

## Chapter 2

# Animal Health Markets and Opportunities: Companion Animal Landscape

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**Abstract** In the future, the global market for companion animal health products is expected to further grow and become more specialized. The major drivers will be the continued strengthening of the bond between owners and their animal companions, increasing companion animal owner awareness, and increasing companion animal owner demands and expectations for companion animal care. This chapter discusses the background knowledge that is required to enable a formulator to differentiate their drug products through novel delivery technologies which address the future companion animal global market needs with the goal of increasing companion animal owner compliance and thus enhancing efficacy.

## 2.1 Introduction

Companion animals (dogs, cats, and horses) have come to play an important part in the lives of many people. They provide companionship and a sense of responsibility, demand care and attention, and respond with affection. Although somewhat controversial, a number of studies have shown that owning a companion animal is associated with positive health benefits [1–3], such as lower blood pressure [2], reduced anxiety [4], reduced cardiac arrhythmias [2], greater psychological stability [5, 6], and improved well-being [7]. In addition, animal-assisted therapy has a number of recognized benefits and is becoming mainstream in a number of areas of human health care [8]. It is therefore no surprise that the bond between companion animals

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**Table 2.1** Key areas affecting the market for companion animal products

<i>Consumers (companion animal owners)</i>	<i>Veterinarians</i>
Economy	Human health advances
Insurance	Regulations
Mobility	Inventory
Travel	Evidence-based medicine
Human–animal bond	Individualization of treatment
Increased diversity of species kept	Emerging diseases
Increasing demands/anthropomorphism	Dispensing/prescription only medicines
Internet	Pharmacies
Pet shops	Technology
Over-the-counter products	Consolidation
Quality of life	Corporate practices
Spend	Practice management
Alternative therapies (herbal, nutraceutical)	Improved medicalization
<i>Disease</i>	<i>Animal health market</i>
Collaboration between medical and veterinary sciences/“One health”	Consolidation
Altered parasite habitats/pathogen distribution	Emerging markets
Diagnostics	Increasing costs
Resistance	Regulation and harmonization
Prudent use guidelines	Pharmacovigilance
Restrictions on use	Intellectual property
Therapeutic vaccines	Generics
Chronic disease	Distribution
	Pet food
	Nutraceuticals

and people is continuing to strengthen and with it the market for products, including pharmaceuticals and vaccines, which contribute significantly to the health and well-being of these animals.

Any look at potential opportunities in the companion animal market, particularly with respect to where formulation may play a role, has to be guided by developments that have shaped this segment over the last few decades. Some, but not all, of the advances have followed, at least in terms of active ingredient or in some instances delivery technology, other market sectors, particularly the much larger market for human health products [9]. Finally, the regulatory framework for veterinary products guides and defines product requirements and approvals around the world. Advances have also been driven by companion animal owner (consumer) and veterinary demand for products that make administration simple, with the aim of maximizing owner compliance; to try to ensure fulfillment of the veterinary professional’s prescribed course of treatment. The numerous approvals of products for companion animals in the last decade reflect the fact that this market segment continues to be attractive [10].

The landscape of the animal health market for companion animals consists of a number of key areas that are not mutually exclusive (Table 2.1).

## 2.2 The Market and Its Players

The market for companion animal health products has grown by around 2.5% per annum in nominal terms since 1992 [9] and has been the main driver of growth in the animal health market globally. The market declined in 2009 due to the negative impact of recessionary conditions but can be expected to stabilize again as and when global economic conditions do so [11]. More than three-quarters of the companion animal market is concentrated in the USA and Europe, where (in alphabetical order) five of the top ten world markets are located (France, Germany, Italy, Spain, and the United Kingdom) [9].

The global animal health market is consolidated with the top ten players controlling by far the majority share of the market. For many years the largest players in the companion animal market have been Merial and Pfizer. The market has seen considerable acquisitions and mergers. Proposed mergers and acquisitions are monitored very carefully by governments around the world (such as the Directorate-General for Economic and Financial Affairs in the European Union and the United States Federal Trade Commission) to protect the consumer from reduced competition, price increases, and reduced innovation. A number of the mergers in animal health have been undertaken to meet human health business objectives—by companies that are players in both sectors, such as Pfizer, Merck, and Sanofi Aventis [12]. Merial, formed in 1997 as a joint venture between the animal health divisions of two human health businesses (Sanofi Aventis's Rhone Merieux and Merck's MSD AgVet), became a wholly owned subsidiary of Sanofi Aventis in 2009. Pfizer purchased Pharmacia Upjohn in 2003 and Wyeth in 2009, driven by its human health strategy. Intervet was purchased by Schering-Plough in 2007 and the resultant Intervet/Schering-Plough Animal Health became Merck (MSD, outside the USA and Canada) Animal Health in 2011, following the 2009 purchase of Schering-Plough by Merck. Elanco (briefly known as Lilly for companion animals) entered the companion animal segment strongly in the USA in 2007 and increased their presence in this market outside the USA through their purchase of Janssen in 2011. Consolidation of the players in this segment is likely to continue [13].

## 2.3 Dispensing and Distribution

The dispensing of medicines has been under discussion for many years. In some countries, such as Italy, veterinarians have a restricted ability to dispense and pharmacies dispense the majority of veterinary prescriptions as well as handling over-the-counter products. The role of the pharmacist has increased in many countries, although training on veterinary species may not have increased in a commensurate fashion [14]. Pharmacists are trained specifically on a number of subjects including

the process of standardizing the dispensing of medicines with, for example, particular focus on length of treatment course [15] where veterinarians focus on the animals under their care and must have a veterinarian–client–patient relationship. With increasing debate and regulation, dispensing may move further into the realm of the pharmacist, which, in many countries, will lead to a potential loss of income for practicing veterinarians.

The internet forms part of the daily lives of many. It has altered business—including the dispensing of medicines and shopping for healthcare products—and communication. Internet pharmacies supplying veterinary medicines to the consumer have been present in a number of countries [16–18] for at least a decade and challenge the veterinarian–client–patient relationship. The internet is here to stay and will continue to confront traditional distribution channels.

## 2.4 Companion Animal Ownership

Companion animal ownership is continuing to increase. Sixty-two percent of US households now own a companion animal (excluding horses), equating to 72.9 million homes [19]. Many other countries are witnessing higher than ever rates of companion animal ownership, including emerging markets such as Brazil, China, India, Mexico, and Russia. Spending on companion animals is also continuing to increase. In the USA, spending has increased from a total of US\$23 billion in 1988 to an estimated US\$51 billion in 2011 [19]. Around 25% of this spending was on veterinary care (including medicines) and a further 20% on over-the-counter products and supplies [12], with the remainder on food, accessories, etc. This trend is being mirrored in other countries.

The population of traditional companion animals, especially dogs and cats, has at best increased only marginally in the last decade but the willingness of companion animal owners to spend more on their animals' health and the ability of veterinarians to meet that need have continued to be key drivers of this market. There are differences between, and even within, countries in the attitudes of companion animal owners towards veterinary visits, with some visiting their veterinarian for disease prevention while others only do so for treatment [20, 21]. In many markets, much of the potential for growth in companion animal veterinary care appears to be related to an increase in spend per animal rather than to an increase in patient numbers [21, 22]. However, in times of economic hardship, there may well be limitations in the willingness of owners to spend on veterinary care as opposed to general companion animal care [11]. Thus, many companion animal practices have developed more creative alternatives to allow companion animal owners to pay for treatment [23].

There is a whole range of other animals that people keep as companion animals, such as rabbits, ferrets, guinea pigs, other small mammals, pet birds, reptiles, and ornamental fish. There is a thriving industry around the care and management of these companion animals. The number of so-called exotic companion animals

presented to veterinarians has increased [24]. However, there is far less data on their numbers and few, if any, veterinary products indicated specifically for use in them. For example, around a decade ago, it was estimated that there could be as many as 5 million pet rabbits owned by 2.2 million households in the United States [25] yet there are still few veterinary products indicated for use in this species.

## 2.5 “One Health”

Collaborative ventures unifying medical and veterinary sciences in areas such as clinical care, disease surveillance and control, education, and research fall under the banner of “One Health” [26]. Climate change, changes in the ecology of parasite habitats, increasing host- and vector-interactions, increased travel by companion animal owners, and importation of animals from endemic areas may be responsible for an increase in the geographical distribution of parasites and an increased risk of vector-borne infection outside traditional endemic areas. This includes not only alterations in the distribution of ticks, such as *Rhipicephalus sanguineus* [27], *Dermacentor reticulatus* (in Europe), and *Amblyomma maculatum* (in the United States) [28] and an increased risk of tick-borne diseases, such as Babesiosis [29], but also changes in the distribution of other vectors and vector-borne diseases, such as Leishmaniasis [30, 31] and heartworm (*Dirofilaria* sp.) [32]. Warm summers suitable for *Dirofilaria* transmission—particularly *D. repens*—in Europe may become the norm [32].

Other parasites, particularly the metastrongyloid lungworms [33, 34] and *Trichuris vulpis* [35] also appear to be spreading and/or may be more prevalent than previously suspected. There are also parasites that pose a significant public health risk, such as *Toxocara* [36] and *Echinococcus multilocularis* [37]. The need for awareness, monitoring, and a good understanding of epidemiology and pathogenesis of companion animals to ensure appropriate year-round control measures has been highlighted by two independent, nonprofit organizations (the Companion Animal Parasite Council (<http://www.capcvet.org>) and the European Scientific Counsel Companion Animal Parasites (<http://www.esccap.org>)).

## 2.6 Resistance

One potential cause of loss of efficacy is resistance. This is inherent to many organisms, such as bacteria and fungi as well as to parasites, and is merely selected for by use, particularly if that use is at concentrations, or in a manner that leads to concentrations, below those that are required to kill sufficient numbers of the target organism. Selection of strains that are tolerant, or able to endure unusually large doses of a poison or toxin, is the first step en route to resistance, heritable genetic adaptation

in the population that results in decreased susceptibility to chemotherapeutic agents, such as antibiotics and pesticides.

There is also concern about the transfer of genetic material coding for multidrug resistance between different species of bacteria [38–41]. For example, in the last 5–7 years, methicillin-resistant *S. pseudintermedius* (MRSP)—an important opportunistic pathogen of companion animals, especially dogs—has emerged, mainly due to clonal spread, as a significant problem [42]. Although reports of colonization and infections of humans with MRSP are relatively rare, the multidrug resistant characteristics of these bacteria mean that they pose a significant risk to animal health but potentially also to human health [43]. There are also methicillin-resistant *Staphylococcus aureus* (MRSA) strains infecting companion animals that are related to clones of MRSA from humans [43]. Many veterinary associations have developed prudent use guidelines promoting appropriate and selective use of antibiotics in companion animals [42]. In future, there may be restrictions on the use of some antibiotics in veterinary medicine and this may extend to companion animals too.

There is evidence that there has been selection for a single-nucleotide polymorphism in the gene encoding a P-glycoprotein transporter in *Dirofilaria immitis*, leading to a homozygous guanosine (“GG-GG”) genotype, which is, when present at a high frequency, phenotypically insensitive to high doses of macrocyclic lactone or, in other words, macrocyclic lactone drug resistant [44]. A microfilarial suppression test can be used to identify the presence of resistant parasites and, perhaps more importantly, map the geographic distribution of this issue [44]. If widespread resistance is indeed an issue, alternative strategies and treatment options will be required in the near future to prevent unnecessary suffering of dogs. There may be a simple, cost-effective, and safe tool to manage infected cases. The endosymbiont *Wolbachia* alters the inflammatory and immune responses to *D. immitis* infection and appears to offer a target for conventional antibiotic treatment [45].

