

Wildlife Contraceptives: A Regulatory Hot Potato

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ABSTRACT: Changing cultural values and increasing urbanization in the United States are curtailing traditional wildlife management tools used to effectively manage conflicts between human and wildlife populations. Because of this trend, the USDA Wildlife Services, National Wildlife Research Center (NWRC) began developing wildlife contraceptives in 1991. Since that time, NWRC scientists have steadily worked toward the goal of developing and registering contraceptive products that are practical to use, safe for the treated animal, and present little risk to humans, nontarget animals, and the environment. Working cooperatively with Innolytics, LLC, OvoControl G™ was recently registered for reducing the hatchability of Canada goose eggs. Another product developed by the NWRC, the single-shot GonaCon™ Immunocontraceptive Vaccine is poised to begin the registration process. A third product, DiazaCon™, soon will be tested for field efficacy and should begin the registration process within the year. Between 1996 and the present, the regulatory agency responsible for wildlife contraceptives has been the Food and Drug Administration, Center for Veterinary Medicine (CVM). Working under this premise, the NWRC has progressed toward fulfilling CVM's regulatory requirements by conducting field efficacy studies and a target animal safety study. NWRC explored various registration options with the CVM, and also with the USDA APHIS Center for Veterinary Biologics (CVB). Through this process, it became clear that wildlife contraceptives were incompatible with CVM's regulatory process, and outside the regulatory authority of CVB. In response, CVM and the U.S. Environmental Protection Agency (EPA) negotiated an agreement on contraceptive uses. The EPA will assume regulatory authority of contraceptives used for wildlife and feral animals. The CVM will retain authority over all uses in captive animals including livestock, companion animals, and zoo animals.

KEY WORDS: cervids, contraception, GonaCon™, urban wildlife, wildlife management

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INTRODUCTION

Changing cultural values and increasing urbanization in the United States are curtailing traditional wildlife management tools used to effectively manage conflicts between human and wildlife populations. Because of this trend, the U.S. Dept. of Agriculture, Wildlife Services, National Wildlife Research Center (NWRC) embarked on an effort to register a wildlife contraceptive in 1991. At that time, Dr. Russell Reidinger, Director of the NWRC, approved a wildlife contraceptive project to be headed by Dr. Dan Thompson. The focus of this project was the development of an immunocontraceptive based on porcine zona pellucida (PZP) for use in free-ranging wildlife populations. Shortly thereafter, Dr. Thompson hired Dr. Lowell Miller as the immunologist in charge of vaccine development. Since Dr. Thompson's retirement in the mid-1990s, Dr. Miller has been the leader of the NWRC wildlife fertility control project.

During the early years of the NWRC wildlife contraceptive project, efforts were directed at developing a product for approval with the Food and Drug Administration's (FDA) Center for Veterinary Medicine (CVM). Recently, regulatory authority over wildlife contraceptives was transferred from the FDA to the U.S. Environmental Protection Agency (EPA). This manuscript relates the story of how wildlife contraceptives became somewhat of a regulatory hot potato, describes how federal regulators now view wildlife contraceptives, and recounts the history to date of NWRC scientists' efforts to register a wildlife contraceptive. Specifically, NWRC hopes to register a single-shot immunocontraceptive and an orally-delivered chemical fertility control

agent within the next two years.

REGULATORY AUTHORITY OF CONTRACEPTIVES

In response to the public's call for cleaner water and air, President Richard Nixon in 1970 established the Environmental Protection Agency (U.S. Code 1970). Among other things, this action transferred regulatory authority to regulate pesticides from the U.S. Department of Agriculture to the EPA. However, there were certain products with pesticidal uses that the FDA maintained they had authority to regulate. Recognizing that the reorganization decreed by President Nixon did not provide adequate guidance for separation of responsibility over pesticides, in 1971 the EPA and FDA entered into an agreement outlining "Matters of Mutual Responsibility" (DHEW 1971). This agreement was later amended in 1973 to further define regulatory responsibilities (DHEW 1973). No mention of regulatory authority over contraceptives was included in any of the agreements. At that time, there was one wildlife contraceptive formally registered for use in wildlife populations in the U.S. Avitrol Corporation held the registration through EPA for Ornitrol™ (20,25-diazacholesterol dihydrochloride) for managing urban pigeon populations. It was orally administered in corn-based bait. At the registrant's request, the registration for Ornitrol™ was cancelled in 1993.

