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Subject: **PRCOPVA.001 - Top 5 Pet Food Nutraceuticals.**

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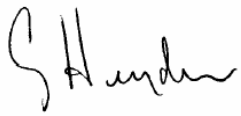
Signed for and on behalf of UniQuest Pty Limited



Mr Gary Heyden

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Executive Summary

Section I: The Most Common Canine and Feline Diseases and Their Associated Nutraceutical Use

One of the most common diseases affecting dogs and older cats is osteoarthritis. Nutraceuticals such as glucosamine, chondroitin sulphate and pentosan polysulphate are commonly used as adjunct therapies in the management of osteoarthritis to alleviate pain and to retard the progression of the disease. The omega-3 fatty acids, which are found in fish and fish oil, are also commonly used nutraceuticals in veterinary medicine. Currently, the omega-3 fatty acids are used in the management of allergic dermatitis, canine aging and cognitive dysfunction syndrome, chronic renal disease, and cancer therapy. Recent studies have demonstrated that dogs fed increased levels of the amino acid arginine, in combination with the omega-3 fatty acids, have an improved quality of life and an increased survival time. Another amino acid, L-carnitine, appears to play an important role in preventing the potentially damaging accumulation of lipids in the liver of cats undergoing rapid weight loss. Significantly, L-carnitine has been shown to encourage the preferential loss of body fat over lean muscle mass during weight loss in cats and dogs. L-carnitine is also effective in the treatment of dilated cardiomyopathy in L-carnitine-deficient dogs. Taurine is an essential amino acid that is commonly added to commercial diets to ensure normal cardiac, reproductive and retinal health in cats, and to prevent cardiac disease in American Cocker Spaniel dogs that are pre-disposed to a taurine deficiency.

Section II: The Most Common Nutraceuticals in Veterinary and Human Medicine

Glucosamine, chondroitin sulphate, pentosan polysulphate and the omega-3 fatty acids are the most commonly used nutraceuticals in veterinary medicine. Arginine, carnitine and taurine are amino acids that are found in all pet foods, but may be added at increased levels to achieve a therapeutic effect. Typically, the inclusion of nutraceuticals is more prevalent in premium-grade pet foods and in veterinary prescription diets, rather those diets available through supermarkets. In Australia, the most common brands of premium and veterinary prescription pet foods are Hill's Prescription Diets, Iam's, Eukanuba Veterinary Diets, Royal Canin Veterinary Diets, Waltham Veterinary Diets and Australian-owned Advance. In the United States, Hill's, Eukanuba, Iam's, Royal Canin and Waltham similarly hold significant percentages of the pet food market, in addition to Nestlé Purina Veterinary Diets and Pedigree Veterinary Diets, which are not available in Australia. Hill's, Pedigree and Nestlé Purina are the most popular Western brands in the Japanese market, along with the Japanese brands Nippon Pet Food, Nisshin Pet Food and Unicharm Pet Care.

Section III: Nutraceuticals and Bioactives in Pet Foods Available in Australia, U.S.A. and Japan

The most significant nutraceuticals and bioactives currently used in veterinary medicine are glucosamine, chondroitin sulphate and pentosan polysulphate (collectively known as glycosaminoglycans), the omega-3 fatty acids, carnitine, taurine and arginine. With the exception of pentosan polysulphate, all are present in most premium and veterinary prescription diets. Pentosan polysulphate is usually administered via injection since it has a very low bioavailability when ingested.

Section IV: Potential Yields of Nutraceuticals and Opportunities For Collaboration With Existing Companies

The highest natural sources of carnitine are skeletal muscle and heart. Interestingly, Hill's uses synthetic carnitine to adjust their diets to ensure sufficient levels of carnitine are present. Skeletal muscle, thymus, heart, liver, and kidney are all significant sources of arginine; however, the red meat or poultry used in the manufacture of the pet food normally provides sufficient arginine without the need for additional supplementation. Rich sources of taurine include bovine gall, liver, heart and skeletal muscle. While Eukanuba and Iam's may supplement their foods with naturally-derived taurine, both Hill's and Advance use synthetic forms of taurine in their diets. Although bovine trachea is an excellent source of both chondroitin sulphate and glucosamine, Hill's and Eukanuba both use poultry meal as their source of chondroitin sulphate and glucosamine, while Advance uses glucosamine extracted from mussel shells. Pentosan polysulphate is commercially produced via synthetic processes and is not included in pet foods.