Failures in the control of fleas on dogs and cats are common [46] and are frequently due to inappropriate control measures [46, 47]. There is considerable variation in the susceptibility of flea strains to insecticides [47] and differences between colony flea strains (adapted to being kept in the laboratory) and field strains [46]. There are reports of flea strains that are, or appear to be, tolerant to some of the insecticides that have been used for a number of years for flea control [48]. Variation in susceptibility may result in differences in the ability to control flea infestations [47]. Some of these differences may reflect true resistance in field strains [48–51], although this has not yet been documented definitively. Factors that may play a role in the failure to control flea infestations [46, 47] include failure to reapply treatment at appropriate intervals, as well as the complex biology of the flea, including the relationship between it, its host, and the environment [46, 47]. Treatment failures have been documented, and if widespread resistance becomes a reality, then this will pose a significant challenge in the management of flea infestations. Appropriate strategies, such as product rotation, which has already been implemented for equine anthelmintics, and combining active ingredients, as is used currently for extending the spectrum of ectoparasite activity [52–54], may need to be developed and new agents will be of increasing importance.

## 2.7 Market Segments

Companion animals are living longer [55, 56], and their care often mirrors the trends in human health care. Diagnosis and disease monitoring in veterinary medicine, particularly for companion animals, has also followed trends in human medicine. Diagnostic imaging techniques, such as ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI), have become commonplace and many veterinary practices have in-house analyzers for clinical chemistry and hematology, as well as rapid patient-side tests, e.g., for infectious agents.

There are parallels between certain conditions, such as overweight and obesity and their consequences, between companion animals and their owners [57, 58]. It is therefore no surprise that the companion animal segment is considered to be the animal health segment that is most like the human pharmaceutical sector, with many of the innovations in human medicine, at least in terms of new chemical entities, subsequently adapted and tailored to suit companion animals.

Dogs and cats have been used for many years both in the study of the pathophysiology of human disease and as laboratory animals during the development of products for human health. In fact, there may be some areas where companion animals provide a better model of disease for human medicine than rodents, particularly where a naturally occurring disease in companion animals, such as neoplasia [59–61], is similar to that in humans. Similarly, cats are a good model for human type 2 diabetes [62] but have different lipid metabolism and do not develop the typical metabolic syndrome [63]. In contrast, there are areas where rodents and humans are probably not good models of companion animal disease, such as congestive heart failure and diabetes [64] in dogs.

Infection (viral, bacterial, and parasitic) is still one of the greatest challenges facing companion animals. Chronic, age-related conditions, such as congestive heart failure in dogs, chronic kidney disease in cats, endocrine diseases, such as hyperadrenocorticism in dogs and to a lesser extent in horses, hyperthyroidism in cats and diabetes mellitus in dogs and cats, and osteoarthritis in companion animals, are being diagnosed with increasing frequency. Still veterinary medicine lacks large-scale epidemiological studies that define prognostic endpoints, allowing evidence-based therapeutic decisions. Although there have been research efforts in this area, for example, in chronic kidney disease in cats [65], the drive for properly designed and controlled evidence-based studies is likely to continue and this will ultimately benefit the companion animal population.

There are, of course, many examples where advances in human medicine have been applied to the treatment of dogs, cats, and horses. These agents may be developed for similar indications in companion animals as in humans (Table 2.2). There are also a number of agents where development has been completed for companion animals but not necessarily in human medicine, such as some of the coxibs. Finally, there are also a number of agents used in companion animals that are not available in human medicine. This is particularly notable in the parasiticide arena where many

**Table 2.2** Selected examples of agents approved in human health and/or companion animal health

Agents approved for use in human and companion animal health	Angiotensin converting enzyme inhibitors—enalapril, benazepril, ramipril
	Antibiotics—penicillins (e.g., ampicillin, (potentiated) amoxicillin) cephalosporins (e.g., cefadroxil, cephalexin), aminoglycosides (e.g., amikacin, gentamicin), diaminopyrimidines (e.g., trimethoprim)
	Antiemetics—domperidone
	Antifungals—nystatin, azoles (e.g., clotrimazole, miconazole), posaconazole
	Antiprotozoal—miltefosine
	Corticosteroids—betamethasone valerate, hydrocortisone aceponate, mometasone furoate
	Diuretics—furosemide, spironolactone
	Ectoparasiticides—synthetic pyrethroids—permethrin, deltamethrin
	Gastric acid inhibitors—cimetidine, omeprazole
	Hormones—estriol, thyroxine
	Intravenous anesthetics—propofol
	Nonsteroidal anti-inflammatory drugs—meloxicam
	Macrocyclic lactones—ivermectin
	Mercaptoimidazoles—thiamazole, carbimazole
	Phosphodiesterase inhibitors—pimobendan <sup>a</sup>
	Receptor tyrosine kinase inhibitors—masitinib
	Anthelmintics—emodepside, fenbendazole, febantel
Agents approved for use in animal health not approved for use in human health	Antibiotics—cephalosporins (e.g., cefquinome, cefovecin), fluoroquinolones (e.g., enrofloxacin, marbofloxacin, orbifloxacin, pradofloxacin)
	Antiemetics—maropitant
	Ectoparasiticides—imidacloprid, S-methoprene, pyriproxyfen, fipronil, indoxacarb
	Endectocides—moxidectin, selamectin, milbemycin oxime
	Intravenous anesthetics—ketamine
	Microsomal triglyceride transfer protein inhibitors—dirlotapide, mitratapide
	Neuroleptics—detomidine, dexmedetomidine, medetomidine, romifidine, xylazine
	Phosphodiesterase inhibitors—propentofylline
	Receptor tyrosine kinase inhibitors—toceranib

<sup>a</sup>Also a calcium sensitizer

agents have been developed for endo- and ecto-parasite control from agents used in crop protection (Table 2.2). This may, in part explain why there are many drugs developed for the treatment of dogs, cats, and horses that are not major franchises in human health. Access to compounds developed for use in humans may not be immediately forthcoming even for animal health companies that have a parent human pharmaceutical company. For example, the introduction of angiotensin II receptor antagonists in human cardiovascular medicine [66] has not yet followed in companion animal cardiovascular medicine.



## 2.8 Market Evolution

Twenty years ago the landscape for companion animal products was completely different. The key drivers were infectious agents—viral, bacterial, and parasitic, leading to well-developed and established segments for biologicals or vaccines (predominantly against viral and bacterial agents), antibiotics and parasiticides (against internal and external parasites). Nowadays, parasiticides and pharmaceuticals, including anti-infectives and other pharmaceuticals, represent the largest category, followed by biologicals.

Infectious diseases are still very important in companion animals worldwide. Traditionally, modified live and/or inactivated vaccines are available against many viruses and some bacterial pathogens. Technological developments have led to the use of recombinant viral vaccines for companion animals, such as those incorporating canary pox [67] or myxoma [68]. Perhaps more importantly, vaccination of companion animals, particularly dogs, against rabies has reduced not only this devastating illness in this species but also in humans through reduction in rabid dogs bites and wildlife reservoirs, the latter through oral vaccination campaigns over the last 20 years [69]. Protective (sterile) immunity to some pathogens—such as feline herpesvirus [70] and feline calicivirus—remains elusive. More recently, vaccine research has focused on more recently described viruses, such as feline immunodeficiency virus (FIV), other types of pathogen, such as *Borrelia burgdorferi sensu lato* and *Leishmania infantum* [71–74], and emerging diseases such as West Nile virus. One of the important challenges remains the ability to differentiate between infected and vaccinated animals. One possible approach would be the introduction of so-called marker-vaccine type technology, where the immune response to the vaccine is different from that to the infection, allowing the differentiation of vaccinated and infected animals by means of a simple patient-side test. This is something that is already available in the livestock market and will likely emerge within the companion animal arena. Despite the wide availability of effective and safe vaccines there are still large numbers of young puppies that succumb to serious disease due to parvovirus and distemper virus infections which take hold prior to the onset of active immunity, perhaps where maternal derived antibody has interfered with the ability to respond. There are no antiviral drugs approved for use in companion animals.

Vaccines against *Leishmania infantum*, the causal agent of canine leishmaniosis, have been available in Brazil for a number of years [71, 72] and, more recently, in the European Union [73, 74]. This represents a breakthrough and is also a potentially significant step forward in the fight against this zoonotic disease—where the dog forms a true reservoir for the disease in humans—that poses a significant public health concern because it leads to significant human morbidity and mortality on an annual basis [75]. As in human medicine, vector control is also likely to remain of critical importance.

Therapeutic vaccine technology has also appeared. Here veterinary medicine lead the way with the USDA granting conditional approval of the first therapeutic

cancer vaccine for the treatment of melanoma in dogs [76]. The future increase in the vaccines market is mainly due to the positive approach towards preventive treatment rather than curative one.

### 2.8.1 Compliance

If there is a common theme driving developments in the different segments of the companion animal market it is compliance—the willingness to follow a prescribed course of treatment. When talking about companion animals this means that the companion animal owner has to be willing and able to do this. Although studied extensively in human medicine, few studies have actually focused specifically on assessing owner compliance and many of these have looked at short courses of antibiotic treatment and not long-term medication [77–80]. Interestingly, there is a suggestion that a longer interval between vaccinations (even when this is mandatory rabies vaccination) from 1 to 3 years [81] may actually improve compliance with vaccination. Compliance with heartworm prophylaxis including heartworm testing and recording date of treatment administration has considerable room for improvement [82] and may account for some of the apparent failures of prophylaxis in recent years [44].

Compliance can be improved by reducing treatment frequency or by making treatment easier to administer (and/or remember) as well as by removing the need for the owner to administer follow-up treatment. There are examples of this that utilize the unique interaction between the species and the innate properties of new chemical entities—unique active ingredients. But this can also be addressed through combining active agents (to reduce the number of medications that have to be administered), drug delivery, and value-added services, such as electronic reminder systems.

### 2.8.2 Enteral and parenteral administration

Oral drug delivery is common and usually straightforward, particularly in the dog. While many of the tablets available are conventional formulations, flavored, often chewable, tablets for oral administration are also available in a number of market segments. For example, the standard approach to heartworm (*Dirofilaria immitis*) prevention has, for many years, been the monthly administration of a low dose of macrocyclic lactone (e.g., milbemycin oxime, ivermectin, or moxidectin) formulated as a flavored, and often, chewable tablet. This capitalizes on two things: the exquisite susceptibility of microfilariae to low doses of these compounds and the relatively long half-life inherent to these lipid soluble molecules. Newer nonsteroidal anti-inflammatory drugs (NSAIDs), such as carprofen [83, 84] and meloxicam, brought better safety profiles through being better tailored, both in strength and formulation, to suit companion animals. The solid, and later flavored, oral dosage

form of carprofen was taken a step further by the honey flavored oral suspension of meloxicam, bringing low dosage, easy to administer, although later there was a move from drop-wise administration to a syringe calibrated in body weight. A number of coxib nonsteroidal anti-inflammatory drugs (NSAIDs) are now approved for, predominantly oral use, in dogs [85–87]. Mavacoxib is particularly interesting because it has an inherently long half-life, meaning that it only requires oral administration once per month [88].

Thyroxine supplementation for the treatment of primary hypothyroidism in dogs has also traditionally been administered as conventional tablet formulations, originally developed for use in humans. One of the drawbacks is that a number of different tablet sizes required to be stocked to allow accurate dosing. Liquid formulations of thyroxine enable the dose to be tailored using a dosing syringe [89]. This formulation not only reduces the inventory veterinarians require to stock but also has been shown to be suitable for once-daily administration to dogs, presumably based on achieving higher peak plasma concentrations following oral administration as a result of the absence of a dissolution phase, thus offering a compliance benefit to the owners of hypothyroid dogs [89, 90].

Another way to reduce the frequency of oral administration is to formulate existing active ingredients in prolonged release formulations. For example, conventional tablet formulations of the mercaptoimidazoles thiamazole (methimazole) or its prodrug carbimazole have to be administered two or even three times daily, at least when starting treatment, for optimal efficacy [91] in the management of feline hyperthyroidism [92]. A sustained-release tablet formulation of carbimazole, with prolonged absorption kinetics resulting in a higher area under the curve and more sustained plasma concentrations of thiamazole has been approved for once-daily administration to cats [93, 94].

Fixed dose combination tablets, such as those used for the treatment of hypertension in humans, have not to date been developed for use in veterinary medicine. These would potentially help to simplify oral administration in situations, such as canine congestive heart failure, where multiple medications are required.

