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Registration of wildlife contraceptives in the United States of America, with OvoControl and GonaCon immunocontraceptive vaccines as examples

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Abstract. Overabundant wildlife populations have the potential to adversely affect wildlife habitats or pose risks to human health and safety through disease transmission and collisions with vehicles and aircraft. Traditional methods for reducing overabundant wildlife, such as hunting and trapping, are often restricted or infeasible in urban and suburban areas. Additional management options are needed. For the past 15 years, scientists with the US Department of Agriculture's (USDA) Wildlife Services' National Wildlife Research Center have been developing and testing contraceptive agents. This research has resulted in the development of several reproductive inhibitors and has forced regulatory bodies to determine where the regulatory authority for wildlife contraceptives will reside. The regulatory authority for contraceptives for wildlife and feral animals has recently been moved from the US Food and Drug Administration (FDA) to the US Environmental Protection Agency (EPA). The first contraceptive registered by the EPA since this move was OvoControl-G for reducing the hatchability of Canada goose eggs. OvoControl was registered in 2005 by Innolytics, LLC working in cooperation with the National Wildlife Research Center. A similar product, OvoControl-P, was registered in 2007 as a contraceptive technique for pigeons. Another product developed by the National Wildlife Research Center, GonaCon immunocontraceptive vaccine, is in the registration process for managing white-tailed deer populations. This manuscript will describe the products that have been and are currently undergoing registration as contraceptives in the United States of America, and the data required for those products.

Introduction

In the United States of America (USA), wildlife damage management is an important part of the wildlife management profession that is conducted on a national level by the US Department of Agriculture (USDA)/Animal and Plant Health Inspection Service (APHIS)/Wildlife Services (WS) program. The WS program is directed by the Animal Damage Control Act of 1931 to protect American agriculture and other resources from damage caused by wildlife. Wildlife Services employs personnel in most states to provide both technical assistance and direct control of damage.

For most of the last century, federal and state wildlife conservation agencies in the USA have focussed on increasing populations of many species of wildlife, with the result that many species, such as white-tailed deer (*Odocoileus virginianus*) and Canada geese (*Branta canadensis*), are now locally overabundant. Overabundant wildlife can cause ecological damage or human–wildlife conflicts, including damage to agricultural commodities, transmission of diseases to humans or livestock, and safety issues such as aircraft strikes. Wildlife damage managers are called upon to resolve this broad range of problems caused by wildlife.

Many of the problems associated with overabundant wildlife occur in suburban or urban areas where regulation of wildlife populations through conventional means, such as hunting, translocation, or culling has not been feasible or is illegal. Other management options are needed, and a growing interest in non-lethal methods for population management of overabundant wildlife species has fostered research in wildlife contraception.

For the past 15 years, scientists with the USDA's Wildlife Services' National Wildlife Research Center (NWRC) have been developing and testing contraceptive agents for wildlife. NWRC scientists have steadily worked towards the goal of developing and registering contraceptive products that are practical to use, safe for the treated animal, and present little risk to humans, non-target animals and the environment. This research has resulted in the development of several reproductive inhibitors and has forced regulatory bodies to determine where the regulatory authority for wildlife contraceptives will reside. The present paper describes the products that have been registered and are currently undergoing registration as contraceptives in the USA, and the data required for registration of those products.

Regulation of wildlife contraception drugs in the USA

Between 1996 and 2006, the regulatory agency responsible for wildlife contraceptives in the USA was the Food and Drug Administration, Center for Veterinary Medicine (CVM).

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Working under this premise, the NWRC progressed towards fulfilling US Food and Drug Administration (FDA)'s regulatory requirements by opening Investigational New Animal Drug (INAD) files for several contraceptives; these INADs allowed interstate shipment of test material and allowed research to be conducted on field efficacy and target animal safety. During this time, it became clear that wildlife contraceptives were incompatible with FDA's regulatory process, partly because they are placed out in the environment on free-ranging wildlife, a situation the FDA does not normally encounter with human, livestock or companion animal drugs. In response, FDA and the US Environmental Protection Agency (EPA) negotiated an agreement on contraceptive uses in wild animals. Beginning in 2006, the EPA assumed regulatory authority over contraceptives used for wildlife and feral animals (Eisemann *et al*. 2006). The FDA Center for Veterinary Medicine (CVM) will retain authority over all uses in captive animals including livestock, companion animals and zoo animals; the regulatory authority is Section 512 of the Federal Food Drug and Cosmetic Act (FFDCA). This change is beneficial for the registration of wildlife contraceptives because the EPA has more expertise than the FDA in environmental risk assessment, including effects on non-target species.

