October 2008

Dear Reader,

Thank you for your interest in contraception and non-surgical sterilization for cats and dogs. ACC&D is pleased to be able to make Contraception and Fertility Control in Animals available as a resource to you. AlcheraBio LLC—the author of this report—has generously agreed to let us share the report in its original form, as well as supporting our work to update the document.

Please note that this document has not been updated since it was published in 2002 and that some information is out of date. Neither ACC&D nor AlcheraBio take responsibility for the accuracy of this information. However, we believe that there is valuable learning in this report and that it can serve as a meaningful resource for those seeking to better understand this area. ACC&D is in the process of updating sections of the report which are relevant to fertility control in cats and dogs. The updated version will be posted on our web site at www.acc-d.org once it is available (anticipated to be mid-2009).

We extend our gratitude to AlcheraBio LLC for the use of Contraception and Fertility Control in Animals, and we hope that you will find it to be a useful resource in your learning.

Please visit www.acc-d.org for more information about contraception and non-surgical sterilization in cats and dogs.

Sincerely,

Karen Green
Director of Outreach
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Contraception and Fertility Control in Animals

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30 September 2002

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The people at MoldaveDesigns (Jenn Birchby, Lauren Cook, and Jay Moldave) are responsible for the design and production.

As animal lovers we would also like to thank our animals – past, present, and future – for driving our interest in this field. They are all castrated or spayed, and perhaps they would have preferred a nonsurgical alternative.

Linda Rhodes, VMD, PhD

Katherine Moldave, MBA

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continued

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1.0 Introduction

1.1 Scope of the Report

This report is a compilation of public material on the subject of contraception and fertility control in animals. Sources include scientific literature, government publications, company web sites and other internet pages, and discussions with some of the leaders in the field. We have included references, not as a comprehensive review of the literature, but to serve as a beginning for those interested in delving further into the subject.

To help the reader not trained in reproduction, we have included a glossary of relevant scientific terms. A list of some interesting web sites is also included.

Although we have tried to be thorough, it is possible that we have overlooked some fact or research readers feel should have been included, or included a statistic that's become outdated – for these oversights we offer our apologies in advance. We trust readers will find that the important sources, topics and opinions are well-covered in this report. Please note that a discussion of the use of abortifacient drugs to terminate an established pregnancy is beyond the scope of the document.

We have included an overview of the basics of control of reproduction and a review of the types of treatments that have been available commercially over the years, or have been investigated by the experts. We include the major commercially important species – dogs, cats, cattle and horses, and an overview of wildlife.

To complement the scientific and technical material, there is a review of the work of various companies that have done research and development in this field, including some thoughts on the history of product development by animal health companies over the years. We've discussed some of the market issues and characteristics that companies will want to look at as they consider developing, commercializing and/or marketing a contraceptive product, and we also present an overview of some special regulatory considerations that, in our opinion, apply to these types of products.

Finally, we offer some speculation about where the field is headed and where it might be five years from now. Although the speculation is our own, it is based on conversations with several leaders in animal contraception.

This report is written for the lay reader, but we hope that veterinarians, researchers, organizations, animal health professionals, and human health companies working on contraception and fertility control also find it useful. We feel strongly that in order to bring the decades of research in this field to fruition with products that can be used commercially, both the science and the business must come together. We hope this report contributes to that process.

1.2 Brief Review of the History of Contraception and Fertility Control Research in Animals

The "pill" was a breakthrough in contraception for women. Daily treatment with low-dose estrogen or estrogen/progesterone combinations became a widely adopted method for human reproductive control. But for animals, no such solution has reached commercialization. Why is this?

Research has been published for more than 30 years showing that nonsurgical contraception for animals is possible. Since daily treatment with steroids is impractical for all species, other methods have been explored. A variety of approaches have been used in many species of animals, including early laboratory work in rodents and studies on dogs, cats, cows, and monkeys. Much of this work was directed towards exploring contraceptive approaches for humans, but some of it was clearly geared towards creating alternatives to surgery for animals.

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Given that research has been so promising, why aren't there several approaches in the marketplace?

Various methods of contraception have been shown to be effective, but efficacy is not enough. To move an idea from the lab into the marketplace, the technology must be effective and safe, and a number of other requirements must also be met. For a company to decide to take a product forward, a technically feasible, stable formulation must be developed and large-scale manufacturing must be possible. The regulatory path must be clear and relatively low risk, and the cost of development reasonable. The market must be clearly defined and the cost of the final product must be low enough to make the investment attractive (i.e., generate appropriate profit margins). Money must be available to complete the project and support an initial marketing campaign. Finally, a company or a group of investors must be willing to take the risk of a long and expensive development project.

Other means of developing a contraceptive for pets or wildlife can be imagined. For example, a humanitarian, nonprofit organization could subsidize the development and registration costs for a product that may not be commercially feasible, and such a product could be provided at cost to spay clinics and shelters for use in feral animals. Early stage companies and humanitarian organizations could collaborate to bring a product through the riskier stages of development, and then partner with a larger company for distribution and sales, with the profits of such a venture subsidizing the contraception of feral animals. To date, in spite of millions of dollars of nonprofit-sector money spent on animal welfare each year, there has been little progress in reaching a commercial product.

Over the years, technical issues and pitfalls have stood between various approaches and the marketplace. In addition, there are sociopolitical factors that have undoubtedly slowed the advance of contraception and fertility control in animals.

In the early 1980s, when some of these methods were being tested in research laboratories, the large pharmaceutical companies were dismantling their reproductive biology research groups. Controversy over the side effects of intrauterine devices in women and debate over abortion and contraception in general led companies to shy away from the entire field.

Animal health research and development groups working on reproduction were also downsized. In animal health companies, decision makers were generally not interested in nonsurgical contraception. Many felt that the "spay" and castration were the drivers that brought clients to the veterinary practice. Providing an alternative, they worried, could have a negative impact on the number of new clients coming in the door. Nonsurgical contraception also suffered from the fact that when each company looked at what other industry leaders were doing, nobody seemed to be working in this area, which also reinforced the negative perception – if this is such a good idea, why aren't our competitors doing it? Over the years, some of the animal health companies have supported research on progesterone-type drugs, GnRH (gonadotropin releasing hormone) vaccines, and GnRH agonists, but none has yet taken any project to completion.

We think the market has changed, perceptions have changed, the social climate has changed, and the time is ripe for progress on products for nonsurgical contraception for animals.

Interestingly, many of the potential products have not changed, and the technologies driving their development include three approaches that have at least a 25-year history in the literature:

- Gonadotrophin releasing hormone (GnRH) agonists
- GnRH vaccination
- Zona pellucida (ZP) vaccination

Currently, there are additional potential approaches under investigation. To help readers understand the basics of how approaches to contraception and fertility control work, we offer a brief review of the physiology of the reproductive system in Section 2, and in Section 3, details of the various approaches are provided.

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2.0 The Physiology of Reproductive Control in Mammals: Overview of the Major Systems that Control Reproduction

The purpose of this brief overview is to give readers the background necessary to understand how the potential products for contraception and fertility control work. This is an oversimplification of a wonderfully complex system, but the material should serve to orient non-biologists reading this report.

2.1 Brain

The major control center for reproduction is the brain, where specific neurons in the hypothalamus synthesize gonadotropin releasing hormone (GnRH) under a number of influences, such as light levels, body condition, age, and the blood levels of various hormones. One of the most interesting things about brain secretion of GnRH is that it is secreted in pulses and not continuously. The pulses are important – if GnRH is not delivered in pulses, it does not have the normal effect on the reproductive system. This small fact becomes important in understanding one of the leading approaches to animal contraception – the GnRH agonist.

GnRH is a decapeptide (small protein made up of 10 amino acids) that acts directly on the pituitary gland. GnRH is considered the master hormone that controls the release of the major reproductive hormones. Interfere with GnRH, and you interrupt all reproduction in both males and females. In fact, not only is reproduction interrupted, but the reproductive behaviors – estrus in females and sexual and mounting behavior in males – are disrupted as well.

2.2 Pituitary Gland

The pituitary gland has specific cells – the gonadotrophs – that have receptors for GnRH that bind the peptide. The regulatory system is highly complex, and at the risk of oversimplifying, we can say that once the GnRH binds to its receptor on specific pituitary cells, it causes the release from the pituitary of two other protein hormones – luteinizing hormone (LH) and follicle stimulating hormone (FSH), which are secreted into the blood. As the brain gives off pulses of GnRH, these pulses reach the pituitary and cause the pituitary to give off pulses of LH and FSH.

2.3 Gonads (Ovaries and Testes)

Once the pituitary gland secretes LH and FSH, they travel in the blood to the gonads – ovaries in females and testicles in males. These two hormones bind to receptors on the gonads. They coordinate the estrus cycle (heat) or the menstrual cycle of the female and are important in the production of estrogen and progesterone. In the male, LH and FSH are important for sperm maturation and stimulating testosterone production.

When the steroid hormones (estrogen, progesterone and testosterone) are secreted from the female or male gonads, these hormones travel in the blood to the brain, where they turn off the secretion of GnRH. This is called negative feedback For example, GnRH causes the pituitary to make more LH, which stimulates the testes to make more testosterone, which goes to the brain and causes the brain to make less GnRH. Levels of LH go down, because the pituitary doesn't get the GnRH signal. When the LH in the blood falls, no testosterone is made. As blood levels of testosterone decrease, the brakes are off the GnRH in the brain, and the system kicks in to make more GnRH, and so on. This is how the system is regulated.

The system is more complex in the female, but the essential message is the same. The estrogen and progesterone produced in the ovary are the negative feedback signals for GnRH. It is not important for this report to detail the complex regulation of the estrus and menstrual cycles. However, this negative feedback concept is important in understanding contraceptive technology. Giving progesterone, for example, will shut down production of GnRH, via negative feedback, interrupting fertility.

In the ovary, where the eggs are produced, each egg is surrounded by a protective coating called the zona pellucida (ZP). The zona pellucida is made up of several glycoproteins, that is, complex proteins with various sugar molecules attached. From recent work in molecular biology, we know that in each species there are different, but similar, zona pellucida proteins around the egg. For example, the zona pellucida from a pig is similar to, but not exactly the same as, the zona pellucida of a cat. This fact is important in understanding a leading method for animal contraception – vaccination with porcine zona pellucida (PZP).

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3.0 Approaches to Contraception and Fertility Control

This section provides an overview of various approaches to contraception and fertility control, based on the physiology described in Section 2.

There are basically three general areas for intervention:

- In the brain – controlling GnRH and its effects
- At the pituitary – controlling GnRH receptors, the cells that secrete GnRH, or the release of LH and FSH
- In the gonads – controlling the steroid hormones (testosterone, estrogen, progesterone) either by administering steroids, removing the gonads, or interfering with fertilization or sperm production

In order to evaluate the commercial promise of each approach, we give a general idea of which approaches are further along in development and which have not been investigated in depth for animals. Details on the various research approaches and their advantages and disadvantages are provided by key species in Section 4.

3.1 Gonadotropin Releasing Hormone (GnRH)

There are three considerations governing interventions at the level of GnRH:

- Potentially effective in both males and females
- Potentially work across species, because GnRH is highly conserved (i.e., the DNA coding for GnRH is similar among mammals)
- Suppress the secretion of the steroid hormones and therefore suppress sexual behavior as well as fertility

3.1.1 GnRH agonists

Effective GnRH agonists, which mimic the effect of native GnRH but have a longer half-life, have been developed and are available as generic peptides. Examples are leuprolide and goserelin, which were developed to suppress testosterone as a treatment for prostate cancer in men.

Agonists work by initially mimicking GnRH, which causes a down regulation of the GnRH receptors in the pituitary gland. The continuous administration of agonists results in a complete suppression of GnRH effect since to be effective, GnRH must be "seen" by the receptors in the pituitary cells.

These peptides are given by injection or subcutaneous implantation, and implants for humans have been developed that are effective for one month to one year (see table entitled GnRH Agonists for Use in Humans on page 6). For example, Lupron Depot® (TAP Pharmaceuticals) comes in a monthly, every three-month or every four-month depot injection. In 2000, Alza announced the approval of Viadur®, a once yearly leuprolide acetate implant for the treatment of prostate cancer. This implant is placed subcutaneously, and releases the GnRH agonist via osmotic pump technology.

A disadvantage of the GnRH agonist approach is that initial administration in females usually results in estrus behavior or estrus stimulation, followed by suppression of estrus until the implant runs out or is replaced. In males, there is a testosterone increase for a week or so. The effect on behavior in male animals is not documented. (When GnRH agonist implants are used for treatment of prostate cancer, they initially result in a stimulation of testosterone, which aggravates the condition, causing increased bone pain from metastatic tumors and a stimulation of tumor growth, before the GnRH suppression begins. This initial stimulation is called a "flare.")

Because of the mechanism of action of GnRH agonists, it is important to understand that these drugs may take several weeks to suppress fertility fully after an initial stimulation. They would therefore not be effective in situations in which an immediate suppression of fertility is desired. Once the agonist is removed, either by removing an implant, depletion of the active drug, or stopping daily administration of the injectable form of the drug, the timing of the return to fertility is quite unpredictable. There is a great deal of variability regarding when the receptor population on the gonadotrophs returns to normal function. So, although a minimum duration of efficacy can be determined, it is difficult to predict when the effects will wear off for each individual animal.

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GnRH Agonists

Advantages	Disadvantages
Proven to suppress fertility in males and females	Initially cause stimulation of sexual behavior and may cause signs of estrus in females
Suppress sexual behavior – females will not come into heat during treatment, males will behave as castrates	Need to be given continuously to achieve effects
Active compounds available as generics (GMP manufactured)	No patent protection for common active drugs
Have been demonstrated to be effective in a variety of formulations, including depot injections, microspheres, and implants	A commercially viable product may need to provide 6-12 months of efficacy for convenience
Reversible – when the drug is discontinued, reproduction should resume within a reasonable period of time (could be used in animals intended for breeding)	If lifetime contraception is desired, multiple treatments will be necessary
	Slow onset of activity (generally a few weeks) and variable reversibility time frame

GnRH Agonists for Use in Humans

Trade Name	Active Compound	Duration or Dosing Schedule	Route	Manufacturer
Lupron Depot®	Leuprolide	1 month, 3 months or 4 months	IM*, microspheres	TAP Pharmaceuticals**
Viadur®	Leuprolide	1 year	SC* implant	Alza Corporation
Eligard™	Leuprolide	1 month (7.5 mg)	SC using a polymer formulation	Sanofi-Synthelabo and Atrix
Eligard	Leuprolide	3 month (22.5 mg)	SC using a polymer formulation	Sanofi-Synthelabo and Atrix
Synarel®	Nafarelin	Once a day	Nasal solution – spray	GD Searle
Supprelin®	Histrelin	Once a day	Injection	Roberts Pharmaceutical Corp.
Not yet assigned	Histrelin	1 year	SC implant	HydroMed Sciences***
Zoladex®	Goserelin	3 month	SC implant	Astra Zeneca
Suprefact®	Buserelin	Every 8 hours	Nasal solution – spray	Shire Pharmaceuticals
Suprefact	Buserelin	Once a day	Injection	Shire Pharmaceuticals
Suprefact	Buserelin	2-3 months	SC implant	Aventis

** IM = intramuscular; SC = subcutaneous*
*** a joint venture of Abbott and Takeda Chemical Industries*
**** in Phase III clinical development*

3.1.2. GnRH antagonists

GnRH antagonists block the GnRH receptor on the pituitary cells. These drugs are small peptides that have a structure very similar to that of GnRH. Most of the small peptides work in all species, due to the highly conserved structure of the GnRH. Cetrorelix is an example of a much-studied GnRH antagonist that has activity in monkeys, dogs, rats and people (for a review, see Reismann 2000). A recent publication describes a new antagonist called acyline that is potent in people at very low doses (Herbst 2002).

Some attempts have been made to synthesize GnRH antagonists that are small molecules rather than synthetic peptides (DeVita 2001). Unlike the peptide drugs, which are effective in all species, the small molecule antagonists have been shown to have different biological actions on the GnRH receptors of different species (Cui 2000).

Why were GnRH antagonists developed when available agonists work so well? The answer is that the initial stimulation side effect caused by agonists can be avoided by using antagonists instead. Unlike the GnRH agonists, which can take several weeks to produce a suppressive effect, the antagonists suppress the reproductive hormones immediately.

This type of drug needs to be given daily by injection or via high-dose implant. If a potent antagonist could be formulated into an implant with a long duration, this approach has the advantage that it begins working almost immediately (within hours), and an antagonist would not cause initial stimulation of sexual behavior.

GnRH Antagonists

Advantages	Disadvantages
Proven to suppress fertility in males and females	Need to be given continuously to achieve effects
Suppress sexual behavior – females will not come into heat during treatment, males will behave as castrates	No depot or long-acting formulations have been developed for use in animals
Reversible – when the drug is discontinued, reproduction should resume within a reasonable period of time (could be used in animals intended for breeding)	Some antagonists may cause histamine release in dogs (see Section 4.1.8), humans and other species
Effective within a short period after treatment initiation (12-48 hours)	

GnRH Antagonists for Use in Humans

Some examples of compounds that have been studied are antide, cetrorelix and ganirelix (Antagon™, Organon Corporation). Cetrorelix was approved by the Food and Drug Administration (FDA) in the US in 2000 as an injectable treatment for infertility (Cetrotide,™ Astra Medica). Both Cetrotide and Antagon are used for short-term treatment to suppress GnRH to prevent premature ovulation in women undergoing controlled ovarian stimulation for fertility treatments.

Neurocrine BioSciences, a small San Diego company, has successfully completed a Phase I human clinical trial with a small molecule GnRH inhibitor that can be taken orally once a day. The company is targeting endometriosis and prostate cancer. A new compound, acyline, has recently been tested in humans (Herbst 2002). To our knowledge, these compounds are not under development for animals.

Trade Name	Active Compound	Dosing Schedule	Route and Formulation	Manufacturer
Cetrotide™	Cetrorelix	1-4 days*	Injectable	Astra Medica
Antagon™	Ganirelix	1-4 days*	Injectable	Organon
Not yet assigned	Not yet assigned	Once a day	Oral	Neurocrine Biosciences**
Not yet assigned	Acyline	Not known	Injectable	Not known

* only short duration needed for use in fertility treatments
**not yet approved – in Phase I human clinical trial

3.1.3 GnRH-toxin conjugates

Another approach to suppressing GnRH involves ablation of the gonadotrophs, which are the cells in the pituitary that have GnRH receptors. Coupling GnRH to a toxin or protein-synthesis inhibitor is a way of delivering the toxin or inhibitor directly to only one type of cells – those that have GnRH receptors. The concept is that when the GnRH plus toxin/inhibitor binds to the GnRH receptors on the pituitary target cells (gonadotrophs) the toxin will be released only to those cells, causing them to die (Nett 2002, Ball 2002). Then, theoretically, permanent sterility would result.

A potential issue related to this approach is the specificity of the toxin delivery. The pituitary gland is full of other important cell types such as cells that make thyroid hormone, growth hormone, and hormones that stimulate the adrenal gland, among others. Showing that the GnRH-toxin conjugate is safe to other pituitary cells would be important for successful development. Also, assuring that conjugation is reliable, both in the bottle and in the body, is important so animals don't get exposed to free toxin.

3.1.4 GnRH vaccines

For at least 30 years (for a review, see Gonzalez 1989, Thompson 2000), various academic and industry laboratories have been trying to make effective GnRH vaccines. It is difficult to raise an effective immune response to a small self peptide (that is, a peptide that is normally present in all mammals and not seen as "foreign" by the immune system).

The main approach has been to couple the small GnRH peptide to a large foreign protein. A number of variations have been used. The hope is that the animal's immune system will experience the coupled protein as foreign and make antibodies against the complex, some of which will bind and inactivate GnRH.

In general, these preparations, when tested in laboratory animals, dogs, and other species, required multiple injections, generated a weak, short-lived antibody response, and failed to provide a response in some animals. Examples of new approaches that have been explored include a synthetic GnRH vaccine with T-helper epitopes (Sad 1993) and the use of a recombinant GnRH antigen (Robbins 2002). These newer approaches may ultimately avoid the multiple injections previously needed to cause the response and may therefore be more practical.

GnRH vaccines have been used in human clinical trials to treat prostate and breast cancer and other endocrine-related disorders (Talwar, 1997, Ferro 1998, Ferro 1999).

In order for GnRH vaccines to be effective, the treated animal (or human) must develop an immune response. This process is variable and it can take several months before immunity develops fully. Therefore, GnRH vaccination may result in a slow onset of infertility. Also, once booster injections have been discontinued, it is likely to take a relatively long time until the GnRH suppression wanes, and the rate at which the immune response declines will probably be highly variable among individuals.

GnRH Vaccines

Advantages	Disadvantages
Proven to suppress fertility in males and females	Immune response may be inconsistent in individual animals
Suppress sexual behavior – females will not come into heat during treatment, males will behave as castrates	Depending on the formulation, might cause injection site reactions
Reversible – when the vaccination boosters are discontinued, reproduction should resume	Difficult to predict when reproduction would resume after cessation of treatment, as timing would depend on the gradual decrease in circulating antibodies to GnRH
May be possible to achieve effect with two initial injections a few weeks apart, followed by an annual booster	Multiple boosters may be needed to develop and maintain effect
	Slow onset of activity (may be over two to three months) as animal mounts immune response

3.2 Zona Pellucida, Egg and Sperm Vaccines

Creating an immune response to some component of the egg or sperm could theoretically cause infertility by interfering with the fertilization of the egg, sperm transport, and/or binding of sperm to the egg. This approach to fertility control works in either the ovary or the reproductive tract, and in most cases is effective only in females.

Since the effect is dependent on the animal mounting an immune response, the suppression of fertility will be gradual, likely over several weeks or months. In addition, the effect can be expected to wear off slowly, resulting in a gradual resumption of fertility over several months or even years, depending on the formulation. This waning effect, or "reversibility," is likely to be variable among individual animals.

Sexual behavior should not be affected by this approach, as the whole cascade of hormones that controls sexual behavior remains normal in vaccinated animals. In other words, female animals should still come into estrus (heat) and show normal mating behavior, but not become pregnant. In situations in which mating behavior is unwanted (for example, pet female cats), this approach would not be useful.

3.2.1 Zona pellucida vaccines

Many years of research have been devoted to exploring the use of vaccination with components of the layer of proteins that surrounds the egg – the zona pellucida (Skinner, 1984, 1996). The zone around the egg that looks transparent is made up of several glycoproteins, that is, proteins with various sugar molecules attached in specific ways to the protein. In each species, the zona pellucida proteins are similar but not exactly the same (for a review, see Prasad 2000). In some species, the cDNA (complementary DNA, synthesized *in vitro* from messenger RNA, which is a "template" for protein synthesis) of the zona proteins has been isolated and sequenced, so the exact amino acid sequences of the proteins are defined.

For veterinary applications, most research has been done using pig zona pellucida (PZP) purified from pig ovaries obtained from slaughterhouses. The PZP can then be formulated in a variety of ways and is injected into animals to raise an immune response. Various injection schedules have been used in various species (see Section 4 for details in each species). Fertility is blocked for some period of time, and booster vaccinations are generally required to maintain the infertility.

Zona pellucida vaccines have, in some cases, caused a side effect of inflammation of the ovary. This phenomenon might be due to raising an immune response to the zona on the eggs in the ovary. If the zona pellucida preparations were not sufficiently purified, they might have contained other components of ovarian tissue, which could account for this effect – an effect that has not been seen in all studies. Other forms of ovarian pathology were seen in a study using a sub-component of the zona pellucida (Paterson 2002), in which a disruption of the follicles occurred. This could result in irreversible sterility.

This approach, though effective as a contraceptive, does not affect sexual behavior. Females will still come into estrus (heat). Also, for obvious reasons, this approach is not effective in reducing the fertility or sexual behavior of males.

Although there are many papers published on the use of zona pellucida vaccines, there is no commercial product available at this time. The most extensive use of these vaccines is in wildlife, where they have been successfully used for many years to reduce fertility and overpopulation (Section 4.5.3).

Using PZP obtained from slaughterhouse material is a disadvantage because it is difficult to manufacture PZP under GMP (Good Manufacturing Practice), a requirement for commercialization. Although the cDNAs for various zona pellucida proteins have been cloned (Harris 1994, Yonezawa 2001), they are hard to manufacture as biologically active recombinant molecules because of their specific glycosylation patterns (Gahlay 2002). However, in order to achieve commercialization, a manufacturing method that does not involve isolation of PZP from slaughterhouse material may be required. Second generation ZP vaccines using recombinant or synthetic zona protein antigens are under investigation (Dunbar 2002).

Zona Pellucida Vaccines

Advantages	Disadvantages
Suppress fertility in females (in some studies and not others)	Ineffective in males
Reversible – when the vaccination boosters are discontinued, reproduction should resume (may depend on the antigen used)	Immune response may be inconsistent in individual animals, and may vary depending on the preparation of the antigen
	Depending on the formulation, might cause injection site reactions
	Difficult to predict when reproduction would resume after cessation of treatment, as this would depend on the gradual decrease in circulating antibodies to ZP
	Multiple boosters may be needed to maintain effect
	Will not affect sexual behavior – animals will still come into estrus and have normal heat cycles
	May be difficult to manufacture under GMP conditions
	Slow onset of activity (may be more than two to three months) as animal mounts immune response

3.2.2 Vaccination against egg proteins

Other proteins within the egg might be used to elicit an immune response and cause infertility. It is important to identify proteins that are only expressed in the egg. If they are found in other organs as well, such as liver or kidney, they could not be used for a vaccine because other tissues would be adversely affected by the immune response.

If novel, egg-specific proteins could be identified, they might be used to generate an immune response and inhibit fertility. If such proteins could be isolated and the cDNA cloned, it might be possible to make a recombinant antigen to be used as a vaccine.

Why is a recombinant antigen desirable? It is unlikely that ovary extracts would be a practical source of material for the type of manufacturing needed to make a product that would be approved by worldwide regulatory authorities, who require cGMP manufacturing. Manufacturing could be streamlined with a well-defined, simple, recombinant protein.

Dr. Scott Coonrod, from the Department of Cell Biology at the University of Virginia, has constructed dog and cat ovarian cDNA libraries and has begun the process of isolating proteins to be expressed for immunogenicity and fertility trials (Coonrod 2002).

3.2.3 Vaccination against sperm proteins

Researchers have been investigating proteins that are only expressed in sperm, with the goal of using these proteins as the basis of anti-fertility vaccines (for an overview see Naz 2000, Frayne 1999). As in the case of the egg proteins, the idea is to find proteins that are not expressed anywhere in the body, except sperm, to decrease the potential side effects of using these vaccines to generate an immune response. Unlike the zona pellucida or egg protein vaccines, sperm vaccines aim to generate what is known as a mucosal immune response, in which the lining of the reproductive tract in females produces anti-sperm IgA type antibodies, which could then bind to the sperm and prevent conception. In recent studies in mice (Naz 2002), relatively long-term contraception (approximately 300 days) was achieved after vaccination.

Some studies have shown that in other laboratory animals, immunizing females with unique sperm proteins can cause them to mount an immune response to sperm, which then inhibits fertility (hamsters: Gaudreault 2002; monkeys: Deng 2002; guinea pigs: Primakoff 1988). This approach has been attempted in males as well, but caused testicular inflammation.

Although this approach could theoretically be applied to most animals, no studies showing efficacy in dogs, cats, cattle, horses or wildlife have been published, although there is early research in some species (Moore 1997).

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Egg and Sperm Proteins

Advantages	Disadvantages
Suppress fertility in females (in some studies and not others)	Ineffective in males
Reversible – when the vaccination boosters are discontinued, reproduction should resume (may depend on the antigen used)	Immune response may be inconsistent in individual animals, and may vary depending on the preparation of the antigen
Defined recombinant proteins easier to manufacture under GMP	Depending on the formulation, might cause injection site reactions
	Difficult to predict when reproduction would resume after cessation of treatment, as this would depend on the gradual decrease in circulating antibodies
	Multiple boosters may be necessary to maintain effect
	Will not affect sexual behavior – animals will still come into estrus and have normal heat cycles
	Slow onset of activity (may be more than two to three months) as animal mounts immune response

3.3 LH Receptor Vaccines

If an immune response can be raised against the receptor of a hormone, it could block the action of that hormone. As hormone receptors are not foreign, the immune system must be "fooled" into mounting an immune response, creating challenges similar to those encountered in trying to generate an immune response to GnRH or zona pellucida. Some research has been done using LH receptors as a vaccine (Saxena 2002). When a bovine LH receptor preparation was implanted in dogs, the dogs mounted an immune response, causing a reduction in fertility (see Section 4.1.4).

This approach, theoretically, would be similar to vaccination with GnRH, in that both fertility and sexual behavior should be blocked. It has the disadvantage of using an implant containing purified LH receptors from bovine ovaries obtained from slaughterhouses, a difficult approach to commercialize because of GMP manufacturing regulations.

LH Receptor Vaccines

Advantages	Disadvantages
Suppresses estrus in females	Not shown to be effective in males
Suppresses sexual behavior – females will not come into heat during treatment	Was given in silastic implants at high doses
Reversible – when the drug is discontinued, reproduction should resume within a reasonable period of time; could therefore be used in animals ultimately intended for breeding	Difficult to manufacture under GMP without defining recombinant antigen
	Immune response may be inconsistent in individual animals and may vary depending on the preparation of the antigen
	Depending on the formulation, might cause injection site reactions
	Difficult to predict when reproduction would resume after cessation of treatment, as this would depend on the gradual decrease in circulating antibodies to LH receptors

3.4 Sex Steroids

Estrogen, progesterone and testosterone are the main sex steroids needed for sexual function. A variety of synthetic versions of the sex steroids are used for therapeutic purposes in both human and animal medicine (Okkens 1981). For the purposes of this discussion, we use the term "estrogen" to refer to all the synthetic estrogenic compounds, and use the term "progesterone" to refer to all synthetic progesterone-type drugs. Similarly "androgen" is used to refer to any testosterone-like drug.

Birth control pills for women are either estrogen alone or estrogen/progesterone combinations, and are given as a daily pill or as patches or implants.

These drugs work through negative feedback on the brain (see Section 2.3). They reduce the levels of GnRH and impair fertility. They also have local effects on the reproductive tract that interfere with fertility. However, they may have a number of side effects, and in some species these side effects can make them undesirable therapies (details are discussed in Section 4 by species).

The need to give daily or long-acting treatment and the fact that side effects vary according to species and treatment are the main disadvantages of manipulating sex steroids for contraception or fertility control (Rutteman 1992).

3.4.1 Progesterone*

Progesterone-type compounds (progestins) in the form of injections, oral solutions, or daily feed additives have been developed for veterinary applications (see Section 4 for details by species).

Theoretically, progesterone receptor antagonists, such as the abortion pill RU486, could be used to affect reproduction in animals, but there are few references in the literature to their use in animals. Abortifacients are beyond the scope of this report.

* refers to all synthetic progesterone-type drugs (progestins)

3.4.2 Anti-androgens, anti-estrogens and aromatase inhibitors

There are drugs that either interfere with the production of testosterone or estrogen or inhibit binding of testosterone or estrogen to their receptors.

These compounds are used to treat prostate and breast cancer in people. In general, they have not been used in animals, so efficacy for animal contraception is unknown. Most of the compounds for humans require daily pills or injections – in some cases several times a day – and are impractical for veterinary use. They are not discussed further in this report.

Progestational and Androgenic Drugs

Advantages	Disadvantages
Suppress estrus and fertility in females	Side effects may be seen (e.g., pyometra in dogs with progesterone-type drugs, clitoral enlargement in dogs with androgens)
Can be given as a daily oral treatment or by long-acting injection	Time of administration during the estrus cycle is important and may determine side-effect profile, so accurate staging of the estrus cycle may be crucial in some species
Drugs availablein some markets that have been approved for use in dogs, cats, cattle, horses, and ferrets	May cause unacceptable residues in food animals if used incorrectly

3.5 Chemical Sterilants

For many years, substances have been available that can be injected directly into the testicle to cause atrophy. They serve as an alternative to castration in farm animals. From a practical point of view, these agents have been difficult to use. They often cause pain, and if dosage is not adjusted correctly, can cause sloughing of the skin over the injection site.

A zinc gluconate formulation, neutralized by arginine, that does not show these undesirable side effects has been developed as a chemical castration agent and has been tested in a large number of male dogs. (Wang 2002. For more information, see Section 6.2.1).

Summary of Fertility Control and Contraception Strategies in Animals

Approach	Duration	Route of Administration	Comments
GnRH vaccine (GnRH conjugated to protein, GnRH recombinant protein, or GnRH T-epitopes)	6-12 months	IM* or SC**	Effective in males and females. Difficult to attain 100% efficacy and requires one year duration to make commercially viable. Typically requires multiple initial injections. Suppresses mating behavior.
GnRH agonist (peptide)	1-12 months	SC implant or injection	Effective in males and females. Implants need to be replaced at intervals. Initial burst of mating behavior (two weeks) followed by suppression of behavior and fertility. Used in human prostate cancer treatment.
GnRH antagonist (peptide or small molecule)	Variable	SC implant or injection, oral	Effective in males and females. Suppresses mating behavior. Little research in animals.
GnRH toxin conjugates	Permanent (some data suggest not)	SC	Effective in males and females. Proof-of-concept studies in dogs published. Suppress mating behavior. Target animal safety concerns need to be defined.
LH receptor vaccine	3 months or more	SC	Effective in males and females. Early research stage. Suppresses mating behavior.
Zona pellucida vaccines	Variable	IM or SC	Effective only in females. Most forms require multiple injections, though some formulations show duration of several years in some wildlife species. Normal estrus behavior retained. Pig ZP may not be effective in dogs and cats, but is used in horses and wildlife.
Sperm vaccines	Variable	IM or SC	Effective only in females. In early research stage. Theoretically normal mating behavior.
Progesterone-type drugs, androgen analogs	Variable	Oral or injectable	Approved for use in some species and countries. Side effects are unacceptable in some species.