Traditional chemotherapeutic regimens for the treatment of canine leishmaniosis have relied upon pentavalent antimonials that have to be administered by injection [95]. Recently, the alkyl phosphocholine miltefosine, originally developed for the treatment of cutaneous neoplasia in humans and used for the treatment of leishmaniosis [96], has been approved for the treatment of leishmaniosis in dogs [97]. This has the advantage that it can be administered orally, rather than by injection. In addition, the antiemetic dopamine D2 receptor antagonist domperidone, which can be administered orally on a daily basis, has also been shown to modulate the course of leishmaniosis in dogs [98].

There are a number of potential novel approaches to insulin delivery that avoid the need for parenteral injection, such as the oral, nasal, and transdermal routes [99] with technologies such as nanotechnology [100], which, if proven feasible and cost effective, will facilitate owner compliance. Some of these [101] have been investigated in dogs and would simplify treatment considerably but have not yet been achievable outside experimental settings. Although inhalation has been used as a route of administration for insulin in humans [99, 102], this has not been highly

acceptable to patients [99] and is not necessarily easier to administer than subcutaneous injection in veterinary patients. With earlier diagnosis of diabetes in cats, there may also be a role for oral hypoglycemic agents if these can be formulated suitably to permit relatively infrequent and easy administration.

A recent advance in companion animal ectoparasite control is spinosad, a naturally occurring spinosyn from the crop protection field [103]. Spinosad is a systemically active compound that is administered once monthly in oral tablet form to dogs for the control of fleas [104, 105]. This active or more correctly its market dynamics has to some extent shifted the market dynamics within the flea control segment. It is probable, given the success of this innovative approach, that further advances will be seen in this field. Future developments in this field are also likely to come from the crop protection field and will continue to focus on easy application and increasing compliance.

Traditional ectoparasiticide products were applied as powders, sprays, and collar formulations. Many of these formulations suffer from a relatively short duration of action and thus require frequent application to avoid gaps in protection. In the early 1990s, lufenuron, a benzoylurea, was shown to be effective against developing stages of fleas after oral administration once monthly [106–109] and as a long-acting (6-monthly) injectable formulation [110], relying on subcutaneous tissue reservoirs for sustained activity.

Compliance with year-round heartworm preventive administration is poor [82]. The development of a sustained-release injectable active over 6 [111] or 12 months [112] reduces the need for companion animal owner compliance. In human contraception, solid dosage forms for oral administration on a daily basis have in part been replaced by implant-technology releasing progestogens over a period of months [113] to years [114]. In veterinary medicine, gonadotropin analogs delivered using this type of technology have been approved for use in dogs and horses [115–117] and have further advanced this technology further by the utilization of a biodegradable formulation [116], precluding the need for (surgical) removal. This type of technology, which may be applicable to other market segments, is interesting because it provides prolonged action with minimal intervention.

Traditionally injectable antibiotic formulations had to be administered on a daily basis. The inherent long duration of activity of a cefovecin, an extended-spectrum cephalosporin, in dogs and cats [118] has allowed the development of a formulation that maintains concentrations above the *ex vivo* minimum inhibitory concentration (MIC) of *Staphylococcus pseudintermedius* for around 12 days in dogs [119] and *Pasteurella multocida* for around 14 days in cats [120]. Although the cost of this long-acting injectable agent is higher than a course of potentiated amoxicillin tablets, this may be offset by the lack of need for owner compliance with the former and thus a lower rate of treatment failures [121], at least for uncomplicated bacterial infections. However, there is some concern, particularly for pathogens that are less susceptible, that concentrations may be below the MIC for prolonged periods leading to emergence of resistance [122].

Carprofen and meloxicam injectable has been used for a number of years as a tool in the management of perioperative pain in cats [123, 124] and robenacoxib

[125] has recently been added to this therapeutic armory. However, what is still missing in this field is the ability to reliably detect and monitor pain in this species. The fact that cats either show few signs or fall almost into a rage makes conducting trials in clinical cases particularly challenging. Although models have been developed to reliably measure and assess the effects of this class of agent in the cat, the step from this into clinical efficacy and safety field trials and beyond into routine use in clinical veterinary practice is still in its early stages.

### 2.8.3 *Topical application*

Topical application is commonly used for local action in the skin. Corticosteroids are used commonly for topical treatment of skin disease in companion animals, particularly dogs. Many topical formulations are oil-based suspensions for application into the external ear canal or creams and ointments for topical application to the skin. Nongreasy gel [126] and spray [127] formulations are also available. The latter may even provide an alternative for oral ciclosporin (also referred to as cyclosporine, cyclosporin A, or cyclosporine), a calcineurin inhibitor, in the management of allergic skin disease (atopic dermatitis) in dogs [128]. Novel calcineurin inhibitors are available and may facilitate improved treatment outcomes and compliance through their efficacy profiles and improved formulations (less frequent dosing).

The use of corticosteroids in dermatology, allergy, and asthma, particularly in humans, is frequently limited by potentially serious side effects, related to the effects of these agents on carbohydrate, protein, and fat metabolism and the immune system. The anti-inflammatory effects of the corticosteroids are presumed to be mainly due to the inhibition of transcription by the glucocorticoid receptor, while the side effects, in the main, are due to activation of transcription. A number of newer agents, such as hydrocortisone aceponate [127] and mometasone furoate [129], are available for topical use in dogs. These improve on the potency of older agents, such as betamethasone valerate [130, 131], but without necessarily an increase in side effects. For example, mometasone furoate is potent but does not dramatically interfere with allergy tests in dogs, following application into the external ear canal at the recommended dose rate for 7 days [132]. Research efforts in human medicine have focused on developing so-called dissociated steroids, where the anti-inflammatory effects and adverse effects are uncoupled (the so-called transrepression hypothesis), with the delivery of an agent that has anti-inflammatory effects without the major side effects associated with prolonged, high dose use of the current corticosteroids [133]. This area has yet to yield suitable steroidal agents and has led to efforts to develop nonsteroidal agents that are glucocorticoid receptor ligands [133, 134]. It remains controversial as to whether this is in fact achievable [133, 134] and the cost constraints in animal health may lengthen the time before which these agents would be seen in animal health, should such a breakthrough be reached. There could be a significant role for such agents in

veterinary dermatology, particularly in the management of atopic dermatitis, for these agents as and when they become available.

In the late 1970s, it was noted that some candidate herbicides had insecticidal activity. Insecticides used in crop protection suffered from user (and consumer) safety concerns, environmental persistence, and rapid development of tolerance. This led to concentrated efforts to develop custom-designed chemicals that specifically target the insect nervous system bringing with them improved user safety, reduced environmental persistence, and, hopefully, slower development of resistance. These new compounds (imidacloprid and fipronil) were both insect neurotoxins, with rapid effects against susceptible adult insects [135]. Fipronil was developed as a spray formulation for the treatment of fleas on dogs and cats [136]. This was soon followed by the development of low volume spot-on formulations of imidacloprid [137, 138], permethrin [139], and fipronil [140] for companion animal ectoparasite control. Following application the lipophilic active agents persist within the stratum corneum, the viable epidermis, and in the pilo-sebaceous units [141, 142]. These products have changed the small animal ectoparasiticide segment forever. Today, there are many such products, which often have their origins in crop protection. A recent entry to this segment is indoxacarb—the only oxadiazine insecticide available in animal health and the only agent that is a pro-insecticide, requiring enzymatic activation or bioactivation (decarbomethoxylation) in the insect (purportedly by esterases and/or amidases) to produce a highly insecticidal active metabolite [143]. Indoxacarb is only weakly active in its parent form, has short environmental persistence, and is essentially detoxified by mammalian hepatic enzymes (by hydroxylation of the inandone group and hydrolysis of the carbomethoxy group) with the insecticidal activity residing in the *S*-isomer [143].

There are also a number of parasiticides that can be applied topically for systemic activity [144]. The use of these agents solely or in combination with more traditional topical ectoparasiticides has extended the spectrum of activity of the traditional spot-on product to include internal parasites (such as heartworm) as well as other ectoparasites, such as mites [145, 146].

Topical application has the advantage that it can get around the need for oral administration—which may be of particular use in the cat. Anthelmintics have traditionally been administered as oral tablets and more recently as flavored tablets in dogs and cats [147–149]. Emodepside is a semisynthetic derivative of a natural *N*-methylated cyclooctadepsipeptides [150] produced by the fungal microflora (*Mycelia sterilia*) of *Camellia japonica* leaves that inhibits nematode pharyngeal pumping [151]. This has been developed as a novel spot-on formulation for cats [152], removing the need for oral administration. Similarly, thiamazole, for the treatment of feline hyperthyroidism, can be delivered topically instead of by orally administered tablets. Extemporaneously prepared formulations using pluronic lecithin organogel appear to be associated with fewer gastrointestinal side effects [153] presumably associated with poor skin penetration with the majority ingested orally by the cat during grooming [154]. Recently, a novel lipophilic topical formulation of thiamazole appears to have met the high quality standards required for commercialization [155].

Demodectic mange was traditionally treated with amitraz, a formamidine insecticide, which, despite its efficacy at insect and tick octopamine receptors [156], is fraught with difficulties in producing a user-friendly formulation and user- and patient-related issues due to its agonist effects at alpha-2 adrenoreceptors in mammals [157]. The advent of spot-on products containing amitraz [158] was a step forward, although the risk of systemic side effects and strong chemical smell are still drawbacks. The efficacy of spot-on products versus demodectic mange remains a challenge, with currently marketed products requiring to be administered more frequently than is required to control other ectoparasites (e.g., every week to 2 weeks) [159–161]. Thus, there is still significant room for improvement to ensure compliance with treatment. There are new developments in the formamidine insecticides, but it remains to be seen whether these newer compounds have good efficacy but fewer side effects and drawbacks.

## 2.9 Delivery Devices

Injection devices, with or without a needle, have been around for decades [162] although only the former have been in routine use for subcutaneous administration in the last 25 years [163, 164]. These devices have helped to improve both patients' quality of life and compliance with therapy [164]. It has only been very recently that this technology has been adapted to veterinary use [165–167].

Percutaneous drug delivery in the form of patches has been used in human medicine since the mid-1980s. Following the availability of opioid patches for transdermal delivery in humans, these agents have been investigated for use in veterinary medicine [168]. Although this type of technology makes drug delivery easy, it is not particularly suitable for use on an outpatient basis in dogs and cats [169]. There have been advances in this area [170], but this means of delivery is not yet in widespread clinical use; however, further advances can be expected as a means of delivering pain control without injection is desirable.

Products for the treatment of otitis externa in dogs generally contain an antibiotic, antifungal, and corticosteroid. Many of the agents have been used for many years, but there are a number of novel agents, such as the triazole antifungal posaconazole and the corticosteroid mometasone furoate [129]. These products are usually delivered in a drop-wise fashion into the external ear canal from a conventional plastic bottle. Recently, an antimicrobial-corticosteroid preparation has become commercially available in a pump [171], which simplifies treatment administration although limited in terms of only being able to administer one dose volume irrespective of the size of the patient. In addition, expandable ear wicks for use with aqueous therapeutic agents similar to those employed in human medicine [172] and ear packing have become popular means of reducing the need for intervention by companion animal owners in the treatment of this chronic, often allergy-based, condition. Many veterinary dermatologists compound their own formulations combined with either an ear wick or ear packing enabling the treatment to remain in situ in the external ear



canal while absorbing exudate for a period of a few weeks following cleaning of the external ear canal. To date, this type of longer acting delivery technology has not yet become widely available commercially. Given the frequency of this indication and its chronicity, it is likely that further advances will be seen in terms of improved delivery perhaps bypassing the companion animal owner, in this field.

## 2.10 Food Interactions and Diet

One way of simplifying administration for many companion animal owners is the administration of the treatment with food. The potential of food and/or feeding status to alter drug absorption and thus systemic availability has been recognized for a long time. Food can impact the pharmacokinetics of a drug through several mechanisms, including, but not limited, to enhancement in drug solubility, changes in gastrointestinal physiology, or direct interaction with the drug. Some of these effects, such as cation chelation by the tetracyclines, have been long known [173]. Significant food effects complicate the development of new drugs, especially when clinical plans require control and/or monitoring of food intake in relation to dosing. In many cases, little is known about the drug–food interaction. This effect can either be positive [93, 174–179]—absorption is enhanced by the presence of food in the gastrointestinal tract—or negative [85, 176, 180–182]. There are models available that can help predict the qualitative effect of feeding status on drug absorption [183]. Developing specific formulations, such as a self-emulsifying drug-delivery system, so that food–drug interactions are reduced, minimized, or avoided, may offer a possibility in future [184, 185]. But, perhaps more importantly, knowledge about the effects of feeding status on drugs used in companion animals needs to be investigated further.

