, *Canis lupus baileyi*). Certainly none of the animals in zoos can be considered food animals, and all drugs administered to collection animals are under the direct supervision and on the order of the licensed zoo veterinarian.

Under the Federal Animal Welfare Act zoos are included under the provision of Class "C" (exhibitor). However, the precise regulations for the use of experimental drugs or nonlabel use of drugs for most captive exotic species is not specifically addressed in this act. The Act states: "*Animal* means any live or dead dog, cat, nonhuman primate, guinea pig, hamster, rabbit, or any other warm blooded animal, which is being used for research, teaching, testing, experimentation, or exhibition purposes, or as a pet." Thus, the use of experimental contraceptive drugs in warm-blooded zoo animals nominally falls under the Animal Welfare Act, and that would include the use of noncommercial drugs being used experimentally. Accordingly, this interpretation requires that zoos provide oversight through an Institutional Animal Care and Use Committee (IACUC) or a similar body before experimental contraceptive drugs are applied to collection animals. Any contraceptive drug or vaccine that is registered under an FDA-issued Investigational New Animal Drug Application (INADA) or a New Animal Drug Application (NADA) falls within this interpretation. Most zoos already comply, although the oversight committees are often given names other than IACUC, such as animal care committee. This institutional responsibility is in addition to compliance with other federal regulations regarding the use of experimental drugs, through use under an INADA or NADA as discussed earlier.

FREE-RANGING WILDLIFE

One of the most poorly understood aspects of free-ranging wildlife contraception is the regulatory process. The regulatory oversight for the testing and application of contraceptive drugs becomes considerably more complicated with free-ranging wildlife because of issues such as ownership of animals, legal authority for managing the animals, classification of some species (such as the white-tailed deer,

Odocoileus virginianus) as food animals, and the often confusing management authority between state and federal entities. Depending upon the species in question and the location of that species, one or more regulatory agencies at the federal, state, or local level may be involved. Regardless of species or location, any experimental contraceptive drug for use in free-ranging wildlife that crosses state lines and jurisdictions must adhere to the FDA–CVM regulations regarding experimental drugs, that is, INADA or NADA requirements. Research in general with free-ranging wildlife is exempt from the federal Animal Welfare Act and therefore from oversight by the institutional IACUC. Within academic institutions engaging in animal research, there must be an IACUC, and in most but not all of these universities, the institutions have chosen to require IACUC approval for research with free-ranging animals regardless of whether they legally fall within the domain of the Animal Welfare Act. This decision is simply a responsible action on the part of the institutions, which seek to meet the intent of the Animal Welfare Act rather than the letter of the law.

The "ownership" of the species is of vital importance, and therefore the nature of the environment will dictate the regulatory issues. Historically, nonmigratory wildlife not living on federal land is legally under the management authority of state fish and wildlife departments on both nonfederal public and private land. Thus, a potential wildlife contraceptive project on nonfederal land must have approval by the particular state wildlife agency before any additional steps can take place. The two requirements most often quoted by state wildlife agencies are prior "approval" by the FDA and a requirement for marking each treated animal.

Few state agencies have understood the FDA regulatory process and the meaning of an INADA in the context of wildlife contraception, which has led to immense problems. The state usually assumes "approval" means that a drug has passed through the entire FDA drug-testing process and has been approved for sale as a commercial product. Even after they learn the nature of the INADA, which *authorizes* the use of an experimental contraceptive drug in a particular setting, the word experimental causes confusion and often concern. Beyond the state agency, county, municipality, and even park regulations must also be considered. Quite a few potential deer contraceptive projects have not materialized because of local firearms ordinances, which also apply to capture guns, or in a few cases the ordinances had to be altered for this specific purpose.

For animals living within certain federal reservations, such as national parks, national forests, wildlife refuges, Bureau of Land Management lands, and military reservations, however, there are individual and specific requirements for the testing and application of contraceptive drugs to free-ranging wildlife above and beyond those of the state, and these regulations vary from unit to unit. Managers of

wildlife on federal reservations have the legal right to manage their wildlife as they see fit, without interference by state agencies. However, the federal agency may voluntarily choose to seek state cooperation and state approval. Thus, contraceptive projects on federal lands may become extremely complicated depending on the actions of their managers.

Some domestic and foreign national parks maintain ethics committees, similar to IACUCs, to review and approve, modify, or reject research proposals. For example, elephant contraceptive research in South Africa's Kruger Park required approval by both a South African National Parks Board research committee and an ethics committee. Similar contraceptive research with wild horses in two US national parks required review and approval by the Resource Management Division of the parks. White-tailed deer contraceptive research and wild horse contraceptive research in two national parks in the United States required additional approval by the regional scientist for each region.