* IM= intramuscular
** SC= subcutaneous

4.0 Fertility Control Technologies by Key Species

In this section we will review the main strategies used for reproductive control by species. Information is included on methods currently in use and methods in research and development. Comments on important aspects of each method are provided, with an assessment of the risks, side effects, and benefits of each approach.

4.1 Dogs

4.1.1 Ovariohysterectomy

This surgical procedure removes both ovaries and the entire uterus. Commonly called a "spay," it is performed under general anesthesia and requires considerable training and expertise. Risks include unexpected consequences of anesthesia, infection, prolonged healing times, and other common complications of surgery. However, when spays are done by an experienced veterinarian, complications are rare. The pain subsequent to surgery is stressful to animal and owner alike and is generally treated with anti-inflammatory drugs. Obviously, ovariohysterectomy results in permanent sterility, with no further behavioral estrus.

Unwanted side effects of surgery include obesity, which can be managed with diet and exercise, and, in a small percentage of bitches (10% - 20%) urinary incontinence occurs within about three years of spaying (Thrusfield 1985, Arnold 1989).

Practitioners vary regarding their advice about when the surgery should be performed, with some preferring to spay dogs before sexual maturity and others opting to wait until the dog has had her first estrus. There is some evidence that removal of the ovaries is protective for mammary carcinoma, perhaps by reducing lifetime exposure to estrogen (Schneider 1969). Owners frequently wait, however, until the dog displays evidence of a first estrus cycle, or heat, before bringing her to the veterinarian for the surgery.

Ovariohysterectomy is a labor-intensive procedure that requires equipment and expertise and involves the staff of the hospital to assist the surgeon. Current aseptic technique requires drapes, sterile instruments, gloves, gown and mask, adding to the cost of the procedure. Many practitioners also perform presurgical blood work, and animals must return to the clinic for a post-surgical checkup and suture removal, which also adds to the expense (see Section 5 for more information on costs).

4.1.2 Castration

Castration is the surgical removal of both testicles. Generally, recovery is uneventful, but complications such as excessive bleeding, infection, and delayed wound healing can occur. Castration results in permanent sterility, as well as decreased sexual behavior and aggression in some dogs. Some veterinarians recommend this surgery for dogs that have not yet reached sexual maturity, to prevent them from developing aggressive behavior, but there is controversy regarding the relationship of aggressive behavior to sex steroids, and castration may not always produce decreased aggression.

The surgery is done under general anesthesia, and usually is less time consuming and labor intensive than the ovariohysterectomy. However, the same requirements for aseptic technique, presurgical blood work, and post-surgical checkup add costs to the procedure (see Section 5 for information on costs).

Castration prevents the male dog from developing benign prostatic hypertrophy (BPH), and is commonly used as a treatment for intact dogs that develop the disorder. Weight gain can be an unwanted side effect of castration, so the post-castration diet needs to be adjusted to prevent this.

4.1.3 Chemical castration

Zinc solutions that cause testicular degeneration and permanent sterility have been developed for direct intratesticular injection. One such solution is being commercialized and is under review by the FDA/CVM (Center for Veterinary Medicine) in the US (see Section 6.2.1 for more details).

4.1.4 Luteinizing hormone receptor vaccination

Very little has been published on this approach. One paper (Saxena 2002) discusses vaccination of dogs with bovine luteinizing hormone (LH) receptors derived from cattle slaughterhouse ovaries. The material was delivered in silastic implants packed with purified bovine LH receptors. Dogs did mount an immune response to the LH receptor, which interfered with fertility and the estrus cycle. However, dogs in this study were not bred, so contraceptive effect can only be inferred.

4.1.5 Progesterone*

Various progestational drugs have been used for contraception and to suppress sexual behavior in the female dog. These drugs act, in general, via several mechanisms, which may include suppression of GnRH through negative feedback (see Section 3.4), or by direct effects on the uterus, sperm transport, or other mechanisms.

Side effects of the progesterone-type drugs can include (Barragry 1994):

- Pyometra
- Increased incidence of mammary tumors in bitches
- Increased sodium and water retention
- Lethargy
- Weight gain
- Diabetes
- Changes in hair coat (loss and discoloration)

The severity of side effects depends mainly on when in the estrus cycle the progesterone is administered. Other factors determining the side effects include the drug used, whether given orally or by depot injection, and the duration of the treatment. Because of concern about unacceptable side effects, these drugs are not commonly used in the US. However, with careful management, including vaginal smears to determine the stage of estrus, they are used successfully, with minimal side effects, by veterinarians in the EU.

Progesterone drugs can be given either orally or by injection. They include proligestone, megestrol acetate, medroxyprogesterone acetate, delmadinone acetate, and chlormadinone acetate.

Megestrol acetate (Ovaban® Tablets, Schering-Plough), given orally, is used to prevent estrus in bitches. During daily treatment, estrus is prevented, and usually recurs about 4-6 months after medication is stopped, depending on the stage of the estrus cycle when treatment began (Burke 1975).

Medroxyprogesterone acetate (Depo-Provera®, Pharmacia) is given by injection, usually every five to six months during anestrus, or as tablets orally once a day. If the precise dose is calculated on a weight basis and the drug used only during anestrus, side effects are minimized (Bryan 1973; Jochle, personal communication). The label directions indicate that the tablets should not be administered for more than two consecutive treatments, making this an impractical long-term solution for contraception.

Delmadinone acetate is potent orally and systemically. It is used to prevent estrus when given no earlier than three months after the last estrus period, and no later than two months before the next estrus. It is not available commercially in the US.

Proligestone (Covinan/Delvosterone®, Intervet), used as a single depot injection, can prevent estrus for up to five months. This product is not approved for use in the US, but is approved in Europe.

What of the use of progestational drugs to suppress testicular function and inhibit male fertility? No drugs currently on the market are labeled for that use. Theoretically, progesterone-type drugs could be used for this purpose, but would be expected to have some of the adverse side effects seen in females, such as lethargy, weight gain, sodium and water retention, and elevated blood glucose (diabetes). Various progesterone and androgenic drugs were studied for their short-term effects in male dogs, and some dose combinations did reduce fertility (England 1997).

Progesterone receptor antagonist drugs have been used to abort pregnancies in bitches mated by accident (mismating), but are not effective in contraception and fertility reduction and are not discussed further in this report (see Galac 2000 and Hubler 2000 for additional details).

* refers to all synthetic progesterone-type drugs (progestins)

4.1.6 Androgen

Mibolerone (Cheque® Drops, Pharmacia) is a synthetic androgen for prevention of estrus. The product works via negative feedback (see Section 2.3) to suppress GnRH. It is not recommended for use in the dog before the first estrus cycle (it may stunt growth), nor should it be used in breeding bitches. The label states Cheque Drops should be discontinued after 24 months of use, making it unsuitable for owners wishing to have continuous contraception for their bitches. Treatment must be started at least 30 days before the next estrus, or the treatment may not be effective. One of the side effects, clitoral enlargement, is due to the androgenic effect of the drug.

4.1.7 GnRH agonists

GnRH agonists have been investigated for use as contraceptives for a number of years, and many studies concluded that this approach was very promising for suppressing fertility in male and female dogs (McRae 1985, Vickery 1985, Vickery 1989). A number of compounds have been shown to be effective for use in the dog, and many types of formulations have been studied (Lacoste 1989, Ogawa 1989). Some formulations demonstrated up to three months of suppression (Okada 1994, Ravivarapu 2000). Several small peptide synthetic GnRH compounds are available as generic drugs.

Although research has been done using dogs, it appears that much of it was in support of the development of drugs for humans. GnRH agonists have been developed in a variety of slow-release

forms for use in human medicine, and are used to suppress testosterone in the treatment of prostate cancer and to suppress estrogen in the treatment of endometriosis (see Section 3.1.1).

Use of a GnRH agonist in female dogs may result in the induction of estrus when treatment is initiated, depending on the progesterone status of the bitch. For a commercial product, this is clearly an unwanted characteristic, but there may be ways to mask it until the suppression takes effect. A recent report studied the use of short-term progesterone treatment in conjunction with GnRH agonist for suppressing this initial estrus response to treatment (Wright 2001). The study confirms that bitches treated with deslorelin implants do exhibit estrus, and that co-treatment with megestrol acetate blocks this estrus.

It might be possible to use a GnRH antagonist to block the initial estrus, but this approach has not been studied (see Section 4.1.8).

In male dogs, use of a GnRH agonist will result in suppression of circulating testosterone and will cause shrinkage of the prostate gland. This may be a significant clinical advantage for dogs with benign prostatic hypertrophy, a common condition of older male dogs. Today, dogs with clinical signs of prostate disease are typically castrated to shrink the prostate, so treatment with a GnRH agonist could benefit dogs suffering from this condition and be particularly useful in dogs intended for breeding at a later date. Currently, there are no drugs approved for this use in dogs.

Given the variety of GnRH analogs developed, approved, and marketed for human health, it is hard to understand why no veterinary application has been developed, though recent information indicates that an agonist implant, using deslorelin (a peptide GnRH agonist) in a lipid formulation, could become available for use in fertility reduction in dogs (Trigg 2002; see Section 6.2.9).

4.1.8 GnRH antagonists

Another method of blocking the action of GnRH is to make a small peptide or molecule that is similar in structure to GnRH, but sits on the GnRH receptor and blocks it. These types of compounds have been developed, and although several products have been approved for use in humans, GnRH antagonists have not been tested extensively in the dog and none are approved for use in dogs (Reismann 2000).

The GnRH antagonists don't cause the initial stimulation seen with treatment with GnRH agonists. Antagonist suppression of sex steroids is almost immediate, and this is considered an advantage.

Like other methods that suppress testosterone, treatment with antagonists will cause shrinkage of the prostate gland in male dogs. One common side effect seen in early research studies in dogs was a release of histamine, both systemically and at the injection site. This was also seen in humans treated with early compounds. Newer compounds do not have this effect.

4.1.9 GnRH protein synthesis inhibitor conjugates

A novel approach to control of GnRH that involves the use of GnRH conjugated to a protein synthesis inhibitor has been investigated by Dr. Terry Nett, of the College of Veterinary Medicine, Colorado State University, Ft. Collins, Colorado, US (Nett 2002). It is being commercialized by Gonex, Inc., and is described in Section 6.2.5.

4.1.10 GnRH vaccines

GnRH vaccines have been tested extensively for their contraceptive effects in dogs (Faulkner 1975, Gonzalez 1989). Dogs have been immunized with various GnRH peptides coupled to such large proteins as ovalbumin, thyroglobulin, keyhole limpet haemocyanin, and tetanus toxoid. In addition, various adjuvants have been used, including Freund's complete adjuvant, water and oil adjuvants, aluminum hydroxide and CpG (Schanbacher 1983, Singh 1985, Vickery 1989, Ladd 1994, Baker 2002).

After 30 years of research, why is there no commercialized vaccine available for use? The main technical hurdles have been:

- Inconsistency of the immune response in dogs
- Need for multiple injections to maintain results
- Injection site reactions due to the use of adjuvants
- Difficulties in formulating the antigen and consistent conjugation of GnRH
- Inconsistency in the duration of effect among treated dogs
- Difficulty and expense of doing large-scale, multi-year studies in dogs

There is some indication that a GnRH vaccine is under commercial development (see Section 6.2.8, MetaMorphix) but it is unclear whether it is being developed for dogs, as the only publicly released data are contained in a study on cats (Robbins 2002).

It is probable that GnRH vaccines, like other treatments that suppress testosterone in males, will cause shrinkage of the prostate gland in male dogs and therefore would be useful in the treatment of benign prostatic hyperplasia.

4.1.11 Zona pellucida vaccines

Like the GnRH vaccines, zona pellucida vaccines have been in the research stage for many years (Mahi-Brown 1982, 1985). Because of the easy availability of cattle and pig ovaries from slaughterhouses, pig and cattle zona pellucida preparations were most commonly used as the vaccine antigen (Gwatkin 1980). In early studies, variability of purification procedures led to inconsistent results.

In some studies, bitches vaccinated with pig zona pellucida (PZP) showed marked ovarian pathology, but the mechanism was undefined. Some evidence suggested that it was due to a cell-mediated immune response, but it may have also been due to the presence of other ovarian proteins in the antigen preparation (see Fayer-Hosken 2000 for a more complete discussion).

Using PZP to immunize dogs has yielded inconsistent results. Some dogs have shown inhibition of fertility (Gwatkin 1980). In more recent work, although a significant anti-PZP antibody response was detected, moderate and inconsistent inhibition of pregnancy was seen in mated bitches (Liu 2002). The ovaries of bitches immunized with PZP appeared normal. It may be that when the dog generates serum antibodies to the PZP, the antibodies do not bind to the dog zona pellucida, and therefore do not block conception.

The dog zona pellucida proteins are ZP1, ZP2 and ZP3, as in other species, and the sequences of these proteins have been reported (Harris 1994).

Others are approaching this problem using molecular biological techniques. By defining the genes that code for dog zona pellucida glycoproteins and then creating recombinant dog-specific zona pellucida proteins, researchers may be able to create a more species-specific antigen that might prove more effective as a contraceptive. Some preliminary published research shows positive results (Srivastava 2002).

The advantage of using a recombinant protein is that it can be manufactured under more defined conditions, without the variability that is inherent in slaughterhouse-sourced material. The disadvan-

tage is that the zona pellucida proteins are glycosolated, and it is likely that their glycosylation pattern is important to their biological action. Achieving accurate, species-specific glycosylation in a recombinant manufacturing system is challenging. Various approaches to second generation zona vaccines will include new types of antigens (Dunbar 2002), and possibly new formulations.

The main technical hurdles to commercialization of a zona pellucida vaccine for dogs are:

- Inconsistent efficacy with the porcine zona pellucida antigen
- Difficulty developing recombinant antigens for use in dogs
- Inconsistency of the immune response
- Ovarian pathology seen in some studies but not others
- Need for multiple injections to maintain results
- Injection site reactions due to the use of adjuvants
- Inconsistency in the duration of effect among treated dogs
- Difficulty in scaling up manufacturing of porcine zona pellucida under GMP
- Difficulty and expense of doing large-scale, multi-year studies in dogs

4.1.12 Sperm vaccines

Very little has been published regarding sperm vaccines for dogs, as the dog sperm-specific proteins have not been studied to any great extent. However, a recent paper described the dog form of the sperm antigen, PH20 (Sabeur 2002). This is the sperm antigen that has been shown to be effective as the basis for an immunocontraceptive vaccine in guinea pigs (Primakoff 1988).

No studies have been published on the effects of immunizing bitches with canine PH20. However, with the antigen well defined, such studies are theoretically possible and might lead to an alternative for contraception. The advantages and disadvantages of such an approach would be similar to those of a zona pellucida vaccine.

4.2 Cats

Research on controlling fertility and contraception in the cat has lagged significantly behind dog research. The few studies that have been published on cats are reviewed briefly below. Theoretically, the advantages and disadvantages of each approach to dog contraception reviewed in Section 4.1 should also apply to cats. However, with so few publications, confirmation of that assumption must await further research.

While we have not differentiated between "domestic" and "feral" cats in this section, contraception and fertility control issues pertaining to feral cats are discussed separately in Section 5.1.2.

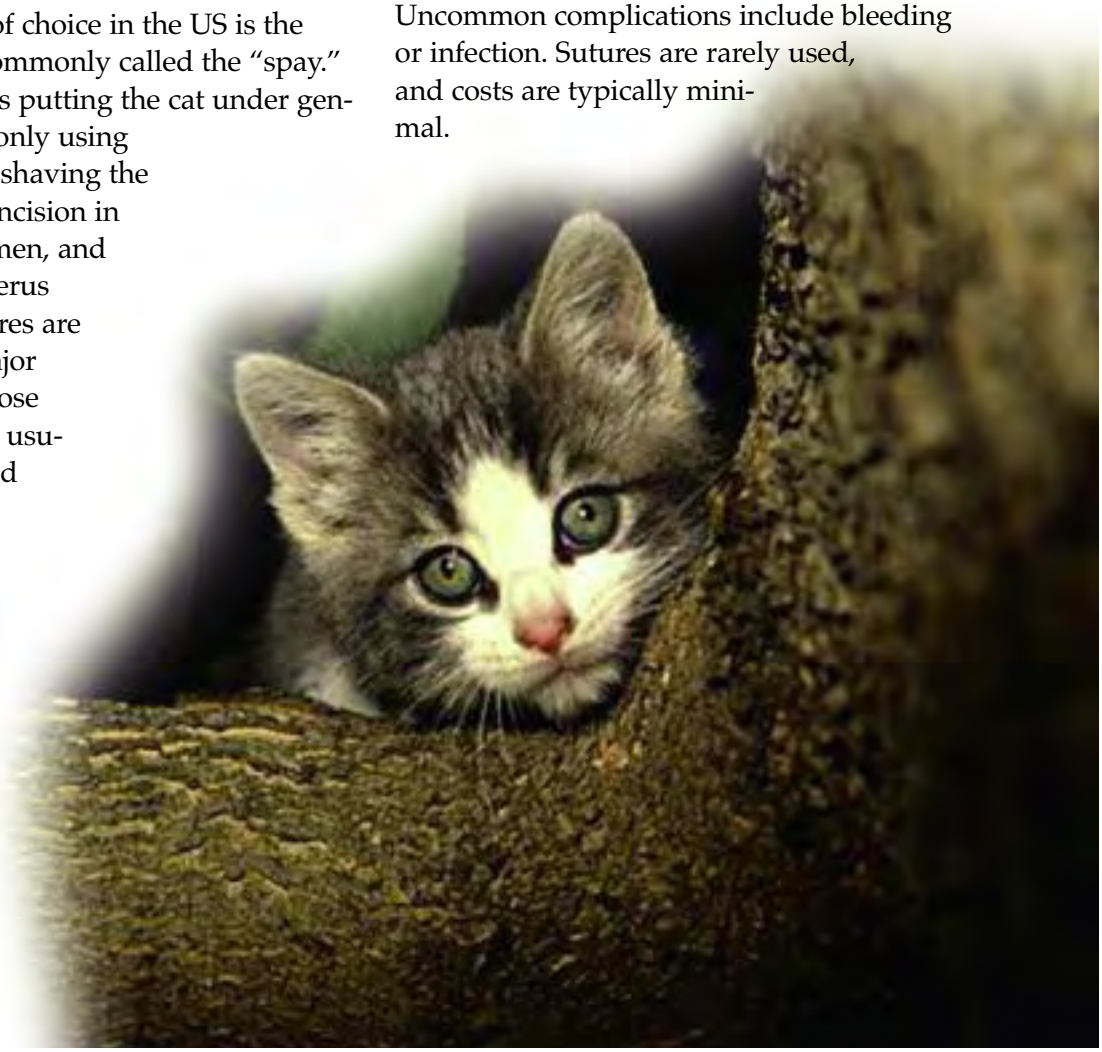
4.2.1 Ovariohysterectomy

For cat owners who do not want their cats to have kittens and who don't want to tolerate estrus behavior, the method of choice in the US is the ovariohysterectomy, commonly called the "spay." The procedure involves putting the cat under general anesthesia (commonly using injectable anesthetics), shaving the abdomen, making an incision in the center of the abdomen, and removing the entire uterus and both ovaries. Sutures are placed to tie off the major blood vessels and to close the abdomen. Animals usually remain hospitalized overnight for observation, and go home the next day. Generally, veterinarians use non-absorbable sutures, so the owner will bring the cat back to the practice about two weeks post-surgery for examination of the healing wound and removal of the sutures.

In Europe, fewer spays are performed, and the procedure typically used is the left lateral flank spay technique. This technique also is done under general anesthesia. The left side of the animal is shaved, and the incision is made high in the left flank. Although there are no good data available to confirm the observation, some veterinarians feel that this surgery is more cost-effective and time-efficient, and has a reduced risk of evisceration. However, if complications such as bleeding occur, visualization is poor using this approach.

4.2.2 Castration

Cat castrations are quick surgeries, and are usually done under general anesthesia using injectable anesthetics. Cats recover rapidly from the operation, and complications are rare. Uncommon complications include bleeding or infection. Sutures are rarely used, and costs are typically minimal.



4.2.3 Progesterone*

There are no progesterone-type drugs currently approved for use in the cat in the US.

Megestrol acetate (Ovaban) is not approved for suppression of estrus in cats in the United States, but it is used in the EU. In cats, its side effects include cystic endometritis, alopecia, polyuria, polydypsia and various other metabolic and endocrine changes. Frequent use can increase the risk of mammary tumors. In some countries, proligestone (Covinan or Delvosteron, Intervet) is approved for use in cats. Proligestone is a second-generation progesterone, and compared to earlier drugs of this type, is supposed to have fewer adverse side effects. It is indicated for suppression and postponement of estrus in the queen and given by subcutaneous injection.

* refers to all synthetic progesterone-type drugs (progestins)

4.2.4 GnRH vaccines

Theoretically, since GnRH is highly conserved across species, a GnRH vaccine developed for use in dogs should be effective in cats, although cats may react to adjuvants differently than dogs.

In a small study involving six male cats immunized with GnRH antigen (GnRH conjugated to tetanus toxoid) in an adjuvanted formulation, five of the six developed anti-GnRH antibodies, but there was little or no effect on serum testosterone levels, even after multiple injections (Ladd 1994).

In another study in 30 male cats using GnRH conjugated to ovalbumin (Enright 1995), cats were immunized at 0, 4, 8 and 12 weeks of the study. The study was carried out only until week 20, so long-term effects were not observed. In the high-dose group, good suppression of serum testosterone and testicular sperm production was seen.

One recent study presented data using a recombinant GnRH vaccine in prepubertal cats (Robbins 2002). Fifteen male or female cats were given the GnRH antigen subcutaneously in a 0.25 ml dose. Injections were administered at 8 and 12 weeks of age and again at approximately two years of age. All immunized cats developed anti-GnRH antibodies, with a significant booster effect seen at two years. No reproductive activity was seen in immunized females, testosterone was suppressed in males, and testicular and ovarian function was suppressed for the duration of the study. This recent study raises hopes that an effective GnRH vaccine might be commercially viable for use in cats (see Section 6.2.8).

4.2.5 GnRH agonists

Deslorelin, a GnRH agonist, has been shown to effectively suppress ovarian activity in cats, but the duration of suppression was variable (Munson 2001). The drug was given via a long-acting subcutaneous implant to 10 mature female cats (and compared to 10 untreated controls), and animals were observed for fourteen months.

Treatment with deslorelin, as expected, initially stimulated estradiol release, followed by estradiol decrease. Return to estrus was variable as the treatment wore off, ranging from 7.5 to up to 14 months or longer (six animals had not yet returned to estrus at the end of the study). Some cats that demonstrated slightly elevated estrogen levels were given a second implant. Additional work will be needed to understand this variability and adjust the implant dosage in order to produce more consistent results among treated cats.

4.2.6 Zona pellucida vaccines

Zona pellucida vaccines have not been widely studied in cats. The commonly used pig zona pellucida (PZP) antigen is not effective in preventing pregnancy. Although cats can react to PZP by producing serum anti-PZP antibodies, these antibodies do not appear to interact with feline zona pellucida (Jewgenow 2000, Gorman 2002).

A better antigen choice for a zona pellucida vaccine in cats might be a cat-specific zona protein or combination of proteins. As yet, there are no published studies on the cloning of these proteins, so this approach is still in the early research stage.

4.3 Cattle

In general, producers want to optimize fertility in cattle, not suppress it. Dairy cattle are managed aggressively to become pregnant within a few months of calving to maximize milk production. In beef cow-calf operations, increasing fertility maximizes the number of calves.

However, suppression of breeding, sexual behaviors, and pregnancy is desirable in beef cattle operations (see Section 5.2) and approaches are in use or under development.

4.3.1 Ovariectomy

Surgical removal of the ovaries (spaying) has been used to suppress estrus in heifers. Historically, surgeries were done in the field, with no anesthesia, using a flank incision. More modern techniques involve using specialized instruments that grasp the ovaries through an incision in the vaginal wall (Habermehl 1993). Complications can be severe, and include bleeding, infection, pain, decreased feed intake leading to acidosis, and even death. However, if an ovariectomy is performed by a skilled operator, complications are minimal. Compared to less invasive methods, ovariectomy is labor intensive and therefore costly.

The main advantages of spaying are that it makes heifers easier to handle in the presence of bulls or steers, it avoids the losses associated with pregnancy, and the spayed heifer may bring a premium price (Bopp 2002). The major disadvantage is the slower rate of gain (about 10% slower than intact heifers) and increased feed required (about 8% more than intact heifers) to achieve the same weight.

A common technique is to implant spayed heifers with a growth promotant in markets in which such implants are approved. This allows the advantages of the reduction of estrus and pregnancy, while overcoming the disadvantage of reduced efficiency (Ensminger 1997, Popp 1997).

4.3.2 Intrauterine devices

Used for some years for contraception in women, intrauterine devices prevent pregnancy, probably by several mechanisms. A copper-bearing device has been shown to prevent pregnancy in heifers (Turin 1997). IUDs are not commonly used or approved for use in cattle. Although they prevent pregnancy, intrauterine devices have no effect on the estrus cycle, and therefore do not solve the problem of mounting, or "bulling," associated with heifers in estrus. A skilled technician would have to insert the devices, and complications such as heavy bleeding, infection, and subsequent infertility could be expected.

4.3.3 Castration

Beef bull calves are castrated, usually before 10 months of age. Except in rare cases in which bulls are born from superior cows, dairy bull calves are castrated and raised as steers for meat. There is a variety of methods of castration, and the operation is usually done in the field, commonly with no anesthesia. Timing is important to reduce stress on the animals – fly season is to be avoided. The surgery is relatively easy and quick, but complications such as bleeding, infection, and fly infestation can occur.

4.3.4 GnRH vaccines

Many researchers have published information on the use of GnRH vaccines as alternatives to castration and spaying in cattle (Robertson 1982, Jeffcoate 1982, Robertson 1984, Goubau 1989, Lobley 1992, Wetteman 1994, Bell 1997, Huxsoll 1998, Cook, 2000, Cook, 2001, D'Occhio 2001). Vaccination would be a less traumatic, less labor-intensive method to achieve suppression of sexual behavior and pregnancy in cattle.

Research has shown that both bulls and heifers can be immunized successfully with GnRH. Immunized bulls have shown decreased sexual behavior and behave like steers, with serum testosterone levels significantly reduced. Heifers that respond to vaccination show decreased estrus and mounting behavior, and do not become pregnant when kept with bulls.

Timing of vaccination in relationship to the stage of growth is important, and various schedules have been proposed (Adams 1996). Feedlot performance of treated cattle has been studied, and although feed efficiency is somewhat reduced, generally the meat produced is superior in some characteristics, such as tenderness (Adams 1992).

Researchers at the Lethbridge Center in Alberta, Canada, have recently published data showing good efficacy of a recombinant fusion protein antigen GnRH vaccine (Cook 2000, 2001). These studies were done in collaboration with Biostar, the Canadian company that was acquired by MetaMorphix, Inc. (see Section 6.2.8). No product resulting from these studies is on the market at this time.

In the United States and Europe, no commercial product is available. In Australia, a GnRH vaccine was approved in 1992 for use in cattle (Vaxstrate, developed in a collaboration by Arthur Webster, Pty. Ltd., Peptech Ltd., and CSIRO* but no longer marketed). The vaccine involved a two-dose protocol (5 ml subcutaneously, followed by a 5 ml booster within 4-16 weeks) and was shown to prevent pregnancy in about 80% of cows for up to about 200 days after the second injection (Hoskinson 1990). The need to re-muster cattle for a second treatment, injection site issues, variability in duration, and pricing issues are believed to have contributed to the decision to discontinue marketing the product.

* Commonwealth Scientific and Industrial Research Organization

4.3.5 GnRH agonists

Since the agonists that are available work well in a wide variety of species, there is no reason to suspect that they would not be effective in cattle. A recent Australian research paper reviewed the use of GnRH agonists and investigated the use of a GnRH agonist "bioimplant" in heifers, showing that pregnancies were prevented for periods of 3 to 12 months, using various doses, and that this effect was reversible (D'Occhio 2000). The article states "It is likely that commercial bioimplants will be available within the next 3 to 5 years." As one of the co-authors (TE Trigg) is with Peptech Animal Health (see Section 6.2.9), this statement may be significant.

GnRH agonists can be used short-term to induce ovulation, and may be useful in controlling and optimizing reproduction in dairy cows and in embryo transfer work. These uses are not covered in this report.

4.3.6 Progesterone*

Melengestrol acetate (MGA) is an orally active progestational compound fed to heifers to decrease behavioral estrus. The compound prevents ovulation by inhibiting the preovulatory surge of luteinizing hormone via negative feedback (Imwallel 2002). MGA Premix (Pharmacia), a feed additive, is approved for use in the US and label indications are for increased rate of weight gain, improved feed efficiency, and suppression of estrus in heifers fed in confinement for slaughter. It is available as a solid material with soybean hulls or as a liquid (in propylene glycol) to be added to feed. Many studies demonstrate the efficacy of this treatment, as well as the effects on carcass quality and feed efficiency.

MGA can also be used in heifers intended for breeding, but for no more than 24 days. Once MGA treatment is stopped, heifers will typically come into heat within about a week, and if bred on this heat will have a reduced conception rate. At subsequent estrus, conception should be normal.

Management is important for effective use of MGA. If heifers go off feed for any reason, they may not consume the medication, and then will display estrus within a week. If medication is withdrawn inadvertently, all treated animals will show heat synchronously, which could create a problem. The slaughter withdrawal time in order to avoid residue in the meat is 48 hours, and this timing requirement can cause problems if animals intended for slaughter 48 hours after MGA is withdrawn are in fact not slaughtered in that time period. All the heifers may come into estrus just before a delayed slaughter time, say three to five days later, resulting in excess bruising due to mounting activity among animals cycling together.

* refers to all synthetic progesterone-type drugs (progestins)

4.4 Horses

Castration of male horses has been used to modify undesirable sexual behavior. Many colts and stallions may not perform up to their athletic potential due to such behavior.

Fillies and mares may also have unpredictable behavior during the breeding season. Estrus-related behaviors vary among female horses and often include nervousness, squealing, agitation, and squatting and urinating. These behaviors are inappropriate for animals involved in shows, racing or training, or eventing. Suppression of estrus via progesterone type drugs has been used.

Because the mare is a seasonal breeder whose estrus cycle usually begins in the spring and continues through the summer, control strategies do not need to be implemented throughout the entire year, but only during this four-to-six-month period.

In several parts of the US, wild horses are reproducing at an unsustainable rate and contraception strategies have been investigated for the control of those populations (see Section 4.5).

4.4.1 Castration

Horses can be castrated using local anesthetics while they are standing or they can be cast on their side using general anesthesia. The surgery is usually routine, but complications can include bleeding, infection, and evisceration of bowel through the incision, which can be serious enough to result in death. Post-surgical pain is common and may be treated with anti-inflammatory drugs. Animals may take several weeks to recover fully and be ready for training or riding.

Usually, castration eliminates unwanted aggression and sexual behavior in stallions, but persistent activity such as mounting and ejaculatory behavior can continue in some geldings. The term "proud cut" is used to describe these geldings, implying that the castration was not complete; but there is evidence to suggest that 20% - 30% of geldings display stallion-like behavior even after proper castration (Smith 1973, Voith 1979). It is not known if this behavior is due to production of androgens by the adrenals or other sources, or merely a behavior trait of some geldings.

4.4.2 Progesterone *

Various steroid drugs have been used for long-term suppression of estrus in show and racing mares (for a review, see Squires 1993). Progesterone in oil-based formulations, sometimes in combination with estradiol, has been employed as an intramuscular injection, but progesterone and progesterone/estradiol are not approved for that use in horses and are unavailable commercially.

Altrenogest (Regu-Mate®, Intervet) is a synthetic progesterone used for controlling estrus in mares. It is administered as a solution either in the feed or directly by mouth on a daily basis to suppress estrus. Once the treatment is discontinued, mares will come into estrus in about four to five days and breed normally.

Proligestone (Delvosteron) is a long-acting, injectable, second-generation progesterone-type drug sometimes used in Europe for estrus suppression, but it is not labeled for this use, and it has shown questionable efficacy (Neely 1988).

* refers to all synthetic progesterone-type drugs (progestins)

4.4.3 GnRH vaccines

For many years, studies have been done on the effects of vaccinating horses with a GnRH vaccine to suppress fertility. As in dogs, the difficulties presented by some formulations include variability in the duration of the effect and the need for multiple injections to raise an immune response.

GnRH vaccination in horses would be useful in management situations in which longer term reduction in sexual behavior and fertility is needed. As it takes weeks to months to mount an immune response, this approach would require careful timing to manage behavior for a specific event such as a show or race. With the duration of the immune response variable, there is a need for multiple boosters to maintain effect, and the timing of reversibility is not easily predicted.

Formulations including Freund's complete adjuvant have typically been necessary to achieve results (Safir 1987), and this adjuvant is not acceptable for a commercial product. Various publications from Australia (University of Queensland and Peptide Technology Pty. Ltd., see Section 6.2.9) reported testing of a GnRH-conjugate vaccine in horses (Dowsett 1991, 1993, 1996). Injections were given two to three times to stimulate immunity in colts and fillies. Various adjuvants and formulations were tested, including an implant. The treatment was effective, but variable, with the longest reported efficacy lasting around 32 weeks. In some experiments, the immune response was shown to wane, and fertility resumed, indicating the reversibility of the treatment.