Our attempts at identifying companies within Australia that extract nutraceuticals for supply to the pet food industry were unsuccessful due to issues of confidentiality whereby nutrition companies were not willing to divulge their suppliers.

Section V: Investigation of Regulatory Requirements Involved With the Production of Nutraceuticals for Inclusion into Pet Foods

In Australia, pet foods require registration with the Australian Pesticides and Veterinary Medicines Authority (APVMA) only if the food is advertised as being therapeutic, rather than nutritional, by actively claiming to "prevent, treat, alleviate or cure" disease. If therapeutic claims are not made by the company, registration is not required.

In the USA, both the Food and Drug Administration (FDA) and the Association of American Feed Control Officials (AAFCO) are responsible for the regulation of pet foods and their

ingredients. Similarly to the situation in Australia, pet foods do not require registration as drugs so long as the labelling of the food does not make therapeutic claims.

Within the European Union, only those food additives that have been scientifically evaluated by the European Food Safety Authority and subsequently listed on the Community Register For Feed Additives can be included in pet foods and marketed. Currently, carnitine, taurine, the omega-3 fatty acids and the omega-6 fatty acids are listed on the register.

Section I: The Most Common Canine and Feline Diseases and Their Associated Nutraceutical Use

The most prevalent use of nutraceuticals in veterinary medicine is for the treatment of osteoarthritis in dogs and older cats. Glucosamine, chondroitin sulphate and pentosan polysulphate contribute significantly towards alleviating pain and retarding the progression of osteoarthritis. The omega-3 fatty acids - docosahexaenoic acid and eicosapentaenoic acid - which are found in fish and fish oil are commonly used as adjunct therapies in the treatment of cancer. The roles of the omega-3 fatty acids in the management of chronic renal disease, canine aging and cognitive dysfunction syndrome and allergic dermatitis have also been well documented. Preliminary studies have suggested a valuable role for L-carnitine, a co-enzyme found in high concentrations in red meat extracts, in preventing the potentially lethal accumulation of lipids in the liver of cats undergoing rapid weight loss.

Introduction

Nutraceuticals, as defined by the North American Veterinary Nutraceutical Council, are “non-drug substance[s] that [are] produced in purified or extracted form and administered orally to provide agents required for normal body structure and function with the intention of improving the health and well-being of animals” [1]. The use of nutraceuticals in human medicine, as an adjunct to more conventional therapy, is a rapidly emerging field that has progressively gained significant research and clinical focus since the late 1980’s [2]. A key argument for the use of nutraceuticals in both human and veterinary medicine is that they have the potential to decrease the adverse side-effects of conventional drugs by allowing for a lower effective dose to be used [3, 4]. Currently, the market availability of nutraceuticals for veterinary use represents only a small fraction of the products available for human medicine; however, it is only to be expected that as more people look to nutraceuticals for their own health, they will want - and indeed expect - the same options for their pets. This review discusses the most prevalent diseases affecting cats and dogs in developed countries, including Australia, the United States of America and Japan.

A significant number of these diseases affect animals that are considered senior - that is, over 7 years of age. With the ever-increasing range of medical and surgical treatments available to canine and feline patients, the average lifespan has increased. As a result, diseases of older patients are increasingly important. The strong human-animal bond between pets and their owners is reflected in owners seeking advanced treatment for their pets and committing substantial financial resources to their pet's health. Finally, particular attention is given to those diseases for which nutraceuticals are currently employed in the treatment regimen. We have also included diseases for which there are no current nutraceutical therapies because we believe that, given their prevalence, these diseases are an important focus for future nutraceutical applications.

The Most Common Canine and Feline Diseases With Associated Nutraceutical Use

Osteoarthritis

Prevalence: Dogs: 20% if over 1 year old [5]; Cats: 90% if over 12 years old [5].

Nutraceuticals Used: glucosamine, chondroitin sulphate, pentosan polysulphate.