Within national parks, the remote delivery of contraceptive drugs may only be performed by persons who have been trained in the chemical immobilization course sponsored by the US National Park Service or its equivalent. Each researcher must then be certified within the national park where the research project is occurring, by passing a delivery equipment test and receiving written certification by the superintendent of the park.

In all these federal reservations, the National Environmental Policy Act (NEPA) requires an environmental impact statement (EIS) or an environmental assessment (EA) before contraceptive drugs may be applied to free-ranging wildlife. This requirement is the responsibility of the managing agency. Within the Department of the Interior, which includes the National Park Service, the Bureau of Land Management, and the Fish and Wildlife Service, the primary research mission rests with the Biological Resources Division of the US Geological Survey. Approval for wildlife contraceptive projects may also require some level of review and approval by this group, as certainly is the case for the Bureau of Land Management in regard to wild horse contraceptive research.

Two final regulatory levels remain within the domain of free-ranging wildlife contraception, and, although neither carries the force of law, they remain the most powerful influences on whether wildlife contraception research occurs or is applied. The first of these influences originates from the research team and brings into focus ethical considerations. Often wildlife contraceptive research groups are asked to consider projects with specific species or in locations where there are clear ethical dimensions that are not resolved. Should deer be subjected to fertility control because they eat ornamental shrubbery or because a municipality will not reduce a speed limit in a high-density area? Should wolves be subjected to

fertility control because they consume caribou for which a state sells hunting licenses? Should seals be subjected to fertility control because they eat food items for which commercial fishermen compete? Should an endangered species ever be contracepted? Who makes the decisions, and what are the criteria for decision making? These are but a few of the ethical issues surrounding wildlife contraception, and the research team must be prepared to accept the responsibility of an ethical evaluation of its potential actions. One serious question that all scientists must ask, and this certainly applies to those engaged in wildlife contraception, is whether the agency for which the research is being carried out plans to use the technology responsibly.

Finally, there is what we might call the "court of public opinion," which is without doubt the most powerful regulatory force of all. In the final analysis, wildlife does not belong to state agencies, or to park superintendents or to animal welfare groups, and certainly not to the scientists who pursue this seemingly bizarre approach to wildlife management. None has exclusive claim to wildlife. In the final analysis, wildlife belongs to a larger public, and their concerns and ideas cannot be ignored.

Perhaps this is nowhere a larger issue than with the concept of white-tailed deer contraception in urban areas of the United States, where it has reached epic proportions. Much of the conflict seems to be centered about the general concepts of lethal versus nonlethal approaches, although the larger issue of whether to manage at all often surfaces. Regardless of the larger public's right to have a say in the management of the wildlife it ultimately owns, a good deal of the information surrounding wildlife contraception comes to the public from highly sensationalized media hype. Nevertheless, once the public makes a decision, whether correct or incorrect, whether in the best interests of the wildlife or not, this body can create intense political pressures from the highest levels of government. Animal lovers lobby for nonlethal control, while hunters and state wildlife agencies fear a loss of hunting opportunity. Ranchers want fewer wild horses on land that they use for livestock grazing, and horse advocacy groups want more horses. Some segments of African society see elephants only as an economic commodity that can bring income from hides, meat, ivory, and hunting, but an equally large segment sees elephants as national treasures and seeks nonlethal controls. In each case the various public groups act to utilize the political process and place pressures upon state and federal legislative bodies to bring about the mode of management that each seeks.

The salient point of bringing into focus the regulatory forces of the public domain is that the scientist must navigate a careful course through these forces if the technology is ever to be applied. It is a fact that most scientists engaged in wildlife

contraception start out by examining only the biological possibilities. They usually do not get very far down the research road before the legal constraints become obvious, and then, often, a good deal of research is lost because it cannot be used, perhaps because the contraceptive agent can pass through the food chain, or because it is unlikely that any oral wildlife contraceptive will ever be approved by the FDA unless it is species specific. Even if they get past the legal constraints, many scientists soon find that the weight of public opinion usually runs against highly stressful procedures, or that the expense of a particular approach is beyond the reaches of the public entities which want to use this technology, or that lack of information or even misinformation has armed the public with incorrect perceptions about the contraceptive or delivery process. In the end, public opinion is much like a mold into which the scientist must design the research and application to fit, and if the scientific community does not understand the precise shape of that mold before they start, not much will result from even the best scientific achievement.

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