In more recent studies using a GnRH-bovine serum albumin vaccine and a commercial adjuvant in mares (Dalin 2002) and stallions (Malmgren 2001), variable results were seen. Multiple injections were used to induce an immune response, and a small number of animals were used in each study. Libido was not totally suppressed in stallions, and the mares continued to show estrus, but with irregular duration and frequency.

GnRH vaccination was reported to be effective in suppressing undesirable behaviors associated with estrus in mares by a group in Australia (Walker 2002) and in fact this research has resulted in the mid-2002 launch of a commercial GnRH vaccine in Australia and New Zealand (see Section 6.2.4 for more information). The vaccine, called Equity™, is a product of CSL Ltd. and is labeled "Oestrus Control Vaccine for Horses." It is an analog of GnRH linked to a carrier protein. Iscomatrix® is used as an adjuvant. The label indication is "an aid in the control of oestrus and oestrus-related behaviour in fillies and mares not intended for breeding."

Equity is given as two injections four weeks apart. The label indicates that the effect will be seen "within about two weeks following the second dose of vaccine in most horses" and suppression of the estrus cycle should last "at least three months and in a percentage of horses . . . for six months or longer." The label also points out "the extent and duration of effect of booster doses of vaccine have not been studied." Therefore, it is not known how mares will react to a second treatment the following year. It is to be expected that CSL will be conducting follow-on studies to extend the label for multiple treatments. Equity is not labeled for use in male horses. Whether clinical trials are underway in males is not known at this time.

4.4.4 GnRH agonists

There is a GnRH agonist approved for use in the horse (deslorelin, Ovuplant®, Ft. Dodge Animal Health in the US), but it is used to induce estrus, not to suppress it. Ovuplant is used to stimulate ovulation when a large follicle is present on the ovary.

There is some indication that deslorelin can cause down regulation of the gonadotropins in the pituitary gland of the horse because it has been associated with reduction in circulating FSH (Johnson, 2000, Farquhar 2001). Theoretically, if larger doses of the drug were given over a longer period of time, suppression of estrus might be achieved, as it is with the same drug used in dogs (Trigg 2002). In the horse, much larger doses may have to be delivered to be effective.

A few studies have been done investigating the use of GnRH agonists in the horse, and data show that, similar to the effects seen in other species, fertility can be suppressed (Montovan 1990, Fitzgerald 1993).

4.4.5 GnRH antagonists

In order to be effective, a GnRH antagonist would need to be given on a regular basis. Frequency of dosing would depend on the pharmacokinetics of the particular drug used. This might be practical as a short-term treatment, useful to suppress unwanted behavior in a stallion or in a mare in estrus before a show or race. In theory, the effect should be fully reversible, and treated animals could subsequently be used for breeding.

Because the effects of an antagonist are seen quickly after initiation of treatment, this approach might be more practical for short-term use. In contrast, the GnRH vaccine or agonist might take weeks to achieve the suppression of libido and fertility.

In studies done in the UK, the GnRH antagonist antarelix was used to suppress fertility in stallions (Hinojosa 2001) and mares (Watson 2000). In this short term-study (eight weeks) stallions treated with the antagonist demonstrated decreased libido and histological evidence of testicular suppression. The compound was effective in reducing testosterone within 48 hours after treatment was initiated. Mares showed lengthening of the estrus cycle and suppression of estradiol. The authors were investigating the use of the antagonist more as a research tool than as a commercial treatment.

4.4.6 Zona pellucida vaccines

The porcine zona pellucida antigen has been tested and shown to be effective in wild horse populations. Mares treated with a vaccine delivered via darts showed a reduction in fertility. Fewer foals were delivered in treated animals. More details regarding wild horse vaccination are provided in Section 4.5.

4.5 Wildlife

Contraception and fertility control in wildlife can play an important role in creating and maintaining the balance among animals, humans, and the environment. Strategies for addressing overpopulations of indigenous species and the presence of unacceptable numbers of pest species depend, at least in part, on the development, availability, and effectiveness of humane approaches to population control. An in-depth review of the field of wildlife contraception is beyond the scope of this report. However, we would like to highlight the main approaches used in a variety of species, and comment on some of the pros and cons of each approach.

Examples of Wildlife Contraception Research

Institution	Species	Method	Comments
Australasian Fauna Laboratories, Macquarie University, NSW, Australia	Koalas, kangaroos (*Macropus giganteus*), wallabies (*Macropus eugenii*) and deer	GnRH agonist (deslorelin) implant	Efficacy in kangaroos for up to one year
Institute for Zoo Biology and Wildlife Research, Berlin, Germany	Bears	Antiprogestereone J956	For interruption of early pregnancy
Marsupial CRC, Australia	Wallabies, possums, kangaroos	Recombinant zona pellucida, species-specific sperm antigens	
Medical College of Ohio, US	Wild horses (*Equus caballus*)	Porcine zona pellucida vaccine	In collaboration with Zoo Montana
National Wildlife Research Center, United States Department of Agriculture, Ft. Collins, Colorado, US	White-tailed deer (*Odocoileus virginianus*), coyotes (*Canis latrans*)	GnRH vaccine, porcine zona pellucida vaccines	Working on longer acting formulations
Perth Zoo, South Perth, Australia	European red fox (*Vulpes vulpes*)	Sperm vaccine	Bait systems and recombinant protein
Pest Animal Control Cooperative Research Centre, Australia	Fox, mice (*Mus domesticus*), rabbit	Sperm vaccine, porcine zona pellucida vaccine	
University of California at Davis, US	Tule Elk (*Cervus elaphus nannodes*), wild horses	Porcine zona pellucida	
University of California at Davis, US	Blacktail deer	GnRH vaccine	
University of Georgia, Athens, GA, US	Elephants, others	Porcine zona pellucida vaccine	
Wildlife Contraception Center for North American Zoos, St. Louis, MO, US	Zoo animals	Various methods	
Zoo Montana – Science and Conservation Center, US	Wild horses, deer, more than 95 species of captive animals	Porcine zona pellucida vaccine	

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4.5.1 Dart delivery systems

Darts and "bio-bullets" have been used to deliver contraceptive vaccines. This method is most effective in locations with physical borders ("confined"), and less effective in mobile wildlife populations in open areas. The viscosity of a given formulation and/or the volume needed can make this type of delivery impractical. Some dart systems have marker dye incorporated to allow short-term identification of treated animals to help prevent re-treatment. Ranges are limited and it can be impossible to tell if the animal was hit at all unless a spot of blood appears at the target site.

4.5.2 Bait delivery systems

If an effective contraception could be delivered to wild populations via some type of bait, it would obviate the need for capturing or darting animals and might decrease the cost of population control significantly. However, baiting systems have some significant disadvantages:

- Ensuring that only the target species will be affected
- The treatment must be very safe, as it is likely that any one animal could be exposed to an overdose of the baited treatment relatively easily
- The bait must be in a stable form that can be left in the field without degrading over time
- The dose of the vaccine or drug must be low enough to enable its incorporation into the bait in a reasonable volume

For immunocontraception, oral exposure to the bait may trigger an immune response that is ineffective, or in some cases, more effective, when compared to an injectable antigen. Oral exposure can trigger a mucosal antibody response, which results in the production of IgA in mucosal surfaces such as the reproductive tract lining. This may significantly enhance the efficacy of, for example, an anti-sperm vaccine. The specific immunogenicity of each antigen will probably vary depending on the route of exposure and the species. For instance, researchers at Perth Zoo in Australia have been investigating the use of *Salmonella typhimurium* recombinant proteins expressing various fox sperm antigens (Bradley 1997, Bradley 1999). They have shown that both systemic IgG and a mucosal immune response in the female reproductive tract can be stimulated.

For fox control in Australia, *Salmonella* and canine herpes virus are being investigated as oral delivery methods for zona pellucida antigens (see www.pestanimalcrc.org.au).

4.5.3 Porcine zona pellucida vaccines

One of the most widely used and successful wildlife contraception approaches has been the use of porcine zona pellucida vaccine. This approach has been used in a variety of species (see Barber 2000, Kirkpatrick 1997, and Section 3.2.1 for details of mechanism of action). Since the zona pellucida vaccine is only effective in females and does not prevent them from coming into heat, females continue to cycle, attract males, and breed even though they do not become pregnant (McShea 1997, Heilmann 1998). This sexual activity may affect the overall behavior of the group and these effects should be evaluated on a species-by-species basis.

Porcine zona pellucida vaccines have been used in the field for many years, yet none have been approved in the US by the FDA/CVM and none are commercially available. The main reason is the difficulty of getting approval for the manufacturing of the vaccine – the efficacy and safety have been amply demonstrated. Since the active antigen is a purified zona from pig ovaries obtained from slaughterhouses, there are a number of technical hurdles to making the production process into one that can be conducted under GMP. It is unlikely that a commercial zona contraceptive vaccine will be approved unless a recombinant antigen can be used, since recombinant proteins are more easily produced under GMP.

Many of the formulations of porcine zona pellucida contain Freund's complete adjuvant, which presents another obstacle to approval in the US by the FDA/CVM as this adjuvant is not acceptable in a registered product. Alternative formulations will need to be developed to pursue regulatory approval, necessitating a substantial testing program to ascertain whether efficacy will be reduced without the Freund's.

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Using a contraceptive vaccine in wild animals, in zoo settings, or to treat animals unlikely to become sources of food for humans raises no human safety concerns, other than inadvertent self-injection while administering the vaccine. However, using these vaccines to control urban and suburban wildlife such as deer, that might enter the human food chain, raises a number of issues. Although it is unlikely that humans eating deer treated with contraceptive vaccines will have any adverse effects, this will need to be proven to the satisfaction of regulatory authorities before these products can be used on deer or other animals that could be consumed by people.

Other safety concerns include the effects on predator species eating treated prey. For example, if a fox or wolf eats a deer recently treated with a long-acting zona pellucida vaccine, will there be any ill effects on the predator's reproductive capacity? This environmental exposure will also have to be considered when attempting to obtain regulatory approval.

The Science and Conservation Center (SCC) at ZooMontana, under the sponsorship of more than 15 foundations and federal agencies, is working on refining the currently used porcine zona pellucida contraceptive vaccine. According to its website (www.zoomontana.org), the SCC is producing larger quantities of the vaccine, testing for contamination, and, in collaboration with other researchers, increasing the efficacy of long-term contraception through a single inoculation (Turner 2002). As of 1996, the organization had worked with more than 60 zoos to contracept rhinoceros, zebra, hippopotamus, bison, wild horses, and deer (Kirkpatrick 1996), and the SCC reports that the total is now 87 zoos and > 95 species.

The National Wildlife Research Center (NWRC) of the United States Department of Agriculture has been investigating the use of porcine zona pellucida vaccines in white-tailed deer. NWRC has been trying new adjuvants to attempt to develop a formulation that will require fewer boosters and show multi-year efficacy (Fagerstone 2002).

The Pest Animal Control CRC (see Section 6.2.3) is working with zona pellucida antigens for control of fox and rabbit populations in Australia. *Salmonella* bacteria and canine herpes virus are being explored for antigen delivery to foxes, while the myxoma virus, genetically modified to include a zona pellucida gene, is being tested for use in rabbits. Similar approaches are being developed for controlling overpopulation of the common house mouse.

Using a similar approach, the Marsupial CRC is researching the use of sperm and zona pellucida antigens for fertility control of kangaroos and wallabies. Researchers have cloned and expressed brushtail possum zona pellucida proteins (ZP2 and ZP3) and established systems to produce and purify recombinant zona pellucida antigens in order to evaluate their effectiveness for contraceptive vaccines (see section 6.2.3).

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4.5.4 GnRH agonists

Deslorelin implants are being developed for contraception in dogs and cats (see Sections 4.1.7, 4.2.5 and 6.2.9) and these implants have been studied for their effects on fertility in wild animals in a zoo setting. Animals treated included male and female cheetahs, a female leopard, lionesses, wild dogs, male sea otters, and male and female red and grey wolves. Results were variable but promising. It is likely the optimal dose will have to be determined for each species and sex (Bertschinger 2001).

Deslorelin implants have also been used to suppress estrus in female elephants (Brown 2001) and for contraception of wild carnivores in southern Africa (Bertschinger 2001). GnRH agonist implants are also being used at the St. Louis Zoo to control the population of lion tailed macaques (www.stlzoo.org/content.asp?page_name=contraception).

Because of the difficulty predicting duration of effect and timing of reversibility, this approach would not be ideal for use in non-confined wildlife population control, although it is already being tested in free-ranging felids (Bertschinger 2002).

4.5.5 GnRH–protein synthesis conjugates

If a single-shot sterilizing treatment were available, it would solve the problem of having to re-treat hard-to-catch animals in the wild. GnRH has been conjugated to a plant-derived protein-synthesis inhibitor called pokeweed antiviral protein (PAP). Theoretically, the GnRH-PAP conjugate should be a permanent approach (see Section 3.1.3 for mechanism and Section 6.2.5 for information on commercialization), but initial testing in dogs showed unexpected recovery of function. GnRH-PAP conjugate treatment has been investigated for its contraceptive effects in captive mule deer (Nett 2001).

4.5.6 GnRH vaccines

GnRH vaccines could be useful in both males and females of most species, because GnRH is highly conserved in mammals (for details on mechanism of action, see Section 3.1.4). Unlike the zona pellucida vaccine approach, GnRH vaccine treatment will reduce sexual behavior and sex steroid levels, so animals will behave as castrates; females will not come into estrus and males will show limited or no breeding behavior.

At the National Wildlife Research Center in Colorado, US, extensive studies of a GnRH vaccine on reproduction in white-tailed deer have been underway for several years. Treatment has led to significantly reduced fawning rates and altered estrus behavior in females, with infertility lasting up to two years without boosting. The bucks showed no sexual activity, and either dropped antlers early or remained in velvet (Miller 2000).

4.5.7 Anti-progesterone

Progesterone receptor antagonists can be used to interrupt pregnancy in progesterone-dependent species. In a study in Germany, a progesterone receptor antagonist was used to prevent early embryo implantation in bears kept in a zoo. The drug was given by injection, and was effective in aborting early pregnancies (Jewgenow 2001).

4.5.8 Progesterone*

Since progesterones are used mainly in zoo settings, they are generally not approved for use in wildlife and are not available commercially for this use, they will not be reviewed here in detail.

A contraceptive used to inhibit reproduction in feline species in zoos is the melengestrol acetate (MGA) implant, originally used in 1975 by Dr. U. Seal (Seal 1976) for contraception. For more than 20 years, various dosages of the MGA implant have been used.

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Dr. Seal filed the first INAD (investigational new animal drug) permit for MGA and provided free implants to zoos. Dr. Ed Plotka assumed responsibilities for implant production and distribution in 1990, the INAD permit was transferred to his name, and a modest fee per implant is now charged. Dr. Plotka provides the FDA with documentation on the use of the implants and asks people who use the implants to submit use data. However, as these implants are not being made under GMP conditions, it is unlikely that they will be developed for commercial use.

Undesirable side effects, similar to those seen in pets, have been seen in treated animals. The first long-term study on the adverse effects of MGA was initiated by Dr. Linda Munson in 1984. Her findings revealed endometrial hyperplasia and inflammation, increased incidence of endometrial, myometrial and mammary cancer in treated animals and, as also seen in pets, an association with weight gain and diabetes (Munson 2002).

For an excellent summary of the uses of progesterone-type drugs in various species, refer to the American Zoological Association Contraceptive Advisory Group's 2001 recommendations (www.stlzoo.org/content.asp?page_name=CAGdatabase).

* refers to all synthetic progesterone-type drugs (progestins)

4.5.9 Sperm vaccines

Using sperm antigens as a basis for immunocontraception has been shown to work in a research setting, but has not been effectively employed for wildlife control. A group in the United Kingdom published preliminary information on screening a cDNA library from grey squirrel (*Sciurus carolinensis*) testes to identify sperm antigens that could be used for immunocontraception. This group also reported investigating various adjuvants for use in such a vaccine (Moore 1997).

The PH20 sperm antigen has been cloned from the European red fox (*Vulpes vulpes*) but no immunocontraception work with the antigen has been published (ten Haven 1998).

The Marsupial CRC is also exploring sperm antigen vaccines for control of marsupial populations (www.marsupialcrc.org.au).

4.5.10 Vaccine antigen for contraception produced in plants

A PhD student at the Murdoch University-based State Agricultural Biotechnology Centre in Perth, Australia has been reported to be genetically engineering plants that could be used to reduce the fertility of rabbits, a major Australian pest species. Plants are modified to produce an animal protein for use in a vaccine to create an antibody response that will cause the rabbit immune system to "attack" its own eggs as foreign cells. Cut plant material is soaked in a solution of soil bacteria, *Agrobacterium*, which has been modified to contain the rabbit DNA. The bacteria infect the plant material and transfer the animal DNA into plant cells where it integrates into the plant DNA. The plant tissue is regenerated in culture using hormones to grow shoots and then transferred to a tub containing hormones that promote root growth. Once the plant roots, it is transferred to soil. It is unclear whether or not the project has proceeded to a point at which the animal protein has actually been delivered to the target animal (www.comm.murdoch.edu.au/synergy/0303/rabbits.html).

5.0 Marketing Overview and Issues

The "contraception and fertility control market" is, in fact, many markets at various stages of development. After some false starts and decades of research, it appears that several commercially viable products for specific applications in contraception and fertility control in animals may be within reach in certain markets (e.g., Addison Laboratories, MetaMorphix, Inc., Peptech Ltd.– see Section 6), and CSL Ltd. has launched a product for mares in Australia and New Zealand. Because no single technology is suitable for all species and segments of the market, researchers are continuing to refine long-standing approaches and pursuing relatively early stage technologies as well. Significant challenges to serving the broad market exist.

The unmet needs in the companion- and production-animal contraception and fertility control market represent opportunities for animal health companies. Historically, however, "big pharma" animal health has been reluctant to develop products either for these market segments (see Section 6) or so-called low-profit segments such as feral animals and wildlife.

Aside from the traditional obstacles to developing, delivering, and commercializing pharmaceutical and biological products (e.g., cost, business and competitive risks, scale-up and manufacturing issues, overall length of time it takes to develop products and obtain approval), contraception and fertility control in animals present specific challenges.

The combination of different technologies, diversity among stakeholders, and the presence of very visible low-margin segments presents a challenge that can be expected to keep marketing managers awake at night. What kinds of things will they be thinking about?

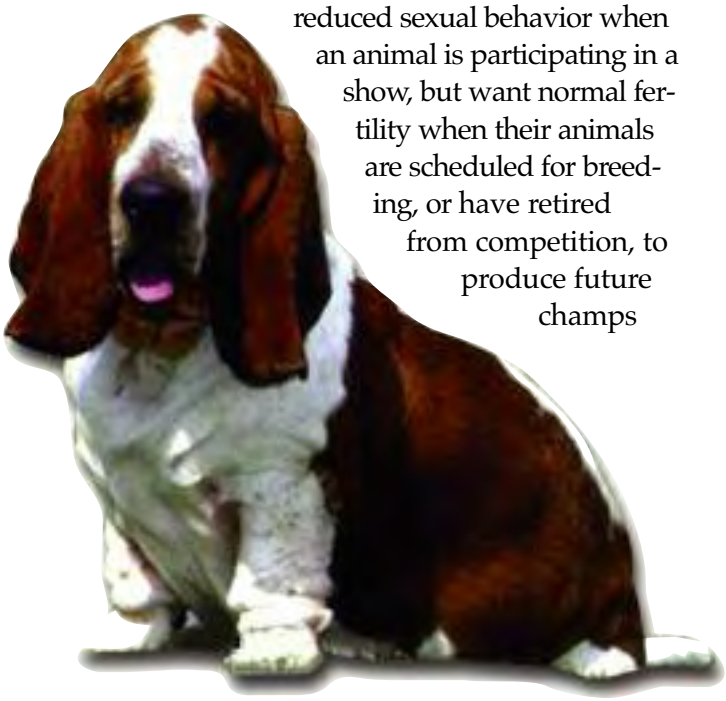
There is no single approach, formulation, technology, or product

It is an understatement to say that the needs of the wildlife community, companion animal owners, shelters, livestock producers, and the veterinary professionals who serve these groups differ, so it is not surprising that there is no single product or approach to contraception and fertility control in animals that "fits all."

There are important end-user preferences that affect the ultimate attributes of products – short-term, long-term, or permanent sterilization; injection, implant, or oral formulation; daily or long-term treatment; suppression or maintenance of sexual and sexually related behavior.

In general:

- Spay/neuter clinics would like something inexpensive, easy to administer, 100% effective, and permanent for feral and adoptable animals
- Companion animal veterinarians want a treatment that brings pet owners back to the practice on a regular basis and is dependable, safe, profitable, and provides the long term health benefits associated with surgical spaying and neutering
- Some pet owners may prefer a permanent solution, and others object to the permanence of sterilization or may wish to breed their animals some day and therefore would like an approach that "wears off." For pet owners, suppression of sexual behavior is important – they don't want their female dogs and cats coming into heat, and owners of male dogs want to reduce mounting and aggression
- Breeders (i.e., reputable breeders), owner/breeders, and show animal owners need the flexibility of reliable fertility control and reduced sexual behavior when an animal is participating in a show, but want normal fertility when their animals are scheduled for breeding, or have retired from competition, to produce future champs



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- Horse owners and veterinarians want fertility control that reduces undesirable behavior in males and eliminates behavior associated with females coming into heat
- Livestock producers want approaches that will minimize bulling and other sexual behaviors and their negative effects on productivity and meat quality
- Wildlife control organizations want permanent, single-dose contraception that minimizes the need for capture and restraint (although segments of the humane and animal welfare/rights community may want a reversible product which may be perceived as more humane by some)

(See Section 3 for a review of the contraception and fertility control technologies that have been investigated by researchers around the world, and Section 4 for a discussion of their applicability to key species.)

There are many potential customer segments and stakeholders – even within a given group there are different needs, and there are societal factors, too

Just as there is a range of technologies at different stages, there is a range of stakeholders, that is, groups with an interest in contraception and fertility control in animals, including:

- Animal health companies
- Biotechnology and life sciences companies
- Foundations
- Humane, shelter, and rescue organizations
- Wildlife groups and zoos
- Veterinary schools and research institutions
- Veterinarians
- Pet owners
- Show animal owners
- Breeders
- Producers and producer organizations
- Regulatory agencies
- Animal welfare and animal rights groups with a variety of philosophies
- The animals themselves

Since stakeholder characteristics, beliefs, needs, and wants vary among and within customer and key influencer groups, the need for extensive market research, targeting, prelaunch programs, and public relations will add to marketing costs and complexity

Companies interested in pursuing opportunities for contraception or fertility control in animals will want to have a thorough understanding of market size and market characteristics. Knowledge about stakeholder interactions and factors that drive the price/value relationship for each end-user segment under consideration will also be important. Companies will need to consider which approach best fits where a given company is, where it wants to be, and how it wants to get there.

Deciding what technology to embrace and how to define and approach such a complicated marketplace can be something of a "balancing act" – weighing company culture, strategic direction, internal resources, and existing customer base and product portfolio to determine the most commercially and strategically viable approach. In order to help optimize the potential of any opportunity, this analysis would be undertaken as a part of the long-range planning process, ideally before initiating product development or forming alliances, but certainly before final decisions regarding product attributes are made.

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In summary: The attributes of a given product are a combination of the inherent characteristics of the technology behind that product; the needs, plans and competencies of the company or companies involved; and the needs of the mix of groups that influence the dynamics of the particular market segment. There's nothing unusual about that, in and of itself – but in a market as complicated as contraception and fertility control in animals, each segment brings its own set of challenges, and, in addition to the typical costs related to product launches, first-in-market companies can be expected to bear the market-definition, education, and public relations costs inherent in bringing "pioneer" products to market.

Potential customer segments have different expectations

Technical characteristics, advantages, and disadvantages of the approaches under development vary from species to species (see Section 4), the "ideal" product differs among end-user segments (i.e., customer groups), and there are also considerations that don't relate strictly to product attributes.

For example, a contraceptive technology that produces permanent sterilization in male dogs will work on a pet dog as well as a stray dog. But some of the needs of the shelter community and low-cost spay/neuter clinic are different from those of a veterinarian with some percentage of clients who want permanent sterilization for their male dogs – the shelter needs to desex animals quickly and economically before adoption or release; the veterinarian needs a certain margin to cover overhead and make a profit. Consequently, cost is an issue that could serve as a basis for mutually beneficial realignment among stakeholders.

For instance, the foundations, organizations, and agencies that have supported research by zoos and academic institutions could reallocate some of their resources to underwriting the costs of the products used in shelter and spay/neuter settings once products are approved for commercial use. Shelter and spay/neuter groups might unite in buying groups that could bring volume business to companies that have products to sell. Insurance companies in the US, which pay customers more than $1 billion a year in claims related to deer-vehicle collisions, could work with groups implementing population-control strategies for suburban wildlife. Joint ventures, partnerships, or "consortium companies" could be formed to take on different aspects of the development, commercialization, and marketing process – an approach that is already in use in the human health arena.

Of course the opportunities for realignment and alliances will depend on who brings what products to market and in what order, but these types of models may evolve to serve important but traditionally "non-profit" segments such as wildlife and stray, abandoned, and feral cats and dogs.

5.1 Dogs and Cats

Nonsurgical contraception of dogs and cats is regarded as a market with significant potential due to the sheer numbers of animals worldwide, the percentage of animals that are not spayed or neutered, the fact that pet owners spend an increasing amount of money on their animals, and the progress of ongoing research and development efforts to create products that offer nonsurgical approaches for pets and stray or feral animals.

There are plenty of pet dogs and cats in many nations (see Sidebar: Pet Stats: Ownership of

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Companion Animals, page 42). Often, pets are considered family members – spending on pets is significant and growing in many parts of the world.

For example:

- Pet-owning households in the US are expected to spend a total of ~$30 billion on their pets in 2002 – $1 billion more than in 2001. Dog owners will spend approximately $864 per dog and cat owners will spend $644 for each cat. The greatest expense will be for veterinary care, followed by food and pet supplies. Grooming, crates, cages, treats, and pet-owner educational materials round out the major categories of spending. The majority of pet owners purchased a gift for a pet in the 12 months prior to the study. (www.starnewspapers.com/star/spbiz/all/281bz2.htm, http://www.appma.org/press/fact_sheets/fact_sheet_03.asp)
- Australian pet owners spend AU$3.3 billion on their pets. Forty-nine percent is spent on pet food, 21% on veterinary care, 7% on pet care products and equipment, and 14% on nonveterinary pet services. Australians spend a yearly average of AU$542 per pet dog and AU$333 per pet cat (www.petnet.com.au).
- In 1998-1999, Brazilians spent $1.5 billion on their pets and Germans spent $5.3 billion (www.ufacusa.com).

In addition, there is evidence that significant numbers of veterinarians who already spay and neuter dogs and cats in North America, Australia, and major markets in Europe would be willing to use a nonsurgical approach, assuming that products are safe, humane, effective, profitable, and less intrusive than surgery.

As noted earlier in this report, researchers have indeed been working in this area for 30 years, and animal health companies have investigated the market periodically (see Section 6). But the fact that, for example, there are no immunocontraceptives available yet for male and female dogs and cats in spite of the number of approved products for humans (e.g., GnRH agonists) indicates that it

is difficult to develop such products (see Section 3 for technical issues and Section 8 for regulatory issues). Marketing these products can be expected to present challenges too, from characterizing "the market" to defining the "ideal" products for major segments (i.e., permanent and nonpermanent products for male and female cats and dogs) and positioning and pricing them properly with the target customer groups.

Let's look at the potential customer groups for contraception and fertility control products in dogs and cats: pet owners (5.1.1); shelter, humane, rescue, and advocacy groups (5.1.2); reputable breeders and show animal owners (5.1.3); and veterinarians (5.1.4).

5.1.1 Pet dog and cat owners

5.1.1.1 How do pet owners feel about controlling reproduction in dogs and cats?

At this point, the primary method of preventing conception in dogs and cats in the US is surgical spaying or neutering (see the Glossary, Appendix 2). Cultural differences influence pet owners' willingness to contracept their dogs and cats surgically. Presumably a certain percentage of pet owners who are willing to spay and neuter their animals will choose nonsurgical alternatives once they are available.

The reasons some pet owners do not sterilize their pets provide insight into:

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- The potential for nonsurgical approaches to be embraced by people whose animals would otherwise remain intact
- The nature and complexity of the marketplace segmentation and education that veterinarians, advocacy organizations, and companies ultimately marketing these products will have to do

5.1.1.2 Dynamics of the Spay/Neuter Decision

A survey of pet owners in the US by the National Council on Pet Population Study and Policy (NCPPSP) (www.petpopulation.org) indicates that 40% of owned dogs and 23% of owned cats have not been spayed or neutered.

Numbers from the Purina Pet Institute (www.purina.com) tell us that although 56% of dog owners and 63% of cat owners rank "reducing the pet overpopulation problem" as the number one pet ownership issue, 34% of dog owners and 15% of cat owners have not had their animals spayed or neutered – in spite of public service announcements, campaigns by humane organizations, pleas from celebrity spokespeople, low-cost spay and neuter services, voucher programs, and checkout-line coin canisters featuring photos of abandoned puppies and kittens.

Furthermore, 20% of owners spayed or neutered their pets only after their animals had produced at least one litter. (www.thepetpress.la.com/articles/earlyage.htm)

Using the percentages of intact pet dogs and cats from the Purina Pet Institute and NCPPSP surveys, we can estimate the number of non-neutered/nonspayed pet dogs in the US alone is between 20 million and 24 million; the number of intact pet cats is between 11 million and 16 million – significant numbers in the eyes of any business development or marketing manager.

But these same managers will wonder why these animals haven't been spayed or neutered, and what the chances are that alternatives to surgery would encourage owners to embrace contraception and fertility control for their pets.

In the US, pet owners who haven't spayed or neutered dogs and cats cite the following reasons:

- Just haven't done it yet
- Want to breed the pet(s) some day
- Pet(s) is/are too young
- Procedure is cruel
- Can't afford it
- It's not natural

So the questions are: would they accept a nonsurgical alternative and why or why not?

Justification for Inaction	Dog Owners	Cat Owners	Would they accept a nonsurgical alternative?
Just haven't had it done yet	30%	27%	**Depends on the real reason(s)**. These owners might: • view spaying or neutering as too inconvenient and time consuming • dislike the idea of major surgery even though they don't consider it cruel • believe that their animals should produce one litter before they're sterilized Veterinarians and companies with reproduction control products need to understand the dynamics of the disconnect in those pet owners who say controlling overpopulation is important yet don't alter their pets. The availability of effective, safe alternatives to surgical spaying and neutering can be expected to appeal to pet owners who are uncomfortable with surgery or believe it's too inconvenient or cruel, but such products will not counter the "one litter" myth. Once products are available, companies, veterinarians, and advocacy groups that want to target the "one litter" consumer group will collaborate to educate owners who are holding off until their pets have a litter – such litters are the source of an estimated 400,000 relinquished puppies in the US each year, which account for 10% of the dogs that enter the shelter system (www.naiaonline.org).
Want to breed the animal(s) some day	21%	5%	**Yes.** Dogs and cats whose owners wish to breed them eventually are good candidates for nonpermanent ("reversible") contraceptive products that eliminate undesirable mating-related behavior but permit a return to fertility and normal mating behavior at some time in the future. Such an approach can be expected to appeal to owners of show dogs, who understandably do not want to have to deal with sexually-related behaviors during competitions. To be commercially viable, such products will have to cause no harmful effects on the treated female or on subsequent litters. Issues related to use of a given product on a breeding animal will have to be addressed, including: • no effect on future fertility (sperm count, estrus cycle, and ability to become pregnant) • no effect on offspring • the need for pre-treatment pregnancy-status determination by blood test or ultrasound • effects on pregnancy if the product is used in a pregnant animal
Animal(s) too young	13%	20%	**Yes.** However, for companies that will be marketing products shown to be safe for use in young dogs and cats, the marketing challenge will be fourfold: • teaching owners that animals younger than six months of age can be treated without ill effects • educating owners about the benefits of nonsurgical approaches • demonstrating that the long-term health benefits of surgical sterilization also apply to nonsurgical approaches • gaining the confidence of veterinarians who have not begun to alter dogs and cats younger than ~6 months of age[1]

[1] Although the American Veterinary Medical Association endorsed early spaying or neutering "as a feasible solution to decreasing pet overpopulation and the tragedy of resulting deaths" in 1993, private small animal veterinarians have not universally adopted the practice. Beginning in the late 1980s, systematic studies as well as in-practice experience have shown that "initial concerns regarding the health, development and safety of the patient have been shown to be groundless" (Mackie 2002). This can be expected to be true of nonsurgical methods of contraception and fertility control approved for use in young animals as well, although this will have to be confirmed with clinical research.