The EPA is responsible for regulating pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Registration of a contraceptive 'pesticide' by the EPA involves two processes. The first is registration of a technical grade active ingredient (TGAI), which is the base chemical used to formulate products. Registration of the TGAI requires submission of a series of data requirements that fall into several broad categories (Fagerstone 1990; Ramey *et al*. 1994): (1) Product Chemistry studies that provide a profile of the physical and chemical characteristics of the pesticide product; (2) Wildlife and Aquatic Organisms studies to determine toxicity to non-target species, primarily in the laboratory but also in actual field studies; (3) Toxicology or Human Health Hazard studies to assess potential hazards to humans according to duration and route of exposure to the pesticide; (4) Environmental Fate studies to monitor the movement, degradation and metabolism of the pesticide in soil, water and air; and (5) Residue Chemistry studies to determine pesticide residues in plants or animals, allowing EPA to determine allowable tolerances for pesticide residues on food items. The second process in the registration of a contraceptive agent is the registration of an end-use product (EP), which is the final formulation incorporating the technical active ingredient. Registration of the end-use product requires submission of a limited number of product chemistry studies specific to the final product formulation, a series of toxicology studies to identify any worker hazards that could be associated with the final formulation, and laboratory and field product performance studies that assess the effectiveness of the product for uses identified on the product label.

The EPA registration process can take several years and potentially can cost several million dollars, depending on the proposed use patterns. The time frame for product development and registration can be quite long (Fig. 1). For example, research began on nicarbazin (NCZ) as a potential bird contraceptive in 1999 and a registration was completed by 2005. Research began on development of an injectable gonadotrophin-releasing hormone (GnRH) immunocontraceptive vaccine in 1994 and a registration with the EPA for the final product, GonaCon, is anticipated to occur in 2009. Generally, EPA will take ~18 months to make a regulatory decision once a new technical ingredient registration package for a non-food, outdoor use is submitted.

Typically, 48 to 60 individual data requirements (which could cost up to US$2 700 000) must be met before registering a new active ingredient with the EPA. This cost does not include product development work before embarking on the registration process. However, the EPA may request fewer registration requirements for an injectable immunocontraceptive vaccine than for an oral product because an injectable product poses less risk of negative impact to air, water and soil, or to non-target animals. Additionally, infertility agents used in potential food species, such as deer and geese, will potentially cost more to register than those targeting non-food species because of the need to show that any residues in meat pose no human safety risks. Registration costs were reduced for both OvoControl and GonaCon because of their limited use patterns. And costs were lowest for GonaCon because it is an injectable product with no exposure to the environment or to non-target animals.

Contraceptive 'pesticides', regardless of whether they are injectable vaccines or orally delivered baits, will probably all be restricted-use products for use only by certified pesticide applicators, which means applicators who have received training approved by the EPA or a designated state agency in pesticide application techniques and safe handling procedures. The certified applicator designation will be required for several reasons: (1) to ensure the humane treatment of the animals (i.e. knowledge of darting, trapping, and other capture methods); (2) to limit potential hazard to the person administering some products through proper handling; and (3) to minimise potential for inappropriate use or non-target hazards. Because wildlife are owned by the public in the USA and managed by federal and/or

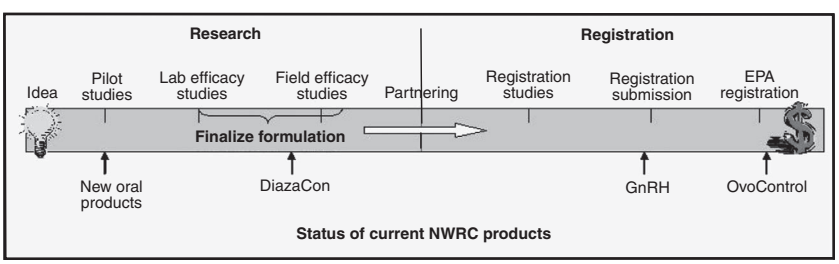

Fig. 1. Product development and registration process.

state wildlife agencies, pesticide labels may require that these agencies be consulted for permits or authorisations before use.

