August, 2001

SpayVac

RESEARCH PRODUCT INFORMATION

SpayVac™ *is a single dose immunocontraceptive vaccine that confers contraception in female mammals for multi-year periods.*

- Cost-effective tool for wildlife population management
- Alternative method to culling wildlife populations
- Effective alternative to spaying domestic pets
- No invasive surgery required

SpayVac™ is a result of patented innovations in vaccine biotechnology at the Department of Biology, Dalhousie University, Halifax, Nova Scotia, Canada. **ImmunoVaccine Technologies Inc.** is pursuing the commercial development of this vaccine for several mammalian species. SpayVac™ is currently available to wildlife and veterinary researchers, zookeepers and game managers for use in research trials only.

PRODUCTS

- **SpayVac™ original formulation**. A multi-year, single dose immunocontraceptive vaccine, which contains porcine zona pellucida (ZP) and Freund's Complete Adjuvant (FCA) adjuvant. This formulation is considered the 'gold standard' for research purposes only.
- **SpayVac™ improvements**. Vaccine formulations which contains PZP and a non-FCA, US FDA-approved adjuvant. Several formulations are in development.
- **SpayVac™ reversible**. Suitable for use where only short-term, temporary contraception is desired. Requires a primary dose and 1-2 initial boosters, plus annual boosting.
- **SpayVac™ for birds.** A vaccine formulation in development which uses the avian equivalent of ZP.
- **SpayVac™ for fish.** A vaccine formulation using a teleost homolog of ZP.

SERVICES

18 **Titer testing**. Ongoing monitoring for ZP (or equivalent) antibody titers in the blood serum of test animals is available.

19 **Wildlife contraception project design and management.** Full expertise available in all aspects of SpayVac™ wildlife fertility control, either in captive or wild settings.

WILDLIFE APPLICATIONS

18 Available delivery methods include:

Injectable syringe
Darts
Jab sticks

19 Doses can be shipped pre-measured and ready for use.

20 Wildlife biologists and reproductive physiologists available for consultation regarding population dynamics, capturing, tagging, census, behavior, and health.

COMPANION ANIMALS

18 Single-dose vaccine products in development.

19 Point-of-use blood titer test kits for annual monitoring in development.

SUPPORTING PERFORMANCE DATA

18 Performance data for 10 mammalian species available upon request.

SHELF-LIFE

18 6-month minimum shelf-life at -20 to 5 ^{0}C for ready-to-use formulation.

19 Freeze dried formulation available upon request.

SHIPMENT

18 Via courier, or per client instructions.

PRICING

18 Please inquire.

CONDITIONS

This product is available under a Material Transfer Agreement for research purposes in non-human mammals only. Nothing disclosed herein is to be construed as a recommendation to use this product in violation of any patents or regulations. Neither ImmunoVaccine Technologies Inc., Dalhousie University or TerraMar Environmental Resources Ltd. accept any obligations or liabilities for consequential damages arising out of or in connection with the use or performance of this research-phase product or other direct or indirect damages with respect to any loss.

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Answers to Frequently Asked Questions About Wildlife Applications for SpayVac™

How does SpayVac™ work? The antigens in SpayVac™, porcine (pig) *zona pellucida* (PZP) proteins, cause a treated female mammal to produce antibodies that adhere to the surface *(zona pellucida)* of her ova (eggs) and prevent sperm from binding, thus blocking fertilization.

What is SpayVac™ composed of? SpayVac™ is made up of three components: the antigen (PZP extracted and purified from pigs ovaries), liposomes (cholesterol and lecithin), and an adjuvant, to stimulate the immune response. Except for the PZP antigen, all other components have been previously approved in other vaccines. However, PZP has been incorporated into research vaccines for >20 years.

Does SpayVac™ affect the well-being of treated animals? Because SpayVac™ results only in antibodies that block sperm binding, the effects on treated animals are minimal. The largest changes relate to the fact that most treated animals will not become pregnant, and in some species (e.g., White-tailed Deer), repeated estrous cycles result in repeated matings. The result may be an extended breeding period and increased mating activity. Increased longevity of treated wild horses has been also been reported. PZP vaccines have been used safely in wildlife and zoo animals for about 20 years and are regarded as safe.

Is SpayVac™ environmentally safe? Unlike hormone contraceptives, which can find their way into the food chain, PZP protein antigens and the resulting antibodies are harmless to the environment. PZP antigens and antibodies are digested like any other proteins by humans, predators, scavengers, and microbes.