Osteoarthritis is a common cause of lameness in dogs and older cats, and is characterised by varying degrees of joint pain and dysfunction [6,7]. It has been estimated that 20% of dogs over 1 year of age, and as many as 90% of cats over 12 years of age, show some degree of osteoarthritis [5]. Osteoarthritis is mediated by a low-grade inflammatory process that gradually results in abnormal cartilage and bone remodelling, with ultimate cartilage loss [6].

Glucosamine is an aminosaccharide precursor to the glycosaminoglycans (GAGs) that are essential components of articular cartilage. While normal cartilage cells (chondrocytes) synthesise glucosamine, those in the cartilage of animals with osteoarthritis cannot [8]. In addition to its structural role in cartilage formation, glucosamine also appears to play an important role as an anti-inflammatory agent [3, 6]. Glucosamine has also been shown to inhibit the formation of matrix metalloproteases (MMPs), enzymes which are responsible for the active destruction of cartilage [3, 6]. Clinical studies in humans and horses have demonstrated that oral glucosamine inhibits the degradation of cartilage [3].

Chondroitin sulphate is a glycosaminoglycans associated with articular cartilage. In dogs and humans, oral administration of chondroitin sulphate decreases the inflammation associated with osteoarthritis[3,6,8]. Chondroitin sulphate also inhibits the activity of destructive metalloproteases, and promotes the synthesis of glycosaminoglycans and collagen [3, 8]. The actions of glucosamine and chondroitin sulphate appear to be synergistic in ameliorating the progression of osteoarthritis [8].

Another glycosaminoglycan, pentosan polysulphate, also induces the synthesis of cartilage components and attenuates cartilage degradation via similar mechanisms to those described for glucosamine and chondroitin sulphate [8]. However, pentosan polysulphate has the additional benefit of thrombolytic and fibrinolytic activity, which is thought to increase blood flow through the joint synovium and subchondral bone, thus encouraging synoviocyte and chondrocyte survival and normal function [6, 8]. Pentosan polysulphate is widely used in veterinary medicine for arthritis. It is not currently used in petfood since it has a low oral availability; rather, it is administered via injection.

Presently, non-steroidal anti-inflammatory drugs (NSAIDs) form the mainstay of therapy for dogs and cats with osteoarthritis. However, long-term use of NSAIDs, as is required in the treatment of osteoarthritis, is associated with significant side-effects such as gastric ulceration and impaired renal blood supply [7]. Furthermore, most NSAIDs inhibit glycosaminoglycan synthesis and so, while controlling the pain and inflammation associated with osteoarthritis, actually aid in the progression of the disease [7]. Glucosamine and chondroitin sulphate have been shown to have a longer duration of action than NSAIDs, and when used as adjuncts allow for an equivalent level of pain relief to be achieved with a lower dose of the NSAID and so fewer concomitant side effects [8].

Cancer

Prevalence: Dogs: 50% if over 10 years old [5]; Cats: precise prevalence unknown, but less than dogs [5].

Nutraceuticals Used: omega-3 fatty acids, arginine.

The most commonly used nutraceuticals in both human and veterinary cancer therapy are the omega-3 fatty acids - docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) - which are found in fish and fish oil. In dogs undergoing chemotherapy for lymphoma, or radiotherapy for nasal tumours, diets supplemented with high levels of omega-3 fatty acids afforded significantly increased disease-free intervals and longer survival times [9]. During chemo- and radio-therapy, dogs receiving the omega-3 fatty acids were also less affected by the wasting syndrome normally associated with neoplasia [9]. Similarly, in rats fed diets supplemented with omega-3 fatty acids, growth of tumours of the colon, liver, lung, prostate and mammary tumours was inhibited, and there was a decrease in the propensity for these tumours to metastasise[9]. *In vitro,* omega-3 fatty acids decrease the activity of metalloproteases which are thought to be involved in tumour growth and metastasis [9]. Furthermore, they appear to decrease the vascular supply to solid tumours and to promote the apoptosis or programmed death of tumour cells [9].

Arginine has also been found to have beneficial effects in canine cancer patients when combined with omega-3 fatty acids. Dogs fed increased dietary arginine in combination with omega-3 fatty acids had an improved quality of life and increased survival times [12].

Chronic Renal Disease

Prevalence: Dogs: 0.9% [5]; Cats: 1.6% if less than 15 years old, 15% if over 15 years old [5].
Nutraceuticals Used: omega-3 fatty acids.