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Justification for Inaction	Dog Owners	Cat Owners	Would they accept a nonsurgical alternative?
Procedure is cruel	5%	5%	**Maybe**, if the pet owner views the actual surgical procedure, rather than the outcome, as what is "cruel."
Can't afford	5%	18%	**Maybe**, especially if the reluctance reflects a combination of affordability and concerns about surgery, rather than a simple unwillingness to spend money on the pet. Some pet owners for whom the charge for a spay or neuter in a veterinarian's office would be too high may be better able to afford a less expensive, but recurring charge – for instance, for annual boosters. They may also be concerned about the quality of surgical procedures done in low-cost clinics or shelters, so they choose to leave the pet sexually intact. In fact, there is a wide range of spay/neuter options and pricing available for pet owners from free or low-cost clinics and shelters as well as private veterinarians. (See Sidebar: A Sample of Spay/Neuter Costs, page 43.) When the cost of surgery is divided by the average life span of a pet dog or cat, the per year expense is negligible. Pet owners who don't spay or neuter their animals due to expense may not have thought about the potential costs of that decision – for example, the costs of repairing property damage caused when a male dog digs his way out of the yard to pursue a female in heat; injures or is injured by a competing male dog, necessitating veterinary care; or gets picked up by the local "dog catcher" and impounded; or the costs of female animals damaging furniture or carpeting when in heat (http://www.spcala.com/). While companies marketing contraception and fertility control products should be aware of the price/value concerns of pet owners, it may be difficult to capture those pet owners who have not taken advantage of free or low cost surgical spaying or neutering programs that, in some cases, even include other important health services.
Not "natural"	3%	7%	**Depends** on what "not natural" means to individual owners. Is it the cessation of sexual function and/or sexual behaviors, is it the changed appearance in males, or is it a presumption that animals should be left "as nature intended?" • *Sexual function*: if it is important that the pet has the potential to reproduce, the owner could consider products that are non-permanent • *Sexual behaviors*: if it is important that the pet behave "naturally," the owner could consider an approach that prevents reproduction but does not alter behavior • *Appearance of male dogs and cats*: there is a product called Neuticles, which are testicular implants that can be used to preserve the appearance of male cats and dogs that have been surgically castrated; nonsurgical alternatives should, in some cases, shrink the testes but they would still be present • "*nature no matter what*." for pet owners who are unwilling to consider any type of reproduction control for their pets, responsible pet ownership and management of reproduction and sexually related behaviors are the only options if litters are to be avoided

statistics: Purina Pet Institute (www.purina.com)

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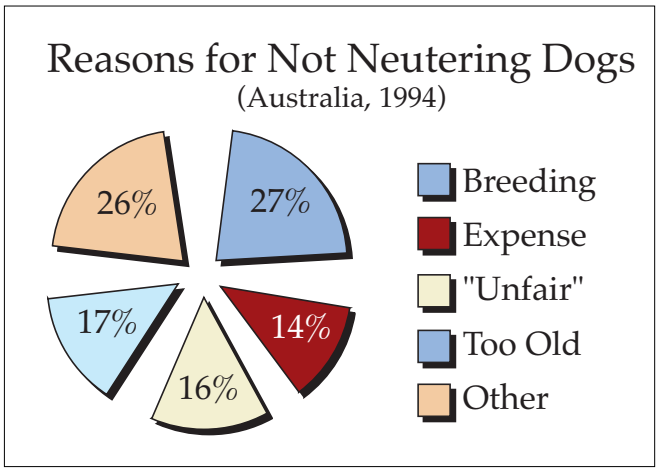
In Europe, spaying and neutering is much less common than in the US, and in fact it is rare (and illegal) in the Scandinavian countries and in Germany, where pets are typically left intact and the emphasis is on responsible pet ownership and managing the reproductive behaviors of pets. In the remainder of northern Europe, the spay/neuter rate among pets is about 50% though it varies in individual countries. In the UK, the spay/neuter rate is approximately 50%. In spite of a relatively common disposition among European pet owners against surgical sterilization of their pets, younger veterinarians are performing spays and neutering and can be expected to do so as long as the procedures are profitable. (Jochle, personal communication) In Latin America, surgical sterilization, particularly of male dogs, is generally not viewed favorably by pet owners.

A 1994 survey indicated that 75% of domestic cats and just over 50% of domestic dogs in Australia were "neutered" (these numbers include spays). The reason cat owners cited most often (46%) for not neutering was that it was too expensive.

The top reason dogs had not been neutered was that owners intended to breed them (27%). Others included expense, perceived "unfairness" to the animal, and a belief that the animal was too old (www.abs.gov.au).



5.1.1.3 Is there an ideal product?

Surgical sterilization will continue to be preferred by pet owners who want one-time, close-to-100% effectiveness against reproductive activity and sexual behaviors and prefer not to immunize or implant their animals.

There is no single product concept among the technologies currently at various stages of development that will capture the market among remaining cat and/or dog owners who wish to control reproduction in their pets.

However, the eventual availability of several alternatives to surgical intervention can be expected to appeal to both major groups of dog and cat owners: those who would opt for surgery if it were the only option available, and those who would do nothing if surgery were the only option available. Therefore, companies that will market these products will be courting customers who are simply going to switch the method by which they control reproduction in their pets as well as customers who would not contracept their pets surgically.

An "ideal" product would require a single administration that would not be traumatic for the animal and would be effective for a predictable amount of time. It would suppress unwanted behavior and be safe for animals and the humans who administer it, as well as for any litters that are born after the effects of the product on the adult animal "wear off." There would be a simple in-office test the veterinarian could administer to verify an individual animal's response and assess the need for re-treatment after a certain period of time.

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What types of issues could affect the "ideal" product characteristics for different types of pet owners?

- Permanent versus nonpermanent ("reversible")
  - Permanent: Pet owners who do not wish to breed their animals.
  - Nonpermanent: Pet owners who plan to breed their animals, show animal owners, responsible breeders – these potential customers will be concerned about how long it will take for products to work and then wear off.
- Contraception/fertility control with or without sexual behaviors
  - For many pet owners, one of the reasons for using contraception or fertility control for their pets is to eliminate unwanted sexual behaviors.
  - Some pet owners may wish to avoid unwanted litters, yet feel that it is inappropriate to interfere with an animal's natural behaviors.
- Implant versus injection
  - Injection: Injections can cause transient pain to the animal, though it can be mitigated by the location of the "shot." Recent reports of vaccine-associated fibrosarcoma may have made cat owners more aware of the potential for problems at the injection site. Ideally, marketed products will be based on formulation technology that will minimize injection pain and injection site reactions. For immunocontraceptives, the number of boosters required to initiate immunity and the number of boosters thereafter may affect acceptance.
  - Implant: Implants have the same potential for transient pain as injections. In addition, owners may find it unacceptable to feel an implant beneath the skin when they pet their dog or cat, so a rigid or large implant would likely be unacceptable. However, should "soft" implants be developed and approved, they may be more difficult to feel, and therefore, more acceptable. Should an owner wish a soft implant removed, for instance, to restore fertility prior to breeding, the implant may be located via ultrasonography.
- Dogs versus cats
  - Variation in cultural attitudes towards dogs and cats may influence the ultimate product mix. Some cultures "value" one species more than the other, and expenditures not only by owners but also by animal health companies may reflect that. Owners may demonstrate more resistance to contraceptive technologies for male dogs than for tomcats, as is the pattern in some parts of the world when it comes to surgical castration.
  - Physiological differences between dogs and cats may affect the relative viability of a given technology. For instance, cats appear to be more sensitive to adjuvants present in certain injectable products.
  - Overall, less research on these technologies has been undertaken in cats than in dogs, so it is unclear whether the technologies that appear most promising in dogs will be applicable to cats as well.

(See Section 5.1.5.1: Issues that affect marketing of contraception and fertility control for dogs and cats, and Section 5.1.5.2: Issues and benefits for dogs and cats by technology, to understand the tradeoffs that are likely to occur as products are developed for the pet owner market.)

Despite the difficulty posed by the variability in pet owner preferences, the fact that more than one approach to contraception and fertility control in dogs and cats is being developed may mean that ultimately, overall rates of contraception in pets will increase, animal health in general will improve, and, hopefully, there will be fewer unwanted, stray, relinquished, and abandoned animals.

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Pet Stats: Ownership of Companion Animals

Please note that much of the information presented in this sidebar is from web sites and some is undated. Therefore, it would be advisable to verify these figures via additional sources if they are to be used for planning purposes.

United States

It has been estimated that currently there are more than 60 million pet dogs and 71 million pet cats in the US, compared to 54 million pet dogs and 44 million pet cats in 1981. By the early 1990s, the number of pet cats was more than 62 million, surpassing the number of dogs, which remained stable.

As of 2001, households with at least one cat or dog outnumbered households without a cat or dog, 55% to 45%. Sixteen percent of households owned at least one cat and one dog, and most cat-owning households had two cats. Fifty-nine percent of pet owners celebrate their pets' birthdays; 83% of pet owners refer to themselves at their pets' "mom" or "dad," 90% would not date a person who doesn't like their pets, and 36% have named a guardian for their pets.

Europe, the Pacific, and South America

There are 47 million cats and 41 million dogs living in European households.

Area	Dogs (million)	Cats (million)	Comments
UK	6.1	7.5	Dog ownership has been declining, while cat ownership is increasing. Forty-five percent of households in the UK own some type of pet. Among dog-owning households, 79% have one dog; the rest have two or more. Among cat-owning households, 62% have a single cat and the rest have two or more. More people between ages 35 and 44 are cat owners while more people between 45 and 54 are dog owners. The bulk of owned dogs are medium (26%) and large (44%) sized. Small dogs (21%), toy dogs (6%), and giant dogs (4%) round out the population. Dog ownership is higher in urban locations. Approximately 59% of pet dogs are purebreds.
France	8.1 – 8.4	8.7 – 9.0	There is at least one pet cat or dog in > 50% of households. Forty-one percent of dogs and 37% of cats live in rural households; 30% of dogs and 28% of cats live in cities and towns with fewer than 100,000 residents; and 29% of dogs and 35% of cats live in cities of 100,000+ people. About 53% of families that own companion animals have one dog or cat; 45% have a dog and a cat. The majority of people who own a dog and/or cat say they acquired the animal(s) because they love animals, they like the companionship, and/or they want the pets for their children.
Germany	5.0	6.8	The number of dogs is declining while the number of cats increases. There is at least one pet in approximately 40% of German households. Dog and cat owners in Germany spent $5.3 billion on their pets in 1998-1999.
Spain	3.3	2.5	
Australia	4.0	3.0	Australia boasts the largest percentage of pet ownership in the world, with pets in 66% of households. Three million of those pets are cats; 4 million are dogs. A survey of the health status of pet-owning humans versus non-pet-owning humans in Australia estimated that the presence of a dog or cat saved AU$2.2 billion dollars in health care expenditures in 1994-1995.
Japan	10.0	7.5	Pet ownership rose 50% between 1990 and 2000 and 5% between 1999 and 2000. Approximately 37% of the people own at least one pet – ~18% of households have a dog; ~12% have a cat.
Brazil	23.0	10.0	Dog and cat owners in Brazil spent $1.5 billion on their pets in 1998-1999.

Sources: Pet Food Institute (www.petfoodinstitute.org), Pet Food Manufacturers' Association (www.pfma.com), European Pet Food Industry Association (www.fediaf.org), www.facco.fr, www.petnet.com.au, www.dogsncats.asn.au, www.feralcat.com, www.ahi.org, http://members.iinet.net.au, American Animal Hospital Association 2001 Pet Owner Survey, www.vetevents.com/acac, Petfood Industry 6/01 Electronic Newsletter, www.ufacusa.com

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A Sample of Spay/Neuter Costs

Please note that much of this information comes from organization websites, and that some of it is undated. Therefore, it would be advisable to verify these figures via additional sources if they are to be used for planning purposes.

Species	Procedure	Country	Cost
Cat	Neuter	France	equivalent of $200
Cat	Spay	US (midwest)	$80
Dog	Spay	Japan	¥20,000 to ¥30,000
Dog	Neuter	Japan	¥15,000 to ¥20,000
Dog <100 lbs	Spay	US	$150
Dog	Neuter	US (affluent community)	$250
Large dog	Spay	UK	£80-£145

Sources include: messybeast.com, news.bbc.co.uk, ARKBARK, canismajor.com, Polley 2002, and northstarnet.org.

Examples of subsidized or low cost spay/neuter services in the US

In many places around the world, subsidized or low-cost spay and neuter services are available.

Area	Program
Dallas, TX	Cat owners could have their male cats neutered at the local Humane Society clinic for a mere 5 cents as part of a February 2002 promotion.
Broward, Miami-Dade, and Palm Beach counties, FL	Cats are spayed for $35 or neutered for $25 and dogs spayed for $39 - $89 or neutered for $39 - $64 courtesy of the Pet Aid League.
Putnam County, FL	$65 buys a spay or neuter, vaccinations, heartworm test, and microchip* for a dog, and a spay or neuter, vaccinations, feline leukemia test, and microchip for a cat.
Mariposa, CA	An SPCA program requires a $10 co-pay for spaying or neutering by a veterinarian chosen by the owner.
Lincoln County, OR	The Animal Control Division of the sheriff's office offers impounded animals for adoption. Unaltered dogs cost $65, including a veterinary checkup, a distemper/parvo vaccine, a puppy tag or dog license, and a $45 voucher for spaying or neutering; unaltered cats cost $40, including a veterinary checkup, a distemper vaccine, and a $25 voucher for spaying or neutering.

*used for identification

5.1.2 Shelter, humane, rescue, and advocacy groups

Please note that for the sake of convenience, we're using the term "shelter community" to include the above-named types of organizations. Note also that the issue of hoarders[2] is outside the scope of this report.

The groups that deal with "unwanted" animals are diverse, and their needs are diverse, but all are involved in dealing with issues presented by the presence of abandoned, stray, free-roaming, and feral animals. There is long-standing global debate about how many dogs and cats make up these populations, how many "adoptable" and "unadoptable" animals are euthanized each year, what can and should be done about it, and the degree to which contraception and fertility control can influence the overall dynamics of what is typically called "overpopulation."

[2] Hoarding is the "pathological collecting" of animals, most frequently cats, dogs, farm animals, and birds. (Patronek 1999).

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There is general agreement, however, that the number of animals is large – in many instances larger than the population of dogs and cats counted as pets – and that many adoptable animals are euthanized. Furthermore, many of these animals are sexually intact.

While in some parts of the world, poisoning and/or shooting stray and feral cats and dogs are accepted practices, groups in many countries attempt to deal with issues of population control, abandonment, and relinquishment of cats and dogs in ways that are regarded as more humane. As part of this effort, research into contraception and fertility control for animals has been conducted at a number of academic institutions (see Section 7) and funding for developing nonsurgical approaches to contraception and fertility control in animals has come from sources such as foundations, government agencies, humane organizations, philanthropists, and in some cases, animal health companies. As noted, large animal health companies have not pursued contraception and fertility control in animals aggressively in the past (see Section 6).

The market served by the shelter community is complex for a number of reasons. Any company, large or small, established or new, that contemplates marketing products for use in shelter-type situations will want to be aware of some of the forces and ongoing debates that influence how shelter, humane, rescue, and advocacy groups view contraception and fertility control for dogs and cats.

Factors influencing the development, adoption, and use of animal health products by the shelter community include:

- Ascertaining what reproduction control technologies best fit the needs of shelter and feral animals
- Cultural, philosophical, and resource issues
- The potential for commercializing, manufacturing, and marketing products profitably for a market segment in which "low cost" has always been assumed to be a requirement

5.1.2.1 How many cats and dogs pass through the shelter system, where do they come from, and what happens to them?

The World Health Organization has developed four categories to characterize dog populations (cited on www.jeevashram.org/ecollage.html):

- *Restricted/supervised*: pets; dogs that are dependent on owners who keep them under supervision
- *Family dogs*: dependent on owners, who restrict them only partially
- *Neighborhood or community dogs*: partially dependent on people; movement unrestricted
- *Feral dogs*: independent or dependent on human-generated waste and garbage; movement unrestricted

The Humane Society-US (HSUS) includes the following cats in its "free-roaming" category:

- Owned cats that are allowed to roam
- Owned cats that have become lost
- Previously owned cats that have been abandoned
- Quasi-owned cats that roam freely and are fed by residents
- So-called working cats that serve as mousers

HSUS notes that feral cats are unsocialized animals "who may be one or more generations removed from a home environment and who may

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subsist in a colony of similar cats," and that it can be difficult to differentiate between free-roaming and feral cats (www.hsus.org).

The popular and professional literature is ripe with statistics and although there is some degree of disparity among them, it is agreed that shelter and "street" or "feral" populations consist of owned animals that have been at large, previously owned animals, free-roaming animals that are fed by humans, "unsocialized" animals that receive some support (e.g., food and even medical care) from humans, and "unsocialized" animals that haven't had homes or support from people (see Sidebars: Who Winds Up in Shelters – and Who Gets Out, pages 49 and 50 and A State Looks at Its Dog Population, page 51).

The ability of non-neutered/unspayed free-roaming (or owned) dogs and cats to produce large numbers of puppies and kittens is impressive:

- Female cats produce 5.7 kittens/year that survive to adulthood; a pair of breeding cats can be responsible for > 420,000 offspring in a 7 year period (www.feralcat.com); in nine years, a female cat, her mate and all of their offspring, producing 2 litters/year with 2.8 surviving kittens/litter, can produce more than 11 million offspring in 9 years (www.spayusa.org)
- A female dog, her mate, their puppies, and their puppies' puppies can produce 67,000 dogs in 6 years (www.spayusa.org)

- A cat or dog that has a litter that then has a litter can be responsible for 50 – 200 kittens or puppies in a year (www.goodnewsforpets.com)

It has been estimated that as many as 60% of non-neutered pet cats become feral within three years (www.feralcat.com). A survey by the American Pet Products Manufacturers Association indicates that 40% of pet dogs and 29% of pet cats are outside at least part of the time, providing those that are intact with plenty of opportunity to mate and produce unwanted litters (New 2002).

Estimates of the number of abandoned, stray, or feral cats in the US vary. Feralcat.com estimates that there are 60 – 100 million; Alley Cat Allies estimates the number at between 30 and 60 million; and Centonze and Levy estimate that stray and feral cats account for 35% to 45% of the entire known cat population (Centonze 2002). Here are some numbers from around the world:

- There are an estimated 1 million abandoned, stray, or feral cats in the UK (www.feralcat.com); 400,000 in New Orleans, Louisiana, US (Mechler 2002), and 12 million feral cats in Australia, 400,000 of which are in New South Wales (www.npws.nsw.gov.au).
- Free-roaming cats produce 70% of the kittens brought into US households (www.saveourstrays.com) from various sources.
- 5% of pet dogs in the US are taken in as strays; 24% of pet cats are taken in as strays (www.purina.com).
- There are an estimated 50,000 street dogs in Sofia, Bulgaria; and, until half of them were reported killed recently, 200,000 in Bucharest, Romania (Mechler 2002).
- In Tokyo, the number of stray dogs decreased from 529,000 in 1975 to 134,000 in 1999 and the number of stray cats increased from 68,000 to 276,000 (www.snips.8m.com).

Although less humane methods are also employed, many communities and organizations deal with free-roaming cats in one of four ways (definitions from Slater 2002):

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- *Trap, remove, euthanize* – This is regarded as a short-term approach unless the sources of food and shelter that attracted the cats in the first place are removed. Otherwise, any cats that avoid the process remain in the area and continue to reproduce and the trap-remove-euthanize cycle can continue.
- *Trap, remove, and relocate to another colony or a sanctuary* – This is a difficult process because suitable locations must be found and obtained and the stress of relocation can compromise the health of the cats. In some cases, cats can be socialized and adopted, but the socialization process is time consuming.
- *Trap, neuter, and return/release* (TNR) – This alternative requires the assistance of veterinarians, who surgically sterilize the cats and notch or tip the ear for identification purposes, as well as caretakers, who feed and monitor the colony on an ongoing basis. Monitoring is necessary to identify any new cats moving into the colony. At its most comprehensive, this strategy is extended to TTVARM, which stands for Trap, Test, Vaccinate, Alter, Release, Maintain, and is geared toward stabilizing and managing feral/unowned cat colonies to help reduce unwanted reproduction and control disease (Cat Fanciers Association, www.cfain.org).
- *"Wait and see"* – This strategy, which typically occurs by default, can result in expenditures on the part of local agencies and governments to gather, transport, and euthanize the animals.

What might all these facts and figures mean?

Reproduction control isn't the only important factor

In spite of the availability of surgical sterilization, a survey showed that "sexually intact" dogs and cats were two to three times more likely to be relinquished by owners in the US than dogs and cats that had been spayed or neutered (New 2002). Another source indicates that 55% of surrendered dogs and 47% of surrendered cats are intact (www.ohlonehumanesociety.org). Although these statistics focus on the US, it is likely that owner failure to neuter pets that are unsupervised at least part of the time is an important contributing factor to shelter populations in general.

The bond between pets and owners can be fragile, and that contributes to shelter populations

Profiles of the dogs and cats relinquished at shelters in the US indicate that 47% of surrendered dogs and 40% of cats are five months – three years old. Thirty percent of relinquished dogs are purebred (www.ohlonehumanesociety.org). Thirty-seven percent of surrendered dogs and 30% of surrendered cats were owned between seven months and one year, and 96% of surrendered dogs had never had obedience training (www.karyngarvin.com). The age range of these animals could be an indication that many pet owners simply don't know enough about expected behaviors, including sexually related behaviors, when they acquire an animal, and the lack of training may indicate that owners haven't invested emotionally in their pets.

5.1.2.2 Organizations dealing with unwanted animals play different roles

There are groups all over the world dealing with unwanted dogs and cats. Some are affiliated, some unaffiliated; some specialize in species or breeds, some deal with "adoptable" animals only, and some with a wide variety of animals; some are bare-bones operations in areas in which community and government support is thin and others are fairly well-supported models for increasing spaying and neutering and adoption rates.

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Philosophies and funding levels differ. Organizations deal with a variety of relinquisher demographics, and the size and composition of unwanted cat and dog populations vary. Furthermore, the tools at a given organization's disposal differ.

According to the Humane Society of the United States, "the relationships among many organizations have been in danger of coming to a standstill" because of the "ongoing and highly visible debates about the words we use to define ourselves." (Lawson 2002).

What many involved in these debates haven't realized, according to the HSUS, is that "if we can reach a point where all organizations, regardless of their labels, are on the same page when it comes to professional standards of animal care, responsible adoption processes, financial and moral support from their communities and local government, and proactive prevention programs that seek to keep pets in homes, we will not have to argue anymore about how to reach our utopia. We will have arrived" (Lawson 2002).

(See Appendix 3 for websites that provide more information on the issues facing these organizations.)

A detailed review of the ways in which shelter systems deal with the dogs and cats in their care is beyond the scope of this report (see Lawson 2002 for more information), but it is important to note that cultural, public health, and economic factors influence many of the issues related to dealing with unwanted cats and dogs. Therefore, a company considering marketing a contraception or fertility control product for use in what may be called the "shelter" market must identify and consider these factors, as well as alliance opportunities, early in the planning process.

Alliances are becoming part of the mix in the shelter community as the various types of organizations realize that cooperation is critical to dealing with issues of unwanted cats and dogs.

As a result, some of the "puzzle pieces" are coming together, and the shelter community has formed a variety of mutually beneficial partnerships. For example, an animal control agency may send "adoptable" animals to the local shelter, while shelter personnel send animals who are too ill or aggressive for adoption to the animal control agency – this reduces the potential for unnecessary euthanasia of animals in the custody of the animal control agency and helps optimize the resources of the shelter, which seeks to find homes for adoptable animals.

5.1.2.3 Technologies useful for shelter and feral animals

Although sterilization as a condition for adopting dogs and cats is not universal, surgical spaying is encouraged in countries such as the US and UK. A number of US shelters "and virtually all rescue groups sterilize dogs before making them available to buyers, and many shelters that do not do the surgery before the animals leave do require that the new owner do so. Some advocacy groups . . . demand laws that require spay and neuter of all dogs and cats unless people buy permission to keep their animals intact. Others seek to require shelters to spay and neuter all animals that leave their premises to avoid unwanted litters in the future" (www.canismajor.com). In California in the US, neuter-before-adoption (NBA) legislation enacted in 2000 requires that all animals adopted from shelters be sterilized (www.thepetpress-la.com/articles/earlyage.htm), and such requirements exist in at least 21 states (Slater 2002).

Issues related to surgery are similar for pets with owners and shelter animals: neutering and spaying are surgical procedures and therefore can

be risky, time consuming, costly, and labor intensive (see Section 4.1.1). However, while pet owners may want to preserve the possibility of breeding their pets in the future, shelters may put a higher premium on permanent sterilization. Therefore, effective nonsurgical methods of permanent sterilization that eliminate unwanted mating-related behaviors, offer the same long-term health benefits of surgical sterilization, are affordable, do not require recapturing animals for re-treatment, and are close to 100% effective could be attractive to this segment (see Section 5.1.5.1).

Nonsurgical sterilization may be acceptable in some countries and to animal welfare groups that oppose surgical procedures on the grounds that the procedures are "mutilation." In European countries, pharmacological approaches to population control have focused on the use of oral and injectable progesterone-type drugs in female dogs and cats because "surgical intervention . . . is often regarded by owners as inhumane and degrading to a companion animal" (Jochle 1994). Currently used progesterone-type drugs are less desirable for shelter situations because they require careful monitoring over time of the estrus cycle of the bitch or queen to be effective, and are not effective in males.

In locations in which trap-neuter-release and similar programs are in use, only a permanent nonsurgical method of sterilization described above would be useful, as it would be unlikely that animals could be recaptured periodically for repeat treatments. Animals returned to feral colonies should be vaccinated against rabies and, if possible, identified in some way to prevent their recapture and re-treatment. Some programs use ear notching for this purpose. In fact, effects of accidental re-treatment would have to be understood and addressed to the satisfaction of regulatory agencies before a product could be labeled for use on feral animals and before organizations with TNR and similar strategies would actually use it.

While some organizations indicate that the ability of lay people to administer a product in the field would be a factor affecting the use of a potential product (Mechler 2002), regulatory, human safety, and liability issues can be expected to restrict use to veterinarians. Furthermore, the desire to limit the need to capture and handle feral animals may make oral (bait-based) vaccines high on some organizations' wish lists (Mechler 2002), but again, regulatory, human safety, and liability issues can be expected to restrict this in certain major markets, including the US and Europe.

5.1.2.4 Cultural, philosophical, and resource issues

These issues include, but are not limited to:

- Availability of funding
- Type of organization
- Nature and additional needs of the dog and cat populations (e.g., rabies control, vaccinations)
- Location (e.g., rural, suburban, urban; local economics)
- Degree of community, governmental, and local veterinary participation and support
- Potential to collaborate with other organizations to provide a wider range of services
- Differentiating between intact animals and stray, abandoned, and feral animals that have already been sterilized

Some of the philosophical issues that have sparked controversy within the shelter community include:

- The so-called "no kill" controversy – some organizations define the concept as not euthanizing adoptable animals and others have defined "no kill" as not euthanizing any animal admitted to the facility. The issue of euthanizing or not euthanizing animals that are not good candidates for adoption due to illness or behavior is part of the "no kill" debate.
- The utility of TNR programs versus capture and euthanasia in dealing with populations of free-roaming and feral animals.
- The degree to which "overpopulation" continues to be a significant problem, particularly in dogs, in some parts of the US and the UK. In some instances, the shelter community is

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involved in "importing" animals from other facilities to satisfy the demand for young dogs.

- The degree to which the shelter community should focus more on preventing relinquishment and less on dealing with overpopulation.
- Whether or not people who obtain dogs from sources other than shelters or rescue groups are by default failing to decrease shelter/rescue populations.
- Opposition to surgical intervention *per se*, on the grounds that it is mutilation, isn't natural, or is performed merely for the convenience of humans.

5.1.2.5 Commercializing, manufacturing, and marketing products profitably

Can companies commercialize, manufacture, and market products profitably in a market segment in which "low cost" has always been assumed to be a requirement? Although this cannot be ruled out, it is likely that animal health companies will focus first on pet owners and the veterinary community that treats their cats and dogs. Animal health companies work hard to retain their veterinary customers, who would be dissatisfied with a pricing structure that enabled shelters to essentially compete with them for clients.

However, alliances among animal-related funding sources, the shelter community, and animal health companies could help create a structure in which the cost of contraception and fertility control could be subsidized – in fact, many existing "low-cost" spay and neuter programs are actually subsidized, which means the difference in what the shelter, pet owner, or prospective pet owner pays and the actual cost is made up in some way (Slater 2002). In addition, once several nonsurgical approaches are commercialized and approved for use, competition may bring pricing down. This would enable the shelter community to take advantage of affordable products that will then have a history of safe and effective use by the veterinary community behind them.

Who Winds Up in Shelters – and Who Gets Out?

Please note that much of the information presented in this sidebar is from websites and is undated. Therefore, it would be advisable to verify these figures via additional sources if they are to be used for planning purposes.

The issue of stray, abandoned, relinquished, and feral dogs and cats is not particular to any one country, culture, economic level, climate, or philosophical view of animals. With some exceptions, it is a global phenomenon to which significant resources are already devoted. Below is a sample of some of the statistics cited by various agencies and organizations. Please see Appendix 3 for websites with additional figures and information about approaches to this issue in a number of countries.

- The Humane Society of the US estimates that only 15% - 30% of dogs and 2% - 5% of cats entering US shelters each year are reclaimed by owners (www.hsus.org).
- In the UK, where identification methods such as tattoos and microchips are more commonly used than in the US, an estimated 51% of dogs picked up are returned to their owners (www.snips.8m.com), though it is feared that mandatory microchipping may encourage pet abandonment by owners who simply won't visit the vet for the chip (www.vetsonline.com/html/veterinary_news).
- In Japan, some pet owners view pets as "disposable;" a pet can be considered a status symbol for first-time home buyers and certain breeds are regarded as trendy – when the trend changes, people switch breeds, creating unwanted animals. There are very few shelters or means by which even animals with ID tags are returned to their owners (ARKBARK).

Dogs and Cats without Homes: A Worldwide Issue

	Who Winds Up in Shelters	Who Gets Out
Canada	SPCA* shelters in British Columbia had been euthanizing 18,000 animals each year, but half were euthanized because of a lack of space . . .	. . . so the 32 shelters put together a plan to "increase hours of operation, develop foster programs, subsidize spay/neuter surgeries, and implement a new system for … better analysis of temperament [that] will allow more appropriate, lasting placements."
Hong Kong	30,000 dogs and cats are euthanized annually.	2,000 (6%) are adopted. Hong Kong is implementing a spay/neuter, adoption, and education program that is expected to double the percentage of adoptions by the summer of 2003.
South Africa	The kennel operation of the Durban SPCA admitted about 4,800 cats and 5,800 dogs in the one-year period between May 2000 and April 2001 for a total of about 10,600. 76% were strays and 22% were relinquished.	• 1% of the cats and 14% of the dogs were reclaimed • 7% of the cats and 15% of the dogs were adopted • 93% of the cats and 67% of the dogs were euthanized
The Netherlands	In 1996, the number of stray cats admitted to The Netherlands' 110 shelters increased 25%, from 23,500 to 31,000, in five years . . .	. . . so the Dutch Society for the Protection of Animals started a four-pronged campaign: • encouraging spaying and neutering • subsidizing the procedures • trapping/neutering/releasing 3,000 feral cats and desexing 30,800 of the shelter cats • implementing an adoption campaign that resulted in homes for more than 5,000 cats
United Kingdom		The Cat Protection League rescues more than 70,000 stray cats each year and the RSPCA finds homes for around 80,000 animals.
United States	An estimated 8 million – 10 million cats and dogs enter shelters in the US each year. 47% of surrendered dogs in the US and 40% of surrendered cats are 5 months – 3 years old; 37% of surrendered dogs and 30% of surrendered cats are owned between 7 months and 1 year of age; 96% of surrendered dogs have never had obedience training.	Between three million and five million of the cats and dogs entering shelters are adopted. • 15% of pet dogs are obtained from shelters; 2% are obtained from rescue groups • 16% of pet cats in the US are obtained from shelters; 2% are obtained from rescue groups In Los Angeles, California, 60,000 animals are euthanized each year. In New York City, shelters euthanized 39,000 animals in 1999. 80% of domestic cats taken to shelters are euthanized in the US.

* Society for the Prevention of Cruelty to Animals

Sources: www.spcadbn.org/za, www.snips.8m.com, www.icawc.org, www.hsus.org, www.purina.com, www.vetsonline.com, www.rspca.org.uk, www.idausa.org, www.purina.com, www.feralcat.com, www.geocities.com/heartland/estates/8208/overpopulation.htm

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A State Looks at Its Dog Population

A 1997 report on a survey of county animal control agencies, humane societies, and municipal animal control divisions in the state of Ohio (US) indicated that 10% of the state's estimated 2.2 million dogs and 5% of its cats were in the hands of an animal control agency or humane society at some point during the year.

How many dogs entered the "shelter system?"

More than 214,000 dogs entered the "shelter system." About 66% (142,000) were strays, which was defined as unlicensed dogs roaming freely. Another 32% (69,000) were relinquished, and 1% (2,500) were cruelty or neglect cases.

What kinds of facilities did they go to?

County shelters admitted 61.3%, municipal facilities admitted 26.4%, and humane societies admitted 5.3%. About 7% (15,000) were transferred from one type of facility to another.

What happened to all of these dogs?

Sixty-one percent of the dogs were ultimately euthanized, 14% were reclaimed by owners, and 24% were adopted.

At the time of the survey, how were the agencies trying to deal with population control and identification issues among the dogs?

Six percent of the county shelters and 15% of the humane societies spayed or neutered all dogs prior to adoption. Sixty-five percent of the county-operated shelters and 42% of humane societies utilized certificates that could be redeemed at veterinary clinics. A combination of sterilization before adoption and certificates was also used.

- 39% of county shelters scanned incoming dogs for microchip identification; 3% implanted chips in dogs that were eventually adopted or claimed by owners
- 56% of humane societies scanned and 8% performed microchip implants
- 30% of dogs adopted from municipal animal shelters were spayed before leaving the facility; 50% of these shelters scanned for microchips

What role does veterinary care play?
Forty-one percent of the agencies said they had access to veterinary services.

What needs were identified by these organizations?

- Improved legislation: 63%
- Increased funding: 58%
- Facility improvements: 51%
- In-service education: 44%
- Public relations: 40%
- Veterinary services: 40%

Sources: www.acs.ohio-state-edu/osu/newsrel/archive/ and www.canismajor.com

5.1.3 Show animal owners and dog and cat breeders

Responsible commercial breeders, owner/breeders, and owners of show dogs who wish to control when their animals come into heat are likely to prefer a fertility control method that has a predictable duration but is not permanent. In addition, any contraception or fertility control product for female cats and dogs whose owners want to breed them at some time in the future will have to be shown to be free of negative effects on subsequent fertility, litter size, and quality, or on the long-term health and fertility of the offspring. Furthermore, products that do not also suppress sexual behaviors would not be appropriate for this market.