How much experience is there with SpayVac™? SpayVac™ was developed in the early 1990s by scientists from Dalhousie University in Halifax, Nova Scotia, Canada. It was first tested on several species of seals, and much experimental work was conducted using laboratory rabbits. In Grey Seals, SpayVac™ has provided contraception for at least 6 years. In a 2-year study of Fallow Deer, SpayVac™ has been 100 % effective. Recently, studies have been expanded to include Domestic Cats, White-tailed Deer, Barbary Sheep, Horses, Grizzly Bears, and Wolves. Over the past 20 years, conventional PZP vaccines have been tried successfully on over 100 mammalian species. SpayVac™ has been successful in producing contraceptive antibody levels in every species in which it has been tested.

How often do treated individuals have to be inoculated to maintain contraception? In long-term experiments with Grey Seals, SpayVac™ has been effective for at least 6 years with only a single inoculation. As of April 2001, SpayVac™ has been 100% effective in Fallow Deer for 2 years. Experiments with other species have not yet extended beyond 1 year. We expect that SpayVac™ will have multi-year effectiveness in most species of mammal, but the exact duration probably will vary according to species, adjuvant, and antigen dosage. Only with testing over many years will we have precise answers to the question of duration of efficacy.

What is the difference between SpayVac™ and conventional PZP vaccines? Conventional vaccines use PZP proteins (antigens) and an adjuvant (immune response stimulant). SpayVac™ uses exactly the same antigens and often the same adjuvant. The critical difference is that the PZP proteins in SpayVac™ are encapsulated in liposomes to protect them while they are being carried to the immune system.

Liposomes have several applications in human medicine, including Rogaine™ (a hair growth drug) and a flu vaccine that can be delivered as a nasal spray. Liposomes have been used for many years and are recognized as safe components of therapeutics.

In practical terms, the most important difference SpayVac™ and the conventional PZP vaccine is performance. SpayVac™ is the only vaccine to achieve multi-year contraception with just one administration. The conventional vaccine initially requires a primary inoculation followed by 1 or 2 booster within a few weeks, with annual boosters afterwards. Although the conventional vaccine has been used in trials on deer at a number of locations, the requirement to hold animals for extended periods to administer initial boosters (or relocate and "dart" free-ranging animals) and to administer annual boosters makes the conventional vaccine generally impractical.

Because only a single administration is required, SpayVac™ will be much less expensive to use than conventional vaccines and will involve much less stress for treated animals. The greatest expense in implementing fertility control is in catching and holding animals. Each capture treatment involves stress and a risk of injury to both animals and workers.

What is an adjuvant and which adjuvant is used in SpayVac™? Adjuvants are materials that are incorporated into vaccines to enhance the immune response. Trials of the conventional PZP vaccine have routinely used Freund's Complete Adjuvant (FCA), which is recognized as the "gold standard" of adjuvants and is used widely in vaccine research. FCA has also been used in trials of SpayVac™. Although FCA is a very powerful adjuvant, some individual animals may respond adversely, although no adverse responses have ever been observed in SpayVac™ trials. Fortunately, SpayVac™ performs well with other adjuvants that have regulatory approval for routine use. While we may continue to use FCA for research purposes, other adjuvants, with regulatory approval, would be used in SpayVac™ formulations intended for routine use.

Will SpayVac™ provide long-term contraception with a single administration in White-tailed Deer? Although we need to conduct large-scale, multi-year trials on White-tailed Deer, the answer is "YES!" We conclude this because:

1 SpayVac™ with liposome-delivered PZP and an approvable adjuvant has resulted in high antibody titers and complete contraception in captive White-tails at Penn State University.
2 The conventional PZP vaccine has been proven on White-tails in numerous field and captive trials.
3 SpayVac™ has worked with a single administration in all mammal species tested to date.

There is every reason to believe that SpayVac™ will also be effective on other deer species, such as Elk, Mule Deer, and Black-tailed Deer. However, we cannot know the answer for certain until long-term trials are conducted.

Are there limitations to using SpayVac™ to manage wildlife fertility? Yes. For the foreseeable future, it will be practical to treat only small populations that are isolated and accessible. The present state-of-the-art requires that all treated animals be captured and marked before being treated, and this will be very difficult to achieve in most situations. Implementing population management with SpayVac™, while less expensive and less stressful on treated animals than using the conventional vaccine, will still be more expensive than culling. And in contrast to culling, contraception will not immediately reduce the number of animals.

Can SpayVac™ be safely administered to pregnant animals? Yes. SpayVac™-elicited antibodies affect only unfertilized eggs. There is no effect on pregnancies already in progress.

Does SpayVac™ have any effect on the DNA of treated animals? No. As with any other immune response, there is no effect on the genes of treated animals.

Does SpayVac™ works on males as well as on females? SpayVac™ will elicit antibody production in males, but because males do not have ovaries, they do not possess eggs or *zona*

pellucida proteins. Thus SpayVac™ has no useful effect on males.