A further role has been ascribed to the omega-3 fatty acids in the management of chronic renal disease. Cats and dogs with renal insufficiency have increased blood pressure in the glomerular capillaries of the kidney, which is triggered by the production of inflammatory mediators prostaglandin E_2 and thromboxane A_2 [10]. This increase in intraglomerular pressure is the primary cause of progressive renal damage [10]. Omega-3 fatty acids, reduce the production of prostaglandin E_2 and thromboxane A_2 in dogs with chronic renal disease, thus decrease intraglomerular pressure and slow the progression of renal disease [10].

Canine Aging and Cognitive Dysfunction Syndrome

Prevalence: Dogs: 50% if over 11 years old [5].
Nutraceuticals Used: omega-3 fatty acids, vitamins C and E, and β-carotene.

Aged dogs often display aberrant behaviours such as destructiveness, increased vocalisation, decreased social interaction, loss of housetraining, disorientation and sleep disturbances; together, these behaviours form the canine cognitive dysfunction syndrome [11]. Brains of aged dogs show oxidative damage to proteins and lipids which, in turn, is thought to impair neuronal function [11]. Omega-3 fatty acids, vitamins C and E, and β-carotene function as antioxidants, preventing oxidative damage to cellular lipids and proteins [11]. Aged dogs that were fed diets rich in antioxidants displayed improved cognitive function and a slower decline in learning and memory, as compared to aged dogs fed control diets [11].

Allergic Dermatitis

Prevalence: Dogs: 15-20% of all consultations [12]; Cats: 15-20% of all consultations [12].
Nutraceuticals Used: omega-3 fatty acids

Allergic dermatitis, including flea-allergy dermatitis and atopy, is the most commonly diagnosed skin disorder in dogs and the third most prevalent skin disease in cats [12]. Both flea-allergy dermatitis and atopy are the result of a hypersensitivity reaction that induces inflammation of the skin [13]. This inflammatory response causes itching which sets in progress a cycle of self-traumatising behaviours ultimately resulting in skin trauma, hair loss and secondary bacterial

infections [13]. A common manifestation of skin allergy is inflammation of the outer ear (otitis externa). Otitis externa is one of the most common diseases seen in small animal practice and is often very refractory to treatment[13].

Omega-3 fatty acids decrease the production of inflammatory agents and so provide a valuable adjunct to conventional therapy which typically consists of antihistamines and glucocorticoids (steroids). In the majority of cases, animals require long-term treatment, and prolonged use of glucocorticoids at anti-inflammatory levels is associated with adverse side-effects such as a decrease in white blood cells, increased urination and drinking, weight gain and gastric ulceration [13]. Thus, the use of omega-3 fatty acids may permit a lower dose and less frequent administration of glucocorticoids, while still suppressing the inflammatory response.

The Most Common Canine and Feline Diseases Without Associated Nutraceutical Use

Obesity

Prevalence: Dogs: 25% of dogs presented at clinics [12]; Cats: 25% of cats presented at clinics [12]. The prevalence of overweight and obese dogs and cats is increasing, in parallel with the increase in the human population. Currently, 60% of Australian adults are obese or overweight and unpublished data suggest 40% of dogs and cats are obese or overweight.

The adverse effects of obesity include a range of endocrine disturbances (diabetes mellitus, hyperadrenocorticism and hypothyroidism - all of which are discussed below), decreased immune function, difficulty breathing (dyspnoea), difficulty in giving birth, high blood pressure (hypertension), degenerative joint and orthopaedic disease and cardiovascular stress [12].

Treatment involves feeding a reduced calorie diet and increasing exercise. In cats, rapid weight loss can result in the deposition of lipids in the liver which can cause liver disease [5]. The addition of increased levels of L-carnitine, a co-enzyme found in high concentrations in red meat extracts, to the diet has been shown to prevent lipid accumulation in the liver of cats undergoing rapid weight loss, thus facilitating safer dieting [12]. Furthermore, overweight cats supplemented with carnitine lost weight more rapidly than cats that were not supplemented. [12]

Diabetes Mellitus

Prevalence: Dogs: 0.2 - 0.25% [5]; Cats: 0.5% [5].