Appropriate diet has been used to support traditional pharmaceutical therapy for decades in the form of, for example, salt restriction in cardiac disease. So-called prescription diets have been available commercially for more than 20 years. Recently, an iodine-restricted diet has been commercialized for the management of hyperthyroidism in cats. Iodine restriction is not new and is used on a short-term basis for 1–2 weeks prior to radioactive iodine therapy in humans [186]. Long-term dietary iodine restriction is controversial as iodine deficiency has a number of well-documented effects including hyperthyroidism and goiter [187] and may have negative effects on cardiovascular health [188]. That said, similar to diets that, by managing carbohydrate intake for diabetic cats, can potentially alter insulin requirements [189, 190], the iodine-restricted diet presents a potential breakthrough in the sense that approaching therapy by means of dietary control is a likely target for future development. In future, further therapeutic diets may become available.



## 2.11 Individualized Treatment and Pharmacogenomics

Antibiotic treatment has been targeted to suit the individual for many years through the use of bacterial culture and antibiotic susceptibility testing. More recently, surrogate parameters have been used to establish clinical and epidemiological break-points. For time-dependent antibiotics (e.g., penicillins and cephalosporins) the time above the minimum inhibitory concentration ( $T > MIC$ ) is used to predict clinical efficacy [191]. For time-independent (otherwise known as concentration-dependent) agents (e.g., aminoglycosides, fluoroquinolones) the ratio of  $C_{max}$  to MIC and/or AUC to MIC is used [191]. Finally, the “mutant selection window” hypothesis postulates that a specific drug concentration zone exists where antibiotic exposure selects for mutant bacterial strains with reduced drug susceptibility [192]. This approach, using the ratio of AUC to the mutant prevention concentration (or MPC—the MIC of the least susceptible mutant in a colony), focuses on maintaining drug concentrations throughout the dosing interval to try to decrease the emergence of resistance [192]. Although there has been some research in this area, to date there is little data on the use of surrogate parameters in veterinary medicine. It is expected that there will be further advances in this area of pharmacokinetic–pharmacodynamic integration to better tailor therapy to suit the individual patient.

The impact of the ATP binding cassette (ABC) transporter protein superfamily on drug pharmacokinetics and pharmacodynamics has been increasingly recognized. P-glycoprotein (P-gp), the product of the ABCB1 (formerly the multidrug resistance or MDR1) gene, is among the most well-characterized drug transporters, particularly in veterinary medicine. P-gp is expressed by a variety of normal tissues, including the intestines, brain capillary endothelial cells, renal tubular cells, and biliary canalicular cells, where it functions to actively extrude substrate drugs [193]. In this capacity, P-gp limits oral absorption and the entry of many drugs into the central nervous system as well as enhancing their excretion from the body. Many drugs used in veterinary medicine are substrates for P-gp, including many chemotherapeutic agents and macrocyclic lactones. A naturally occurring, four base pair deletion mutation in the ABCB1 gene occurs in many herding dog breeds, including collies, Australian shepherds, and Shetland sheepdogs [194–200]. The mutation (ABCB1-1 $\Delta$ ) renders affected animals extremely susceptible to adverse effects of P-gp substrates at doses well below those tolerated by dogs with the wild-type genotype because they are unable to transport these agents from the brain back into the blood [194, 196, 198–200]. Further investigation of this area will likely lead to more targeted individual therapy.

While inter-individual variation in drug metabolism is well recognized in human medicine, there is an ongoing debate on population kinetics in veterinary medicine. Population kinetic studies are not mandatory but provide further evidence to support field efficacy and safety trials based on selection of the correct dosing regimen [174]. It is likely that individualization of treatment will continue to develop and in future there may even be specific product information for subpopulations within a species.

## 2.12 Generics, the cascade and compounding

Animal health companies invest up to somewhere in the region of 10% of their annual turnover into research and development [9]. In fact, the cost of development has increased by more than 150% [9]. Costs and complexity are likely to continue to increase in line with human health, despite the fact that the animal health market is far smaller than its human counterpart.

### 2.12.1 *Generics*

A generic veterinary product is a product with the same quantitative and qualitative composition (i.e., active substance and pharmaceutical form) that has been demonstrated, in appropriately designed bioavailability studies, to be bioequivalent to the reference product. Bioequivalence is a complex area [201]. The assumption is that if two products are bioequivalent then the pharmacological effects, in terms of safety and efficacy, should be more or less the same. However, there are tremendous implications for other important parameters, particularly those related to efficacy, because the pharmacokinetics of the reference and generic product are generally not identical. In addition, there are a number of situations, such as active agents with highly variable pharmacokinetics, prolonged-release formulations, and topical products, where straightforward bioequivalence calculations may not be appropriate [202–205].

In human health, the launch of generic products, after data and patent protection of reference products have expired, has significant financial impact. Thus, it is no surprise that the protection of intellectual property frequently leads to litigation [206]. In animal health, the protection of intellectual property is equally as important as it is essential to recoup product development costs [207], which are in the region of €50 to 200 million (or around US\$65 to 265 million) per product [9]. Authorized veterinary generics exist legitimately and can be used by veterinarians in the same way as other authorized veterinary medicines. Human medicines (including generics) that are similar to the authorized veterinary medicines may not be used unless there is no suitable veterinary medicine available.

There are generic products in many segments of the companion animal market as a number of the active ingredients found in key reference brands no longer benefit from intellectual property protection. Generic entrants make market segments increasingly crowded and, although price tends not to fall as dramatically as it does in human medicine, the pricing structure within a segment is generally altered. Some reference brands have still been able to maintain a competitive edge by adding additional claims, changing formulation (e.g., from traditional tablets to flavored chewable tablets or by adding additional active agents [52]). Given the costs incurred in and time required (around 8–12 years) [9] to develop new animal health products, it is likely that intellectual property, not only in and around new chemical entities but also on formulations and manufacturing processes, will remain an important and highly competitive, and potentially litigious, area.

### 2.12.2 *The cascade*

European Union legislation is designed to ensure the quality, safety, and efficacy of veterinary medicines. It has, however, been recognized that there are circumstances where the benefits of treatment with unauthorized medicines outweigh the potential risks. This, legal exemption, is known as the “prescribing cascade” and is intended to increase the range of medicines available for veterinary use.

The cascade provides a legal mechanism that allows veterinarians to use their clinical judgment to prescribe a suitable medicine where no authorized veterinary medicine exists. If there is no medicine authorized for a specific condition, the veterinarian caring for the animal may prescribe another product, such as one licensed for use for another condition, another species, in another country or for human use, subject to specific conditions, including where appropriate import requirements. It is only if there is no such medicine available that a medicine can be prepared extemporaneously (by definition provided, made, or adapted as an expedient; make-shift) by a veterinarian, pharmacist, or the holder of an appropriate authorization to manufacture.

The choice of medicine under the cascade should be based on clinical grounds and not on cost. Thus, it is not possible to choose a product approved for use in humans just because it is cheaper than a veterinary product. The cascade not only applies to the choice of medicine but also, for example, to the dose rate chosen. Any variation to what is stated on the license of an approved veterinary product would constitute off label (or extra label) use.

### 2.12.3 *Compounding*

The extemporaneous manufacture (or compounding) of medicines for use in animals, frequently by so-called compounding pharmacies, is far more common in the United States [208] than in the European Union [209]. Compounding is generally considered to be an option when the compounded product provides an individual patient with a significantly different product than that available commercially, such as a product compounded to facilitate dosing of an animal with a body weight lower than targeted by the commercially available tablet sizes or one without a coloring agent or excipient to which a particular individual is allergic. In general, since compounded products are exempt from standard approval requirements, including those relating to manufacturing quality [210], it is not intended that they be advertised or promoted.

The responsibility of ensuring that the medicine used is both safe and effective is the responsibility of the veterinarian caring for the animal [208]. Compounding, while it may be appropriate for the optimal treatment of specific cases, is by nature not intended for widespread use as it can be fraught with potential pitfalls, particularly with regard to pharmaceutical quality [208, 211]. Excipients may differ, batch testing may not be performed, long-term testing of the stability of the finished product

is often not conducted, and the shelf life before and after opening [212, 213] and optimal conditions for storage may not be known [212–214]. For example, it has been shown that compounded protamine zinc insulin seldom conforms to the United States pharmacopoeia (USP) [215]. In general, there is a dearth of public or published information on the content and characteristics of extemporaneously prepared products, even those in almost routine use for companion animals in the United States.

There generic products in many segments of the companion animal market as a number of the active ingredients found in key reference brands no longer benefit from intellectual property protection. Generic entrants make market segments increasingly crowded and, although price tends not to fall as dramatically as it does in human medicine, the pricing structure within a segment is generally altered. Some reference brands have still been able to maintain a competitive edge by adding additional claims, changing formulation (e.g., from traditional tablets to flavored chewable tablets or by adding additional active agents [52]). Given the costs incurred in and time required (around 8–12 years) [9] to develop new animal health products, it is likely that intellectual property, not only in and around new chemical entities but also on formulations and manufacturing processes, will remain an important and highly competitive, and potentially litigious, area.

## **2.13 Regulation and pharmacovigilance**

### **2.13.1 Regulation**

The quality, safety, and efficacy of animal health products have to be demonstrated and undergo scientific review by the regulatory authorities before such products can be granted a license. The process ensures that only those products of a defined standard, which have been tested thoroughly and reviewed carefully, reach the marketplace [9]. As part of this process a file or dossier containing all of the data pertaining to all of the studies conducted with a product is submitted to the competent authority.

In the United States, the Department of Agriculture (USDA) is responsible for vaccine registration, at least for those products that are for the prevention of infectious disease [216]. Within the same jurisdiction, the Environmental Protection Agency (EPA) is responsible for the regulation of pesticides, including products with topical activity for the control of ectoparasites on dogs and cats, and the Food and Drugs Administration's (FDA) Center for Veterinary Medicine (CVM) is responsible for the regulation of pharmaceutical products, including pesticides that work systemically and thus require a veterinary prescription [216]. The European Medicines Agency is the central body with groups responsible for the approval of human and veterinary medicines. The centralized procedure is obligatory for medicinal products derived from biotechnology and for other products where a new chemical entity and/or delivery or formulation technology is used [9].

Product approval is not a one-off procedure but ongoing work is required to defend the licenses of existing products, which utilizes around 35% of animal health companies' annual budget for research and development [9]. Not only that, but requirements are, in general, increasing and becoming more stringent [9]. With the increasing complexity of the regulatory constraints, it is expected that, at least for innovative and novel animal health products, the time to market and costs will continue to increase. A number of initiatives have promoted harmonization. Under the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH), the US, European Union, and Japan, observed by Canada and Australia/New Zealand, have worked towards harmonization of the technical data requirements prior to granting market authorization [217]. This has led to a number of guidelines that have been implemented, including one for veterinary medicinal products including vaccines.

Other initiatives have aimed at promoting innovation and increasing the number of approved veterinary medicinal products, such as the EMA initiative for assisting micro-, small-, and medium-sized pharmaceutical businesses [218]. At least 31 companies (16 in animal health and 15 companies developing products for both human and veterinary medicine) have met the strict criteria for the Small- and Medium-Size Enterprise (SME) initiative. However, the success rate of these concerns has been lower than for larger enterprises, mainly due to quality issues [218]. To address a gap in animal welfare, minor use, minor species (MUMS) regulations have been put in place to cover not only these so-called minor species but also less common [minor] use of products in major companion animal species [219–221].

### ***2.13.2 Post marketing surveillance***

Pharmacovigilance (or post marketing surveillance) involves the monitoring, researching, assessment, and evaluation of suspected adverse effects of veterinary medicinal products (including lack of expected efficacy and effects in human users). Data is collected not only throughout the development of a veterinary medicinal product but also after a product has been granted approval. Many countries have well-established spontaneous reporting systems that allow veterinary healthcare providers and users to report suspected adverse drug reactions. These reporting systems apply to all medicines used in animals whether within the label for a veterinary medicinal product or relating to off (or extra) label use.