Currently some owners of show dogs use progesterone-type products to suppress the estrus cycles of animals that are likely to come into season at inconvenient times. Using progesterone-type drugs in dogs successfully requires close monitoring of the estrus cycle and is labor intensive. (See Section 4.1.5 for a discussion of progesterone-type drug use in dogs. Progesterone-type drugs as injections are also available for cats. See Section 4.2.3 for a discussion of progesterone-type drugs used in cats.)

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5.1.4 Veterinarians

Veterinarians are key to the commercial success of new animal health products – they have to embrace a product and use it in their practices, and they're on the front line in educating their clients about the characteristics and benefits. For a contraception/fertility control product to be attractive to veterinarians, it must be safe and effective, be relatively easy to use, and generate profits for the business.

Will clients be willing to pay for an innovative nonsurgical contraceptive or fertility control product? In the US, there are relatively recent, reliable data that show that dog and cat owners are willing to take their animals to the veterinarian and pay reasonable costs for treatment.

An American Veterinary Medical Association survey (AVMA Center for Information Management 1997) indicates that in 1996:

- Dog owners in the US spent an average of $74 per vet visit and an average of $129 per dog on veterinary care
- Cat owners in the US spent an average of $67 per vet visit and an average of $81 per cat on veterinary care
- 89% of dog-owning households visited a vet in the previous two years
- 73% of cat-owning households visited a vet in the previous two years
- 23.4% of dog-owning households reported spending between $200 and $499 and 21.5% spent between $100 and $199 on veterinary services in 1996
- 18% of cat-owning households reported spending between $50 and $99 and 17% spent between $100 and $199 dollars on veterinary services in 1996

Further, the survey report estimated that:

- Total expenditures on veterinary services for dogs in the US in 1996 were ~$7 billion
- Total expenditures on veterinary services for cats in the US in 1996 were ~$4 billion

Even 37% of caretakers of feral animals, as previously noted, are willing to pay for veterinary services, including sterilization (Centonze 2002).

Additional information on pet owner expenditures for spaying and neutering in various markets can be found in the Sidebar entitled A Sample of Spay/Neuter Costs, page 43.

The AVMA survey also indicated that in 1996, 7.6% of the most recent veterinary visits by US dog owners and their dogs were to have the dog spayed or neutered, down from 8.4% in a 1991 survey. Among cat owners, 14% of the most recent visits to the vet were to get the cat spayed or neutered, down from 19.6% in 1991. During the same time frame, the percentage of visits for flea and/or tick control increased from 13.5% to 16.7% for dogs and 9.5% to 12.4% for cats.

While there is a belief among some that vets in the US don't want to "give up" the surgical spay/neuter because the procedure brings animals and their owners to the clinic, anecdotal information and the AVMA survey indicate that the ongo-

ing issue of flea and tick control is bringing dog and cat owners to the practice or clinic on a regular basis and therefore may be replacing the spay/neuter as the service around which veterinarians can build their practices.

Veterinarians can also enhance the level of services they provide by playing a role in educating new pet owners about what to expect in terms of dog and cat behaviors and strengthening the human-animal bond, thereby contributing to a decrease in relinquishment and abandonment rates. (See Sidebar A Look Into the Future: Daisy Visits the Vet, page 54).

It is estimated that in the US, preserving the human-animal bond could increase veterinary income by at least $2 billion a year.

"Simply put, if animals don't remain in their homes, they can't be cared for by veterinarians as [the animals] age. They also can't use or consume products sold by pharmaceutical or pet industries" (Olson 2002).

What are the key characteristics that any product intended for use by companion animal veterinarians will have to have to be successful?

- *Profitability* – Operating a veterinary practice entails carrying a variety of fixed costs, and although those costs vary depending on the location and nature of a given practice, surgical sterilization consumes time and resources that could be employed more effectively. A product that enables veterinarians to make a good margin and frees time to see additional patients could turn a relatively expensive procedure for the veterinarian into a solution that benefits owner, pet, and vet alike.
- *Safety to humans* – Veterinary professionals administering contraceptives must be assured that these products can be used safely. Companies contemplating developing and/or marketing such products may also wish to consider including a delivery device that would limit the possibility of accidental self-injection as part of the product concept.
- *Animal safety* – Veterinarians are charged with protecting the welfare of the animals they treat, and products must be proven to be safe to their satisfaction.
- *Offer the same health benefits as surgical spaying and neutering* – The long-term health benefits of surgical sterilization have been documented, and they contribute to the overall quality of life for pets and peace of mind for their owners. A contraceptive product that failed to offer the same positive benefits would have a difficult time gaining acceptance.
- *Minimal liability* – Liability is clearly a concern of veterinarians in instances in which an animal does not respond to a product as expected. In addition, products with durations that vary according to the responses of individual animals (e.g., contraceptive vaccines) should be labeled so that they can be re-administered at the minimum effective time frame safely in all target animals. While the labeling required by regulatory authorities will help veterinarians understand the expected effectiveness of new contraceptive and fertility control products, in-office testing (for example, for serum anti-GnRH antibodies in the case of a GnRH vaccine) to monitor how well products are working may help vets gain confidence and minimize concerns about liability. Companies marketing such products can also help build confidence by ensuring that veterinarians have client-education tools that delineate the potential for incidence of failure.

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A Look into the Future: Daisy Visits the Vet

One Practitioner's Approach to Client Education

Assume it's happened – a new product has been approved in the US for suppressing estrus and providing contraception in dogs. The product happens to be a GnRH vaccine that is launched with a label claiming efficacy in 90% of treated dogs after two injections, one month apart. The contraceptive effect lasts up to a year. Annual boosters are recommended. The only safety issue is that 10%-20% of animals show pain at the injection site, of two to five days duration. The product is launched with a rapid, in-office blood test that measures anti-GnRH antibodies in whole blood.

How would a veterinarian educate his or her clients in the use of such a product?

Let's take a look at a routine visit by Mrs. Curtis and her dog Daisy, a six-month-old apricot purebred miniature poodle. Mrs. Curtis and Daisy have been coming to Dr. Jones for puppy care since Daisy was born.

Dr. Jones is performing the physical exam when Mrs. Curtis asks, "When do I spay her? I'm worried she is going to come into heat."

Dr. Jones says, "Let's see, she's six months old, she can come into heat in the near future. Mrs. Curtis, we have a good alternative to the spay surgery. It's the latest technology for birth control. We can give Daisy a birth control injection. Thirty days later she'll get a second birth control injection, and then 30 days after that, you bring her in for a blood test to make sure it took. We can do the blood test right here in the office."

Mrs. Curtis is surprised and amazed. "So we don't have to spay? And then she never comes into heat?"

"Yes, this is instead of the spay. Each year we'll give her another birth control injection. Usually it only has to be given once a year. It doesn't always work, but we'll know that by a simple blood test. And then we make a decision – shall we continue with the birth control injection, or shall we do the spay?"

Mrs. Curtis asks, "What do you think Doc, what do you recommend?"

Dr Jones replies, "I think it's a great alternative to the surgery – you don't have to worry about anesthesia, keeping your dog in the hospital, separation anxiety, pain, sutures, or wearing that big collar after surgery for a week or so. Avoiding surgery altogether is a good thing – we don't have to remove her organs."

Mrs. Curtis begins to understand, "So if I choose this birth control injection, and I want to breed her in a few years, could I?"

"Yes" says Dr. Jones, "in most cases, if you don't give the injection to Daisy each year, she will gradually resume her natural cycle and come into heat, but we don't know exactly how long that might take."

Mrs. Curtis is still worried about Daisy. "Is it safe?" she asks. "Are there any side effects?"

Dr. Jones tells Mrs. Curtis, "Some dogs have some discomfort or tenderness in the leg at the injection site, but it's pretty minor and if it bothers her, we can give her a baby aspirin once a day until it gets better. You know what, Mrs. Curtis, I have some literature here that explains it in more detail. Take it home, read it with your family and give me a call in a couple of days about your decision."

Mrs. Curtis goes home happy that she has a choice.

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5.1.5 Summary and conclusions: dogs and cats

5.1.5.1 Issues that affect marketing of contraception and fertility control for dogs and cats

The following table is intended as a guide and is not to be considered exhaustive.

Customer Group	What's Important to Them
Pet owners	• Need for suppression of unwanted sexual behaviors • Concern about effects in very young animals • Reassurance that new technologies and products are effective • Reassurance that nonsurgical methods offer the same health benefits as surgical sterilization • Reasonable treatment schedule • Reassurance that there are no harmful effects on treated animals
Shelters/humane organizations/ advocacy and rescue groups	• Eliminating "objectionable" behaviors (e.g., yowling, spraying, roaming, fighting) that contribute to pet abandonment • Cost and the potential need for partnerships that help defray costs • Ease of use • Single treatment • Human and animal safety • Effectiveness (permanent sterilization) for adoptable animals and animals treated in trap-neuter-release programs
Breeders* and show animal owners	• Predictable duration of effect • Predictable onset of effect • Flexibility (show schedule versus breeding schedule) • Effects on treated animals and subsequent litters • Any harmful effect if a pregnant animal is treated
Veterinarians	• Effectiveness • Animal safety • Cost and profitability • Vets may prefer a nonpermanent approach that brings clients to the clinic regularly (note that pet owners may prefer permanent sterilization) • Debunking the "one-litter-before spay" myth • Liability, related to effectiveness of permanent and reversible products; reversibility of nonpermanent products within a given time frame • Delivery device(s) that ensure human safety

**refers to reputable breeders*

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5.1.5.2 Issues and benefits for dogs and cats by technology

Contraception and fertility control technologies for dogs and cats are reviewed in Sections 4.1 and 4.2 respectively. Please note that although theoretically these approaches should apply to contraception and fertility control in cats, significantly less research has been done in cats.

Technology/Products	Potential Benefits	Issues

Progesterone-type drugs	• Suppress estrus and fertility in females
	• Oral or injectable
	• Nonpermanent
		• Unwanted short- and long-term side effects
		  • mammary tumors
		  • water retention
		  • lethargy
		  • weight gain
		  • pyometra (uterine infection)
		  • diabetes
		  • hair loss and discoloration
		• Cannot be used long term
		• Precise timing of administration required for some products; owner and vet must monitor estrus cycles
		• Females only; not available for males

Androgens	• Nonpermanent • Suppress estrus and fertility in females	• Not recommended for use before first estrus cycle • Side effects (e.g., clitoral enlargement) may occur • Treatment must start at least 30 days before the next estrus
GnRH agonists	• Suppress fertility and sexual behavior in males and females • Effective in a variety of formulations • Effects wear off when drug is discontinued • Should offer same health benefits as surgical spaying/neutering (e.g., shrinkage of prostate in males, decrease in mammary tumors and pyometra in females)	• Onset of activity not immediate – may be a few weeks • Duration of activity variable among animals • May cause initial stimulation of estrus in females; this might be blocked by initial use of a GnRH antagonist or progesterone • Requires continuous administration • Many products approved for use in humans

Continued

Technology/Products	Potential Benefits	Issues
GnRH antagonists	• Suppress fertility and sexual behavior in males and females • Effective in a variety of formulations • Effects wear off when drug is discontinued • Should offer same health benefits as surgical spaying/neutering (e.g., shrinkage of prostate in males, decrease in mammary tumors and pyometra in females) • Effective shortly after initial administration	• Require continuous administration • Rapid onset of activity • Return of fertility should be quick and predictable after cessation of treatment • Some drugs may cause histamine release in dogs • Depot or long-acting formulations for animals not developed • Limited data available in dogs and cats • Two products approved for use in humans (daily injections)
GnRH vaccines	• Suppress fertility and sexual behavior in males and females • Effects wear off when boosters are discontinued • May be possible to achieve effects with two initial injections a few weeks apart, followed by an annual booster • Have been tested on dogs and cats • Should offer same health benefits as surgical spaying/neutering (e.g., shrinkage of prostate in males, decrease in mammary tumors and pyometra in females)	• Potentially inconsistent immune responses among individuals (may not be able to achieve near 100% efficacy) • Possible injection site reactions • Reversibility time frame difficult to predict • Multiple boosters may be required • Slow onset of activity (weeks to months) • Efficacy could be compromised in animals that are immunosuppressed
GnRH toxin conjugates	• Suppress fertility and sexual behavior in males and females • One dose should produce permanent sterility • Should offer same health benefits as surgical spaying/neutering (e.g., shrinkage of prostate in males, decrease in mammary tumors and pyometra in females)	• Theoretically permanent, although some dog data indicate some recovery may be seen • No cat data available

Continued

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Technology/Products	Potential Benefits	Issues
Zona pellucida vaccines	• Some studies demonstrate suppression of fertility in females • Effects wear off when boosters are discontinued	• Not effective in males • Does not affect sexual behaviors (i.e., estrus cycle) • Difficult to predict time frame for resumption of fertility • Need for multiple injections to achieve results • Possible injection site reactions • May be difficult to achieve GMP manufacturing with a slaughterhouse-derived antigen • Porcine ZP antigens may not be effective in dogs and cats
Vaccination against sperm/egg proteins	• Suppress fertility in females	• Issues similar to those in zona pellucida vaccines • Research at an early stage
Chemical sterilants	• Permanent sterilization • Effective in 100% of treated animals	• May require sedation of some dogs • Only used in males • Not tested on cats • Some side effects of vomiting in early trials • Not reversible
LH receptor vaccine	• Suppresses estrus in females • Effects wear off when drug is discontinued	• Early stage research • No trials in cats • Only administered in silastic capsules • Antigen derived from slaughterhouse material, difficult to achieve GMP manufacturing

5.1.5.3 Marketing issues in cats and dogs – the bottom line

As discussed earlier in this report, the history of research in contraception and fertility control for cats and dogs is a long one. Researchers have continued to explore nonsurgical alternatives, knowing that such products could offer significant advantages in population control for dogs and cats. This research has been of interest not only to organizations that have long been involved in the welfare of animals and creating awareness of population control issues, but also to the new organizations that continue to be founded worldwide.

Research continues, the quest for funding of low- or non-profit segments continues, and debate about population figures and the relative value of population control strategies continues – but there are some common factors that marketers may want to consider when assessing what would be required to serve pet owners and the shelter community. These include:

- Dealing with an unusually fragmented market in terms of customer groups, cultures, societal factors, and desired product profiles
- Understanding clearly the limits of a given technology in terms of the marketing opportunities it presents – and doesn't present
- Making a commitment to supporting the veterinary profession, the shelter community, and pet owners by developing, sponsoring, and supporting programs that strengthen the bond between people and companion animals
- Implementing public relations and education activities that target each customer group and its key influencers
- Developing creative, mutually beneficial collaborations and alliances

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5.2 Cattle

Current practices of spaying heifers and castrating bulls are less than ideal. If a new nonsurgical method were developed with the appropriate attributes, there is a large market waiting to take advantage of it. The sheer size of the cattle market, coupled with the intensive and semi-intensive management practices common in beef production, make for a very attractive market for a product that could reduce stress on the animals.

It is estimated that there are approximately 121 million cattle in Canada and the US combined (National Agricultural Statistics Service, August 2002).

In January 2001, the worldwide cattle population was estimated at approximately 1 billion animals; broken down as follows (USDA, cited on www.cattle.ca/CanFax/statistics.htm):

Area	Cattle Population (million)
India and China	444
Brazil, Argentina, Columbia, Mexico, Venezuela, Uruguay	270
United States and Canada	110
Former Soviet Union, France, Germany, Turkey, UK	93
Australia and New Zealand	37
South Africa	14
Other	70
Total	**1,038**

5.2.1 Beef cattle

Beef cattle producers are in the business of generating optimum feed efficiency and weight gain in the minimum amount of time for the least cost and fewest inputs. Any compromise in productivity is felt keenly when the animals are sold, and when animals injure other animals, producers incur labor and medical costs and performance is reduced.

"Bulling" and "buller-rider syndrome" are colloquial terms used to describe behaviors that tend to occur in intensively managed beef cattle operations, such as feedlots, where animals are housed in large groups. Animals display the sexual behavior of chasing and mounting each other. When cattle mount the rear quarters of other cattle, it often results in bruising of the hind quarter and back muscles. Bulls, steers and heifers may all exhibit bulling, and the behavior is usually seen when heifers come into estrus. They eat less, mount other heifers, are harder to handle, tend to convert feed to weight less efficiently and therefore grow more slowly, and may become pregnant, which decreases their value. In fact, heifers that can be guaranteed open when they're sold have commanded a $50 to $75 advantage (Bopp 2002). Bulling is disruptive, can cause injury, and can add to labor costs by necessitating the segregation of instigators.

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Ovariectomy, also known as spaying, is a common method of preventing bulling and its associated effects (see Section 4.3.1). Spayed heifers tend not to gain weight as quickly as their unspayed counterparts, but in countries in which growth-promoting implants are approved, producers use a combination of spaying to prevent estrus and implanting to maintain productivity. Another approach currently available in some markets is the use of the progesterone-type drug MGA (melengestrol acetate) in the feed, which decreases behavioral estrus (see Section 4.3.6).

Researchers have investigated using GnRH vaccines to reduce estrus and associated behaviors in heifers. A product called Vaxstrate was launched for female cattle in Australia in the early 1990s (see Section 4.3.4) but is no longer on the market due to the need for two doses, variability in duration of effect, and injection site reactions. Nonetheless, it was the first product of its kind for use in cattle, and demonstrated that the GnRH concept has commercial potential.

GnRH vaccines and agonists could also be used in place of castration of beef bulls. Surgical castration is a stressful procedure, usually done in a field setting without anesthesia. The procedure cannot be done during times when fly infestation is possible, as fly strike can cause significant morbidity and mortality. A nonsurgical alternative would be a significant advantage because it would enable a producer to achieve a castration-like state at any time of the year, and reduce the stress on the bull calves, which would increase the health and productivity of the animals.

GnRH vaccination could add to labor and handling of cattle if it required more than one injection for efficacy. As it takes time for an immune response to become effective, calves would have to be vaccinated early to allow the immune response to develop before shipment to feedlots.

The use of GnRH agonists in cattle has been investigated (D'Occhio 2001). (See Section 4.3.5). These drugs would be given via implants and do cause effective suppression of testosterone in bulls, and of estrus and pregnancy in heifers. Their advantage is they only require handling once to be effective, and within a week or so, GnRH suppression can be achieved. However, duration of activity would have to be compatible with management practices in the feedlot so that re-implantation would not be necessary.

Use of the GnRH agonist implant may result in tissue residues depending on how rapidly it is cleared from the body because it is given in a slow release form. The issues of tissue residues and their impact on human food safety would have to be defined in order to develop a commercial product. If a long withdrawal time is needed, during which the effect wears off, the product would be less desirable.

Surgical neutering (castration) is performed on beef bull calves destined for feedlots. Researchers have investigated the use of GnRH vaccines that could obviate the need for castration, but no product is on the market (see Section 4.3.4). A nonsurgical product that could be used in this population would be desirable to decrease the labor and risks associated with this procedure (fly strike, infection). Increasingly, as farmers and veterinarians come under scrutiny by the animal welfare community, alternatives to painful procedures will be emphasized, and a nonsurgical alternative to castration would be preferable to a surgical procedure.

In beef cattle operations it is desirable to suppress breeding, sexual behavior and pregnancy. Producers can be expected to prefer a long-acting or permanent method that is convenient, reliable, does not cause carcass damage, fits with established production schedules and practices, and requires little labor. Long-term effects on the animals are not an issue, since most treated animals will go to slaughter. However, safety in humans who consume the meat is paramount, and any method involving treatment with a drug would have to demonstrate no harmful residues in the meat of the treated animal.

5.2.2 Dairy cattle

Contraceptive products are not used in dairy practice. GnRH agonists have been used in a research setting to induce ovulation for embryo transfer and artificial insemination.

The only dairy management setting in which these products might be useful is in a nonsurgical alternative to the castration of dairy bulls. The same advantages as described above for beef bulls apply.

5.2.3 Issues that affect marketing of contraception and fertility control in cattle

Essentially, companies bringing sterilization products for feedlot animals to the animal health market will be dealing with the same marketing issues presented by many of the products for food-producing animals. The following column lists some of these issues.

Producers

- Maintaining or improving productivity
- Maintaining or improving meat quality
- Fitting in with production practices, including use of hormone implants (where permitted)
- Minimizing labor
- Minimizing handling
- Minimizing bulling and associated loss of productivity
- Demonstrating calculable added value
- Food, handler, and target animal safety
- Producer association, packer, retailer, and consumer buy-in
- Willingness to adapt to new technologies

Producer and trade associations

- No detrimental effects on consistency of product
- Food, handler, and target animal safety
- Increased productivity
- Increased value of end product
- Compatibility with Beef Quality Assurance (US) and similar programs in other markets
- Packer, retailer, and consumer buy-in

Veterinarians

- Demonstrating consistent product performance
- Ease of handling and administration
- Liability
- Food, handler, and target animal safety
- Animal welfare
- Demonstrating calculable added value
- Demonstrating the potential to increase practice income

Packers

- No trim
- No detrimental effects on meat quality
- No residues or food safety issues
- No changes in packinghouse procedures

Consumers

- High quality, consistent meat
- No residues or food safety issues
- Improved animal welfare

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5.2.4 Issues and benefits for cattle by technology

See Section 3 for an overview of technologies and Section 4.3 for details on applications in cattle. Please note that these approaches, when used properly, will prevent pregnancy and provide potential for premium price

Technology	Benefits/Potential Benefits	Issues
Ovariectomy	• Suppresses bulling • Potential for premium price	• Skill required to perform the procedure • Potential complications (infection, pain) • Labor intensive • Expensive • Decreased feed efficiency and slower rate of gain; use of implants to offset, where permitted • Animal welfare concerns
Intrauterine devices		• Early stage, no product available • Would not affect estrus or bulling
Castration	• Limits aggression • Prevents ability to impregnate heifers	• Timing is important to reduce stress • Potential complications (bleeding, infection, fly infestation) • Buller-rider syndrome can still occur among steers in intensive production
GnRH vaccine	• Less traumatic than surgery • Effective in bulls and heifers • Suppresses bulling • Meat may have some superior characteristics • Suppresses testicular function in bulls, growth and carcass traits similar to that of steers	• Feed efficiency somewhat reduced, similar to steers • May cause injection site reactions • May need two injections a few weeks apart to be effective (more labor and increased input costs) • Handler safety issues
GnRH agonist	• Research indicates pregnancy in heifers prevented for 3 to 12 months • Suppresses bulling	vTreatment via implant and therefore may have residue issues • Non-permanent (re-treatment may be required adding to labor costs) • If implant is non-biodegradable may affect slaughterhouse practice
Progesterone-type drug (melengestrol acetate, MGA)	• Suppresses bulling • Improves gain and productivity in intact open heifers (~3% to 7%)	• 48-hour slaughter withdrawal • Use for at least 14 days but less than 24 days • Females come into estrus within two to six days after MGA is removed from feed • Reduced conception rate if bred at first estrus after treatment stops • normal subsequent estrus

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5.3 Horses

Nonsurgical contraception and fertility control for horses represents a niche that could be addressed as a follow-on market by a broadly focused animal health company, in a collaborative relationship with a smaller company specifically geared to the equine market, or by a life sciences company as an outgrowth of competency in a specific reproduction-control technology.

The equine population includes working horses, pleasure and recreational horses, race horses, show horses, wild horses, and horses used for food. (See Section 4.5 for information regarding wild horses.) Horses intended for consumption are not covered in this report, though obviously horses can move into this category from others and human food safety issues could come into play.

In the US, there are about 7 million horses. The Horse Council categorizes them as follows (www.horsecouncil.org/ahcstats.html):

Segment	Percent of US Horse Population
Race horses	10%
Show horses	28%
Recreational horses	44%
Others (e.g., farm, ranch, rodeo, polo, law enforcement)	18%

It is estimated that there are 886,000 horses in Canada: one-third are in Alberta, and 56% are in Alberta and Ontario combined (research commissioned by the Canadian Equestrian Federation 1998).

Equine contraception and fertility control strategies are employed to deal with aggressive behaviors and manage or suppress estrus (see Section 4.4 for a review of technologies).

5.3.1 Males

Some young males "exhibit sexual frustration or self-mutilation tendencies." Unwanted sexual behaviors among stallions include "whinnying, squealing, pushing, rearing, striking, and biting" (www.horsekeeping.com). These behaviors decrease the potential performance of show, race, and working horses.

Typically, the potential of stallions for breeding purposes is assessed relatively early, and only 10% of male horses pass muster (www.horsekeeping.com). The 90% without economically significant breeding potential are surgically castrated. However, should their subsequent performance indicate that they would have had breeding potential, there is no recourse for owners. A reversible nonsurgical approach would be ideal for these animals.

5.3.2 Females

The behavior of fillies and mares can become unpredictable during the spring and summer breeding season. Mares that are in estrus can be treated with progesterone-type products to suppress estrus (see Section 4.4.2) but no long-term solution is available at this time. A reversible nonsurgical approach would be useful for mares intended for future breeding.

GnRH agonists are approved for use in induction of estrus in mares with large follicles on their ovaries (Ovuplant, Ft. Dodge). The product is

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used for timing of breeding as it stimulates ovulation when used short term. No long-term agonist product for suppression of estrus is commercially available.

Not all products used to suppress estrus in mares are approved in all markets and certain products cannot be used in performance and/or racehorses that are in competition. The acceptance and use of new technologies will be subject to review and approval not only by regulatory authorities governing approval of new drugs, but also by the authorities governing performance events and horse racing.

GnRH suppression technologies and zona pellucida vaccines have been studied for their utility in the equine market, and at least one GnRH-based product for horses has been commercialized. In July 2002 CSL Limited, an Australian company (see Section 6.2.4), launched Equity™, a GnRH protein conjugate vaccine labeled as an aid in the control of estrus and estrus-related behavior in fillies and mares not intended for breeding. Equity Oestrus Control Vaccine for Horses helps prevent follicular development in the ovaries. According to the Equity label "the ovaries in vaccinated horses become small and inactive, cyclic oestrus activity commences to decline or will cease within about two weeks following the second dose of vaccine in most horses. Vaccine-induced suppression of oestrus should last for at least three months and in a percentage of horses will continue for six months or longer. If continued anoestrus is desired, additional booster doses will probably be required."

Side effects can include swelling at the injection site, but are said to resolve within a few days.

The label carries a warning regarding accidental self-injection and needle sticks to people administering the product. Equity is supplied in syringes.

5.3.3 Issues that affect marketing of contraception and fertility control for horses

Pleasure horse owners

- Avoiding surgery
- Minimizing or eliminating undesirable behaviors
- Effectiveness
- Target animal safety

Racehorse owners

- Fit with regulations
- Flexible timing (for nonpermanent products)
- Effectiveness
- Maintaining performance levels
- Duration of effect in horses intended for breeding
- Definite reversibility
- Target animal safety

Show horse owners

- Fit with regulations
- Flexible timing (for nonpermanent products)
- Effectiveness
- Maintaining performance levels
- Duration of effect in horses intended for breeding
- Target animal safety

Veterinarians

- Effectiveness
- Convenience
- Target animal safety
- Avoiding surgical complications
- Avoiding risk of injury to vet
- Demonstrating consistent product performance
- Ease of handling and administration
- Liability
- Demonstrating the potential to increase practice income

5.3.4 Issues and benefits for horses by technology

See Section 3 for an overview of technologies and Section 4.4 for details on applications in horses.

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Technology	Benefits/Potential Benefits	Issues
Castration	• Limits aggression and unwanted sexually-related behaviors • Permanent	• Potential complications (bleeding, infection, gut/intestinal prolapse, swelling of hind legs, scrotal abscess several months after castration) • Castrated animals should be separated from fillies and mares until the wound is sufficiently healed

GnRH vaccine	• Effective in males and females of various ages
	• Limits aggression and unwanted sexually-related behaviors
	• No surgery, less stressful
	• Potentially reversible
		• Duration variable
		• May cause injection site reactions
		• May need multiple injections
		• Immune response may take up to several months to suppress, may not be practical for short-term use
		• Effectiveness variable
		  • libido may not be totally suppressed in stallions
		  • mares may exhibit irregular estrus

GnRH agonist	• Effective in males and females • Limits aggression and unwanted sexually-related behaviors • Research indicates suppression of fertility is possible • Reversible	• Little published work • Effective within one to two weeks of treatment • Duration of effect unpredictable • Likely that relatively large dosage will be required for effectiveness • Dosage probably by implant
GnRH antagonist	• Effective in males and females • Limits aggression and unwanted sexually-related behaviors • Could be practical for short-term use (e.g., prior to a show or a race) • Should be fully reversible, enabling treated animals to be used for subsequent breeding	• Early stage research not focused on treatment for commercialization
Zona pellucida vaccine	• Porcine ZP is effective in wild horses • Potentially reversible	• See Section 4.5 and 5.4
Progesterone-type drugs	• Suppress estrus and unwanted sexually-related behaviors • Can be administered orally, or by injection • Not for long-term use	• Treated mares come into estrus four to five days after treatment ceases and breed normally • Must be given daily • If animal is “off feed,” missed doses may result in estrus • Useful only in females

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5.4 Wildlife

From the suburban woods of New Jersey in the US, where white-tailed deer are colliding with vehicles, serving as one of the vectors for the tick that carries Lyme disease, and devouring expensive shrubbery, to Kruger National Park in South Africa, where the elephants are reproducing at an unsustainable rate, there is a need for population control of wildlife. In Australia, a variety of wildlife species are contributing to erosion and damage to wetlands, trees, and shrubs, and compromising the habitats of native animals; in the UK, an introduced species of squirrel is squeezing out the natives.

Eliminating surplus animals by hunting or poisoning has, in some cases, become unacceptable, illegal, or unsafe, and communities worldwide are looking for humane alternatives.

The list of rapidly multiplying species is long, but here are just a few examples:

- Mice, rabbits, foxes, wallabies, koalas, and kangaroos in Australia
- Possums in New Zealand
- Deer, coyotes, wild horses, bear, and elk in the United States
- Monkeys in Hong Kong and parts of Japan
- Grey squirrels in England and Italy

Controlling wild populations with contraceptive technology presents complex challenges that involve politics, animal welfare and animal rights concerns, funding issues, and community needs as well as technical challenges, and there is a wide range of species to be controlled. (Note that issues related to feral dogs and cats are discussed in Section 5.1.2).

Unlike pets, horses, or cattle in confinement, planning and executing a contraception program for wild animals means taking on additional challenges, including:

- Capturing, identifying, and possibly re-treating animals and training workers to do so
- Producing and safely handling contraceptive treatments that are not available commercially
- Studying population dynamics and developing reliable models to determine how many animals need treatment to stabilize or decrease a target population (Hobbs 2000, Barlow 2001)
- Understanding the effects of contraception on sexual behavior
- Understanding, monitoring, and assessing the response of the target population to the treatment
- Understanding the environmental impact of the product in the field (e.g., will treated prey species, when consumed by predators, cause unintended effects on predator species)
- Understanding and managing public perception of the target species (i.e., as a pest or a valued wildlife species)
- Balancing public acceptance of permanent infertility versus reversible contraception

Finding and treating the animals is one of the most challenging aspects of designing a population control program. No matter what the species, treatment involves locating the animals in the wild, and either darting them with the contraceptive preparation or capturing them to administer it by hand. The proportion of the population that must be treated to achieve a stabilization of the population, and/or a meaningful reduction must be determined. There are concerns that population control efforts could lead to increases in animal numbers rather than decreases because treated animals may live longer and untreated animals may exhibit increased fecundity due to reduced competition for food.

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Ideally, animals that have been treated should be identifiable in some way, so that resources will not be consumed re-treating animals. In order to stabilize or decrease a given population, a large number of animals need to be treated, and more and more resources will be required as the proportion of treated to non-treated animals increases. It may very well be that, in the future, the limiting factor will not be the availability of the contraceptive drug as much as the availability of skilled field personnel to deliver the treatments.

How the animal population responds to the treatment is also of concern – will treated animals exhibit normal behavior? For example, animals treated with GnRH vaccines can be expected to demonstrate suppressed sexual behavior while those treated with zona pellucida vaccine may not, allowing some treated, polyestrus animals to cycle more than usual (e.g., deer will extend their breeding season after treatment but wild horses will not). How will changes such as these affect the social structure of the animals in the wild? Of course, these issues are different for each species, and must be considered before a program is initiated.

Wildlife contraception is also used in zoos, in instances in which a zoo cannot support continued expansion of the population of a certain species and separation of the sexes is not desirable. Zoo contraception is also used to control population genetics and to prevent pregnancies in aged animals or animals that are not candidates for reproduction. In this case, capturing the animals is less of an issue and administration of some type of scheduled treatment could be practical.

Several non-profit organizations have contributed significant funding to developing effective contraceptives for wildlife. For example, the Humane Society of the United States (www.hsus.org) has supported development and use of the porcine zona pellucida vaccine. The Geraldine R. Dodge Foundation has also supported these efforts (www.grdodge.org) through grants to the Science and Conservation Center in Montana where research on porcine zona pellucida vaccine is ongoing.

The Saint Louis Zoo in St. Louis, Missouri is the Wildlife Contraception Center for North American Zoos. According to its website, its "contraception database now contains more than 12,000 records, representing almost 300 species. Plans call for the database to be expanded in order to aid in making future recommendations for newer contraceptive methods and for additional species. It is also important that the Wildlife Contraception Center continue to monitor those contraceptives already in use and to be prepared to track methods that become available." (www.stlzoo.org/content.asp?page_name=contraception)

In 1996, the FDA/CVM weighed in on the regulation of products for use in wildlife in the US, saying "discussions between FDA, the Environmental Protection Agency (EPA), and the Department of Agriculture (USDA) have led to the determination that evaluation of products which interfere with conception in animals and are identified as drugs come under the jurisdiction of the FDA's Center for Veterinary Medicine. The Center acknowledges that the EPA and USDA have expertise in evaluation of certain areas, such as bait and vaccine development, and consults with them as needed. The Center is aware of the problem of population control among certain animal species and encourages the development of products to assist in their management." (www.fda.gov/cvm/index/fdavet/1996/ september96.htm).