How much does SpayVac™ cost? At present, SpayVac™ is not in commercial production and a price has not yet been set. However, the most expensive part of any wildlife contraception program is securing the animals to be treated, and because SpayVac™ requires only a single administration, overall costs will be much less than those involved with the conventional vaccine.

How can I obtain SpayVac™ for use on deer or other wildlife in my area? The responsibility for wildlife management generally rests with state or provincial wildlife agencies. Thus, an early step should be to consult with the appropriate people within the responsible management agency. If there is a desire to try SpayVac™, this may be possible under the provisions for field trials contained in Food and Drug Administration (FDA) rules in the USA, Health Canada rules in Canada, or the rules of the appropriate agency elsewhere.

ImmunoVaccine Technologies Inc. (IVT), Halifax, Nova Scotia, Canada, is commercializing SpayVac™ for use on companion animal and wildlife. TerraMar Environmental Research Ltd., Sidney, BC, Canada, is the "strategic partner" with IVT for research and development of SpayVac™ for wildlife applications.

On what species has SpayVac™ been tested? The following species have been tested as of May 2001: Fallow Deer *(Dama dama)*, White-tailed Deer *(Odocoileus virginianus)*, Horses *(Equus caballus)*, Barbary Sheep *(Ammotragus lervia)*, Grizzly Bears *(Ursus arctos)*, Wolves *(Canis lupus)*, Grey Seals *(Halichoerus grypus)*, Hooded Seals *(Cystophora cristata)*, Harp Seals *(Phoca groenlandica)*, and Laboratory Rabbits *(Oryctolagus cuniculus)*. We hope to begin trials with Black Bears *(Ursus americanus)* and Black-tailed Deer *(Odocoileus hemionus columbianus)* in 2001.

Who can I contact for more information?

Wildlife Applications:

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SpayVac™ Product Information:

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Subj: **Fwd: deer management**
Date: 10/8/2003 12:27:55 PM Central Standard Time
From: wfjt333@swbell.net
To: willhenrym@aol.com
File: **SPAYVAC-Jul01.zip** (17300 bytes) DL Time (45333 bps): < 1 minute
Sent from the Internet (Details)

Note: forwarded message attached.

X-Apparently-To: wfjt333@swbell.net via web80405.mail.yahoo.com; 03 Oct 2003 09:19:24 -0700 (PDT)
Return-Path: <gray@holterra.com>
Received: from mtac3.prodigy.net (151.164.30.67)
by mta805.mail.yahoo.com with SMTP; 03 Oct 2003 09:19:24 -0700 (PDT)
X-Originating-IP: [216.218.210.201]
Received: from launch.server101.com (ns1.giga-sj-001.net [216.218.210.201])
by mtac3.prodigy.net (8.12.9/8.12.9) with ESMTP id h93GJMWg003153
for <WFJT333@swbell.net>; Fri, 3 Oct 2003 11:19:23 -0500 (CDT)
Received: from ci336635a (pcp490236pcs.nash01.tn.comcast.net [68.53.0.208])
(authenticated as gray@holterra.com with LOGIN)
by launch.server101.com (8.11.6/8.11.6) with ESMTP id h93GJHA10862
for <WFJT333@swbell.net>; Sat, 4 Oct 2003 02:19:18 +1000
Reply-To: "Gray Anderson" <gray@holterra.com>
From: "Gray Anderson" <gray@holterra.com>
To: <WFJT333@swbell.net>
Subject: deer management
Date: Fri, 3 Oct 2003 11:23:39 -0500
Organization: Holterra Wildlife Management
MIME-Version: 1.0
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X-MimeOLE: Produced By Microsoft MimeOLE V6.00.2800.1106
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Ms. Taylor -

I have attached the Spayvac drug information sheets released by the company. Please let me know if you need additional information. We don't have specific protocols for deer management because each city provides a unique challenge and different set of constraints. But from our conversation I will give you a list of steps to consider:

Year 1:
1) Permits from city and state - we can assist
2) Defendable population estimate - critically important - we can do these
3) Post-management population levels desired - to set management goals
4)Management methods (socially, logistically, and economically viable) - city council
5) Project implementation - females will be captured and inoculated with Spayvac (~80% of females in the post-management population). The remaining animals will be removed (your choice on methods) until the target population level is reached. Point to remember - the remaining females will be pregnant at this time and will give birth to fawns in the Spring. Spayvac will prevent future pregnancies but will not effect the current fetus. Abortion drugs are available (we have not used them) that will eliminate these pregnancies but the technique is often at

odds with the non-lethal aspects of the overall management - again this is a social and economic issue to be considered and resolved by the council.