Important lessons can be learned about the performance of agents in a population after a product has been launched onto the market. This is related to the use of the product in much larger numbers of animals and reflects potential variance in pharmacokinetics (e.g., rate and extent of absorption) as well as interactions both with other agents and with the altered physiology found in many disease states. The collation of pharmacovigilance data can lead to adjustment of the product license to take into account effects seen when used in the population intended to be treated.

## 2.14 Conclusions

In the years to come, the worldwide market for companion animal health is expected to grow further. It will also continue to become more specialized. Major drivers of this are the continued strengthening of the bond between owners and their animal companions, increasing companion animal owner awareness, and increasing companion animal owner demands and expectations for companion animal care. With increasing urbanization, there will continue to be a shift in the species and type of companion animals kept and, while growth in the care of these species is expected, this will of course be influenced by economic, social, and demographic trends. There is a need for evidence-based studies in companion animals and this, along with increasing global regulatory requirements, will continue to increase product development costs. While new chemical entities will continue to emerge, influenced by the much larger arena of human health, and to challenge traditional delivery concepts, there will also be increased focus on differentiating products through novel delivery technology designed to increase companion animal owner compliance and thus enhance efficacy.

## References

1. Friedmann E, Son H (2009) The human-companion animal bond: how humans benefit. *Vet Clin North Am Small Anim Pract* 39:293–326
2. Arhant-Sudhir K, Arhant-Sudhir R, Sudhir K (2011) Pet ownership and cardiovascular risk reduction: supporting evidence, conflicting data and underlying mechanisms. *Clin Exp Pharmacol Physiol* 38:734–738
3. Wood L, Giles-Corti B, Bulsara M (2005) The pet connection: pets as a conduit for social capital? *Soc Sci Med* 61:1159–1173
4. Jennings LB (1997) Potential benefits of pet ownership in health promotion. *J Holist Nurs* 15:358–372
5. McConnell AR, Brown CM, Shoda TM, Stayton LE, Martin CE (2011) Friends with benefits: on the positive consequences of pet ownership. *J Pers Soc Psychol* 101:1239–1252
6. Knight S, Edwards V (2008) In the company of wolves: the physical, social, and psychological benefits of dog ownership. *J Aging Health* 20:437–455
7. Cline KM (2010) Psychological effects of dog ownership: role strain, role enhancement, and depression. *J Soc Psychol* 150:117–131
8. Palley LS, O'Rourke PP, Niemi SM (2010) Mainstreaming animal-assisted therapy. *ILAR J* 51:199–207
9. International Federation for Animal Health-Europe (IFAH-Europe) (2008) Facts and figures about the European animal health industry. [http://www.ifaheurope.org/files/ifah/document-slides/41/199\\_FFfinal.pdf](http://www.ifaheurope.org/files/ifah/document-slides/41/199_FFfinal.pdf). Accessed 29 Jan 2012
10. Philips M (2007) The pets we love—and drug. *Newsweek* 149:40–41
11. Volk JO, Felsted KE, Thomas JG, Siren CW (2011) Executive summary of phase 2 of the Bayer veterinary care usage study. *J Am Vet Med Assoc* 239:1311–1316
12. Buhr BL, Holtkamp D, Sornsen S (2011) Healthy competition in the animal health industry. *Choices* 26. Accessed 16 Mar 2012
13. Geary TG, Thompson DP (2003) Development of antiparasitic drugs in the 21st century. *Vet Parasitol* 115:167–184

14. Ceresia ML, Fasser CE, Rush JE, Scheife RT, Orcutt CJ, Michalski DL, Mazan MR, Dorsey MT, Bernardi SP (2009) The role and education of the veterinary pharmacist. *Am J Pharm Educ* 73:16
15. McDowell A, Assink L, Musgrave R, Soper H, Chantal C, Norris P (2011) Comparison of prescribing and dispensing processes between veterinarians and pharmacists in New Zealand: are there opportunities for cooperation? *Pharmacy Practice* 9:23–30
16. O'Rourke K (2002) Florida Board of Pharmacy disciplines PetMed Express. Savemax. Internet pharmacies given another chance. *J Am Vet Med Assoc* 220(1583–1584):1604
17. van Herten J (2008) KNMVD sees veterinary court decision about internet pharmacy Medpets in good hands. *Tijdschr Diergeneeskde* 133:815
18. Anonymous (2001) DEA addresses queries about Internet pharmacies. *J Am Vet Med Assoc* 219(4):423–424
19. American Pet Product Association (APPA) (2012) 2011–2012 National Pet Owners Survey. [http://www.americanpetproducts.org/press\\_industrytrends.asp](http://www.americanpetproducts.org/press_industrytrends.asp). Accessed 29 Jan 2012
20. Klumpers M, Endenburg N (2009) Pets, veterinarians, and multicultural society. *Tijdschr Diergeneeskde* 134:54–61
21. Wolf CA, Lloyd JW, Black JR (2008) An examination of US consumer pet-related and veterinary service expenditures, 1980–2005. *J Am Vet Med Assoc* 233:404–413
22. Baguley J (2011) An analysis of the demand for and revenue from companion animal veterinary services in Australia between 1996 and 2006 using industry revenue data and household census and pet ownership data and forecasts. *Aust Vet J* 89:352–359
23. Dunn L (2006) Small animal practice: billing, third-party payment options, and pet health insurance. *Vet Clin North Am Small Anim Pract* 36:411–418, vii
24. Vermeulen P, Endenburg N, Lumeij JT (2008) Numbers of dogs, cats, birds, and exotic animals in veterinary practices in the Netherlands 1994–2005 and possible consequences for the veterinary curriculum. *Tijdschr Diergeneeskde* 133:760–763
25. USDA (2002) US Rabbit industry profile. [http://www.aphis.usda.gov/animal\\_health/emergingissues/downloads/RabbitReport1.pdf](http://www.aphis.usda.gov/animal_health/emergingissues/downloads/RabbitReport1.pdf). Accessed 16 Mar 2012
26. Palatnik-de-Sousa CB, Day MJ (2011) One Health: the global challenge of epidemic and endemic leishmaniasis. *Parasite Vectors* 10:197
27. Parola P, Socolovschi C, Jeanjean L, Bitam I, Fournier PE, Sotto A, Labauge P, Raoult D (2008) Warmer weather linked to tick attack and emergence of severe rickettsioses. *PLoS Negl Trop Dis* 2:e338
28. Teel PD, Ketchum HR, Mock DE, Wright RE, Strey OF (2010) The Gulf Coast tick: a review of the life history, ecology, distribution, and emergence as an arthropod of medical and veterinary importance. *J Med Entomol* 47:707–722
29. Porchet MJ, Sager H, Muggli L, Oppliger A, Müller N, Frey C, Gottstein B (2007) A descriptive epidemiological study on canine babesiosis in the Lake Geneva region. *Schweiz Arch Tierheilkd* 149:457–465
30. Petersen CA (2009) Leishmaniasis, an emerging disease found in companion animals in the United States. *Top Companion Anim Med* 24:182–188
31. Aspöck H, Gerersdorfer T, Formayer H, Walochnik J (2008) Sandflies and sandfly-borne infections of humans in Central Europe in the light of climate change. *Wien Klin Wochenschr* 120(Suppl 4):24–29
32. Genchi C, Kramer LH, Rivasi F (2011) Dirofilarial infections in Europe. *Vector Borne Zoonotic Dis* 11:1307–1317
33. Morgan E, Shaw S (2010) *Angiostrongylus vasorum* infection in dogs: continuing spread and developments in diagnosis and treatment. *J Small Anim Pract* 51:616–621
34. Helm JR, Morgan ER, Jackson MW, Wotton P, Bell R (2010) Canine angiostrongylosis: an emerging disease in Europe. *J Vet Emerg Crit Care (San Antonio)* 20:98–109
35. Traversa D (2011) Are we paying too much attention to cardio-pulmonary nematodes and neglecting old-fashioned worms like *Trichuris vulpis*? *Parasite Vectors* 4:32
36. Rubinsky-Elefant G, Hirata CE, Yamamoto JH, Ferreira MU (2010) Human toxocarosis: diagnosis, worldwide seroprevalences and clinical expression of the systemic and ocular forms. *Ann Trop Med Parasitol* 104:3–23



37. Torgerson PR (2006) Mathematical models for the control of cystic echinococcosis. *Parasitol Int* 55(Suppl):S253–S258
38. Cohn LA, Middleton JR (2010) A veterinary perspective on methicillin-resistant staphylococci. *J Vet Emerg Crit Care* 20:31–45
39. Ewers C, Grobbel M, Bethe A, Wieler LH, Guenther S (2011) Extended-spectrum beta-lactamases-producing gram-negative bacteria in companion animals: action is clearly warranted! *Berl Munch Tierarztl Wochenschr* 124:94–101
40. Murphy CP, Reid-Smith RJ, Boerlin P, Weese JS, Prescott JF, Janecko N, Hassard L, McEwen SA (2010) *Escherichia coli* and selected veterinary and zoonotic pathogens isolated from environmental sites in companion animal veterinary hospitals in southern Ontario. *Can Vet J* 181:963–972
41. Loeffler A, Lloyd DH (2010) Companion animals: a reservoir for methicillin-resistant *Staphylococcus aureus* in the community? *Epidemiol Infect* 138:595–605
42. Prescott JF (2008) Antimicrobial use in food and companion animals. *Anim Health Res Rev* 9:127–133
43. van Duijken E, Catry B, Greko C, Moreno MA, Pomba MC, Pyörälä S, Ružauskas M, Sanders P, Threlfall EJ, Torren-Edo J, Törneke K (2011) Review on methicillin-resistant *Staphylococcus pseudintermedius*. *J Antimicrob Chemother* 66:2705–2714
44. Geary TG, Bourguinat C, Prichard RK (2011) Evidence for macrocyclic lactone anthelmintic resistance in *Dirofilaria immitis*. *Top Companion Anim Med* 26:186–192
45. McCall JW, Genchi C, Kramer LH, Guerrero J, Venco L (2008) Heartworm disease in animals and humans. *Adv Parasitol* 66:193–285
46. Dryden MW, Rust MK (1994) The cat flea: biology, ecology and control. *Vet Parasitol* 52:1–19
47. Bossard RL, Hinkle NC, Rust MK (1998) Review of insecticide resistance in cat fleas (Siphonaptera: Pulicidae). *J Med Entomol* 35:415–422
48. Lemke LA, Koehler PG, Patterson RS (1989) Susceptibility of the cat flea (Siphonaptera: Pulicidae) to pyrethroids. *Econ Entomol* 82:839–841
49. Bass C, Schroeder I, Turberg A, Field LM, Williamson MS (2004) Identification of the Rdl mutation in laboratory and field strains of the cat flea, *Ctenocephalides felis* (Siphonaptera: Pulicidae). *Pest Manag Sci* 60:1157–1162
50. Bass C, Schroeder I, Turberg A, Field LM, Williamson MS (2004) Identification of mutations associated with pyrethroid resistance in the para-type sodium channel of the cat flea, *Ctenocephalides felis*. *Insect Biochem Mol Biol* 34:1305–1313
51. Bossard RL, Dryden MW, Broce AB (2002) Insecticide susceptibilities of cat fleas (Siphonaptera: Pulicidae) from several regions of the United States. *J Med Entomol* 39:742–746
52. Young DR, Jeannin PC, Boeckh A (2004) Efficacy of fipronil/(S)-methoprene combination spot-on for dogs against shed eggs, emerging and existing adult cat fleas (*Ctenocephalides felis*, Bouché). *Vet Parasitol* 125:397–407
53. Otranto D, Lia RP, Cantacessi C, Galli G, Paradies P, Mallia E, Capelli G (2005) Efficacy of a combination of imidacloprid 10%/permethrin 50% versus fipronil 10%/(S)-methoprene 12%, against ticks in naturally infected dogs. *Vet Parasitol* 130:293–304
54. Prullage JB, Tran HV, Timmons P, Harriman J, Chester ST, Powell K (2011) The combined mode of action of fipronil and amitraz on the motility of *Rhipicephalus sanguineus*. *Vet Parasitol* 179:302–310
55. Kraft W (1998) Geriatrics in canine and feline internal medicine. *Eur J Med Res* 3:31–41
56. Bonnett BN, Egenvall A (2011) Age patterns of disease and death in insured Swedish dogs, cats and horses. *J Comp Pathol* 142(Suppl 1):S33–S38
57. Gossellin J, Wren JA, Sunderland SJ (2007) Canine obesity: an overview. *J Vet Pharmacol Ther* 30(Suppl 1):1–10
58. Heuberger R, Wakshlag J (2011) Characteristics of ageing pets and their owners: dogs v. cats. *Br J Nutr* 106(Suppl 1):S150–S153