The material NWRC was developing in the early 1990s was an injectable immunocontraceptive vaccine. Veterinary vaccines traditionally had been registered by either the FDA Center for Veterinary Medicine (CVM),

or if intended for the prevention of disease, the USDA's Center for Veterinary Biologics (CVB). Since the product NWRC was developing was an injectable vaccine, and pregnancy is not considered a disease, the CVM concluded they had regulatory authority over a wildlife immunocontraceptive vaccine. However, because of their history with Ornitrol™, EPA maintained they had authority over products to be used in wildlife. This difference of opinion over regulatory authority left NWRC with no clear path for product registration.

In 1996, NWRC hosted a Workshop titled "Wildlife Contraceptives: The Regulatory Challenge", at the Denver Wildlife Research Center. Representatives from the EPA, USDA, and FDA attended the workshop and agreed to draft a Memorandum of Understanding (MOU) between EPA and FDA outlining regulatory authority of wildlife contraceptives. At that time, FDA was to be responsible for any wildlife contraceptive products.

APHIS REGISTRATION EFFORTS UNDER FDA

Following the Wildlife Contraceptive Workshop, APHIS requested that CVM open Investigation New Animal Drug (INAD) files for two immunocontraceptive vaccines. INADs were opened for vaccines based on porcine zona pellucida (PZP, ZonaCon™) and gonadotropin releasing hormone (GnRH, GonaCon™) in 1996 and 1997, respectively. The INADs allowed testing to be conducted on PZP in "wildlife species" and GnRH in "wildlife species, including deer, coyotes, prairie dogs, and various other rodents." In 1999, APHIS opened a third INAD for another contraceptive agent, 20,25-diazacholesterol dihydrochloride (DiazaCon™) for use in "prairie dogs". An INAD permits an investigational drug to be shipped via interstate commerce, facilitates research on the effectiveness and safety of the drug, and allows FDA the discretion to authorize the use of edible tissues from animals treated with the investigational drug (Code of Federal Regulations 2005a). It also provides for conducting studies on free-ranging wildlife.

Up until 1998, NWRC immunocontraceptive vaccines incorporated Freund's adjuvant into the formulation. Freund's was known as the best adjuvant to induce high antibody response in investigatory vaccines. However, in 1997 FDA made it clear that a vaccine containing Freund's adjuvant would not be registered because it could potentially cause false positive TB skin test results, it could cause severe reactions at injection sites, and because of a concern regarding its potential carcinogenicity. Studies showed that other adjuvants typically used in food animals or humans did not produce an adequate immune response in contraceptive vaccines to cause infertility for a sufficient length of time to make contraception a viable management tool for deer. Consequently, NWRC scientists had to develop a new adjuvant. A new adjuvant based on Johnes's vaccine and containing *Mycobacterium avium* was tested. A GnRH/keyhole limpet hemacyanin-based vaccine coupled with the *M. avium* adjuvant resulted in infertile deer and lasted multiple years following only a single vaccination. The adjuvant and final vaccine preparation were subsequently named AdjuVac™ and GonaCon™, respectively. In 1998, NWRC asked FDA if the new formulation of GonaCon™

could be approved. FDA determined that with the appropriate supporting data, GonaCon™ could be used in animals that might enter the food chain.