Contraceptives registered by the Environmental Protection Agency

Development and registration of OvoControl

The first contraceptive registered by the EPA under the new agreement with the FDA was OvoControl-G (EPA registration number 80224–5), for management of Canada geese. This was registered in 2005 by Innolytics, LLC working in cooperation with Wildlife Services NWRC. A similar product, OvoControl-P, was registered by Innolytics, LLC in 2007 as a contraceptive agent for feral rock pigeons. Both of these end-use products contain the technical active ingredient nicarbazin.

Nicarbazin (NCZ) is a compound approved by the FDA since the 1950s for control of coccidiosis in broiler chickens (Jones *et al*. 1990*a*, 1990*b*). If accidentally fed to breeder or layer hens, NCZ causes reduction in hatchability and egg laying (Sherwood *et al*. 1956). The mechanism of action is due to increased permeability of the membrane between the egg white and egg yolk, which destroys the conditions necessary for development of the embryo (Yoder 2005; Yoder *et al*. 2006). Based on this information, the WS National Wildlife Research Center in 1999 attempted to determine whether NCZ had similar reproductive effects in other avian species. A pilot study was conducted with Coturnix quail (*Coturnix japonica*). Quail were treated with 125 ppm NCZ commercial chicken feed (Koffolk, Tel Aviv, Israel) for 25 days, resulting in a 100% reduction of hatchability by 4 weeks of treatment. This positive result led to an interest in developing a contraceptive for use in Canada geese (Bynum *et al*. 2005).

As goose populations and urban areas in the USA expand and overlap, Canada geese are often considered a nuisance and potential health problem (e.g. fouling land and water, colliding with aircraft). Expanding populations of resident Canada geese that remain in suburban and urban areas year-round often result in increased conflicts with humans. The public is increasingly requesting non-lethal, humane means for managing Canada goose flocks residing near or on airports, golf courses, industrial parks, government sites and city parks.

Based on the positive results with Coturnix quail, a study was performed to assess the absorption of NCZ in Canada geese as compared with chickens and mallards (Bynum *et al*. 2005; Yoder *et al*. 2005). This study showed that application of NCZ to reduce egg hatchability in Canada geese would require use of a much higher dose than that in chickens owing to reduced drug absorption in the goose. Other studies with penned Canada geese pairs in Minnesota (K. C. VerCauteren, unpubl. data) and with wild Canada geese in Colorado (Yoder 2005) showed that if geese ate high enough levels of NCZ, hatchability of eggs could be significantly reduced. However, it proved difficult to develop a field bait that would deliver high enough levels of NCZ, as the NCZ proved to be unpalatable to Canada geese at the concentrations required to achieve effective levels (VerCauteren *et al*. 2000; Curtis *et al*. 2001; L. Clark, unpubl. data).

Eventually a palatable bread-like bait (OvoControl-G) was developed by Innolytics, LLC. The bait is semi-soft, made of wheat flour, dyed yellow and shaped like corn (Bynum *et al*. 2005). Based on the results of pen studies, it was decided that field testing of OvoControl-G was warranted. This field efficacy study was undertaken in February 2004 following EPA protocol approval. At 10 sites in Oregon, wild Canada geese were provided bait for 56 days at a rate of 2500 ppm (Bynum *et al*. 2007). Percentage hatchability at individual nests was significantly reduced by 51% at treated *versus* control sites. Because NCZ can completely inhibit egg production, reproductive success at treated sites was probably reduced considerably more than accounted for by determination of percentage hatchability alone, as some geese did not lay eggs. OvoControl-G, registered with the EPA in 2005, contains 5000 ppm, so birds do not need to consume a large amount on a daily basis to achieve a contraceptive effect.