However, no products have yet been approved because no sponsor has fulfilled all the necessary regulatory requirements. There are several factors that make it difficult for companies to develop products for wildlife:

- Products require approval on a species-

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by-species basis (e.g., products approved for use in deer will not be labeled for use in elk unless elk studies are completed)

- Any target species, such as deer, that might be used for food will require extensive studies to demonstrate human food safety, adding significantly to the cost of the development program
- Wildlife control personnel must be available to administer the product and monitor treated, free-ranging animals
- The market may break down into products causing permanent sterility for "pest" species and nonpermanent products for wildlife species with societal value
- Marketing such products will require significant prelaunch public awareness and education programs that will consume additional resources to support what are likely to be low-volume products

What about pricing? Many people have expressed the opinion that a low-cost treatment is needed for the wildlife market, and therefore companies may shy away from developing a low-margin, small-market product. However, much of the cost of wildlife control is tracking, capturing and handling the animals – the cost of the actual treatment is likely to be a small fraction of the labor costs, even if the per dose price is "high."

It is very difficult to estimate the size of the wildlife market, as it is so diverse. Most research has been done on relatively isolated populations, e.g., deer or wild horse populations on islands, where the population as a whole can be studied. In borderless situations, such as interconnected suburban communities, population control strategies involving capture are much more difficult. The size of the market will certainly depend on the effectiveness of the treatment. Whether the market size is big enough to justify an investment in developing a product will have to be evaluated carefully by any company interested in comercializing a wildlife contraceptive.

Therefore, it seems foreseeable that wildlife markets may be addressed as follow-on opportunities for companies that are deriving income from contraception and fertility control products for other species such as pet cats, pet dogs, and cattle. These companies may be willing to explore wildlife applications of their technologies in collaboration with organizations that already fund wildlife population control projects and groups that are already carrying out wildlife population control programs.

Regardless of species, population control products for wildlife will need to be effective, preferably without the need to boost or re-treat animals. Reversible (i.e., nonpermanent) products may be preferred in some non-pest species. Products must not be intact or biologically active when they pass through the food chain. In addition, products must be safe in target animals, including those that may be pregnant when they are treated, and should be free of long-term negative effects on treated animals. Administration methods that do not require capture are more convenient than those that do, but injury to animals that are treated via darts or "biobullets" should be minimal. Products should not alter the social system within the animal group. Delivery systems that prevent accidental self-treatment by personnel administering the drug or vaccine are desirable. Products for wildlife in remote areas should be packaged in shatterproof containers and have stability profiles that enable them to be stored without refrigeration and used in extreme temperatures.

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5.4.1 When Wildlife Become "Pests" – Some Examples

Location	Pest Species and Impact
Australia	• Mice, particularly the house mouse *Mus domesticus,* cause significant agricultural damage and it is estimated that a major plague could cause crop losses of more than $AU150 million. A breeding pair and its offspring can produce 500 mice in a 21-week period. • Rabbits, an introduced species, are one of the most widely distributed mammals in Australia, where they compete with native animals and damage agriculture. Rabbits cause more than $AU600 million damage to farming annually and are considered the country's most ubiquitous and destructive pest animal; at one time there were 200 million to 300 million rabbits in Australia. A single pair can produce 30 – 40 offspring per year. • The fox population, another introduced species, is distributed in a pattern similar to that of the rabbit because rabbits are one of their sources of food. Another food source is young lambs, and lamb losses due to predation by foxes is estimated at 30% in some areas. A female fox can produce more than 20 cubs in a four-year lifespan. sources: www.pestanimal.crc.org.au, www.nre.vic.gov.au
US	• There were an estimated one-half million white-tailed deer in the US at the beginning of the 20th century – now, there are ~27 million in the US and Canada, thanks to agricultural development, the growth of the suburbs, and a decrease in deer predators. Suburban deer population densities have reached 100 to 200 per square mile, which is 5 to 10 times higher than in the countryside. Deer cause 1.5 million vehicle crashes, several hundred deaths, and about 29,000 injuries per year. They are responsible for property damage that generates >$1 billion in insurance claims each year – making insurance companies an attractive potential source of support for organizations working on deer technologies.. Culls and hunting eliminate about six million deer a year in the US. However, this is a short-range approach and the decreased competition it creates within herds can enable populations to rebound. Culls and hunting are also not viewed favorably by many suburban and urban-fringe communities. Trapping and relocation efforts are costly ($400 - $3,000 per animal) and are not practical or, in many cases, successful. (In the UK, there are more than one million deer versus an estimated 445,000 in the early 1970s). sources: www.fund.org, www.whyfiles.org, www.reason.com, uk.rec.birdwatching at www.xs4all.nl • Coyotes cause economic damage throughout North and Central America. A 1990 survey of lamb losses in 15 western US states indicated that about 9% of the region's six million lambs died. About 60% of the losses were due to predation, and coyotes were responsible for 70% of them. The resulting economic impact was ~$11.4 million sources: Miller 1966
UK and Italy	Grey squirrels, introduced to the UK in 1876, have essentially "ousted" the native red squirrel. Differences in feeding patterns have given the greys an advantage. Greys also carry the parapox virus, which kills red squirrels. Presently, the greys outnumber the reds 66:1. The greys were introduced in Italy in 1948 by a politician returning from the US, and a pattern similar to that in the UK emerged. Predictive models indicate that the range of the grey squirrel will extend from Italy through the Alps and into France. sources: www.nature.com, www.biology.qmw.ac.uk, www.red-squirrels.org.uk, www.wildlifetrust.org.uk

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Location	Pest Species and Impact
Japan and Hong Kong	• In a recreational area of Hong Kong, 1,250 macaques are causing traffic accidents, stealing food, and attacking hikers. Some of the monkeys have even taken ferry trips across the harbor and ended up in the business district. But the population is growing by 5.5% - 10% a year from the 600 monkeys counted in a 1992 survey. The macaques, who roam in bands of 30 to 100 animals, have become accustomed to being fed by humans. Officials are urging people to stop, and have introduced an immunocontraception program. Animals are anesthetized, injected with "an immunovaccine that sterilizes males permanently and makes females infertile for up to five years," microchipped, and released. • In Japan, the population of wild monkeys has increased from 15,000 about 50 years ago to 150,000 today. Animals in Nikko National Park are jumping on the hoods of cars, expecting to be fed by the occupants. Area residents and businesses keep their windows closed, feeding the monkeys has been banned, farmers are trying electric fences, and the governor of the prefecture has indicated an interest in birth control for the monkeys. sources: Brooke (New York Times 2002), Walker (Reuters 2002)

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5.4.2 A Sample of Wildlife Control Philosophies and Strategies

Location	Strategy
Australia	According to Australia's National Feral Animal Control Program (NFACP) "vertebrate pests, such as rabbits, foxes and feral goats now make up about 10% of Australia's mammal fauna. They have adapted and spread into most of Australia's agricultural systems and natural environments. None have been eradicated, despite considerable effort. With available control techniques, it is unlikely to be technically, economically or socially feasible to eradicate any established, widespread pest from the Australian mainland. Therefore the focus of the NFACP is on strategic, sustained best practice management of pest animals where they are causing actual rather than perceived damage." NFACP has set forth the following best practices: • Managing actual rather than perceived impacts[3] • Impact-based management rather than pest-based management (i.e., "in some situations there are more technically, economically and socially feasible ways to reduce damage than killing pest animals") • Strategic management • Group management rather than individual management • Commercial use where appropriate • Humane techniques and strategies source: National Feral Animal Control Program (www.affa.gov.au)
Australia	Koalas on the uninhabited (by people) 15-square-mile Snake Island off the Melbourne coast have no predators, they're healthy, and they're not pests, but the population has outstripped the island's ability to support it. The citizenry opposes culling. Researchers implemented a PZP-vaccine-based immunocontraception program at the end of 2000 to sterilize and then monitor some of the island's 2,400 koalas. This approach has been coupled with a relocation program. sources: www.pestanimal.crc.org.au, www.affa.gov.au, www.discover.com, www.parkweb.vic.gov.au
New Zealand	There are more than 70 million possums in New Zealand, and they consume 22,000 tonnes of vegetation per night. The possum population is present in 90% of the country and continues to climb, since NZ possums have no predators or competition for food. Possums are responsible for damage to forests, the spread of Bovine Tuberculosis (Tb) among cattle and deer, and consuming the eggs and chicks of native birds. Possum control measures include fences, hunting and trapping, ground poisoning, and aerial poisoning. Researchers are testing a virus that is engineered not to replicate and will be sprayed in the possum's face when the animal puts its head in a feed box. In 1998 the New Zealand Parliamentary Commissioner for the Environment assessed possum control progress and set forth the following strategic areas: • Sustained political and public focus, as well as commitment, to substantially reduce Tb levels in cattle and deer herds and to protect native biological diversity • Promotion of . . . national objectives rather than continued arguments about the merits of reducing the national possum population *per se* • Strong commitment from all control agencies to collaborate and share information, research, experiences, and expertise • Better scientific understanding of the role of possums in New Zealand ecosystems, with a greater focus on [their] impact as a predator of native birds • Appropriate policies to ensure the development and testing of delivery systems for possum-specific biological control methods can proceed as soon as possible • Better understanding of community values and beliefs that shape attitudes towards the risks and benefits of control options • A greater effort to inform Maori and other communities about the nature of risk, how it applies to possum impacts and the use of different control methods • Development and implementation of a quality assurance system that permeates the possum control industry and delivers effective, efficient and safe operation sources: www.pce.govt.nz/reports/allreports/possum_mgmt_98.shtml, www.learnz.org.nz, www.frst.govt.nz, www.landcareresearch.co.nz, www.discover.com

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Location	Strategy
South Africa	Elephants in the 13,500-acre Kruger National Park are far from being endangered – in fact, their population growth rate is between 7% and 8%. The herd consumes about 300-600 pounds of food each day per animal. Keeping the park's population stable at 7,500 – 8,000 elephants has meant culling between 500 and 600 animals each year. Some people oppose the culling on humane grounds, while others assert that the culled animals contribute to the local economy. In the late 1990s a project to test an immunocontraceptive approach using PZP began. In 2000, researchers (Fayrer-Hosken 2000) reported that two of 10 elephants treated with the immunocontraceptive were pregnant, a significantly lower conception rate than that of the control-group elephants (89%); another source (Pimm 2001) asserts that data on adult elephant cows indicate an expected conception rate among the general population in the park of about 51%, considerably less. No clear strategy for dealing with managing the elephants has emerged. It may be that ultimately, management strategies will involve a balance of culling and reproduction control. It has also been suggested that "huge, cross-border nature reserves that can accommodate more elephants" may be part of the solution (Adam 2002). sources: Fayrer-Hosken (2000), Adam (2000) and Pimm (2001), cited on www.nature.com, www.aibs.org/biosciencelibrary,
US	At the beginning of the 20th century there were an estimated two million wild horses in the western areas of the US. By 2001 there were fewer than 50,000, and the government's goal is to reduce that number to 27,000 by 2005. The US Bureau of Land Management is charged with balancing the needs of the wild horses with the needs of the environment, which means every so often a certain number of horses are collected and auctioned off for adoption. In the 30 years between 1971 and 2001, about 159,000 were rounded up. Not all rounded-up horses find homes, and sanctuaries take many of them. Wild horses are also found in Maryland, North Carolina, and Virginia. "Birth control" has been emerging as a tool that can help manage these wild herds. Maryland has used PZP-based immunocontraception to help manage its herd at Assateague State Park since 1995. The vaccine has four important characteristics: it is not permanent, it can't make its way into the food chain, it's safe for the mare and, if she's already pregnant when the vaccine is administered, it's safe for the foal as well. Over time the vaccine technology has improved – now only one shot is required instead of two – and research is underway on a sustained-release version that may increase duration to two years. sources: www.vetcentric.com/magazine, http://news.nationalgeographic.com, www.zoomontana.org

[3] "Often impacts will not be quantified at the start of the project. For some situations, NFACP would prefer to support 12-month pilot projects to define: basic pest ecology (e.g., relating movements and density to damage); nature and extent of impact; and, the stakeholders involved in the problem. Monitoring agricultural production responses to pest control during the management phase of field projects should provide some quantification of pest animal impacts and the effectiveness of management strategies" (www.affa.gov.au).

6.0 Review of Companies Developing Products

6.1 Large Pharmaceutical Companies with Animal Health Operations

Historically, "big pharma" animal health has had an "on again/off again" relationship with contraception and fertility control in animals.

For example:

- Pharmacia Corporation, in the late 1970s, provided funding support for research into a chemical sterilant.
- Several large animal health divisions of major human pharmaceutical companies pursued GnRH vaccines in the 1970s and 1980s. One company worked on and then dropped a product concept in the 1970s when it appeared that the potential product would not be commercially viable. A GnRH project at another company in the late 1980s did not produce a product felt to be reliable enough and the project was discontinued.
- The Carnation Company and The Upjohn Company started to develop a mibolerone-based contraceptive dog food in 1975. Carnation was hopeful of approval from the FDA, and planned to distribute the dog food through veterinarians and, eventually, retail outlets. However, the project did not come to fruition, at least in part because of fears that a product for animals might be used to induce abortions in women or cause abortions in women who consumed pet food.

Although it is misleading to say large animal health companies have not been interested in contraception and fertility control in animals, societal factors as well as frustration with technological issues put the market on the back burner while animal health companies worked on products such as antiparasitics, antimicrobials, anti-inflammatories, and vaccines for economically important diseases.

But Now They're Getting More Interested!

In recent years – as the animal health industry continued to consolidate; the companion animal market has grown; the livestock market has matured; and pipelines have typically revolved around improvements and diversification rather than "blockbusters" in major categories – animal health companies seeking new opportunities are assessing, defining, and pursuing contraception and fertility-control technologies and markets.

For example, Pfizer Animal Health announced an agreement with Peptech Animal Health (see Section 6.2.9) in December 1998 in which Pfizer agreed to fully fund a 12-month period of research as well as the development of methods for scaling up manufacture of what was termed Peptech's third-generation, long-acting implant for reversible castration of companion animals. Although that particular alliance ended, Pfizer has not been alone in its interest in contraception and fertility control, and Peptech is continuing to develop its product and pursue opportunities for collaborating with established animal health companies. Protherics PLC (formed by the merger of Proteus International PLC and Therapeutic Antibodies Inc.) formed an alliance with Janssen Animal Health for a GnRH vaccine for use in animals, although according to its website, Protherics has been seeking a new partner as this report goes to press. According to its website, United Biomedical Inc. (UBI) and a publicly unnamed animal health company have an alliance focused on a GnRH vaccine for small animals.

Representatives from some of the top-ten animal health companies – Bayer Corporation, Intervet, Merial Ltd., Novartis Animal Health US, Inc., and Pharmacia Animal Health – attended the first International Symposium on Nonsurgical Methods for Pet Population Control, held in Georgia, US in April 2002.

Top animal health companies have collaborated with smaller animal health and life sciences companies in areas other than contraception and fertility control as well (e.g., Schering-Plough Animal Health with Aphton Corporation for equine anti-gastrin technology; Merial Ltd. with United Biomedical Inc. (UBI) for a vaccine to prevent boar taint; Novartis Animal Health with Evolutec Ltd. for tick vaccines; Intervet with Lion Biosciences for bioinformatics and tagging technology, and Pfizer Animal Health with CyDex, Inc. for a drug formulation technology. Several dozen such alliances have been announced).

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The expected acquisition of Pharmacia by Pfizer will consolidate animal health further, but while the actual number of major animal health players to which researchers and smaller companies can bring products and technologies will decrease, the competition among the top animal health companies for products and technologies with the most potential could well increase. If new approaches to contraception became available through licensing, the larger companies could be receptive to alliances.

6.2 Smaller Animal Health and Life Sciences Companies

The fact that large animal health companies, for the most part, are not pursuing basic R&D in contraception and fertility control in animals, coupled with the fragmented nature of the market, presents opportunities for smaller animal health and life sciences companies to collaborate with partners, or, in some cases, work on their own to develop, commercialize, and ultimately market products.

Some of the companies that have worked in or are working in the area of contraception and fertility control for animals are profiled below. Note that given the large number of life sciences and biotechnology companies working on reproduction and related areas, it is likely that there are additional, unannounced animal health projects underway.

6.2.1 Addison Biological Laboratory, Inc., Fayette, MO, US

Addison Biological Laboratory, Inc. (Addison) is a private company specializing in products for the international veterinary market. The company offers cattle diagnostic services; products for companion animals, cattle, swine, horses, and exotic animals; and a delivery system for use in animals in instances in which administering drugs or vaccines is difficult.

Addison is commercializing Neutersol™, a product based on technology invented by the late Dr. Mostafa Fahim at the University of Missouri Center of Reproductive Science and Technology (Columbia, Missouri, US) and licensed to Addison for marketing.

Neutersol is an injectable product that will be labeled to cause permanent sterility in male puppies 3 - 10 months of age. The product is a solution of zinc gluconate neutralized by arginine (100 mg/ml). When injected directly into the testicles of young male dogs, Neutersol causes the testicles to shrink, which in turn results in atrophy of the testes and epididymis, inhibiting the production of sperm.

Dose is calculated based on testicular width, and a special caliper with dose values that can be read directly from it will be available with the product. The dose range is from 0.2-1 ml per testicle. Animals are treated in the veterinarian's office. Anesthesia is not required for the injection. A mild sedative may be used at the discretion of the veterinarian but is generally not necessary. In clinical trials, 24% (66 of 270) of the dogs received a mild sedative and nearly all of those were at the beginning of the trials. Once the participating veterinarians became comfortable with the technique, sedatives were rarely used.

A study presented at the International Symposium on Nonsurgical Methods for Pet Population Control (Wang 2002) indicates that this treatment is an effective and safe method for nonsurgical sterilization of male dogs regardless of age and breed of the animal. Reported side effects include pain when the testes were manipulated

(5% on 1st day post-injection, decreasing to 2% and 1% on days 2 and 3 post-injection). Other side effects observed were mild, and resolved. An unexpected reaction was that 10 of 270 treated animals (~4%) vomited post-injection. Withholding food and water for 12 hours prior to injection seemed to resolve this problem.

Field trials in dogs have been conducted in Mexico and several sites in the US. According to the company, FDA/CVM is conducting its review of the product. Therefore, Neutersol could become the first FDA-approved nonsurgical approach to sterilization in male dogs.

Although the initial label indication will be for Neutersol for puppies, preliminary studies indicate that the technology can be used successfully in older dogs. Efficacy research has been done in cats and Addison expects to ultimately seek approval for a feline product. Early fieldwork has been conducted in species such as rabbits and horses. The company anticipates that the technology will be effective in any mammal.

www.addisonlabs.com

6.2.2. Aphton Corporation, Miami, FL, US

Aphton Corporation (Aphton: NASDAQ APHT) works with technology that blocks or neutralizes hormones involved in gastrointestinal or reproductive systems. The company is primarily focused on human health. Among its targets are gastric, pancreatic, colorectal, liver, esophageal and reproductive cancers; other gastrointestinal diseases, such as GERD (gastroesophageal reflux disease), peptic ulcers, and NSAID-related (nonsteroidal anti-inflammatory drug) ulcers; and pregnancy prevention.

Aphton has a global strategic alliance with Schering-Plough Animal Health that encompasses the animal applications of Aphton's anti-gastrin immunogen, which neutralizes equine gastrin (equine hormone G17, the hormone that governs acid secretion in the stomach). The target is preventing and/or treating equine gastric ulcers.

Aphton is developing a GnRH vaccine ("pharmaccine") for treating human prostate cancer. This technology may have animal health potential. However, the company's website does not indicate contraception or fertility control collaborations with animal health companies at this time.

www.aphton.com

6.2.3 Cooperative Research Centres (CRC), various locations, Australia

The CRC Program was inaugurated by the Australian Federal Government in 1990 to unite researchers from universities, government labs, including the Commonwealth Scientific and Industrial Research Organization (CSIRO), private industry, and public-sector organizations in long-term collaborations to support R&D and education activities "that achieve real outcomes of national economic and social significance."

There are more than 60 individual CRCs, covering such diverse areas as information and communications technologies, mining and energy, environment, medical science and technology, and agriculture.

Three CRCs are involved in work in contraception and fertility control in animals. Although they are not companies *per se*, they are included here because of their links to companies that ultimately commercialize and market CRC advances.

CRC-Vaccine Technology: CRC-VT, established in 1993, brings scientists and manufacturers together to improve existing vaccine technologies and develop new approaches to human and veterinary vaccines. Its partners are The

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Queensland Institute of Medical Research, CSIRO, Walter and Eliza Hall Institute of Medical Research, University of Melbourne, Monash University, Australian Red Cross Blood Service, LaTrobe University, and CSL, Ltd. (see Section 6.2.4). CSL is the marketing arm of CRC-VT. At the University of Melbourne and CSL, CRC-VT is working on a GnRH vaccine as an alternative to surgical spaying and neutering in companion animals. (See Section 3.1 for a general discussion of GnRH vaccines.)

CRC-VT's GnRH vaccine project is initially focusing on dogs. GnRH is a self antigen (i.e., produced naturally by the animal), and this approach to increasing the immune response to GnRH uses foreign T helper cell (Th) epitopes (See Section 3.1.4). CRC-VT has identified canine Th epitopes that are recognized across breeds and has incorporated them into peptide vaccines. According to CRC-VT, trials in dogs have repeatedly shown that these types of peptide vaccines can elicit high anti-GnRH antibody titers that result in suppression of reproductive hormones. Thus the dogs are rendered infertile, though not permanently. The vaccine has been shown to be highly effective across a variety of breeds of dog, demonstrating the feasibility of the peptide vaccine strategy in an outbred population (CRC-VT Annual Report 2001). In 2001, CRC-VT reported that preliminary trials in dogs indicated that peptide vaccines provide contraceptive effect in male dogs for at least six months.

CRC-VT has alliances with: CRC for the Biological Control of Pest Animals and the Marsupial CRC.

CRC for the Biological Control of Pest Animals: The CRC for the Biological Control of Pest Animals focuses on efforts to develop cost-effective, environmentally friendly, humane biological contraception/fertility control agents to deal with overpopulation of the European rabbit, European red fox, and introduced house mouse in Australia. This CRC is creating oral bait vaccines by genetically modifying carrier viruses to include DNA from key mammalian reproductive proteins. During infection of the pest mammal, these modified viruses cause an immune response to the target animal's own eggs and prevent reproduction.

- Rabbit project: Introduced European rabbits compete with indigenous wildlife for food and shelter and cost Australian farms more than $AU600 million annually. At the Pest Animal CRC, rabbit zona pellucida (ZP) genes are inserted into the *myxoma* virus. Lab studies have shown that female rabbits infected with the resulting virus can be rendered infertile, but field studies have yet to be conducted.
- Fox project: The European red fox is the most important predator species in Australia. In fact, it is believed that lamb loss due to predation by foxes is 30% in some areas. Historically, poison bait has been widely used to control fox populations. Pest Control CRC's goal is to develop a fertility control vaccine that will reduce the need for so-called lethal control. Bait delivery of the virus has been achieved, and efforts are now underway to identify the most effective fox-specific zona pellucida protein for fertility control.
- Mouse project: Uncontrolled populations of mice not only disrupt grain production on between 100,000 and 500,000 hectares each year in Australia, they also invade buildings, live-

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stock pens, and other facilities and are a threat to human and livestock health. Rodenticides are not specific and therefore present a risk to human and non-target-animal health. Again, Pest Control CRC is working with zona pellucida, inserting a mouse zona pellucida gene (ZP3) into murine cytomegalovirus. In the lab, the modified virus rendered mice infertile for > 6 months. Modelling predicts that two-thirds of female mice will have to be sterilized to reduce population growth to the point at which the incidence of "mouse plagues" will also be reduced, and contained field studies are now being initiated to see whether this can be achieved. Another group is studying the mouse virus *ectromelia* (mouse pox) in conjunction with the development of an immunocontraceptive vaccine.

The partners in the Pest Animal CRC are: The Australian National University, CSIRO Division of Sustainable Ecosystems, Adelaide University, The University of Sydney, The University of Western Australia, the Agriculture Protection Board of Western Australia, and the Department of Conservation and Land Management.

Marsupial CRC: The Marsupial CRC is geared to combining molecular biology, biotechnology, and laboratory science with ecological expertise to address issues of managing populations of marsupials in their own habitats. To that end, the Marsupial CRC conducts research in reproduction and physiology to support evolving management strategies in *in vitro* fertilization as well as fertility control. The Marsupial CRC website notes that researchers have identified the gene sequences encoding two key marsupial sperm proteins, a precursor to manipulating reproductive processes in marsupials. Researchers have also shown that male wallabies immunized with sperm produce antibodies that reduce the animals' fertility, indicating the potential of this approach to contraception.

The partners in the Marsupial CRC are Macquarie and Newcastle Universities, Landcare Research New Zealand, Queensland Department of Primary Industries, and Perth Zoo. The CRC has alliances with Boyce Thompson Institute for Plant Research (Cornell University, Ithaca, New York, US) and Arizona State University, Phoenix, AZ, US (plant-based vaccine delivery systems); University of Western Sydney; AgResearch (see CSL, section 6.2.4); Ecoplan Australia Pty. Ltd. (population management of marsupials); University of Vienna, Vienna, Austria (delivery mechanism for immunocontraceptive vaccines); Pest Animal Control CRC (see above); the Western Australian Department of Conservation and Land Management (CALM); and Professor Mike O'Rand at the University of North Carolina, Chapel Hill, NC, USA.

CRC overview: www.crc.gov.au/
CRC-Vaccine Technology: www.crc-vt.qimr.edu.au/
Pest Animal CRC: www.pestanimal.crc.org.au/
Marsupial CRC: www.marsupialcrc.com.au/

6.2.4 CSL Ltd., Melbourne, VIC, Australia

Biocor Animal Health (a CSL subsidiary, Omaha, NE, US)

AgResearch (New Zealand basic science company)

AgVax (autonomous development subsidiary of AgResearch)

Celentis (established by AgResearch to market its discoveries)

CSL Ltd. (CSL), formerly Commonwealth Serum Laboratories, is a public company (Australian Stock Exchange: CSL) founded in 1991. CSL's business model is to develop, manufacture, and market human plasma products, cell culture reagents, human pharmaceuticals and diagnostics, and veterinary vaccines and diagnostics. The company has operations in more than 70 nations. CSL has established 17 wholly owned subsidiaries, one partially owned subsidiary, and a number of alliances and collaborations. Both the parent company (CSL) and its US subsidiary, Biocor Animal Health Inc., are involved in developing and marketing veterinary products. CSL also has a relationship with the linked New Zealand companies AgResearch, AgVax and Celentis.

CSL markets Improvac®, an immunocastration (GnRH) vaccine for male pigs to prevent boar taint in pork. Improvac is a synthetic GnRH conju-

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gated to a diphtheria toxoid carrier protein and has been available commercially since 1998.

In mid-2002 CSL launched Equity™, an equine anti-GnRH vaccine in Australia and New Zealand. Equity is labeled as an aid in the control of estrus and estrus-related behavior in fillies and mares not intended for breeding (see Section 4.4.3). The label states "oestrus-related behaviour varies between horses though it is often characterized by squealing, nervousness, squatting and urinating, increased agitation and clitoral 'winking.' Some horses display aspects of oestrus-related behaviour when they are not in oestrus, but generally this type of behavior is increased during the oestrous period of the oestrous cycle. Following vaccination, ovarian activity is suppressed, leading to markedly reduced oestrus-related behavior in most horses."

Estrus suppression induced by Equity can be expected to last for "at least three months and in a percentage of horses will continue for six months or longer."

CSL also markets disease-prevention vaccines for cats, dogs, cattle, horses, pigs, and sheep, as well as several diagnostics produced by its Biocor subsidiary. Biocor (Omaha, NE, US) is a biologicals company that develops and markets diagnostics and bovine, swine, canine, and feline vaccines.

AgResearch (New Zealand) is a government agency that focuses on agriculture-related science. In October 2000, AgResearch launched Celentis to market its science and technology, and simultaneously announced a strategic alliance with CSL. According to an AgResearch press release, the relationship with CSL offers Celentis access to a worldwide distribution and marketing network and provides opportunities for R&D collaborations. For more information on AgResearch, see its website (URL at the end of this section).

AgVax Developments Ltd., established in 1993, is an "autonomous subsidiary" of AgResearch/ Celentis. AgVax develops and commercializes new technologies stemming from biological research and has its own product line. One of AgVax's products is Androvax, a vaccine that improves fertility in ewes by stimulating antibodies against androstenedione that alter the animals' hormone balance and increase the level of FSH, with subsequent increase in mature follicles and number of lambs.

CSL is the "the industry participant" in the Australian Cooperative Research Centre (CRC) for Vaccine Technologies (see Section 6.2.3). The CRC-VT 2000/2001 annual report describes a project to develop a GnRH vaccine for use in dogs and states that "we have clearly shown that on optimization of dose and number of doses, peptide vaccines can render dogs sterile for at least six months."

According to the CRC-VT 2000/2001 annual report, the chair of the team managing the CRC immunocontraception project is Dr. John Walker of CSL. Several other members of the team are also from CSL. Vaccines resulting from this effort can be expected to be further developed and commercialized by CSL.

www.csl.com.au
www.biocor.com
www.agresearch.cri.nz
www.agresearch.cri.nz/celentis
www.agvax.com

6.2.5 Gonex, Inc., Boulder, CO, US

Gonex Inc. (Gonex) was launched in 1995 to develop GnRH-based technology invented by company founders and patent holders Dr. Terry Nett and Dr. Michael Glodé. Dr. Nett is with the College of Veterinary Medicine and Biomedical Sciences of Colorado State University (Ft. Collins, Colorado, US) and Dr. Glodé is Robert Rifkin Professor of Medicine at the University of Colorado Health Sciences Center (Denver, Colorado, US). Gonex has licensed the rights to the technology and is pursuing applications in animal and human health.

In an April 2002 presentation at the International Symposium on Nonsurgical Methods for Pet Population Control (Nett 2002), Gonex Chief Operating Officer Dr. Paul Jarosz noted that the current animal health objective is to provide the market with an injectable product that can sterilize male and female companion animals via a single injection.

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The company's technology chemically links GnRH to a protein synthesis inhibitor (pokeweed antiviral protein – PAP). This protein is from plant leaves and only has cell-killing activity once inside the target cell. There is some evidence that when outside the cell, PAP has no toxic effect (Schlick 2000).

Linking GnRH to PAP allows the protein synthesis inhibitor to be delivered specifically to gonadotroph cells when the GnRH binds to the GnRH receptor and is internalized as part of normal cellular processes, delivering the inhibitor inside the cell.

The target gonadotroph cells in the anterior pituitary gland synthesize and secrete luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Once destroyed, the gonadotrophs are unable to produce sufficient LH or FSH and therefore the injected animal cannot produce viable sperm or eggs. Studies have confirmed that the compound suppresses fertility in rats, sheep, deer, cats, and dogs. Preliminary data (Nett 2002, Ball 2002) show effective suppression of testosterone in male dogs. Some dogs had increases in serum testosterone after 20 weeks, indicating the gonadotroph cells either recovered function, or new gonadotroph cells emerged in the pituitary. This may be a dose-related effect – according to the company, upcoming studies will assess the duration of effect and ascertain whether there is a dosage that induces permanent sterilization.

Assuming permanent sterilization can be achieved, the Gonex technology might be attractive in situations in which sterilization is desirable, because the technology is effective in males and females and should offer benefits that include reduced incidence of testicular and mammary cancers and elimination of estrus (heat) in females (as will any approach that lowers GnRH).

Gonex anticipates that FDA approval will be achieved within four to five years after an INAD has been filed. Once the product has been established in the companion animal market, Gonex plans to explore the market opportunities in livestock and wildlife. If timed correctly in livestock, a product could ultimately be used to sterilize calves to improve weight gain and avoid unwanted pregnancies in heifers. In the wildlife arena, the Gonex product may have the potential to help control the overpopulation of animals such as deer, coyotes, foxes, raccoons, horses, buffalo, and elk.

www.gonex.com

6.2.6 Immucon, Montreal, QC, Canada

Immucon specializes in reproductive technologies. Specifically, the company developed the P34H Sperm Fertilizing Ability Test diagnostic test for infertility in human males. The product is distributed in Canada and Europe by BIOCHEM Immunosystems (Casalecchio Di Reno, Italy).

According to its website, Immucon is working on oral contraceptives for men and women, and reversible contraceptive vaccines for men, women, and animals. The vaccine for women is expected to be effective for 18 months and it is anticipated that the vaccine for men will be effective for 12 months with a 4-to-6 week "recovery" following the period of contraception. In June 1999, the US Patent and Trademark Office granted a patent for Immucon's male contraceptive technology, which is based on utilizing a fragment of protein P26H, a sperm-binding protein that enables sperm to bind to zona pellucida, to neutralize sperm. No information is provided on the company website regarding the potential vaccine for animals and no animal health collaborations or alliances are noted.

www.immucon.com

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6.2.7 Immunovaccine Technologies Inc., Halifax, Nova Scotia, Canada

Immunovaccine Technologies Inc. (IVT) is developing and commercializing a line of veterinary and human vaccines based on its VacciMax™ platform, which enables the delivery of protected nondegraded antigens to the immune system in a proprietary liposome. According to an IVT company profile, the platform has been designed to provide a rapid, high-quality, long-lasting immune response in a range of applications; minimize injection-site reaction; and eliminate the need for boosters. The technology was invented at Dalhousie University (Halifax, Nova Scotia, Canada).