Once a final formulation for the product was determined, NWRC entered the development phase, where tightly controlled and monitored studies (pivotal studies) were required for FDA review. In addition, FDA required that the product be manufactured under "Good Manufacturing Practices" (GMP) conditions. APHIS was not in the position to manufacture GonaCon™ under GMP. Consequently, a private partner was sought to assist with the development, manufacturing, and marketing. Ultimately, that partner would be ensured some rights to the product. In 2004, a veterinary drug manufacturer expressed serious interest in the vaccine for use in the more lucrative livestock market. APHIS was still on its own to seek FDA approval of the product for wildlife uses.

The pivotal studies required by FDA included dose titration studies, product stability, target animal safety, laboratory and field efficacy, and human food safety. These studies are costly and many are difficult to conduct on free-ranging deer under the conditions required by FDA. Regardless, NWRC began conducting the studies to address their requirements. To date, studies have been or are being conducted to address dose titration, target animal safety, and laboratory and field efficacy; and a protocol has been developed to determine product stability.

The efficacy of GonaCon™ was tested on multiple species during development. Wild pigs are a growing problem in the U.S. To address this issue, the vaccine was tested in domestic pigs as a surrogate for wild pigs. Because NWRC did not have a development partner at this point, this study was conducted on a very small budget. The cooperating researcher asked if the 50 treated pigs could be sold and sent to slaughter to recover some study costs; subsequently, such a request was submitted to FDA. Their response (letter dated Dec. 2002) stated that an investigational exemption for GnRH conjugated to keyhole limpet protein was consistent with public health, and that swine treated with GonaCon™ could be marketed for human use. However, they reminded NWRC that the INAD was for wildlife, and that any further work on domestic animals would require a separate INAD. Three years later, NWRC made a similar request to send to slaughter 20 bison treated with GonaCon™. FDA rejected this request, citing the fact that bison were not under the current INAD (letter dated Aug. 2005).

FDA considers deer to be a potential food source. Despite the previous approval to slaughter swine, FDA regulations require the submission of data to demonstrate no risk to humans from eating vaccinated deer. To begin the FDA human food safety review, NWRC submitted detailed information of the composition and formulation of GonaCon™. After review, FDA responded that "in general the components of the product do not raise a human food safety concern" (letter dated Nov. 2005). They did ask for more information on potential inflammation at the injection site. These data will be obtained from the ongoing target animal safety study.

Despite progress in addressing FDA's animal drug authorization requirements, it was obvious that both parties, APHIS and FDA, were having difficulty with this product registration. More often than not, it seemed as though the investigators would never be able to satisfy FDA requirements, particularly those related to product manufacturing under GMP conditions. At the same time NWRC was working on FDA data requirements, other avenues for registration were being explored.

REGULATORY OPTIONS OUTSIDE THE FOOD AND DRUG ADMINISTRATION

GonaCon™ was being considered by NWRC scientists as a disease vaccine for controlling the transmission of brucellosis in Yellowstone bison. Brucellosis is spread among animals primarily through contact with infected placentas or aborted calves, and through milk of infected animals. If GonaCon™ could be used to render brucellosis-positive bison infertile, the primary route of transmission would be blocked. In combination with a testing and vaccination program, brucellosis might even be eliminated from the herd over time. As the transmission of brucellosis from bison to cattle is of great concern, there could be enormous benefit to both bison and cattle management. GonaCon™ is based on biological material, and veterinary biological vaccines for prevention or treatment of diseases are regulated by the USDA Center for Veterinary Biologics (CVB). Therefore, NWRC asked CVB to consider GonaCon™ a disease vaccine and entertain a license application submitted to their office. CVB responded that GonaCon™ was not consistent with a true disease vaccine but was functionally a contraceptive, and FDA had regulatory authority over contraceptives.