Following the registration of OvoControl-G for management of Canada geese, Avery *et al*. (2006, 2008) tested whether NCZ bait could be used for contraception in the rock pigeon, an abundant exotic species found throughout the world. A bait was developed based on the goose bait that contained 5000 ppm NCZ. It was readily accepted by pigeons and produced desired levels of NCZ in blood plasma of female birds. In pen tests, nesting pairs of rock pigeons exposed to the test bait had a 59% reduction in hatching of eggs after treatment with NCZ. All nestlings produced during the study appeared healthy and normal, there was no mortality among the adult pairs, and birds began to lay fertile eggs after being taken off the treatment. The test showed that, provided sufficient levels are maintained in the blood, NCZ is an effective and safe means to reduce hatchability of rock pigeon eggs. Thus, application of NCZ bait could become an important non-lethal component of integrated management efforts to reduce populations of rock pigeons, particularly in urban and suburban settings. The key to successful population reduction will be devising strategies to ensure target birds receive adequate exposure to NCZ bait. Registration of nicarbazin (OvoControl-P) was granted in 2007 based on these data.

Registration of these Canada goose and pigeon contraceptives with the EPA required the submission of data on NCZ as a technical active ingredient (TGAI), and on NCZ 30% granulated premix as a manufacturing use product (MP) that is formulated onto baits. Thirteen product chemistry studies were required for the TGAI and 17 for the MP (Table 1). Toxicology or human health hazard data requirements for NCZ included six studies for the TGAI and four studies for the MP. Data showed that NCZ has very low toxicity (Bynum *et al*. 2007). Six data submissions were also required for the TGAI to assess potential hazards to wildlife and aquatic organisms. These studies showed that NCZ is practically non-toxic to aquatic animals on an acute basis and is practically non-toxic to northern bobwhite quail and slightly toxic to the mallard on an acute/sub-acute basis (EPA 2005). Thus the likelihood of chronic risk to non-target animals is low and is further minimised by label restrictions. Environmental fate study requirements were met by submitting three studies for the TGAI and one for the MP. Studies showed that NCZ is stable in water and does not leach through the soil. Based on modelling from these studies, the EPA concluded that the environmental exposure from the use of NCZ will be small compared with its use in poultry feed. Residue chemistry studies were not required

Table 1. United States Environmental Protection Agency (EPA) data requirements for GonaCon and OvoControl
The active ingredient (TGAI) for GonaCon is gonadotrophin releasing hormone (GnRH) and the active ingredient for OvoControl is nicarbazin

Data requirement	GonaCon		OvoControl		
	TGAI	EP	TGAI	MP	EP
Product chemistry data requirements					
Product identity and composition		X		X	X
Description of materials used to produce the product		X		X	X
Description of production process	X		X	X	X
Description of formulation process		X		X	X
Discussion of formulation of impurities	X	X		X	X
Preliminary analysis		X			X
Certified limits		X		X	X
Enforcement analytical method		X		X	X
Color	X	X	X	X	X
Physical state	X	X	X	X	X
Odor	X	X	X	X	X
Stability to normal and elevated temperatures, metals, and metal ions			X		
Flammability				X	X
Explodability				X	X
Storage stability		X		X	X
Corrosion characteristics				X	X
pH	X	X	X	X	X
Melting point/melting range			X		
Density/relative density/bulk density			X	X	X
Dissociation constants in water			X		
Particle size and shape			X	X	X
Partition coefficient (n-octonal/water)			X		
Water solubility			X		
Vapor pressure			X		
Terrestrial and aquatic non-target organisms data requirements					
Acute toxicity freshwater invertebrates			X		
Freshwater fish toxicity			X		
Avian oral toxicity			X		
Avian dietary toxicity			X		
Avian reproduction			X		
Earthworm toxicity			X		
Non-target plant protection data requirements					
Aquatic plant growth – algal toxicity			X		
Residue chemistry data requirements					
Chemical identity	X				
Directions for use		X			
Toxicology data requirements					
Acute oral toxicity	X	X	X		
Acute dermal toxicity		X			
Acute inhalation toxicity				X	
Primary eye irritation		X		X	
Primary dermal irritation		X		X	
Dermal sensitisation				X	
90-day chronic dietary			X		
Prenatal developmental toxicity			X		
Mammalian bone marrow chromosomal aberration			X		
Other genotoxic effects			X		
Target animal safety (not required)		X			
Metabolism	X		X		
Product performance					
Laboratory efficacy		X			X
Field efficacy		X			X
Environmental fate data requirements					
Hydrolysis			X		
Leaching and adsorption/desorption			X		
Aerobic soil metabolism			X		
Terrestrial field dissipation					X

TGIA = technical grade active ingredient; MP = manufacturing product; EP = end-use product.

based on the nature of the compound, which clears from body tissue very rapidly.