There are several causes of diabetes mellitus but the end result is insufficient secretion of insulin and/or resistance to the effects of insulin at target tissues [5]. The lack of insulin signalling means that cells cannot absorb glucose, resulting in abnormally high levels of glucose in the blood while, paradoxically, cells are deprived of this essential source of energy [5]. Consequently, proteins and lipids are used for energy resulting in the loss of muscle and fat [5]. In time, lipids

may be converted into ketone bodies, an alternative energy source, that at increased concentrations can cause vomiting, dehydration, acidosis and death [5]. In cats, the most common form of diabetes is analogous to type 2 diabetes, previously called adult-onset diabetes or non-insulin dependent diabetes [5]. This form of diabetes results from obesity and lack of physical activity. Type 1 diabetes is the most common form in dogs and results from immune-mediated destruction of cells which produce insulin [5].

Diabetes mellitus is effectively treated by administering insulin via injection: human, pig or long-acting analogue insulin are best suited to dogs, while long-acting analogue insulin is preferable for cats [5]. It is also important to adjust the animal's diet to provide sufficient calories to maintain ideal body weight and to minimize post-eating glucose concentrations by decreasing carbohydrate content and increasing fibre in the diet.

Hyperadrenocorticism

Prevalence: Dogs: one of the most common endocrine disorders [5]; Cats: rare [5].

The majority of cases (~ 90%) of hyperadrenocorticism are due to tumours or benign growth of the pituitary resulting in an increase in the pituitary hormone adrenocorticotrophic hormone (ACTH) [5]. The increased levels of ACTH induce the adrenals to produce abnormally high concentrations of cortisol. The remaining cases of hyperadrenocorticism are due to adrenal tumours that secrete increased cortisol[5]. The effects of excess cortisol are seen predominantly in the form of increased urination and drinking, increased appetite and obesity, enlarged liver, lethargy, muscle weakness, hair loss, thin skin and bruising [5]. The most effective treatment for both types of hyperadrenocorticism are the drugs mitotane and trilostane which decrease the production of cortisol [5].

Hypothyroidism

Prevalence: Dogs: 0.2 - 0.6% [5]; Cats: very rare [5].

Hypothyroidism is a multisystemic disease that affects the majority of the body's systems, and is seen most frequently in middle-aged, pure-bred dogs [5]. Most cases are due to the gradual destruction of the thyroid via an immune-mediated process or due to atrophy [5]. Dogs commonly show skin abnormalities, obesity, lethargy, weakness, decreased heart rate, cold intolerance and anaemia [5]. Treatment consists of oral supplementation of synthetic thyroxine [5].

Hyperthyroidism

Prevalence: Dogs: rare [5]; Cats: the most common endocrine disease [5].

Hyperthyroidism is one of the most common diseases affecting late middle-aged and geriatric cats [5]. It is due to an enlargement of the thyroid gland, the cause of which is unknown [5]. The resultant increased concentration of the thyroid hormone thyroxine causes an increase in the body's metabolism [5]. Typically, cats present with weight loss, vomiting, diarrhoea, increased heart rate, increased drinking and appetite, dyspnoea, aggression and hyperactivity [5]. Treatment options include drug therapy to decrease the amount of thyroxine produced, surgery to remove a section of the thyroid or administration of radioactive iodine to destroy a portion of the thyroid [5].

Inflammatory Bowel Disease

Prevalence: Dogs: common [5]; Cats: common [5].

Inflammatory bowel disease is a general term that encompasses a number of diseases that are characterised by an infiltration of inflammatory cells into the tissue of the small or large intestine [5]. Inflammation causes damage to the tissues resulting in vomiting, diarrhoea and weight loss [5]. The first step in treatment involves feeding a bland diet in an attempt to eliminate any dietary hypersensitivities[5]. If this fails, anti-inflammatory and immunosuppressive drugs such as corticosteroids may be used [5]. Antibiotics are also often prescribed in combination with corticosteroids [5].

Gingivitis

Prevalence: Dogs: > 80% if over 3 years of age [5]; Cats: > 80% if over 3 years of age [5].