Because the market potential for a deer contraceptive is very small, NWRC was having difficulty finding a manufacturing partner interested in GonaCon™ for this use. Another avenue for providing a limited-market product is through the product's being compounded by a pharmacist upon request by a veterinarian (FDA 2003). Under the compounding pharmacy model, the product is not reviewed or authorized by the FDA. Instead, if the FDA determines the product meets certain criteria, the agency can transfer regulatory authority to state pharmacy boards. As a compounded drug, a veterinarian requests that a pharmacist produce the drug for a specific use. The pharmacist is not allowed to maintain any finished product in stock. The liability for formulating the compounded drug according to specifications rests with the pharmacist, and the requesting veterinarian is liable for ensuring the proper use of the product. NWRC felt GonaCon™ met the requirements of a compounded product and therefore asked FDA if they concurred. FDA did not deny this request to compound GonaCon™. Instead, the discussions that had begun in 1996 between EPA and FDA regarding regulatory oversight were renewed. EPA and FDA agreed to partition regulatory responsibility of animal contraceptives based on the intended use. FDA retained authority over all contraceptives used in domestic animals, livestock, and wild animals held in captivity (i.e., zoos). EPA assumed regulatory authority over contraceptives for use in

wildlife and feral animals, including wildlife opportunistically utilizing zoo property.

NEW DIRECTION FOR WILDLIFE AND FERAL ANIMAL CONTRACEPTIVES

With new and clear direction concerning regulatory oversight of wildlife contraceptives, NWRC has now set goals regarding product approval. The focus is to obtain EPA registration for an injectable immunocontraceptive for use in cervids. The primary emphasis will be the registration of GonaCon™. However, depending upon customer interest, NWRC may also attempt to register a PZP-based product. Future registration efforts for an injectable immunocontraceptive may include wild swine. NWRC may also attempt to register an orally-delivered contraceptive agent (20,25-diazacholesterol hydrochloride) for both birds and mammals. Target species include the monk parakeet (*Myiopsitta monachus*) and the California ground squirrel (*Spermophilus beecheyi*). Future contraceptive research at NWRC will center on developing orally-delivered contraceptive products.

With EPA's recent approval of OvoControl G™, the groundwork has been set for orally-delivered contraceptives. EPA's approach to registration and required data is similar to that for a rodenticide (Code of Federal Regulations 2005b). Data requirements for registration include product chemistry, toxicology, environmental fate and effects, residue chemistry, product performance, and worker protection. NWRC anticipates having to address similar data requirements for any oral contraceptive delivered as a bait. Data requirements could vary depending upon the active ingredient and the method of application. For instance, environmental fate data requirements will be more extensive for broadcast delivery than for products delivered in bait stations. In addition, with EPA's new guideline for endangered species impacts additional data may be required to satisfy nontarget hazard concerns (USEPA 2005).

Registration requirements for an injectable immunocontraceptive vaccine may be very different than a typical EPA registration. An injectable product poses little risk of negative impact to air, water, and soil, and primary nontarget hazards are minimal, as are secondary hazards for a protein-based product such as GonaCon™. If EPA determines the proposed use is a nonfood or feed use, residue chemistry data will not be required. The primary data requirements will be general product chemistry and toxicology. However, a product label would contain precautionary language against accidental injection into humans. GonaCon™ will be a "Restricted Use" product and will be limited to Certified Pesticide Applicators. It will be further restricted to use by state or federal wildlife or natural resource management personnel or persons working under their authority.

NWRC scientists have developed GonaCon™, an injectable immunocontraceptive vaccine that will render a treated animal infertile for multiple years following a single injection. This development makes contraception a viable management tool. Despite this breakthrough, the costs associated with individually vaccinating deer make the technique viable only in select situations. The development of oral contraceptives, such as 20,25-

diazacholesterol dihydrochloride or the recently registered OvoControl G™, makes contraception a truly viable wildlife management tool. With the expertise EPA has in assessing the environmental and human health risk of vertebrate control products, and the history USDA APHIS has with developing and registering products with the EPA, the future of wildlife contraception looks promising for wildlife managers to have access to multiple contraceptive products for use on a variety of species.

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