The company's immunocontraceptive vaccines for female animals, called the SpayVac™ line, consist of porcine zona pellucida antigens and an adjuvant encapsulated in the VacciMax delivery system. Like other anti-zona pellucida vaccines, the antigens in SpayVac elicit antibodies that adhere to the surface of the eggs of the treated female. This prevents sperm from binding, thus blocking fertilization.

A single dose is expected to provide contraception for multi-year periods. IVT has evaluated members of its veterinary SpayVac product line in fallow deer and several species of seals. The vaccine was given as a single dose to animals in the wild, and animals were then monitored for pregnancy. In these studies, a single dose provided a >90% reduction in fertility, with no adverse reactions. Seals show contraceptive effects that extend 10 years post-injection and fallow deer trials show 100% reduction in fertility after 3 years.

The first SpayVac-line vaccine is expected to be commercialized for deer. If the vaccine produces long-term suppression of fertility in deer as it does in seals, deer would not have to receive a yearly booster – a big potential advantage that would result in cost savings and better deer control than that provided by products requiring yearly re-treatment (see Section 5.4).

A disadvantage to using a zona pellucida vaccine is that deer that do not become pregnant during normal rutting season will show normal mating behavior, and most probably will continue to come into estrus at regular intervals until the days lengthen and breeding season is over.

IVT is exploring the companion animal market and asserts that researchers have assessed the platform's effectiveness in 10 species of mammals, as well as birds and fish. Each SpayVac vaccine will require species-specific customization.

However, although the product is effective in wild animals tested to date, a recent study in female cats shows that, while cats treated with SpayVac develop high levels of serum antibodies to pig zona pellucida, this does not result in effective contraception, and cats readily become pregnant (Levy 2002). This indicates that the pig and cat zona pellucida proteins are different enough that pig zona pellucida cannot be used as a contraceptive vaccine antigen in cats. IVT is screening various proprietary zona pellucida antigens in an attempt to deal with this issue.

Although no data have been published on the use of SpayVac in dogs, recent research has cast doubt on the use of pig zona pellucida vaccines in dogs, for similar reasons (Liu 2002). See Sections 3.2.1, 4.1.11 and 4.2.6 for more information.

IVT's animal-health collaborations include:

- TerraMar Environmental Research Ltd. (Sidney, BC, Canada): wildlife applications
- Dr. Julie Levy, College of Veterinary Medicine, University of Florida (Gainesville, FL, US): feline applications
- Dr. Janet Horrocks, School of Engineering and Science, University of Albertay-Dundee (Dundee, Scotland): avian applications

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- Dr. Giulio Soldani, Facolta di Medicina Veterinaria, Universita di Pisa (Pisa, Italy): dog applications
- Hong Kong Department of Agriculture, Fisheries and Conservation (Honk Kong, PRC): applications in macaque monkeys
- USDA National Wildlife Research Center (Ft. Collins, CO, US): applications in white-tailed deer
- Humane Society of the United States (Washington, DC, US): applications in white-tailed deer

www.immunovaccine.com

6.2.8 MetaMorphix, Inc., Savage, MD, US MetaMorphix Canada, Saskatoon, SK, Canada

MetaMorphix, Inc. (MetaMorphix) is a privately held company with three technology platforms: genomics/proteomics, growth and differentiation factor, and immunopharmaceuticals. It was founded in Baltimore in 1994, licensing growth and differentiation factor technology from Johns Hopkins University to develop innovative livestock production technologies for improving growth, feed efficiency, and nutritional value.

The company made headlines in March 2002 when it acquired the animal genomics and genotyping business of Celera Genomics Group (Rockville, MD, US and South San Francisco, CA, US), and then again in June 2002 when it announced an agreement with Caprock Cattle Feeders and Excel Corporation, both part of Cargill Incorporated (Minneapolis, MN, US), an international marketer, processor, and distributor of agricultural, food, and other products. The agreement involves developing and implementing genomic selection tools that MetaMorphix expects will enable cattle breeders and feedlot operators to produce beef that meets consumers' expectations.

MetaMorphix is also pursuing immunocontraception for animals as a result of its 2000 acquisition of the immunopharmaceutical assets of Biostar, Inc. Biostar was a rapidly growing Canadian animal vaccine company working on animal vaccines, products for increasing production efficiency in livestock, and immunological sterilization of companion animals. It sold its animal health vaccine line to Novartis Animal Health Canada Inc. in the same time frame in which MetaMorphix acquired the Biostar immunopharmaceuticals business and established a wholly owned subsidiary, MetaMorphix Canada.

MetaMorphix is currently developing a GnRH vaccine for feline contraception (see Section 3.1.4 for details on GnRH vaccines). In one study of male and female cats, immunization of 8 - 12 week-old kittens followed by immunization at ~ 2 years of age led to the suppression of testicular and ovarian function for at least 25 months (Robbins 2002, see Section 4.2.4). There were "minimal and transient" injection site reactions reported in the kittens, with no morbidity or mortality, and no other adverse events seen. It is likely that an annual booster will be required to maintain infertility.

The MetaMorphix GnRH vaccine has a significant advantage over earlier GnRH conjugate vaccines: the MetaMorphix vaccine is made as a recombinant protein, making the manufacturing process more amenable to scale up and commercialization. According to Dr. Sarah Robbins, speaking at the International Symposium on Nonsurgical Cat and Dog Contraception in Georgia (Robbins 2002), the antigen consists of eight copies of GnRH linked to each end of a proprietary carrier protein. The carrier protein is based on a leukotoxin A fragment from *Mannheimia* (formerly *Pasteurella*) *haemolytica*, with the section of the protein responsible for its toxic effects removed. This makes this greater than a 50 kDa protein, which is large enough to elicit a robust immune response to GnRH.

The combination protein is made in an *Escherichia coli* strain of bacteria, using recombinant technology. Dr. Robbins reported that MetaMorphix has scaled this process up to 100 L production under GMP conditions, with a purification procedure that "satisfies FDA requirements."

In a press release dated August 2000 MetaMorphix listed three development-state GnRH vaccine products acquired upon acquisition of Biostar:

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- CLean™ – eliminates boar taint in male pigs
- NeuterVax™ – a nonsurgical alternative to castration in companion animals
- NeuterVax Cattle™ – prevents heifers in feedlots from entering into estrus

The fact that the company has scaled-up GMP manufacturing capability indicates it may be well on the way toward regulatory approvals. Although MetaMorphix has only released information publicly on the use of the vaccine in cats, it is likely that a dog product is also under development, as there is no reason the technology would not be applicable to all species – and dogs present a significant market.

It can be expected that the approval process will be slower for cattle and pig applications than for companion animal application due to human food safety issues.

Neither MetaMorphix nor MetaMorphix Canada has a website.

6.2.9 Peptech Limited, North Ryde, NSW, Australia

Peptech Limited (Peptech: Australian Stock Exchange PTD) focuses on research and development of peptides and proteins for human and animal health applications. Human health targets include cancer, inflammation, and infection.

The company's animal health work revolves around applications of its proprietary peptide delivery technology for fertility control and contraception.

Ovuplant is Peptech Animal Health's first internationally marketed product. It is a subcutaneous implant of deslorelin for use in horses (see section 4.4.4), the same synthetic peptide GnRH agonist being developed for contraception in dogs. The implant measures 3.6mm x 2.3mm and is preloaded in a disposable syringe-like device that inserts the implant subcutaneously into the mare's neck. Ovuplant is designed to induce ovulation in mares within 48 hours after treatment in order to optimize the timing of breeding or artificial insemination. In this application, it stimulates fertility, illustrating that a GnRH agonist can cause stimulation in short-term applications. (It causes suppression of fertility if it is given as a sustained dose over time; see www.ahs.cqu.edu.au/cbs/biomed/about/studies / ovuplant.htm for references and discussion.)

Ovuplant is registered in Australia, Canada, New Zealand, South America, and the US, where it is marketed and distributed by Fort Dodge Animal Health (Ayerst). Other marketing partners include Ayerst (Canada), Boehringer Ingelheim Vetmedica (Germany), and Tri Agro (Argentina).

The fact that Peptech has been successful in developing a deslorelin implant, manufactures the implant under GMP, and has received international approvals for the product shows that the company is capable of doing the same for a similar product for use in contraception in pets.

Peptech Animal Health is currently working on implants for "reversible" (i.e., non-permanent) contraception in male and female companion animals. Studies in dogs have indicated that the company's sustained-release implant platform can deliver an effective dose of deslorelin, the GnRH agonist, for as long as 12 months. Long-term, continuous administration of GnRH agonists suppresses the activity of the pituitary, reducing the secretion of LH and FSH, curbing the production of reproductive hormones, and, according to Peptech's website, modifying aggressive or antisocial behavior (see Section 3.1.1 for more on the mechanism of GnRH agonists).

Peptech's technology is a lipid formulation that protects the active compound, deslorelin, from degradation following implantation, while releas-

ing it at a relatively constant rate. The implant measures approximately 1cm x 2.3mm and is manufactured by extrusion of a proprietary lipid mixture, which is then preloaded into a unique implantation device. This device is then terminally sterilized. The implant is placed subcutaneously between the shoulder blades. No anesthetic is needed. After placement, the implant softens and becomes difficult to detect by palpation of the animal. However, the implant can be located via ultrasonography for removal if necessary. The implant is not absorbed, but it is non-irritating and can remain in place with no tissue reaction.

Studies over a five-year period have evaluated the use of the implant in adult and prepubertal male and female dogs, prepubertal male and female cats, and mature female cats (Trigg 2002). Various doses have been used and the implants can deliver 3, 6 or 12 mg of deslorelin.

Male dogs

Although the initial product is expected to carry a six-month duration label, studies have shown that contraception in male dogs can be achieved for periods of greater than one year depending on certain aspects of the formulation and the dose. Subcutaneous placement of the implant between the shoulder blades appears to have no negative effects on the subject animals and there were no instances of implantation site reaction, according to Peptech. In most animals, contraceptive effects are established by week two, and by week four post-treatment all animals are under the influence of the drug. This follows an initial stimulation by the GnRH agonist that results in a stimulation of testosterone production. To maintain contraception, an additional implant is administered before the effects of the currently implanted device wear off. However, the variability in the duration of effect is large.

Prepubertal male dogs treated with deslorelin showed a delay in sexual maturity with normal fertility developing after expiration of the implants.

How the owner and practitioner will ascertain the optimal time for reimplantation is not clear – for the six-month-duration product, practitioners may just elect to reimplant dogs every six months. The initial label claim will be for a single six-month treatment, but supplementary filings will be made to support repeat dosing.

The product is reported to be very safe. Tissue reactions are not seen at the site of implant, as the implant is biocompatible. Tolerance studies at 10x the normal dose have been conducted in male and female dogs as part of the FDA approval process, and these studies indicate no significant effects on general health, behavior, food consumption, body weight, and clinical pathology, according to the company. This is consistent with the safety of long-acting GnRH agonist products used in humans.

Clearly, Peptech is actively pursuing regulatory approval of this product in Australia and with the FDA/CVM in the US. When questioned at the International Symposium on Nonsurgical Contraception for Cats and Dogs in April of 2002, Dr. Tim Trigg of Peptech said that the company had "no distributor currently," so at this writing it is unclear who will market the product. It may be that this product will be the first "reversible" contraception launched for use in dogs.

Female Dogs

GnRH agonists generally will stimulate estrus in bitches before down regulating fertility (see Section 3.1.1). Results in female dogs vary, apparently due to varying progesterone levels at the time of administration. Anestrous females with plasma progesterone <5ng/ml showed estrus within seven days of implantation while those with progesterone >5ng/ml did not (Trigg 2001). If bitches are bred on this induced estrus they can become pregnant, but won't carry the pregnancy to term (Wright 2001). If bitches are pregnant when implanted with the GnRH agonist, they will experience no difficulties during whelping and puppies will not be affected.

Peptech has completed a study in female dogs (n = 56) as the pivotal trial for regulatory filing in Australia, and hopes to file before the end of 2002.

As in young male dogs, bitches show a delay in

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sexual maturity with normal fertility developing after expiration of the implants.

Cats

Limited studies have been done in prepubertal male and female cats, and results showed a delay in the hormonal and behavioral traits that indicate sexual maturity. In a study (Munson 2001) with 20 female cats, treatment with the deslorelin implant stimulated an initial ovulation, followed by extended periods of suppression of estrus. It appears that research and development on the cat product is not as advanced as that for dogs.

Cattle

Peptech has collaborated with the Animal Sciences and Production Group of Central Queensland University (CQU, Rockhampton, QLD, Australia) on developing a GnRH agonist implant to provide long-term, reversible suppression of ovarian function in cattle produced in extensive management systems. Twelve-month effectiveness has been demonstrated in female cattle. CQU, Peptech and Vetrepharm Pty. Ltd. (Camperdown, NSW, Australia) have collaborated on a "GnRH agonist-LH protocol" for controlling the timing of ovulation in breeding programs such as embryo transfer. These activities are described on the CQU website. (www.ahs.cqu.edu.au/research/aspg/research.htm).

Other potential applications for Peptech's contraceptive technologies include:

- Benign prostatic hyperplasia (BPH) – this condition is common in male dogs older than six years of age. The current treatment approach consists of surgical castration or daily treatment with human drugs. This condition should be treated effectively by the current GnRH agonist under development, and can be pursued as an additional label claim.
- Incontinence – interesting data have come out of Zurich University (Switzerland) indicating that some spayed females that suffer incontinence have responded to deslorelin therapy.
- Stray dogs – studies in Thailand and Indonesia demonstrated "long-term" prevention of fertility in stray dogs. Approval will be sought for the use of the drug in these countries.
- Wildlife – Peptech technology is being tested on elephants, giraffes, monkeys, lions, tigers, African wild dogs, and other species; some data have been presented to the international wildlife reproduction control community.

Peptech, Macquarie University (Sydney, NSW, Australia), and Bioquest Ltd. (North Ryde, NSW, Australia) have received a grant from the Australian Research Council (ARC) to evaluate a modification of the Peptech technology for use in controlling populations of koalas, kangaroos, and deer via permanent sterilization. Peptech continues to collaborate with Macquarie University and Australia's National Parks and Wildlife Service to assess the use of Peptech technology in situations in which culling and/or relocation are unacceptable.

Peptech has intellectual property and patent applications covering the implant formulation and its application to delivery of GnRH agonists in human and veterinary applications. Patents have been granted for the canine contraceptive in the US, the EU, Australia, and New Zealand and are pending in Canada.
www.peptech.com

6.2.10 Pestat Ltd., Canberra, ACT, Australia

Pestat Ltd. (Pestat), a spin off from the CRC for the Biological Control of Pest Animals (see Section 6.2.3), was established as a public company in July 2002 to commercialize the CRC's discoveries. The company is involved in fertility control for pest animal species and is also developing protein production and intellectual property management capabilities.

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Pestat is working on a mouse-specific virus engineered to produce a mouse fertility protein that the company hopes will induce immunity to the protein and result in infertility in mice. The virus will be incorporated in an oral bait. It is estimated that "mouse plagues" damage between 100,000 and 500,000 hectares of grain crops each year in Australia. In South Australia and Victoria, the 1993 mouse plague caused at least $AU55 million in losses. (http://www.pestanimal.crc.org.au/).

One of Pestat's objectives is to use the mouse fertility control technology as the basis for genetic technology with applications in other pest animal species. Pestat is one of the first companies to receive a Federal Biotechnology Innovation Fund grant.

See Section 6.2.3 for more information about fertility control in mice.

www.pestat.com (site under construction as this report goes to press)

6.2.11 Protherics PLC, Cheshire, England, UK

Protherics PLC (Protherics: London Stock Exchange PTI.L) was created in September 1999 by the merger of two companies, Proteus International and Therapeutic Antibodies. (Prior to the merger, Proteus had been involved in developing a chemical sterilant for cats and in 1994 entered into a collaboration with Ft. Dodge Animal Health (Kansas and New Jersey, US,) for various veterinary applications.)

Protherics' proprietary platform technologies are:

- Polyclonal antibodies for use in acute medical emergencies
- Peptide-conjugate vaccines for use in treating chronic diseases

The firm markets rattlesnake and adder envenomation products (CroFab™ and ViperaTAb® respectively) and DigiFab™ for reversal of digoxin toxicity. A vaccine approach for human hypertension and a product to treat sepsis are under development, as are immunotherapeutics for cancer and kidney failure in humans.

Protherics has also licensed technology to Enfer Scientific Ltd. (Dublin, Ireland) to be developed and commercialized as a test to diagnose bovine spongiform encephalopathy (BSE) in carcasses. In turn, Enfer has an agreement with Abbott Laboratories (Abbott Park, IL, US) to extend sales beyond Ireland into Europe.

A GnRH vaccine (Prolog™) for use in human prostate cancer is in clinical trials in the UK. This work has been carried out in collaboration with ML Laboratories (Warrington, UK), but the project has been under review for its commercial viability due to the apparent need for higher doses of the vaccine than originally anticipated. As of the end of May 2002, Protherics and ML Laboratories were discussing the possibility of applying recent advances in Protherics' technology to test a more potent version of the vaccine. There also may be some intellectual property issues related to Protherics patents for GnRH analogues and their use due to rejection of the European patent application. A Listing Particulars document (http://www.fsa.gov.uk/ukla/ protherics_plc.pdf) notes that while the validity of the patent in the US is probably not threatened, the European decision could prejudice patents granted in the UK, Australia and New Zealand.

Protherics collaborated with Janssen Animal Health (Janssen Pharmaceutica, Beerse, Belgium, a part of Johnson & Johnson) on a GnRH vaccine intended to control fertility and improve meat quality in animals. The Protherics web site notes that the project is in the equivalent of Phase II trials. Under the Protherics/Janssen licensing agreement, Janssen was to have manufactured the active ingredient and any formulated vaccines. Janssen evaluated the vaccine in a number of species and achieved proof of concept in cats. Janssen has opted to discontinue its participation in the project on commercial grounds, and Protherics is said to be exploring other opportunities to develop a vaccine for animals.

www.protherics.com

6.2.12 United Biomedical Inc., Hauppauge, NY, US; subsidiaries in Taiwan and People's Republic of China

United Biomedical Inc. (UBI) is a privately held immunotherapeutics and immunodiagnostics company that employs proprietary processes to design and manufacture synthetic peptide products for human and animal health. UBI technology

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is based on refining peptides to act via the immune system.

UBI has worked on several animal health technologies:

- A synthetic subunit vaccine with proprietary vaccine delivery system to prevent foot-and-mouth disease (FMD) caused by the foot-and-mouth-disease virus (FMDV). UBI also has developed FMDV immunodiagnostics that distinguish infected animals from vaccinated animals.
- A vaccine to "remove" boar taint, which is an odor that can affect consumers' perception of the quality of pork meat. The vaccine is a GnRH vaccine, intended to immunocastrate swine by neutralizing GnRH (see Section 3.1.4 for details on the mechanism). It also acts as a growth promoter. According to UBI's website, the boar taint vaccine "has thus far demonstrated 100% efficacy in large-scale trials conducted in swine." At the end of 1998, UBI announced a licensing agreement with Merial Ltd. (Duluth, GA, US) for developing, manufacturing, marketing, and distributing UBI's GnRH vaccine for preventing boar taint.
- A vaccine to reduce allergy in dogs by decreasing the level of immunoglobulin E (IgE), an allergen-specific antibody that, in a dog, binds to mast cells in the dog's skin. When the dog is exposed to the allergen, the IgE signals the mast cells, releasing histamines that cause the manifestations of an allergic reaction. UBI has collaborated with the veterinary school at North Carolina State University (US) and an undisclosed animal health company to evaluate the effectiveness of its canine allergy vaccine.
- An anti-somatostatin vaccine to promote growth in livestock by stimulating anti-somatostatin antibodies. Somatostatin is a hormone that reduces the release of growth hormone (GH) from the pituitary.
- An immunocontraceptive for male and female companion animals that stimulates immune responses against GnRH and is intended to be long acting but not permanent. The vaccine is an application of UBI's GnRH vaccine technology. It is designed to provide a long duration via administration of single-shot annual boosters. The company is conducting clinical trials of its contraceptive vaccine in dogs in collaboration with an undisclosed animal health company.

In 2000, UBI entered into an agreement to manufacture, sell, and distribute its animal health products in the People's Republic of China through China Animal Husbandry Industry Co. in Beijing.

www.unitedbiomedical.com

6.2.13 Zonagen, Inc., Woodland Hills, Texas, US

Zonagen, Inc., (Zonagen: NASDAQ ZONA) develops products for the reproduction, fertility, contraception, women's health, and urology markets. The company was founded in 1987 to commercialize work done by Dr. Bonnie Dunbar of Baylor University (Waco, TX, US) on a zona pellucida contraceptive vaccine for use in animals and possibly humans. In the early and mid-1990s, Zonagen was reported to be working on Zonavax, a zona pellucida vaccine intended to render animals infertile initially and sterile within six months to two years. Schering AG (not Schering-Plough) was involved in early efforts and, in 1997, Zonagen entered into an agreement with Wyeth-Ayerst Laboratories to develop a recombinant zona pellucida for humans. That agreement was terminated in September 2001 after a primate study produced inconsistent results.

At that time, Zonagen President and CEO Joseph Podolski announced that although he believed modifying the antigen could lead to the desired level of reliable contraceptive effects, Zonagen would suspend further research in this area to focus on small molecule projects believed to be better positioned to provide value to shareholders more quickly.

The company's current website does not refer to Zonavax or animal health applications of Zonagen technology.

www.zonagen.com

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7.0 Academic Research on Animal Contraception: What's New?

Over approximately the last 30 years, academic and government researchers have been investigating animal contraception. The majority of the work has involved immunocontraception – either using GnRH in various forms, or porcine zona pellucida as antigens. Much effort has gone into trying to improve the response to these antigens by changing the antigen, adjusting the immunization schedule, or improving the adjuvants.

So, what's new? There has been some success developing immunocontraceptives that provide adequate efficacy with a single injection (Dalhousie University, Halifax, Nova Scotia, Canada, University of California at Davis, California, US and the National Wildlife Research Center, Ft. Collins, Colorado, US). Some researchers are attempting to develop bait systems for delivery of antigens (Virginia-Maryland Regional College of Veterinary Medicine Center for Molecular Medicine and Infectious Diseases, Virginia Tech, Blacksburg, Virginia, US).

Much research has been done to define novel antigens for immunocontraception. Using molecular biology to define sperm proteins (UC Davis and AFSSA Nancy Wildlife Management Unit, Malzéville, France), egg proteins (University of Virginia, Charlottesville, Virginia, US) and naked zona pellucida DNA (Murdoch University, Perth, Australia) as potential antigens for immunocontraception may have some promise, but will present the same challenges as other immunocontraceptive schemes – the difficulty of raising a robust and long-lasting immune response and the development of an acceptable adjuvant system. New GnRH antigens have also been constructed (Academia Sinica, National Chung Hsin University, Taiwan).

As for fundamentally new physiological targets for contraception and fertility control, we may have to wait for the next generation of research, perhaps with the help of genomics and proteomics.

Some of the research centers working on developing contraceptives and fertility control for animals are listed below, in alphabetical order:

7.1 AFSSA Nancy Wildlife Health and Management Unit, Malzéville, France

This group is focusing on fertility control in the fox, using immunocontraceptives based on sperm antigens.

7.2 Baylor College of Medicine, Houston, TX, US

Dr. Bonnie Dunbar, in the Department of Cell Biology, has been investigating the zona pellucida of various mammalian species for many years, and was a pioneer in developing the zona pellucida immunocontraceptive approach (Dunbar 2002).

7.3 Center for Reproductive Science/Technology, University of Missouri, Columbia, MO, US

Dr. Min Wang has been working to evaluate the safety and efficacy of zinc gluconate neutralized by arginine for use as an intratesticular injection for chemical castration in male dogs. This work has been commercialized by Addison Biological Laboratory (see Section 6.2.1).

7.4 College of Veterinary Medicine at Auburn University, Auburn, AL, US

Dr. Brenda Griffin and Dr. Henry J. Baker of the Scott-Ritchey Research Center are testing a combination of unique GnRH constructs and novel adjuvants to produce infertility and suppression of breeding behaviors in male and female cats and dogs. The adjuvant they are researching is a CpG oligonucleotide, which they claim is "non-

toxic, equal in potency to Freund's adjuvant, and highly effective in enhancing immunocontraceptive protein vaccine response." They have identified specific sequences of these oligonucleotide adjuvants for dogs and cats (Baker 2002).

7.5 College of Veterinary Medicine, Colorado State University, Fort Collins, CO, US

Dr. Terry Nett of the Animal Reproduction and Biotechnology Lab has been working with a variety of contraceptive and fertility control technologies, and most recently has done research in collaboration with Dr. Barry Ball, using GnRH protein synthesis inhibitor technology (see Section 3.1.3) to decrease fertility in male and female dogs (Ball 2002). This technology is being developed by Gonex Pets (see Section 6.2.5).

7.6 College of Veterinary Medicine, University of California at Davis, US

Dr. Irwin K. Liu, professor in the Department of Population Health and Reproduction, has been working on zona pellucida vaccines in many species for a number of years, and recently completed a study showing that dogs immunized with pig zona pellucida were not contracepted effectively (Liu 2002). His group is working on developing single-shot, long-acting zona pellucida-based immunocontraceptive treatments for horses.

Dr. Linda Munson has recently published work on the use of GnRH agonist treatment as a contraceptive in cats (Munson 2001).

Dr. Barry Ball has been working with colleagues to identify sperm proteins in dogs (Sabeur 2002), and also to test the GnRH protein synthesis inhibitor technology in male dogs (Ball 2002). See Sections 3.1.3 and 6.2.5.

7.7 College of Veterinary Medicine, University of Florida, Gainesville, FL, US

Dr. Julie Levy has been researching the population dynamics of feral cats under various management situations in collaboration with Dr. Janet Foley of University of California at Davis. Dr. Levy has also tested SpayVac in cats (see Section 6.2.7).

7.8 College of Veterinary Medicine, University of Georgia, Athens, GA, US

Dr. Richard Fayrer-Hosken, of the Department of Large Animal Medicine and Physiology and Pharmacology, leads a group doing research on the use of zona pellucida vaccine in wildlife.

7.9 Cornell Institute for Animal Welfare, Cornell University, Ithaca, NY, US

Dr. Paul Curtis, extension wildlife specialist in Cornell's department of natural resources, and Dr. Milo Richmond, associate professor in that department, have been investigating porcine zona pellucida and GnRH as antigens for contraceptive vaccines for deer. To increase effectiveness, the vaccines contain Freund's adjuvant, which is irritating to deer and sometimes causes lesions at the injection site. Dr. Curtis tested the effectiveness of a new phosphazene adjuvant that will not produce these side effects, but it did not combine well with the zona antigen.

They are now using a laproscopic surgical technique in deer, in collaboration with faculty from The New York State College of Veterinary Medicine at Cornell University. Dr. Curtis feels that in the long run, this will be less expensive than vaccines because each

deer needs to be handled only once. In his opinion, the expense and time required for boosters make vaccines cost prohibitive.

7.10 Division of Veterinary and Biomedical Sciences and the Department of Microbiology, Murdoch University, Perth, Australia

Investigators are using naked DNA coding for zona pellucida proteins as an antigen for the immunization of the cat. T-cell responses have been seen in a small group of animals, but no long-term contraception trials have yet been reported (Eade 2002).

7.11 Institut für Zoo- und Wildtierforschung, Berlin, Germany

Dr. Katherine Jewgenow and her colleagues are working on antigenic determinants of feline zona pellucida protein 1, and have done research on feline zona pellucida antigen expression. This group has also published research on contraception in bears.

7.12 Institute of Molecular Biology, Academia Sinica, National Chung Hsin University, Taichung, Taiwan

Dr. Jaulang Hwang and colleagues have used linear array epitope technology to develop a vaccine against GnRH. A fusion protein, with 19 repeats of GnRH, fused with the receptor-binding domain of *Pseudomonas* exotoxin A, was used as an antigen and tested in 50 female dogs, with 96% generating high titer anti-GnRH antibodies. As yet, no breeding studies have been done.

7.13 Lethbridge Research Center, Lethbridge, Alberta, Canada

Drs. Cook, Kastelic and McAllister have been conducting studies on the use of GnRH vaccines in cattle in collaboration with the researchers who were originally with the Canadian company, Biostar (now MetaMorphix Canada, see Section 6.2.8).

7.14 National Wildlife Research Center, United States Department of Agriculture, Ft. Collins, CO, US

Dr. Lowell Miller and colleagues have been researching immunocontraception in deer using GnRH and porcine zona pellucida vaccines in various formulations. Studies of up to six years in duration have been carried out on deer herds in semi-confined situations (Penn State University, Pennsylvania, US and Seneca Army Depot, New York, US). Coyote studies at Utah State University have also been conducted. The Center is attempting to develop a single-shot immunocontraceptive using Mycopar®, a licensed Johne's vaccine, as an adjuvant in place of Freund's complete adjuvant (Fagerstone 2002).

7.15 New York State College of Veterinary Medicine, Cornell University, Ithaca, NY, US

Dr. Pat Concannon has worked for many years on canine reproduction and the canine estrus cycle.

7.16 Norwegian School of Veterinary Science, Oslo, Norway

Dr. W. Farstad, Professor in the Department of Reproduction, has published on reproduction in the fox and assisted reproduction in various canid species.

7.17 Rutgers University, New Brunswick, NJ, US

Dr. Larry Katz in the Animal Science Department is researching basic reproductive physiology of deer and has tested the efficacy of GnRH vaccines for deer contraception. He and his group have also investigated the use of GnRH agonists, use of prostaglandins and glucocorticoids to terminate pregnancy, and development of baits to either attract deer for treatment or to provide oral administration of various substances.

7.18 University of Liège, Belgium

Dr. John Verstegen, Professor in the Department of Small Animal Clinical Sciences, is an expert in small animal reproduction and has recently published on the use of GnRH agonists in the bitch (Wright 2001).

7.19 University of Pretoria, Onderstepoort, Republic of South Africa

Dr. Bertschinger and others in the Department of Reproduction have conducted research on reproduction in wildlife and published on the use of a GnRH agonist in wild animals (Bertschinger 2001).

7.20 University of Virginia, Charlottesville, VA, US

Dr. Scott Coonrod in the Department of Cell Biology is working on identifying oocyte-specific proteins in dogs and cats. His group has constructed dog and cat ovarian cDNA libraries and plans to "express recombinant forms of these proteins for use in companion animal immunogenicity and fertility trials." (Coonrod 2002, Berkeley 2002).

7.21 Vertebrate Biocontrol Cooperative Research Centre, CSIRO Wildlife and Ecology, Canberra, ACT, Australia

Dr. Mark Bradley has worked on immunocontraception for wildlife control in Australia, and published on sperm antigens and bait systems. (See Section 6.2.3 for information on other Cooperative Research Centres involved in contraception and fertility control in animals).

7.22 Virginia-Maryland Regional College of Veterinary Medicine, Virginia Tech, Blacksburg, VA, US

Dr. Stephen M. Boyle and Dr. Beverly Purswell are working on developing an orally administered immunocontraceptive vaccine for cats. They've taken a genetically engineered bacterium that could be placed in bait and altered it to express a zona pellucida antigen. To determine the most appropriate antigen, they are defining regions of the zona pellucida that are unique to cats, hoping that this will make the vaccine species specific.

Drs. Boyle and Purswell plan to form the Contraceptive Vaccine Center for Feral and Domestic Cats and "through this center of collaboration experts could pool both information and funding in a more efficient manner, bringing solutions quickly to the table," according to the Alliance for Contraception in Cats and Dogs website. (www.vt.edu/accd/).

8.0 Regulatory Issues: Some Considerations for Evaluating Contraceptives

As with any new animal health product, for optimal return on investment, registration should be pursued in all appropriate markets – typically, North America, Europe, Australia, New Zealand, and Japan represent significant animal health markets. Europe in particular is an attractive market for nonsurgical contraceptive products for pets due to the general reluctance to alter dogs and cats surgically. Close cooperation with the Center for Veterinary Medicine of the FDA is needed to expedite the registration process for new drugs in the United States.

Review of all international regulatory considerations and procedures is beyond the scope of this document. In general, each country has its own procedures for meeting requirements, and it cannot be assumed that once FDA/CVM requirements are met, registration is assured in other markets. For example, even within North America, gaining approval in Canada can entail meeting requirements that differ from those of the FDA.

There is an effort to harmonize registration requirements in the major markets – the US, EU, Japan, and other countries are working together to draft guidelines. For each country, a full regulatory submission has to be prepared to achieve approval for marketing. Typically, agencies require that additional clinical trials be conducted in their own countries, and further safety testing may be needed. Considerable effort on the part of sponsors is needed to reformat regulatory submissions and meet all requirements.

In the US, the FDA/CVM has ruled that all immunocontraceptive vaccines will be reviewed by the CVM, unlike vaccines related to disease prevention, which are reviewed and approved by the United States Department of Agriculture (USDA). Therefore, FDA guidelines govern the approval process in the US. In general, protocols are designed to prove effectiveness and safety and to achieve the best claim structure for products. Before clinical trials commence, the CVM reviews the study protocols to help the sponsoring company understand any necessary changes or additions that might help increase the odds that the protocols will meet CVM requirements.

How quickly approvals can follow after submission of all required documentation varies widely depending on the country, the product, and the quality of the submission. Working closely with the regulatory body during the development of a drug or immunocontraceptive can speed the process in some cases, but it would not be unusual for review to take a year or more for companion animal products and longer for production animal products, for which human food safety is a concern.