Gingivitis is an inflammatory response of the gingiva (the gum tissue that borders the teeth), in association with increased numbers of pathogenic bacteria [5]. The bacteria produce endotoxins that destroy the gingiva [5]. The deposition of plaque is the trigger for initiating gingivitis [5]. As the plaque invades the gingiva, bleeding, swelling and bad breath may be noticed [5]. Gingivitis can progress to periodontitis and tooth loss [5]. The feeding of hard, dry food helps to remove plaque from the teeth, as does the chewing of bones [5]. However, regular brushing is the most effective method of preventing the accumulation of plaque [5]. Yearly dental check-ups, and scaling as required, are also important preventative measures.

Pancreatitis

Prevalence: Dogs: approximately 1% [5]; Cats: unknown [5].

Pancreatitis is inflammation of the pancreas, the cause of which is usually unknown [5]. Animals display lethargy, vomiting, weight loss, abdominal pain, diarrhoea, dehydration and fever [5]. Treatment is aimed at alleviating the symptoms and maintaining nutrition and hydration [5]. Animals are usually given intravenous fluids, antiemetics to prevent vomiting and analgesics for pain management [5]. In some patients, a tube may be inserted into the jejunum (section of the small intestine), to allow food to be delivered into the intestine at a point that bypasses the need for pancreatic activity, thus giving the pancreas time to recover [5].

Urocystolithiasis

Prevalence: Dogs:1.5-3% [14]; Cats: unknown - assumed to be similar to dogs.

The formation of mineral stones, or calculi, in the urinary tract occurs when the urine is supersaturated with minerals [5]. The pH of the urine has a significant effect by influencing the solubility of the minerals[5]. Infection of the urinary tract can predispose animals to the formation of calculi [5]. Two types of calculi are most often seen in cats and dogs: calcium oxalate calculi represent 30-40% of those seen in dogs, and 50-55% of those in cats; struvite calculi constitute 50% of the calculi in dogs and 40% of those in cats [5]. Animals with calculi may show difficulty and pain on urinating, may need to urinate often while only passing small volumes of urine, and there may be blood in the urine [5]. Depending upon the type and location of the calculi, animals may be treated surgically to remove them. Alternatively, commercially available diets may be used to dissolve the calculi (Hill's s/d) and prevent them from reappearing (Hills's c/d). These diets are effective at controlling the pH of the urine and minimising the concentrations of calculus-forming minerals.

Atrioventricular Valve Endocardiosis

Prevalence: Dogs: 5% if 5-7 years of age, >35% if over 12 years of age [5]; Cats: prevalence unknown but has been observed in geriatrics [5].

Atrioventricular valve endocardiosis is a chronic, degenerative disease of the valves between the atria and ventricles of the heart [5]. It is caused by the deposition of mucopolysaccharides within the valve tissue causing it to thicken, stiffen and become distorted [5]. As the heart contracts, blood flows back through the damaged valve rather than being ejected from the heart to the lungs and body. This results in fluid accumulating in the lungs causing coughing and lethargy, and insufficient blood flowing to the body, further compounding the lethargy. While surgical replacement of the affected valve/s is possible, it requires the skill of a specialist surgeon and the availability of heart bypass equipment; thus, drug therapy is the most common

mode of treatment [5]. A low sodium diet and specific drugs are used to decrease blood pressure and improve blood flow from the heart[5]. Further drugs are used to promote regular contractions of the heart [5]. It is also important that exercise is restricted to avoid over-loading the heart.

Hypertrophic Cardiomyopathy

Prevalence: Dogs: very rare [5]; Cats: common [5].

Hypertrophy (thickening) of the left ventricle is common in cats, although its cause is unknown [5]. As the ventricle thickens it is less able to effectively eject blood, resulting in an increased blood pressure in the lungs which can cause pulmonary oedema (fluid in the lungs), the formation of blood clots and a decrease in the volume of blood distributed around the body [5]. Treatment is via drugs aimed at reducing blood pressure, minimising clotting, increasing the relaxation of the ventricle so that it can better fill with blood and obtain a more forceful contraction, and slower beating of the heart to also facilitate more complete filling and ejection of blood [5].

Conclusion

Nutraceuticals already play an important role in veterinary medicine and are used largely to ameliorate the results of mediators of inflammation and oxidative damage. Their most common use is for management of osteoarthritis in dogs and cats. However, there are many diseases which are currently not treated with nutraceuticals. Therefore, as further research identifies the benefits of new and existing nutraceuticals in human and veterinary medicine, the potential of these compounds in the treatment of veterinary disease will expand.