In addition to the TGAI and MP data submissions, the EPA required submission of data to register OvoControl-G and OvoControl-P as end-use products (EP). For registration of the EP, 18 product chemistry studies and one environmental fate study specific to the final product formulation were submitted. In addition, laboratory and field product performance studies were submitted to verify the effectiveness of the products. Advantages of these products are that nicarbazin is specific to egg layers, it is cleared from the body within ~48 h, and the infertility effect is reversible. A disadvantage of the products is that they have to be fed continuously before and during egg laying.

Development and registration of GonaCon

GonaCon is a gonadotrophin-releasing hormone (GnRH) immunocontraceptive vaccine recently developed by the National Wildlife Research Center. GnRH immunocontraceptive vaccines take advantage of the role played by GnRH in regulating mammalian reproduction. GnRH controls steroidogenesis and gametogenesis by stimulating the release of gonadotrophins from the pituitary, triggering the cascade of reproductive hormones that lead to ovulation in females and spermatogenesis in males. GonaCon is a single-shot, multiyear immunocontraceptive vaccine that stimulates the production of antibodies that bind to the GnRH hormone in an animal's body, reducing GnRH's ability to stimulate the release of the sex hormones for normal reproductive activity. As a result, all sexual activity is decreased, and animals remain in a non-reproductive state as long as a sufficient level of antibody activity is present. GonaCon Immunocontraceptive Vaccine suppresses reproduction in treated animals of both sexes (Miller *et al*. 2004*b*). In females, follicular development, ovulation and oestrus are inhibited. In males, testosterone levels are reduced, testicular size and aggressive behaviour decrease significantly and no interest is shown in oestrous females (Miller *et al*. 2004*b*). A single injection of GonaCon can keep female animals infertile for 1 to 4 years without boosting, but infertility is reversible over time as antibody levels decline. Multiple injections increase the longevity of the vaccine.

GnRH is a small hormone that is a weak antigen owing to its low molecular weight and its being a 'self' hormone (Herbert and Trigg 2005). To produce GonaCon, GnRH is made immunogenic by conjugating it to a large, non-self, haemocyanin protein harvested from marine mollusks (Miller *et al*. 2003, 2004*b*). An adjuvant is used in conjunction with the vaccine to achieve an immune response sufficient to provide contraception. The adjuvant used in GonaCon vaccine was developed at NWRC and consists of a modified, USDA-approved vaccine for Johne's disease called Mycopar (Fort Dodge Animal Health, Fort Dodge, IA, USA). Mycopar is approved for use in food animals and therefore does not raise concerns regarding the consumption of GonaCon-treated deer (Miller *et al*. 2004*b*).

The GnRH vaccine has been shown to induce contraception in many mammalian species, including California ground squirrels (*Spermophilus beecheyi*) (Nash *et al*. 2004), domestic cats (*Felis catus*) (Levy *et al*. 2004), domestic and feral swine (*Sus scrofa*) (Killian *et al*. 2003, 2006*c*; Miller *et al*. 2003), wild horses (*Equus caballus*) (Killian *et al*. 2004, 2006*b*), bison (*Bison bison*) (Miller *et al*. 2004*a*), black-tailed deer (Perry *et al*. 2006) and white-tailed deer (Killian *et al*. 2005; Miller *et al*. 2000; Miller and Killian 2001).