59. Hahn NM, Bonney PL, Dhawan D, Jones DR, Balch C, Guo Z, Hartman-Frey C, Fang F, Parker HG, Kwon EM, Ostrander EA, Nephew KP, Knapp DW (2012) Subcutaneous 5-azacitidine treatment of naturally occurring canine urothelial carcinoma: a novel epigenetic approach to human urothelial carcinoma drug development. *J Urol* 187:302–309
60. Thamm D, Dow S (2011) How companion animals contribute to the fight against cancer in humans. *Vet Ital* 45:111–120
61. Withrow SJ, Wilkins RM (2010) Cross talk from pets to people: translational osteosarcoma treatments. *ILAR J* 51:208–213
62. Henson MS, O'Brien TD (2006) Feline models of type 2 diabetes mellitus. *ILAR J* 47:234–242
63. Hoenig M (2006) The cat as a model for human nutrition and disease. *Curr Opin Clin Nutr Metab Care* 9:584–588
64. Catchpole B, Ristic JM, Fleeman LM, Davison LJ (2005) Canine diabetes mellitus: can old dogs teach us new tricks? *Diabetologia* 48:1948–1956
65. White JD, Malik R, Norris JM (2011) Feline chronic kidney disease: can we move from treatment to prevention? *Vet J* 190:317–322
66. Martineau P, Goulet J (2001) New competition in the realm of renin-angiotensin axis inhibition; the angiotensin II receptor antagonists in congestive heart failure. *Ann Pharmacother* 35(1):71–84
67. Poulet H, Minke J, Pardo MC, Juillard V, Nordgren B, Audonnet JC (2007) Development and registration of recombinant veterinary vaccines. The example of the canarypox vector platform. *Vaccine* 25:5606–5612
68. Spibey N, McCabe VJ, Greenwood NM, Jack SC, Sutton D, van der Waart L (2012) Novel bivalent vectored vaccine for control of myxomatosis and rabbit haemorrhagic disease. *Vet Rec* 170:309
69. Blancou J (2008) The control of rabies in Eurasia: overview, history and background. *Dev Biol (Basel)* 131:3–15
70. Cohen C, Artois M, Pontier D (2000) A discrete-event computer model of feline herpes virus within cat populations. *Prev Vet Med* 45(3–4):163–181
71. Parra LE, Borja-Cabrera GP, Santos FN, Souza LO, Palatnik-de-Sousa CB, Menz I (2007) Safety trial using the Leishmune vaccine against canine visceral leishmaniasis in Brazil. *Vaccine* 25:2180–2186
72. Dantas-Torres F (2006) Leishmune vaccine: the newest tool for prevention and control of canine visceral leishmaniosis and its potential as a transmission-blocking vaccine. *Vet Parasitol* 141(1–2):1–8
73. Bourdoiseau G, Hugnet C, Gonçalves RB, Vézilier F, Petit-Didier E, Papierok G, Lemesre JL (2009) Effective humoral and cellular immunoprotective responses in Li ESAP-MDP vaccinated protected dogs. *Vet Immunol Immunopathol* 128:71–78
74. Lemesre JL, Holzmüller P, Gonçalves RB, Bourdoiseau G, Hugnet C, Cavaleyra M, Papierok G (2007) Long-lasting protection against canine visceral leishmaniasis using the LiESAP-MDP vaccine in endemic areas of France: double-blind randomised efficacy field trial. *Vaccine* 25:4223–4234
75. den Boer M, Argaw D, Jannin J, Alvar J (2011) Leishmaniasis impact and treatment access. *Clin Microbiol Infect* 17:1471–1477
76. Kling J (2007) Biotech for your companion? *Nat Biotechnol* 25:1343–1345
77. Adams VJ, Campbell JR, Waldner CL, Dowling PM, Shmon CL (2005) Evaluation of client compliance with short-term administration of antimicrobials to dogs. *J Am Vet Med Assoc* 226:567–574
78. Barter LS, Maddison JE, Watson AD (1996) Comparison of methods to assess dog owners' therapeutic compliance. *Aust Vet J* 74:443–446
79. Barter LS, Watson AD, Maddison JE (1996) Owner compliance with short term antimicrobial medication in dogs. *Aust Vet J* 74:277–280
80. Grave K, Tanem H (1999) Compliance with short-term oral antibacterial drug treatment in dogs. *J Small Anim Pract* 40:158–162

81. Rogers CL (2011) Rabies vaccination compliance following introduction of the triennial vaccination interval—the Texas experience. *Zoonoses Public Health* 58:229–233
82. Rohrbach BW, Odoi A, Patton S (2011) Survey of heartworm prevention practices among members of a national hunting dog club. *J Am Anim Hosp Assoc* 47:161–169
83. Vasseur PB, Johnson AL, Budsberg SC, Lincoln JD, Toombs JP, Whitehair JG, Lentz EL (1995) Randomized, controlled trial of the efficacy of carprofen, a nonsteroidal anti-inflammatory drug, in the treatment of osteoarthritis in dogs. *J Am Vet Med Assoc* 206:807–811
84. Fox SM, Johnston SA (1997) Use of carprofen for the treatment of pain and inflammation in dogs. *J Am Vet Med Assoc* 210:1493–1498
85. King JN, Arnaud JP, Goldenthal EI, Gruet P, Jung M, Seewald W, Lees P (2011) Robenacoxib in the dog: target species safety in relation to extent and duration of inhibition of COX-1 and COX-2. *J Vet Pharmacol Ther* 34:298–311
86. Roberts ES, Van Lare KA, Marable BR, Salminen WF (2009) Safety and tolerability of 3-week and 6-month dosing of Deramaxx (deracoxib) chewable tablets in dogs. *J Vet Pharmacol Ther* 32:329–337
87. Steagall PV, Mantovani FB, Ferreira TH, Salcedo ES, Moutinho FQ, Luna SP (2007) Evaluation of the adverse effects of oral firocoxib in healthy dogs. *J Vet Pharmacol Ther* 30:218–223
88. Cox SR, Lesman SP, Boucher JF, Krautmann MJ, Hummel BD, Savides M, Marsh S, Fielder A, Stegemann MR (2010) The pharmacokinetics of mavacoxib, a long-acting COX-2 inhibitor, in young adult laboratory dogs. *J Vet Pharmacol Ther* 33:461–470
89. Le Traon G, Burgaud S, Horspool LJ (2008) Pharmacokinetics of total thyroxine in dogs after administration of an oral solution of levothyroxine sodium. *J Vet Pharmacol Ther* 31:95–101
90. Le Traon G, Brennan SF, Burgaud S, Daminet S, Gommeren K, Horspool LJ, Rosenberg D, Mooney CT (2009) Clinical evaluation of a novel liquid formulation of L-thyroxine for once daily treatment of dogs with hypothyroidism. *J Vet Intern Med* 23:43–49
91. Trepanier LA (2006) Medical management of hyperthyroidism. *Clin Tech Small Anim Pract* 21:22–28
92. Trepanier LA, Hoffman SB, Kroll M, Rodan I, Challoner L (2003) Efficacy and safety of once versus twice daily administration of methimazole in cats with hyperthyroidism. *J Am Vet Med Assoc* 222:954–958
93. Frénais R, Burgaud S, Horspool LJ (2008) Pharmacokinetics of controlled-release carbimazole tablets support once daily dosing in cats. *J Vet Pharmacol Ther* 31:213–219
94. Frénais R, Rosenberg D, Burgaud S, Horspool LJ (2009) Clinical efficacy and safety of a once-daily formulation of carbimazole in cats with hyperthyroidism. *J Small Anim Pract* 50:510–515
95. Noli C, Auxilia ST (2005) Treatment of canine Old World visceral leishmaniasis: a systematic review. *Vet Dermatol* 16:213–232
96. da Silva SM, Amorim IF, Ribeiro RR, Azevedo EG, Demicheli C, Melo MN, Tafuri WL, Gontijo NF, Michalick MS, Frézard F (2012) Efficacy of combined therapy with liposome-encapsulated meglumine antimoniate and allopurinol in the treatment of canine visceral leishmaniasis. *Antimicrob Agents Chemother* 56(6):2858–2867
97. Guerin PJ, Olliaro P, Sundar S, Boelaert M, Croft SL, Desjeux P, Wasunna MK, Bryceson AD (2002) Visceral leishmaniasis: current status of control, diagnosis, and treatment, and a proposed research and development agenda. *Lancet Infect Dis* 2:494–501
98. Gómez-Ochoa P, Castillo JA, Gascón M, Zarate JJ, Alvarez F, Couto CG (2009) Use of domperidone in the treatment of canine visceral leishmaniasis: a clinical trial. *Vet J* 179: 259–263
99. Heinemann L (2011) New ways of insulin delivery. *Int J Clin Pract Suppl* 170:31–46
100. Reis CP, Damgé C (2012) Nanotechnology as a promising strategy for alternative routes of insulin delivery. *Methods Enzymol* 508:271–294
101. Saffran M, Field JB, Peña J, Jones RH, Okuda Y (1991) Oral insulin in diabetic dogs. *J Endocrinol* 131:267–278