Year 2:
1) Population estimates - monitor management - set goals based on fawn production
2) Implement smaller scale management similar to year 1
3) Project end

Year 3:
1) Population estimate - to monitor project success - not required

I hope this helps. Please don't hesitate to call if you need more information. Talk with you soon.

Sincerely,
Gray Anderson

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Sorry for the delay. I have attached 2 documents released by the company that makes the Spavac contraceptive. This should provide baseline information on the product. I have a scientific publication on the subject but it is 2.9 Mb and is scanned into PowerPoint. If you can handle attachments that size and format, I would be glad to forward that as well.

The biggest thing to know about the use of contraception is that contracepting females is designed to reduce annual fawn production (common sense). This will stabilize the population but not actually reduce the population until natural mortality begins to exceed annual production. So there is going to be a ~5 years time lag before you see results (population decline). This is what was learned at Fire Island. While some call Fire Island a success (the population did decline after about 5 yrs of hard work) others considered it a failure because of the time and money spent to finally get the population to decline.

I consider Fire Island a success from a scientific standpoint because so much was learned. Most importantly was that the PZP used and the annual boosters that were required make the old contraceptive mixture logistically and economically impractical. The new Spayvac formulation has great promise but still requires a huge effort in the first 2-3 years. We are still learning about Spayvac and the drug is still in the process of FDA approval. However, we can use the drug experimentally if the projects fit some basic study design protocol.

I hope this information is helpful. Please don't hesitate to contact me if you would like more information. Also Mark Fraker (contact info on the attachments) is a great resource with the company to discuss the product further. Talk with you soon.

Gray Anderson

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WHY NOT USE CONTRACEPTIVES?

At the present time, in the state of Texas there are no legal means to control populations of deer using contraceptives. Any Texas program involving contraceptive agents must be approved by the Texas Parks and Wildlife Department. No program using these agents has been approved by the Department.

Experimental steroidal fertility control agents have been evaluated in deer reproduction programs in several states. Research conducted on a captive deer herd in Ohio indicated that oral and intramuscular contraceptives reduced deer productivity. However, the reduction was insufficient to prevent growth of the herd.[1] In Kentucky oral doses of microencapsulated contraceptives successfully interrupted deer pregnancies, but high dose requirements and the aversion of deer to treated bait combined with post-treatment pregnancies prevented effective control of the growth of the herd.[2]

Some studies have involved the remote delivery of implants using biodegradable projectiles.[3] However, the limited life expectancy of implants, the expense involved in treatment, and the difficulty of treating an adequate portion of a herd make such efforts impractical at present.[4]

The Humane Society of the United States (HSUS) has seven active field sites where deer contraceptive research is underway. HSUS research is focused on three goals:

(1) develop a vaccine that will provide one to two years of contraception with a single shot;

(2) find a vaccine formulation that uses an immune-system booster acceptable to the Federal Food and Drug Administration;

(3) determine if these treatments can be used to stabilize deer populations, and, if so, under what circumstances. They feel

they are close to success in achieving the first two goals. A key program of administering a one-shot vaccine pellet by dart rifle began last year, with results expected this fall. If successful, this method of delivery would likely be more acceptable to regulatory agencies.[5]

In July 2000, Dr. Scott Coonrod, a wildlife contraception expert from the University of Virginia who has a Ph.D. in animal physiology from Texas A&M University, met with the Lakeway Deer Control Committee. Dr. Coonrod maintained the status of immunocontraception programs make them inappropriate for use in Lakeway at the present time. He said such programs hold hope for the future but not for communities facing an immediate problem. Click on *What's the Problem?* for info about the deer problem in Lakeway.

It is important to remember that, even if available, contraception will have no effect in reducing the size of our existing herd, which is estimated to be nearly 1900 deer. Culling will still be necessary to reduce the population to a level which is healthier for the deer and safer for the citizens of Lakeway. Once we reach that level, we would hope to be able to maintain the herd at that size through fertility control rather than lethal means.

[1]Harder, J. D. and T. J. Peterle. 1974. Effect of DES on reproductive performance of white tailed deer. Journal of Wildlife Management 38(2): 183-196

[2]Matschke, G. H. 1977. Microencapsulaed diethylstilbestrol as an oral contraceptive in white-tailed deer. Journal of Wildlife Management 41(1): 87-91

[3]Matschke, G. H.1980. Efficacy of steroid implants in preventing pregnancy in white-tailed deer. Journal of Wildlife Management 44(3): 756-758

[4]Ellingwood, Mark R. 1988. Connecticut Dept. of Environmental Protection, Wildlife Bureau (Publication No. DR-11)

[5]McElroy, Pat (Humane Society of the United States). E-mail correspondence dated 3/1/2000

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