In many regions of the USA, white-tailed deer populations are locally overabundant (Daigle and Crête 1999). Problems associated with overabundant deer include frequent collisions between deer and motor vehicles (Conover 1997; Etter *et al*. 2000), damage to native and ornamental vegetation (Waller and Alverson 1997; Rooney and Waller 2003), effects on forest community composition (Côté *et al*. 2004) and reduction of avian biomass and diversity (DeCalesta 1994; McShea and Rappole 2000). Although sport hunting remains the most effective means of controlling deer, overabundant deer now inhabit many settings, particularly urban or suburban areas, where hunting is prohibited. In addition, urban and suburban residents often prefer non-lethal wildlife control methods such as contraception (Curtis *et al*. 1993; Warren 1995; Rutberg 1997; Stout *et al*. 1997). Fertility control has potential as a management technique for use in these types of situations, particularly where a large population can be reduced with lethal methods first before fertility control is used to limit population growth.

The WS NWRC has been conducting studies to develop a GnRH vaccine in white-tailed deer for ~10 years. Based on this research, the USDA/Animal and Plant Health Inspection Service will submit an application to the USA EPA during early 2009 for a Section 3 (national) registration of GonaCon as a contraceptive agent for adult female white-tailed deer. GonaCon will be registered as a 'Restricted Use' product, for use by APHIS Wildlife Services or state wildlife management agency personnel or persons working under their authority. GonaCon users will also be required to follow state wildlife regulations and authorisation processes.

During January 2007, an Experimental Use Permit was submitted to the EPA by the NWRC/APHIS requesting the use of GonaCon for experimental purposes at Point Reyes National Seashore for a program to treat fallow deer (*Dama dama*) with contraceptives. This study began in July 2007 and is being conducted in cooperation with the National Park Service and White Buffalo. A second experimental use permit was submitted to the EPA in August 2007 for treating elk in Rocky Mountain National Park with contraceptives. That study began in the winter of 2008 in collaboration with Colorado State University, the National Park Service and the Colorado Division of Wildlife.

Based on a preliminary review of data submitted to obtain the Experimental Use Permits, the EPA has recognised that the product will be limited in use, will be restricted as to who may use it, and will have little or no contact with the environment owing to the nature of the packaging in pre-filled syringes for administration to specific target animals. Limited environmental exposure will reduce the need for excessive and costly studies that will have little or no impact on furthering protection of the environment and human exposure.

The technical active ingredient that will be registered with the EPA is gonadotrophin releasing hormone (GnRH). The studies required for the TGAI include primarily product chemistry studies, of which six are anticipated to be required. One toxicity study will be submitted. Other data requirements have

been or will be waived or will be met by submission of material from the literature on GnRH.

Studies anticipated to be required for the end-use product include 12 product chemistry studies and six standard toxicology studies required to determine any potential hazards to handlers and applicators. Residue studies are not required because the vaccine is made up of proteins, which when consumed, are broken down into amino acids in the gastrointestinal tract that are indistinguishable from amino acids from the metabolism of other ingested proteins, and have no contraceptive effect. During the period when FDA had regulatory authority over wildlife contraceptives, the CVM allowed swine treated with GnRH vaccine in one study to be sent to slaughter and issued a letter to APHIS indicating that 'in general, the components of this product do not raise a human food safety concern'. A target animal safety study was also conducted during the period of FDA authorisation. This was a 20-week study with two groups of white-tailed deer, one of which was given a single injection of GonaCon and one of which was given a single injection at weekly intervals for 3 weeks (simulating a situation where deer could be accidentally dosed more than once during a short period of time). The study concluded that GonaCon is safe for target animals and that unintentional repeated vaccination does not pose threats to the health of female deer (Killian *et al*. 2006*a*). Efficacy data will be required for the end-use formulation. This requirement will be met by submission of data from pen studies with white-tailed deer at Pennsylvania State University (Miller *et al*. 2000; Miller and Killian 2001) and from a field trial conducted in Maryland under Good Laboratory Practices (Gionfriddo *et al*. 2006). The pen studies showed 90–100% effectiveness in reducing fertility during the first year and ~70% effectiveness during the second year. The field trial showed the vaccine to be 88% effective the first year and 47% effective the second (Dr James Gionfriddo, pers. comm.). GonaCon will not replace other management tools but is a tool that can be used to help manage overabundant deer herds or other wildlife in urban and residential areas where other management methods, such as hunting, are not always an option.

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