102. Zarogoulidis P, Papanas N, Kouliatsis G, Spyrtos D, Zarogoulidis K, Maltezos E (2011) Inhaled insulin: too soon to be forgotten? *J Aerosol Med Pulm Drug Deliv* 24:213–223
103. West SD, Turner LG (2000) Determination of spinosad and its metabolites in citrus crops and orange processed commodities by HPLC with UV detection. *J Agric Food Chem* 48:366–372
104. Snyder DE, Meyer J, Zimmermann AG, Qiao M, Gissendanner SJ, Cruthers LR, Slone RL, Young DR (2007) Preliminary studies on the effectiveness of the novel pulvicide, spinosad, for the treatment and control of fleas on dogs. *Vet Parasitol* 150:345–351
105. Robertson-Plouch C, Baker KA, Hozak RR, Zimmermann AG, Parks SC, Herr C, Hart LM, Jay J, Hutchens DE, Snyder DE (2008) Clinical field study of the safety and efficacy of spinosad chewable tablets for controlling fleas on dogs. *Vet Ther* 9:26–36
106. Blagburn BL, Vaughan JL, Lindsay DS, Tebbitt GL (1994) Efficacy dosage titration of lufenuron against developmental stages of fleas (*Ctenocephalides felis felis*) in cats. *Am J Vet Res* 55:98–101
107. Hink WF, Drought DC, Barnett S (1991) Effect of an experimental systemic compound, CGA-184699, on life stages of the cat flea (Siphonaptera: Pulicidae). *J Med Entomol* 28:424–427
108. Hink WF, Zakson M, Barnett S (1994) Evaluation of a single oral dose of lufenuron to control flea infestations in dogs. *Am J Vet Res* 55:822–824
109. Hotz RP, Hassler S, Maurer MP (2000) Determination of lufenuron in canine skin layers by radioluminography. *Schweiz Arch Tierheilkd* 142:173–176
110. Franc M, Cadiergues MC (1997) Use of injectable lufenuron for treatment of infestations of *Ctenocephalides felis* in cats. *Am J Vet Res* 58:140–142
111. Lok JB, Knight DH, Wang GT, Doscher ME, Nolan TJ, Hendrick MJ, Steber W, Heaney K (2001) Activity of an injectable, sustained-release formulation of moxidectin administered prophylactically to mixed-breed dogs to prevent infection with *Dirofilaria immitis*. *Am J Vet Res* 62:1721–1726
112. Holm-Martin M, Atwell R (2004) Evaluation of a single injection of a sustained-release formulation of moxidectin for prevention of experimental heartworm infection after 12 months in dogs. *Am J Vet Res* 65:1596–1599
113. Bhatnagar S, Srivastava UK, Takkar D, Chandra VL, Hingorani V, Laumas KR (1975) Long-term contraception by steroid-releasing implants. II. A preliminary report on long-term contraception by a single silastic implant containing norethindrone acetate (ENTA) in women. *Contraception* 11:505–521
114. Simon P, Sternon J (2000) Etonorgestrel (Implanon) subcutaneous implant. *Rev Med Brux* 21:105–109
115. Meinert C, Silva JF, Kroetz I, Klug E, Trigg TE, Hoppen HO, Jöchle W (1993) Advancing the time of ovulation in the mare with a short-term implant releasing the GnRH analogue deslorelin. *Equine Vet J* 25:65–68
116. Trigg TE, Wright PJ, Armour AF, Williamson PE, Junaidi A, Martin GB, Doyle AG, Walsh J (2001) Use of a GnRH analogue implant to produce reversible long-term suppression of reproductive function in male and female domestic dogs. *J Reprod Fertil Suppl* 57:255–261
117. Rubion S, Desmoulins PO, Rivière-Godet E, Kinziger M, Salavert F, Rutten F, Flochlay-Sigognault A, Driancourt MA (2006) Treatment with a subcutaneous GnRH agonist containing controlled release device reversibly prevents puberty in bitches. *Theriogenology* 66:1651–1654
118. Stegemann MR, Passmore CA, Sherington J, Lindeman CJ, Papp G, Weigel DJ, Skogerboe TL (2006) Antimicrobial activity and spectrum of cefovecin, a new extended-spectrum cephalosporin, against pathogens collected from dogs and cats in Europe and North America. *Antimicrob Agents Chemother* 50:2286–2292
119. Stegemann MR, Sherington J, Blanchflower S (2006) Pharmacokinetics and pharmacodynamics of cefovecin in dogs. *J Vet Pharmacol Ther* 29:501–511
120. Stegemann MR, Sherington J, Coati N, Brown SA, Blanchflower S (2006) Pharmacokinetics of cefovecin in cats. *J Vet Pharmacol Ther* 29:513–524

121. Van Vlaenderen I, Nautrup BP, Gasper SM (2011) Estimation of the clinical and economic consequences of non-compliance with antimicrobial treatment of canine skin infections. *Prev Vet Med* 99:201–210
122. Mateus A, Brodbelt DC, Barber N, Stärk KDC (2011) Antimicrobial usage in dogs and cats in first opinion veterinary practices in the UK. *J Small Anim Pract* 52:515–521
123. Slingsby LS, Waterman-Pearson AE (2002) Comparison between meloxicam and carprofen for postoperative analgesia after feline ovariohysterectomy. *J Small Anim Pract* 43:286–289
124. Morton CM, Grant D, Johnston L, Letellier IM, Narbe R (2011) Clinical evaluation of meloxicam versus ketoprofen in cats suffering from painful acute locomotor disorders. *J Feline Med Surg* 13:237–243
125. Kamata M, King JN, Seewald W, Sakakibara N, Yamashita K, Nishimura R (2012) Comparison of injectable robenacoxib versus meloxicam for peri-operative use in cats: results of a randomised clinical trial. *Vet J* 193:114–118
126. Degim IT, Hadgraft J, Houghton E, Teale P (1999) In vitro percutaneous absorption of fusidic acid and betamethasone 17-valerate across canine skin. *J Small Anim Pract* 40:515–518
127. Nuttall T, Mueller R, Bensignor E, Verde M, Noli C, Schmidt V, Rème C (2009) Efficacy of a 0.0584% hydrocortisone aceponate spray in the management of canine atopic dermatitis: a randomised, double blind, placebo-controlled trial. *Vet Dermatol* 20:191–198
128. Nuttall TJ, Mcewan NA, Bensignor E, Cornegliani L, Löwenstein C, Rème CA (2012) Comparable efficacy of a topical 0.0584% hydrocortisone aceponate spray and oral ciclosporin in treating canine atopic dermatitis. *Vet Dermatol* 23:4–10, e1–e2
129. Horspool LJ, Weingarten A (2011) Novel agents in the treatment of canine otitis externa. *Proceedings SCIVAC International Congress, Rimini, Italy, 27–29 May 2011*. pp 241–243
130. Ghubash R, Marsella R, Kunkle G (2004) Evaluation of adrenal function in small-breed dogs receiving otic glucocorticoids. *Vet Dermatol* 15:363–368
131. Ginel PJ, Garrido C, Lucena R (2007) Effects of otic betamethasone on intradermal testing in normal dogs. *Vet Dermatol* 18:205–210
132. Reeder CJ, Griffin CE, Polissar NL, Neradilek B, Armstrong RD (2008) Comparative adrenocortical suppression in dogs with otitis externa following topical otic administration of four different glucocorticoid-containing medications. *Vet Ther* 9:111–121
133. Clark AR, Belvisi MG (2012) Maps and legends: the quest for dissociated ligands of the glucocorticoid receptor. *Pharmacol Ther* 134:54–67
134. De Bosscher K, Beck IM, Haegeman G (2010) Classic glucocorticoids versus non-steroidal glucocorticoid receptor modulators: survival of the fittest regulator of the immune system? *Brain Behav Immun* 24:1035–1042
135. Moffat AS (1993) New chemicals seek to outwit insect pests. *Science* 261:550–551
136. Postal J-MR, Jeannin PC, Consalvi P-J (1995) Field efficacy of a mechanical pump spray formulation containing 0.25% fipronil in the treatment and control of flea infestation and associated dermatological signs in dogs and cats. *Vet Dermatol* 6:153–158
137. Arther RG, Cunningham J, Dorn H, Everett R, Herr LG, Hopkins T (1997) Efficacy of imidacloprid for removal and control of fleas (*Ctenocephalides felis*) on dogs. *Am J Vet Res* 58:848–850
138. Jacobs DE, Hutchinson MJ, Krieger KJ (1997) Duration of activity of imidacloprid, a novel adulticide for flea control, against *Ctenocephalides felis* on cats. *Vet Rec* 140:259–260
139. Endris RG, Matthewson MD, Cooke MD, Amodie D (2000) Repellency and efficacy of 65% permethrin and 9.7% fipronil against *Ixodes ricinus*. *Vet Ther* 1:159–168
140. Hutchinson MJ, Jacobs DE, Fox MT, Jeannin P, Postal JM (1998) Evaluation of flea control strategies using fipronil on cats in a controlled simulated home environment. *Vet Rec* 142:356–357
141. Cochet P, Birckel P, Bromet-Petit M, Bromet N, Weil A (1997) Skin distribution of fipronil by microautoradiography following topical administration to the beagle dog. *Eur J Drug Metab Pharmacokinet* 22:211–216
142. Chopade H, Eigenberg D, Solon E, Strzemienski P, Hostetler J, McNamara T (2010) Skin distribution of imidacloprid by microautoradiography after topical administration to beagle dogs. *Vet Ther* 11:E1–E10

143. McCann SF, Annis GD, Shapiro R, Piotrowski DW, Lahm GP, Long JK, Lee KC, Hughes MM, Myers BJ, Griswold SM, Reeves BM, March RW, Sharpe PL, Lowder P, Barnette WE, Wing KD (2001) The discovery of indoxacarb: oxadiazines as a new class of pyrazoline-type insecticides. *Pest Manag Sci* 57:153–164
144. Pacey MS, Dutton CJ, Monday RA, Ruddock JC, Smith GC (2000) Preparation of 13-epi-selamectin by biotransformation using a blocked mutant of *Streptomyces avermitilis*. *J Antibiot (Tokyo)* 53:301–305
145. Bishop BF, Bruce CI, Evans NA, Goudie AC, Gration KA, Gibson SP, Pacey MS, Perry DA, Walshe ND, Witty MJ (2000) Selamectin: a novel broad-spectrum endectocide for dogs and cats. *Vet Parasitol* 91:163–176
146. von Samson-Himmelstjerna G, Epe C, Schimmel A, Heine J (2003) Larvicidal and persistent efficacy of an imidacloprid and moxidectin topical formulation against endoparasites in cats and dogs. *Parasitol Res* 90(Suppl 3):S114–S115
147. Kopp SR, Kotze AC, McCarthy JS, Traub RJ, Coleman GT (2008) Pyrantel in small animal medicine: 30 years on. *Vet J* 178:177–184
148. Shoop WL, Mrozik H, Fisher MH (1995) Structure and activity of avermectins and milbemycins in animal health. *Vet Parasitol* 59:139–156
149. Zajac AM (1993) Developments in the treatment of gastrointestinal parasites of small animals. *Vet Clin North Am Small Anim Pract* 23:671–681
150. Weckwerth W, Miyamoto K, Iinuma K, Krause M, Glinski M, Storm T, Bonse G, Kleinkauf H, Zocher R (2000) Biosynthesis of PF1022A and related cyclooctadepsipeptides. *J Biol Chem* 275:17909–17915
151. Harder A, Schmitt-Wrede HP, Krücken J, Marinovski P, Wunderlich F, Willson J, Amliwala K, Holden-Dye L, Walker R (2003) Cyclooctadepsipeptides—an anthelmintically active class of compounds exhibiting a novel mode of action. *Int J Antimicrob Agents* 22:318–331
152. Charles SD, Altreuther G, Reinemeyer CR, Buch J, Settje T, Cruthers L, Kok DJ, Bowman DD, Kazacos KR, Jenkins DJ, Schein E (2005) Evaluation of the efficacy of emodepside+praziquantel topical solution against cestode (*Dipylidium caninum*, *Taenia taeniaeformis*, and *Echinococcus multilocularis*) infections in cats. *Parasitol Res* 97(Suppl 1):S33–S40
153. Hoffman SB, Yoder AR, Trepanier LA (2002) Bioavailability of transdermal methimazole in a pluronic lecithin organogel (PLO) in healthy cats. *J Vet Pharmacol Ther* 25:189–193
154. Sartor LL, Trepanier LA, Kroll MM, Rodan I, Challoner L (2004) Efficacy and safety of transdermal methimazole in the treatment of cats with hyperthyroidism. *J Vet Intern Med* 18:651–655
155. Hill KE, Gieseg MA, Kingsbury D, Lopez-Villalobos N, Bridges J, Chambers P (2011) The efficacy and safety of a novel lipophilic formulation of methimazole for the once daily transdermal treatment of cats with hyperthyroidism. *J Vet Intern Med* 25:1357–1365
156. Evans PD, Gee JD (1980) Action of formamidine pesticides on octopamine receptors. *Nature* 287:60–62
157. Hsu WH, Kakuk TJ (1984) Effect of amitraz and chlordimeform on heart rate and pupil diameter in rats: mediated by alpha 2-adrenoreceptors. *Toxicol Appl Pharmacol* 73:411–415
158. Rugg D, Hair JA, Everett RE, Cunningham JR, Carter L (2007) Confirmation of the efficacy of a novel formulation of metaflumizone plus amitraz for the treatment and control of fleas and ticks on dogs. *Vet Parasitol* 150:209–218
159. Fourie LJ, Kok DJ, du Plessis A, Rugg D (2007) Efficacy of a novel formulation of metaflumizone plus amitraz for the treatment of demodectic mange in dogs. *Vet Parasitol* 150:268–274
160. Fourie JJ, Delpont PC, Fourie LJ, Heine J, Horak IG, Krieger KJ (2009) Comparative efficacy and safety of two treatment regimens with a topically applied combination of imidacloprid and moxidectin (Advocate) against generalised demodicosis in dogs. *Parasitol Res* 105(Suppl 1):S115–S124
161. Heine J, Krieger K, Dumont P, Hellmann K (2005) Evaluation of the efficacy and safety of imidacloprid 10% plus moxidectin 2.5% spot-on in the treatment of generalized demodicosis in dogs: results of a European field study. *Parasitol Res* 97(Suppl 1):S89–S96