8.1 Effectiveness

What claims can the label of a contraceptive product contain? The claims are based on the effectiveness of the product and are backed up by clinical data in the relevant species. Design of efficacy claims and clinical trials to prove them must be coordinated with a clear marketing strategy so that at the end of the development process, the market is defined, product attributes meet market needs as closely as possible, and communication with customer groups can be effective.

For contraceptives and fertility control agents, claim structure must include:

- The species in which the product will be used
- Definition of the intended population for the product (e.g., for male and female dogs over six months of age)
- How quickly the product will show its effect (e.g., for vaccines, how long from the initial injection and any follow-up boosters to full contraceptive effect)
- The length of time for which the product is proven to work (i.e., duration of effect)
- The potential reversibility of the treatment (e.g., will animals regain their ability to breed when treatment is discontinued, and if so, in how long a time)
- How the product is used (e.g., injections, oral dosing, implants)
- The schedule of use (e.g., once every six months)
- Dose (if applicable)

It is important for a developer of a contraceptive drug to make sure that the clinical trials are conducted in the widest possible population of a given species in order to achieve the broadest claim. For example, dogs of various ages should be used for the clinical work, as some veterinarians might want to use a contraceptive in adult animals while others will be interested in treating very young animals. A broad spectrum of breeds should be used in clinical trials.

Duration and potential reversibility of effect will need to be measured in clinical trials.

If the label claim is intended to be "effective contraception for a year," breeding studies of at least a year's length will be necessary. How will efficacy be proven if the label claim is permanent sterilization? Multi-year trials over the lifetime of a pet are not practical, and so a label claim such as this may not be realistic unless the product showed actual tissue destruction of the testicles or ovaries. One strategy that companies developing these types of products might want to implement is to launch a product with a label defining a duration of 6-12 months, and then continue the studies, filing label extensions to increase the duration claim, if possible, or to demonstrate that repeat treatment extends the duration of effect.

What about products that may have a variable onset of and decline in efficacy, such as a GnRH or zona pellucida vaccine that may provide six months of contraception in one animal and two years in another? Even in the best of cases, individual animals in a clinical trial will probably have to be followed for at least a year, making clinical efficacy trials long, labor intensive, and expensive. If claims for continued effects based on booster immunizations are desired, multi-year trials will be needed.

For vaccines, codevelopment of a serum antibody test may be helpful, if serum antibodies can be shown to directly correlate to suppression of fertility. This type of correlation would have to be demonstrated adequately in clinical trials. The veterinarian could then periodically test an animal for anti-zona pellucida or anti-GnRH serum antibodies to predict the need for booster vaccinations.

For agonist implants, efficacy can be expected to be dose-related and easier to predict than that of immunocontraceptive agents, which rely on an animal's innate immune response to treatment. Removal of the implant should predictably be followed by return to fertility, the timing of which will need to be documented.

One of the major reasons pet owners spay or castrate their pets is because the animals are exhibiting unwanted behaviors such as estrus behavior in females, and aggression, mounting, and territory marking in males. To include label claims on their contraceptive products such as "use of this product will reduce aggressive behavior," sponsoring companies would have to conduct well-controlled, blinded behavioral evaluations. Even if it can be demonstrated that the proposed contraceptive suppresses serum sex steroids, such as testosterone in males, it is unlikely that regulatory authorities will allow using this surrogate endpoint to make behavior claims. Suppression of estrus behavior may be easier to document than reduction in aggression. If behavioral claims are desired, clinical trials to evaluate behavior will have to be designed carefully. The newly launched CSL Ltd. product for mares does contain a "behavior claim," stated on the Australian label as follows: "an aid in the control of oestrus and oestrus-related behaviour in fillies and mares not intended for breeding." (See Sections 4.4.3 and 6.2.4).

Female dogs that have ovariohysterectomies early in life show a reduced incidence of mammary tumors, and this is probably due to the lifetime reduction of the exposure of the mammary tissue to estrogens. Very likely this would also be true of dogs treated long-term with contraceptives that also suppress estrogen, such as GnRH agonists, GnRH antagonists, GnRH toxin conjugates, and GnRH vaccines (see Section 3.1).

In order to substantiate this benefit and have such a claim on the label of a product, long term, well-controlled studies in dogs would be needed. Since the positive effect is cumulative over a lifetime and mammary tumors are more common in older dogs, it is probable that studies with hundreds of dogs over at least four to five years might be required to prove this type of claim. It would certainly be to a company's advantage to plan to initiate these types of trials early in the development process, so that a supplemental claim could be filed once such trials are complete. However, the cost of a program of such magnitude would have to be balanced against the commercial advantage of having such a claim.

A claim that should be relatively easy to achieve is the effect of contraceptives that suppress GnRH (and therefore testosterone) on the dog prostate gland. Currently, there is no drug approved for the treatment of benign prostatic hypertrophy in dogs, and for animals with enlarged prostates that are causing clinical signs, castration is the recommended treatment. Upon suppression of testosterone levels, the prostate gland shrinks very quickly – in fact, within a week of surgical castration, a decline in the size of the prostate gland can be measured (Rhodes 1999). It should therefore take weeks to months, rather than years, to see measurable effects on the size of the prostate gland in dogs, making design of a clinical trial to achieve this label claim straightforward.

8.2 Target Animal Safety

Obviously, contraceptive products must be safe for the animals, but what exactly does "safe" mean? Safety is generally proved by doing a study in the "target" animal – that is, the animal species in which the product will be used. The resulting study shows that the normal dose and higher doses, sometimes given multiple times, cause no adverse effects. The study must include a reasonable number of animals of the appropriate ages and of both sexes, if the product is labeled for males and females.

Animals are observed for any behavioral changes, and injection or implant sites are monitored for any signs of irritation, pain or inflammation. During the study, blood tests are usually performed to measure any drug effects on serum chemistry and hematology parameters.

At the end of the study, animals are euthanized and full

necropsies are performed – gross pathology and histopathology are required, along with serum hematology and chemistry and other, more specialized measurements depending on the product. All procedures must be done under Good Laboratory Practices (GLP) guidelines, which increases the cost. Designing the protocol for the study, having it reviewed and agreed to by the FDA/CVM (for submission in the US), completing the study (including the histopathology), and writing up a final report can take a year and up to half a million dollars or more, depending on the species and duration of the experiment.

8.3 Human Safety

In all cases, the safety of the person handling products of these types is a concern. If a vaccine or other injectable product has a long-lasting or permanent effect, the people administering the product will be at risk for self-injection and compromise of their own fertility, and the labeling will have to reflect these issues. Some types of products can be expected to be restricted to use by veterinarians only. These requirements would have to be worked out with regulatory agencies.

Exposure to toxic substances such as chemotherapeutic agents and worries about HIV and other infectious agents in human blood have prompted a number of companies to develop injection technology that protects the person giving the treatment. It should be possible for devices to be developed for veterinary contraceptive injections that would similarly protect the veterinarian or technician giving the injections to animals.

This may become an issue even in the development of the current group of immunocontraceptives (see Section 6) that may be entering larger scale clinical trials in the near future. Veterinary clinics may be reluctant to participate in a clinical trial in which their staff members may be exposed to an experimental contraceptive. Certainly it would decrease the risk of participation if the experimental immunocontraceptive were to be delivered via a device that minimized the possibility of human exposure. In fact, the company that launches its contraceptive vaccine or injectable product along with a safe mode of administration should have a definite commercial advantage.

For cattle, and for horses intended for human food (e.g., in the EU), human food safety needs to be taken into consideration when developing contraceptive products. In general, this means that the sponsoring company must prove that meat or milk from animals treated with the drug (or immunocontraceptive) are safe for human consumption.

In the case of drugs, such as GnRH agonists, this means conducting studies on the pharmacokinetics, metabolism, and excretion of the drug; defining all significant metabolites; studying the amount of drug residue found in edible tissues; and defining the time period over which the drug residue declines. Depending on the drug or the residue levels, long-term toxicity studies in at least two species of laboratory animals must be conducted (usually rats and dogs). For the GnRH agonists that have been developed for human use, these toxicity studies will have already been completed to support human regulatory approval. The toxicity data, along with the residue depletion data, are used to set a withdrawal time – that is, the length of time that must pass between treatment of the animal with the drug and slaughter for human consumption.

For immunocontraceptives, studies may have to be completed to show that if a person consumes the meat from a treated animal, and by chance ingests the injected

dose of the immunocontraceptive, there would be no toxic or contraceptive effects. These types of requirements complicate the regulatory approval of these agents for use in food animals.

8.4 Formulation

Probably the least appreciated, but most important, step in bringing a product through commercial development successfully is developing a formulation. Formulations that are used for research proof-of-concept or initial efficacy studies rarely are suitable for full-scale development.

The final formulation needs to be stable – that is, the active drug or antigen has to remain intact over a reasonable shelf life. Preliminary stability studies need to be carried out at temperatures higher than room temperature and at high humidity to help predict long-term stability. If a proposed injectable is to be delivered in a multi-dose vial, the stability of the product remaining after the first dose is removed must be determined.

The formulation must be non-irritating to tissue when injected or implanted, especially if multiple applications are required (e.g., boosters or repeat implants). The formulation must be cost-effective enough to enable a reasonable profit margin. Sterilization methods must be developed that are effective and do not degrade the active antigen or drug. Analytical methods must be developed under GLP conditions to measure the antigen or drug. If an implant is being developed, release rates of the drug need to be demonstrated under a variety of conditions, and if the product is to be an injectable, syringeability must be good. Injectables for use in cattle or horses must be syringeable at cold temperatures.

Once a few possible formulations have been defined that meet these criteria, efficacy of the final formulation must be reconfirmed in a reasonable number of animals. For a contraceptive product, these efficacy tests can take six months to a year, assuming the product claim is for that time frame. Depending on the fragility of the product (antigen or GnRH agonist), the process of reaching a final formulation can take one to two years, and cost several million dollars.

Separate formulations may be needed for various species, especially for adjuvanted products. These formulations must meet all requirements, even if the active drug or antigen in each different formulation is the same.

8.5 Manufacturing

During formulation development, it is necessary to begin to think about how the product will be manufactured and who will actually do the manufacturing. GMP must be followed to meet worldwide regulatory requirements. Some larger animal health companies have manufacturing facilities that can handle these products and have experience in putting together the data that the FDA/CVM and other regulatory authorities require, but smaller companies may have to locate toll manufacturers.

Many requirements need to be fulfilled, and the details will not be reviewed here. In general, packaging, sterility, reproducibility from lot to lot, stability under a variety of handling conditions, cleaning requirements, and labeling need to be worked out. Data may need to be generated on the safety of the product and its raw materials to people exposed in the manufacturing process. The impact of manufacturing on the environment must be defined. Enough product must be made under GMP conditions to conduct the pivotal safety and field studies. Manufacturing must be scaled up to meet demand once the product is launched.

Each formulation of a product needs its own manufacturing process and documentation, so it is desirable to decrease development time and costs

by developing one formulation that can be used in multiple species. Sterilization of the final product is also important for injectable or implantable products, and methods need to be established and proven not to degrade the active ingredients.

In the case of GnRH agonists and antagonists approved for use in humans, GMP-manufactured bulk drug should be readily available, and development could be restricted to establishing a final formulation and manufacturing process. For immunocontraceptives, manufacturing may be more of an issue, particularly since there may be some antigen preparations that are extremely difficult to purify in bulk under GMP conditions. Using pig ovaries from slaughterhouse material as the source for porcine zona pellucida proteins is an example of an approach that may be useful for research purposes, but will be hard to scale up for commercial use under GMP.

Selecting the right manufacturing process or toll manufacturer can make or break a product, its ability to meet regulatory requirements, and its profitability. Fail to fulfill any of the requirements, and no matter how well the product works, it will not be approved for sale.

The costs and timing of meeting the requirements and getting successfully through the approval process with the FDA/CVM and other regulatory agencies worldwide vary depending on the complexity of the product. In general, manufacturing regulations in Australia and New Zealand are not as demanding as those in Europe and the US. Experienced companies know that assembling the necessary documentation for manufacturing can take a minimum of two to three years and carry a multi-million dollar price tag. In some cases, a factory needs to be built, requiring large capital investment.

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9.0 The Future

In some instances, the work that goes into R&D, scale-up, and pre-commercial activities is public; in others it is not. Sometimes competitive strategy keeps developments and collaborations under wraps and information isn't available to the larger community working in the same area. Therefore, any compilation of public information is, by definition, incomplete, as is an assessment of a given field as a whole.

Once a product is actually launched, common sense can help predict the longer range plan for that product, but prognostication is always a little risky. However, looking into the future is part of what motivates advances, and besides, it's difficult to resist.

9.1 Will a Broad Base of Products Be Available?

The foundation is there – years of academic research and commitment to finding nonsurgical alternatives for contraception and fertility control in animals. Progress has been made – contraceptive vaccines are in use in wildlife species, a GnRH vaccine has just been launched for horses in Australia and New Zealand, and several life sciences companies that are commercializing academic research appear to be at the point at which regulatory agencies are looking at their products.

Dogs and Cats

For the pet market, there are three companies currently conducting clinical trials to meet regulatory requirements for contraceptive products: Addison Laboratory, Inc. (Neutersol, the chemical sterilant for males); MetaMorphix, Inc. (a GnRH vaccine); and Peptech Ltd. (a deslorelin non-biodegradable implant). When these companies will succeed in bringing their products through the regulatory process in the major world markets is not known, but it is possible that all three will be launched, in some part of the world, within the next few years.

Because the technologies will be new to the marketplace, companies may wish to invest in educating consumers and veterinarians to optimize sales. Companies bringing the first few products to market will also take on the task of educating the public about nonsurgical alternatives, and the way in which this is done will influence how eager pet owners will be to embrace this change.

Hopefully, within the next five years there will be several products available – this will benefit veterinarians, who will be able to pick the product that's best for a given pet and its owner; as well as benefitting the companies selling the products. These companies will not only provide products, but will be in the business of educating their veterinary clients, thereby strengthening the relationship between companies and vets. The presence of multiple companies with commercial products could contribute to competitive pricing, too.

As products become available, the organizations that make up what this report has called the "shelter community" will have an opportunity to evaluate their current practices and think about how these new technologies might further feral dog and cat population control. With products available, the funding community (e.g., foundations and humane organizations) may shift from supporting research on contraceptive technology to financing purchase of available products and developing a better infrastructure for their use.

Cattle

A cattle product may be farther off – not due to the lack of efficacy of these approaches in cattle, but due to the added challenge of proving human food safety.

Producers tend to prefer animal health inputs that don't require handling cattle more than once, so a single-dose protocol would have more appeal for this market. Price sensitivity among producers is a factor as well, since the market is subject to financial, supply-and-demand, and climate-related ups and downs – when the market is down, producers cut back on inputs.

Animal welfare and animal rights groups will continue to draw attention to livestock production practices that they consider inhumane, and nonsurgical alternatives to spay and castration may

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help address their concerns. These groups are having an impact by working with grocery chains and fast-food outlets – for example, such efforts have led to a McDonald's corporate "animal welfare policy" (www.mcdonalds.com/corporate/social/marketplace/welfare/index.html). It is possible that this type of collaboration could have an influence on the market for a nonsurgical alternative product for use in beef cattle.

Again, education will be key to encouraging cattle producers to adopt new technology. Any company developing products for the cattle market will do well to utilize field (i.e., clinical) trials as well as demonstration trials under commercial conditions in major markets to show the effect of a nonsurgical alternative on the bottom line – less stress could result in less disease, better weight gain, and fewer production inputs.

Horses

In mid-2002, CSL Ltd. (see Section 6.2.4) launched a GnRH vaccine as an aid in controlling estrus and estrus-related behavior in fillies and mares (see Section 4.4). The product is available in Australia and New Zealand. It remains to be seen if the product will be submitted and approved in the EU and US, but this launch will be an interesting testing ground for the commercial potential of such a product.

It is likely that the label will be extended for use in stallions in the future, as the product was launched with a claim in female horses only.

Wildlife

As for wildlife, there are already research-grade porcine zona pellucida vaccines in use worldwide, but they are not available for use in deer that might be taken for meat, as the human food safety issues have not been addressed. Because of the economics of the market and the high costs of developing a GMP manufacturing process and meeting other regulatory requirements, it may be difficult to bring this type of product to market unless either the regulations are changed or the manufacturing process development is subsidized.

Even with subsidies, developing synthetic zona pellucida antigens, for example, is a difficult technical problem – one on which many groups have worked for many years. There may be some hope that legislation in the US (i.e., the minor species minor use bill now making its way through Congress) may make obtaining approval for products for use in wildlife species less onerous. Currently, the economics of achieving regulatory approval make it unlikely that any company can bring a wildlife product to the market unless the product is approved for use in a more commercially viable species such as dogs or cats.

Administration of contraceptives to wildlife also makes it expensive to enter this market – for example, chasing elephants by helicopter to administer a vaccine and tracking treated elephants to administer a booster is expensive and difficult; prying koalas gently out of trees, treating them and, if necessary, relocating them is costly; and, in general, stabilizing or reducing populations of wildlife species can involve programs that consist of multiple approaches and

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have to satisfy a variety of interest groups.

As better long acting vaccines become available, they will prove very helpful in solving the multiple-capture problem. The limit on the use of such products may well be the lack of trained personnel to administer them. These may be among potential uses of funding from non-profit sources – training for wildlife population control program workers and research into better delivery methods.

Political and social issues related to managing wildlife can be expected to have an impact on what methods are deemed acceptable (e.g., permanent versus "reversible"). For example, there is opposition in the US to using immunocontraception in wild horses from some segments of the public, even when the contraception is well documented to be reversible. There is opposition to deer contraception from hunting organizations and fish-and-game agencies in the US, even while the US Federal government is funding research in that area.

The Australians are developing bait delivery and even viral delivery of antigens for contraception, but these approaches can be expected to present significant regulatory challenges in the EU and US.

One thing is sure in the field of wildlife population control – as the human population expands, there will be more and more need for effective control of so-called nuisance species, and the public will be more willing to pay for it. Hopefully, the dedicated community of researchers who work in this field will continue to develop strategies for regulatory approval of the best products, so that they can be used more widely. Wildlife may evolve as a follow-on market for companies that commercialize products for pets, cattle or horses.

9.2 New Technologies

Finding new antigens from eggs or sperm and using them for immunocontraceptives is an area of research that may yield new contraceptive vaccines, but this approach will face the same challenge as the GnRH or zona pellucida vaccines – how to formulate an antigen/adjuvant combination that, when administered, results in robust, effective, long-lasting contraception.

There is a pressing need for new adjuvants to use with well-defined antigens, and, as basic understanding of animal immunology increases, it may be that effective new adjuvants will be found that will help make immunocontraceptives more effective – perhaps single shot and multiyear.

New transgenic technology is making it possible to synthesize proteins in plants, and various companies, such as Epicyte (San Diego, California, US) and Medicago (Montreal, Quebec, Canada), have shown that mammalian proteins, including human antibodies, can be purified from plants with human genes inserted. This technology raises a host of technical and regulatory issues, but could be a source of "cheap" antigen for future immunocontraceptive products (Smith 1997).

Are there any radically new approaches on the horizon? One could imagine that GnRH production in the brain could be decreased using antisense technology. That is, with the *in vivo* synthesis of antisense mRNA, GnRH production could be suppressed (W. Jochle, personal communication). How could this be achieved? Giving anti-sense oligonu-

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cleotides would not be practical, as they would have to be present within the GnRH neurons in the hypothalamus. Perhaps in the future, technology will be available to create a well-regulated type of gene therapy, which could deliver antisense mRNA for GnRH to the appropriate neurons, controlled by a brain-specific promoter. As gene therapy and understanding of regulation of gene expression mature, approaches such as these might be possible. For now, they remain speculative.

9.3 Issues

Contraception and fertility control products intended for use in animals will be subject to scrutiny as to their potential for use by humans as abortion drugs. How to thwart inappropriate use by humans has been a worry for many years in animal drug development. This issue was in the news recently in the US when it was discovered that people were going to pet shops, purchasing potent antibiotics intended for use in pet fish, and using them to treat human infections and colds. For this reason, it is likely that, in general, nonsurgical contraception products will be labeled for use by veterinarians only.

Furthermore, handler safety will continue to be a crucial factor, requiring delivery devices that ameliorate or at least minimize the potential for accidental self-administration. It would be very likely for an inadvertent human exposure to a GnRH vaccine, for example, to result in some suppression of fertility in human males and females, and exposure of a pregnant woman might result in an abortion. This problem is obviously less of an issue with a GnRH agonist implant, for which the potential for accidental exposure is less than with an injectable. For each potential product, the risk will have to be evaluated carefully.

Pricing will be an issue that each company developing products will have to think about carefully, since most nonsurgical approaches will require multiple treatments to maintain efficacy over time, and the products will have to be marked up for the prescribing veterinarians to make a profit. How much recurring expense will be acceptable to a pet owner, for example, as

opposed to the one-time expense of a surgical sterilization? This will have to be balanced against the advantages of the nonsurgical approach and the health benefits of taking a pet cat or dog to the vet regularly.

The animal rights/animal welfare movement may play an important role in this arena. This influence can be seen in Europe, where castration and spaying are regarded by some as mutilations, and "unnecessary" surgery is considered cruel. The availability of nonsurgical approaches, it can be hoped, will enable the animal rights/animal welfare community to envision an acceptable population control methodology.

Given these issues, are the large animal health companies ready to build on the research, take some risk, and make the investment necessary to commercialize some of the promising work to date? The size of the market, the existence of a significant unmet need, the fact that in many cases the traditional animal health segments (e.g., antiparasitics, antimicrobials, anti-inflammatories, vaccines) are extremely competitive, the fact that several collaborations have been undertaken, and the presence of half of the top 10 animal health companies at the International Symposium on Nonsurgical Methods of Pet Population Control indicate that the answer may be "yes."

However, continuing technical issues, expected regulatory hurdles, the fact that several collaborations involving large animal health companies

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have not come to fruition, and the fact that many "big pharma" animal health companies are looking for opportunities that are in fairly advanced stages of development may mean that it will take one regulatory success in a major contraception and fertility control market to encourage the other large animal health companies to follow suit. The question is: which major company will be the first? Or, will this market become a stronghold for smaller life sciences companies with specific technological competencies?

9.4 The Way Forward

The history of human health tells a story of how technological advances have been turned into effective new ways of managing disease, injury, prevention, and other health issues that affect longevity and the quality of life. This is true of animal health, too. But the stage must be set – practitioners and key influencers informed – before a new approach is actually available and accepted. This is the traditional role of medical- and veterinary-education programs. Through these outlets, and, increasingly, via advertising, the word spreads to the consumer and other members of the public. No matter what contraception and fertility control products become widely available, they will represent "something new" – and therefore something that will be adopted at different rates by different stakeholders.

In this report, we have compiled information that we hope will encourage support for efforts to develop products that can offer alternatives to companion animal owners, veterinarians and livestock producers, and help solve population-control and overpopulation issues in free-roaming, feral, wild, and "nuisance" species. We hope that new, mutually beneficial relationships will form at all levels – research and development, commercialization, and marketing – and across interest groups as work in this field continues. And we hope to see new interest in contraception and fertility control among companies whose human health work may hold promise for broader application – in animals

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Appendix 1 – Glossary

ablation – removal of a part (usually by cutting)

antibody – an immunoglobulin that is made by white blood cells in response to exposure to an antigen

antigen – a substance that is administered to an animal to elicit an immune response (usually refers to a protein substance)

bulling – when cows in estrus mount each other as if to breed; this can cause excessive activity and bruising of the hind quarters (bulls and steers may also show this behavior)

castration – technically, removal of either the ovaries of females or the testicles of males, but the term is commonly used to apply to males and it considered synonymous with "neuter"

cDNA – complementary DNA, which defines the DNA coding sequence of a gene and can be used to define the amino acid sequence of a protein

cell-mediated immune response – specific acquired immunity in which the role of small lymphocytes (white blood cells) of thymic origin (T-lymphocytes) is predominant

depot injection – an injection of a drug that is absorbed slowly over a period of time; this allows a drug to have its effect over days rather than hours

down regulation – in the context of reproduction, used to mean that sensitivity to a hormone is decreased, usually due to a reduction in the number of receptors but sometimes due to the unavailability of receptors to respond to the hormone

estrus – also known as "heat;" the time during which an female animal is ovulating and receptive to breeding by a male; it is characterized by specific hormonal and behavior changes

follicle stimulating hormone (FSH) – one of the hormones of the anterior pituitary that stimulates the growth of ovarian follicles in females and spermatogenesis in males

gonadotropin releasing hormone (GnRH) – the hormone that is produced in the brain, released in a pulsatile manner, and stimulates the pituitary gland to release luteinizing hormone and follicle stimulating hormone. It is a small ten amino acid peptide.

gonadotroph – specific cells in the pituitary gland that have receptors that bind the peptide GnRH. These cells produce follicle stimulating hormone and luteinizing hormone.

good manufacturing practice (GMP) – the list of practices to be followed in manufacturing pharmaceutical products to meet world wide regulatory requirements

heat – also known as estrus (see estrus above)

histopathology – a study of the microscopic appearance of tissues to look for any pathological changes caused by an illness, toxin, drug treatment, etc.

IgA – immunoglobulin type A; made by immune cells in response to exposure to an antigen; this type of immunoglobulin is usually secreted onto mucous membranes of the reproductive tract, nasal passages, etc.

IgG – immunoglobulin type G; made by white blood cells in response to exposure to an antigen; this type of immunoglobulin is circulated in the blood

immunocontraception – causing an animal to become infertile by injecting it with an antigen that causes an immune response to some component of the reproductive system, such as eggs, zona pellucida, sperm or GnRH.

glycosylate – to add various types of sugar molecules to a protein; many proteins are glycosylated.

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luteinizing hormone (LH) – one of the hormones of the anterior pituitary that acts to cause ovulation of mature follicles and the secretion of estrogen in females, and stimulates the testes to produce testosterone in males

luteinizing hormone releasing hormone (LHRH) – another name for gonadotropin releasing hormone (GnRH)

necropsy – dissection of an animal's body after death to examine organs and tissues; usually done to determine the cause of death or to study the effect of treatments (called autopsy when referring to humans)

neuter – common term usually used to mean removal of the testicles of male animals, but can also mean spay in females

oligonucleotide – a relatively small fragment of DNA (usually about 2-20 bases)

ovariectomy – surgical removal of the ovaries; generally called a "spay" when referring to female cattle

ovariohysterectomy – surgical removal of the ovaries and uterus; generally referred to as spay when referring to female companion animals

spay – when used in reference to dogs and cats, spay means ovariohysterectomy, or surgical removal of the uterus and ovaries; when used in reference to cattle, spay means surgical removal of the ovaries

zona pellucida – a transparent, non-cellular layer or envelope of uniform thickness surrounding an ooctye (egg); made up of glycosylated protein

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Appendix 3 – Related Websites

These are some of the websites we found useful during the preparation of this report. Obviously, the list cannot contain every source for information on contraception and fertility control in animals. Furthermore, as we all know, URLs change, move, are removed, and expire. Information found on the web, like all information, should be verified by additional sources and not used as a sole source for decision making. Please review the disclaimer at the beginning of this report. The fact that we've listed a given website here does not imply that AlcheraBio endorses the content of the site, nor does this list include every site consulted in preparing this report.

- **www.aaepmarketview.com**– a market research website of the American Association of Equine Practitioners; contains links to other sources of data as well
- **www.affa.gov.au** – website of the Department of Agriculture and Forestry (Australia); contains information about pest animal impact and management
- **www.ahs.cqu.edu.au** – contains information on cattle projects undertaken by Central Queensland University in Australia
- **www.alleycat.org** – website of an organization specializing in nonlethal control of feral and stray cats via trap-neuter-release programs
- **www.animalnetwork.com/cats/reference/neuter4.asp** – website of Cat Fancy Magazine; this link provides information on contraception for pets in Europe
- **www.animalshelter.org.UK** – website of a UK shelter that traces its history to the late 1800s
- **www.aphis.usda.gov/ws/nwrc/research/immunocontraception.html**: this site reviews contraceptive vaccine development by the National Wildlife Research Center of the United States Department of Agriculture
- **www.appma.org** – website of the American Pet Products Manufacturers Association, Inc.; includes US pet industry facts
- **www.avma.org** – American Veterinary Medical Association; miscellaneous information on all species
- **www.beeflinks.com, www.agric.gov.ab.ca** and **www.usask.ca** – information about issues in the North American beef industry, including buller syndrome
- **www.bengalcat.com** – website of the International Bengal Cat Society, with extensive discussion of "animal rights" and "animal welfare"
- **www.canismajor.com** – website with many categories of dog-related information
- **www.cattle.ca/CANFAX/statistics.htm** – Canadian organization with information about cattle numbers and beef consumption in major markets around the world
- **www.cattle-today.com** – cattle industry information, including breeds of cattle
- **www.cfhs.ca** – website of the Canadian Federation of Humane Societies; provides information about animal welfare issues in Canada
- **www.csiro.au** – website of the Commonwealth Scientific and Industrial Research Organization (Australia) which is involved with several organizations working on contraception and fertility control for animals
- **www.dogsncats.asn.au** – statistics on Australian pets
- **www.dontspay.org** –alternatives to the ovariohysterectomy for pets
- **www.ea.gov.au.** – Environment Australia website; information on predation by feral cats

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- **www.facco.fr** – facts and figures about the pet population and pet owner characteristics in France
- **www.fediaf.org** – facts and figures about pet populations and the pet food industry in Europe; links to similar organizations in Portugal, Spain, Italy, Belgium, Norway, France, and Denmark
- **www.feralcat.com** – website of San Diego CA Feral Cat Coalition; also contains information about feral cats in Australia
- **www.frst.govt.nz** – website of The Foundation for Research, Science & Technology which invests in research, science and technology in New Zealand, including wildlife projects
- **www.goodnewsforpets.com** – a source for "pet news," information on the survey The State of the American Pet
- **www.gov.mb.ca/agriculture/statistics** – website of the Canadian province of Manitoba; contains Canada horse statistics
- **www.healthypet.com** – a pet-information website of the AAHA (American Animal Hospital Association)
- **www.horsecouncil.com** – US horse industry statistics
- **www.hsus.org** – The Humane Society of the United States website contains information about the organization's programs for control of animal overpopulation and its support of immunocontraception. Note that there are many regional and local humane society websites as well.
- **www.icawc.org** – website of the International Companion Animal Welfare Conference
- **www.idausa.org** – website of In Defense of Animals US
- **www.landcareresearch.co.nz** – website of the Manaaki Whenua Landcare Research organization (NZ); discusses fertility control for possums
- **www.marsupialcrc.com.au** – A summary of the Marsupial CRC research on contraceptive vaccines for use in kangaroos, wallabies and possums
- **www.mckeeproject.org** – website of an organization that focuses on animal health in Latin America
- **www.messybeast.com** – an unaffiliated website with information on cat issues
- **www.morrisanimalfoundation.org** – publishes Animal/News
- **www.naiaonline.org** – website of the National Animal Interest Alliance (US)
- **www.ovpr.uga.edu** – go to /rcd/researchreporter/spring98/elephant.html for information on contraception in elephants; also search www.nature.com for additional information on contraception in wild elephants
- **www.parkweb.vic.gov.au** – website of Parks Victoria (AU); contains information about koala relocation programs
- **www.pest.cabweb.org** – Biocontrol News and Information from all over the world
- **www.pestanimal.crc.org.au/** - a summary of the Pest Animal Control CRC in Australia, including its work with fox, rabbit and mouse population control
- **www.petfoodinstitute.org** – website of the Pet Food Institute; contains pet-related statistics (US)
- **www.petpopulation.org** – website of National Council of Pet Population Study and Policy (US)
- **www.purina.com** – presentation of the pet population study in the US

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- **www.pzpinfo.org** – Wildlife Forever, a description of the history of using porcine zona pellucida vaccine for control of wildlife, and a review of the use of the vaccine, including recent projects, with links to other sources of information on wildlife conservation
- **www.rspca.org.uk** – website of the Royal Society for the Prevention of Cruelty to Animals
- **www.saveourstrays.com** – website of The Humane Community of America; information on the companion animal/owner bond
- **www.shkd.org** – website of a Turkish group working with programs for the stray dog population in the Istanbul area
- **www.snips.8m.com** – website of The Spay/Neuter Incentive Project and Sanctuary
- **www.spayusa.org** - website of the Spay USA organization, devoted to increasing the number of pets surgically spayed
- **www.spca.bc.ca** – website of the British Columbia (Canada) SPCA. Note that there are many local and regional ASPCA and SPCA sites.
- **www.spcadbn.org.za** – website of the South Africa SPCA
- **www.stlzoo.org/content.asp?page_name=CAGdatabase** – a comprehensive guide to the use of contraceptives in zoo situations; provided as the recommendations of the American Zoological Society Contraceptive Advisory Group.
- **www.stlzoo.org/content.asp?page_name=contraception** – Information about the St. Louis zoo Wildlife Contraception Center and its database on contraceptive methods
- **www.tufts.edu/vet/cfa/feralbib.html** – free-roaming and feral cat bibliography
- **www.vetinfo.com** – pet information website founded by two small animal veterinarians
- **www.vetmed.vt.edu/ACCD/index.html** – website of The Alliance for Contraception in Cats and Dogs, which hosted the 2002 International Symposium on Nonsurgical Methods for Pet Population Control
- **www.vetsonline.com** – information website of the British Veterinary Nursing Association
- **www.wildlifetrust.org.uk** – website of the British Wildlife Trust conservation charity
- **www.wspa-international.org** – website of the World Society for the Protection of Animals
- **www.zoomontana.org/biology.html** – a summary of the work Zoo Montana is doing for wildlife contraception, including a description of the large scale pig zona pellucida vaccine project, with a bibliography of selected articles related to use of pzp for immunocontraception of wildlife

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