162. Weller C, Linder M (1966) Jet injection of insulin vs the syringe-and-needle method. *JAMA* 195:844–847
163. Bohannon NJ (1999) Insulin delivery using pen devices. Simple-to-use tools may help young and old alike. *Postgrad Med* 106:57–58, 61–64, 68
164. Rex J, Jensen KH, Lawton SA (2006) A review of 20 years' experience with the NovoPen family of insulin injection devices. *Clin Drug Investig* 26:367–401
165. Burgaud S, Guillot R, Harnois-Milon G (2012) Clinical evaluation of a veterinary insulin pen in diabetic cats. *Proceedings World congress WSAVA/FECAVA/BSAVA* 11–15 April 2012. Birmingham, UK, p 499
166. Burgaud S, Riant S, Piau N. Comparative laboratory evaluation of dose delivery using a veterinary insulin pen. *Proceedings World congress WSAVA/FECAVA/BSAVA*, 11–15 April 2012, Birmingham, UK, p 567
167. Burgaud S, Guillot R, Harnois-Milon G (2012) Clinical evaluation of a veterinary insulin pen in diabetic dogs. *Proceedings World congress WSAVA/FECAVA/BSAVA* 11–15 April 2012. Birmingham, UK, p 568
168. Kyles AE, Papich M, Hardie EM (1996) Disposition of transdermally administered fentanyl in dogs. *Am J Vet Res* 57:715–719
169. Hofmeister EH, Egger CM (2004) Transdermal fentanyl patches in small animals. *J Am Anim Hosp Assoc* 40:468–478
170. Reed F, Burrow R, Poels KL, Godderis L, Veulemans HA, Mosing M (2011) Evaluation of transdermal fentanyl patch attachment in dogs and analysis of residual fentanyl content following removal. *Vet Anaesth Analg* 38:407–412
171. Rigaut D, Sanquer A, Maynard L, Rème CA (2011) Efficacy of a topical ear formulation with a pump delivery system for the treatment of infectious otitis externa in dogs: a randomized controlled trial. *Int J Appl Res Vet Med* 9:15–28
172. Clamp PJ (2008) Expansile properties of otowicks: an in vitro study. *J Laryngol Otol* 122:687–690
173. Barza M, Brown RB, Shanks C, Gamble C, Weinstein L (1975) Relation between lipophilicity and pharmacological behavior of minocycline, doxycycline, tetracycline, and oxytetracycline in dogs. *Antimicrob Agents Chemother* 8:713–720
174. Cox SR, Liao S, Payne-Johnson M, Zielinski RJ, Stegemann MR (2011) Population pharmacokinetics of mavacoxib in osteoarthritic dogs. *J Vet Pharmacol Ther* 34:1–11
175. McKellar QA, Galbraith EA, Baxter P (1993) Oral absorption and bioavailability of fenbendazole in the dog and the effect of concurrent ingestion of food. *J Vet Pharmacol Ther* 16:189–198
176. Shiu GK, LeMarchand A, Sager AO, Velagapudi RB, Skelly JP (1989) The beagle dog as an animal model for a bioavailability study of controlled-release theophylline under the influence of food. *Pharm Res* 6:1039–1042
177. Watson AD, Rijnberk A, Moolenaar AJ (1987) Systemic availability of o, p'-DDD in normal dogs, fasted and fed, and in dogs with hyperadrenocorticism. *Res Vet Sci* 43:160–165
178. Campbell BG, Rosin E (1998) Effect of food on absorption of cefadroxil and cephalexin in dogs. *J Vet Pharmacol Ther* 21:418–420
179. Xu C-H, Cheng G, Liu Y, Tian Y, Yan J, Zou M-J (2012) Effect of the timing of food intake on the absorption and bioavailability of carbamazepine immediate-release tablets in beagle dogs. *Biopharm Drug Dispos* 33:30–38
180. Küng K, Hauser BR, Wanner M (1995) Effect of the interval between feeding and drug administration on oral ampicillin absorption in dogs. *J Small Anim Pract* 36:65–68
181. Le Traon G, Burgaud S, Horspool LJ (2009) Pharmacokinetics of cimetidine in dogs after oral administration of cimetidine tablets. *J Vet Pharmacol Ther* 32:213–218
182. Thurman GD, McFadyen ML, Miller R (1990) The pharmacokinetics of phenobarbitone in fasting and non-fasting dogs. *J S Afr Vet Assoc* 61:86–89
183. Parrott N, Lukacova V, Fraczkiwicz G, Bolger MB (2009) Predicting pharmacokinetics of drugs using physiologically based modeling—application to food effects. *AAPS J* 11:45–53



184. Tanno FK, Sakuma S, Masaoka Y, Kataoka M, Kozaki T, Kamaguchi R, Ikeda Y, Kokubo H, Yamashita S (2008) Site-specific drug delivery to the middle-to-lower region of the small intestine reduces food-drug interactions that are responsible for low drug absorption in the fed state. *J Pharm Sci* 97:5341–5353
185. Perlman ME, Murdande SB, Gumkowski MJ, Shah TS, Rodricks CM, Thornton-Manning J, Freel D, Erhart LC (2008) Development of a self-emulsifying formulation that reduces the food effect for torcetrapib. *Int J Pharm* 351:15–22
186. Sawka AM, Ibrahim-Zada I, Galacgac P, Tsang RW, Brierley JD, Ezzat S, Goldstein DP (2010) Dietary iodine restriction in preparation for radioactive iodine treatment or scanning in well-differentiated thyroid cancer: a systematic review. *Thyroid* 20:1129–1138
187. Zimmermann MB, Andersson M (2011) Prevalence of iodine deficiency in Europe in 2010. *Ann Endocrinol (Paris)* 72:164–166
188. Hoption Cann SA (2006) Hypothesis: dietary iodine intake in the etiology of cardiovascular disease. *J Am Coll Nutr* 25:1–11
189. Kirk CA (2006) Feline diabetes mellitus: low carbohydrates versus high fiber? *Vet Clin North Am Small Anim Pract* 36:1297–1306
190. Mori A, Sako T, Lee P, Nishimaki Y, Fukuta H, Mizutani H, Honjo T, Arai T (2009) Comparison of three commercially available prescription diet regimens on short-term post-prandial serum glucose and insulin concentrations in healthy cats. *Vet Res Commun* 33:669–680
191. Toutain PL (2002) Pharmacokinetic/pharmacodynamic integration in drug development and dosage-regimen optimization for veterinary medicine. *AAPS PharmSci* 4:4
192. Blondeau JM (2009) New concepts in antimicrobial susceptibility testing: the mutant prevention concentration and mutant selection window approach. *Vet Dermatol* 20:383–396
193. Macdonald N, Gledhill A (2007) Potential impact of ABCB1 (P-glycoprotein) polymorphisms on ivermectin toxicity in humans. *Arch Toxicol* 81:553–563
194. Geyer J, Döring B, Godoy JR, Moritz A, Petzinger E (2005) Development of a PCR-based diagnostic test detecting a nt230(del4) MDR1 mutation in dogs: verification in a moxidectin-sensitive Australian Shepherd. *J Vet Pharmacol Ther* 28:95–99
195. Geyer J, Gavrilova O, Petzinger E (2009) Brain penetration of ivermectin and selamectin in MDR1a, b P-glycoprotein- and BCRP-deficient knockout mice. *J Vet Pharmacol Ther* 32:87–96
196. Griffin J, Fletcher N, Clemence R, Blanchflower S, Brayden DJ (2005) Selamectin is a potent substrate and inhibitor of human and canine P-glycoprotein. *J Vet Pharmacol Ther* 28:257–265
197. Han JI, Son HW, Park SC, Na KJ (2010) Novel insertion mutation of ABCB1 gene in an ivermectin-sensitive Border Collie. *J Vet Sci* 11:341–344
198. Mealey KL, Bentjen SA, Gay JM, Cantor GH (2001) Ivermectin sensitivity in collies is associated with a deletion mutation of the *mdr1* gene. *Pharmacogenetics* 1:727–733
199. Mealey KL (2008) Canine ABCB1 and macrocyclic lactones: heartworm prevention and pharmacogenetics. *Vet Parasitol* 158:215–222
200. Roulet A, Puel O, Gesta S, Lepage JF, Drag M, Soll M, Alvinierie M, Pineau T (2003) MDR1-deficient genotype in Collie dogs hypersensitive to the P-glycoprotein substrate ivermectin. *Eur J Pharmacol* 460:85–91
201. Martinez MN, Hunter RP (2010) Current challenges facing the determination of product bioequivalence in veterinary medicine. *J Vet Pharmacol Ther* 33:418–433
202. Baynes R, Riviere J, Franz T, Monteiro-Riviere N, Lehman P, Peyrou M, Toutain P-L (2012) Challenges obtaining a bio waiver for topical veterinary dosage forms. *J Vet Pharmacol Ther* 35(suppl 1):103–114
203. Bermingham E, Del Castillo JR, Laines C, Pasloske K, Radecki S (2012) Demonstrating bioequivalence using clinical endpoint studies. *J Vet Pharmacol Ther* 35(Suppl 1):31–37
204. Claxton R, Cook J, Endrenyi L, Lucas A, Martinez MN, Sutton SC (2012) Estimating product bioequivalence for highly variable veterinary drugs. *J Vet Pharmacol Ther* 35(Suppl 1):11–16

205. Modric S, Bermingham E, Heit M, Laines C, Thompson C (2012) Considerations for extrapolating *in vivo* bioequivalence data across species and routes. *J Vet Pharmacol Ther* 35(Suppl 1):45–52
206. Pillai X, Kinney WA (2010) Strategies for strengthening patent protection of pharmaceutical inventions in light of federal court decisions. *Curr Top Med Chem* 10:1929–1936
207. Elliott G (2007) Basics of US patents and the patent system. *AAPS J* 9:E317–E324
208. Boothe DM (2006) Veterinary compounding in small animals: a clinical pharmacologist's perspective. *Vet Clin North Am Small Anim Pract* 36:1129–1173, viii
209. Agelová J, Macesková B (2005) Analysis of drugs used in out-patient practice of veterinary medicine. *Ceska Slov Farm* 54:34–38
210. Anonymous (2007) New recommendations to modernize drug manufacturing. *FDA Consum* 41(4)
211. Lust E (2003) Compounding for animal patients: contemporary issues. *J Am Pharm Assoc* 44:375–386
212. Davis JL, Kirk LM, Davidson GS, Papich MG (2009) Effects of compounding and storage conditions on stability of pergolide mesylate. *J Am Vet Med Assoc* 234:385–389
213. Hawkins MG, Karriker MJ, Wiebe V, Taylor IT, Kass PH (2006) Drug distribution and stability in extemporaneous preparations of meloxicam and carprofen after dilution and suspension at two storage temperatures. *J Am Vet Med Assoc* 229:968–974
214. Nguyen KQ, Hawkins MG, Taylor IT, Wiebe VJ, Tell LA (2009) Stability and uniformity of extemporaneous preparations of voriconazole in two liquid suspension vehicles at two storage temperatures. *Am J Vet Res* 70:908–914
215. Scott-Moncrieff JC, Moore GE, Coe J, Lynn RC, Gwin W, Petzold R (2012) Characteristics of commercially manufactured and compounded protamine zinc insulin. *J Am Vet Med Assoc* 240:600–605
216. Hunter RP, Shryock TR, Cox BR, Butler RM, Hammelman JE (2011) Overview of the animal health drug development and registration process: an industry perspective. *Future Med Chem* 3:881–886
217. Holmes M, Hill RE (2007) International harmonisation of regulatory requirements. *Rev Sci Tech* 26:415–420
218. Carr M (2010) The Small- and Medium-sized Enterprises Office (SME Office) at the European Medicines Agency. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 53: 20–23
219. Mackay D (2004) Vaccines for minor use/minor species (MUMS) in the European union. *Dev Biol (Basel)* 117:141–143
220. Nolen RS (2004) Senators unanimously approve MUMS bill. *J Am Vet Med Assoc* 224:1225–1226
221. Quigley K (2012) Veterinary medicines: what is the MUMS/limited markets policy? *Regulatory Rapporteur* 9:8–9





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