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Section II: The Most Common Nutraceuticals in Veterinary and Human Medicine

The most commonly used nutraceuticals in veterinary medicine are glucosamine, chondroitin sulphate, pentosan polysulphate, and the omega-3 fatty acids. Many of the prescription diets manufactured for the management of specific diseases include these nutraceuticals. Significantly, many of these diets also contain L-carnitine which may function in the prevention of lipid deposition in the livers of obese cats undergoing rapid weight loss, the maintenance of lean body mass during weight loss in dogs, and in the treatment of dilated cardiomyopathy in L-carnitine-deficient dogs. Taurine is an essential amino acid that is routinely added to commercial diets. In cats, a dietary deficiency in taurine has been associated with cardiac, reproductive and retinal disease. American Cocker Spaniel dogs may also be predisposed to taurine deficiency and consequent cardiac disease. Arginine, when combined with the omega-3 fatty acids, has been shown to improve the quality of life and increase survival times of dogs undergoing treatment for cancer. Although the use of nutraceuticals has been embraced by consumers world-wide, their prescribed use by medical practitioners is considerably more limited. Currently, the only nutraceuticals in human medicine that are consistently recognised as having any significant benefits are glucosamine and chondroitin sulphate for the management of osteoarthritis.

Part IA: The Most Common Nutraceuticals in Veterinary Medicine

The most prevalent use of nutraceuticals in veterinary medicine is for the treatment of osteoarthritis in dogs and older cats[1,2,3]. Glucosamine, chondroitin sulphate and pentosan polysulphate are routinely used by veterinarians to alleviate pain and retard the progression of cartilage destruction[1,2,3]. They are used in addition to the non-steroidal anti-inflammatory drugs (NSAIDs) that form the mainstay of treatment for osteoarthritis. The benefit of using glucosamine, chondroitin sulphate and pentosan polysulphate in addition to NSAIDs is that they have a longer duration of action, no marked side-effects, and allow for the desired level of pain relief to be achieved with lower doses of NSAIDs, thus significantly minimising the side-effects associated with long-term NSAID use[3].

The omega-3 fatty acids – docosahexaenoic acid and eicosapentaenoic acid – are potent inhibitors of oxidative cellular damage and inflammation, and so are commonly used as adjunct

therapies in the treatment of cancer[4], canine aging and cognitive dysfunction syndrome[5] and allergic dermatitis[6]. More recently, a role for the omega-3 fatty acids in the management of chronic renal disease has also been described[7]. Diets produced commercially for the management of the above conditions contain significant levels of omega-3 fatty acids (Table 1; see also Part II).

Nutraceutical	Disease	In Prescription Diet
Glycosaminoglycans (glucosamine, chondroitin sulphate, pentosan polysulphate)	Osteoarthritis	Yes
Omega-3 fatty acids (docosahexaenoic acid and eicosapentaenoic acid)	Cancer, chronic renal disease, canine aging and cognitive dysfunction syndrome, allergic dermatitis	Yes

Table 1. Nutraceuticals associated with common diseases and their availability in commercial diets.

Part IB: The Most Common Bioactives in Veterinary Diets

L-carnitine is a normal component of all animal cells, where it is required for energy production; significantly, 95% of the body's carnitine is found in cardiac and skeletal muscles[8]. To ensure optimum health in cats and dogs, carnitine is a common additive to commercial pet diets (Table 2; see also Part II). However, carnitine may serve other roles in addition to normal cardiac and skeletal muscle function. In cats, rapid weight loss can result in the deposition of lipids in the liver which can cause liver disease[8]. The addition of increased levels of carnitine to the diet has been shown to prevent lipid accumulation in the liver of cats undergoing rapid weight loss, thus facilitating safer dieting[8]. Similarly, carnitine may play a role in the maintenance of lean body mass during weight loss in dogs (J. Rand pers. comm.). Carnitine is also used specifically in the treatment of dilated cardiomyopathy in L-carnitine-deficient dogs[8].

Taurine is an essential amino acid required by cats in order to synthesise bile salts[8]. Taurine is also essential for normal function of the retina of the eye, the reproductive system, and the heart, and cats deficient in taurine may show disease in these organs[8]. Dogs, unlike cats, can also use glycine for the conjugation of bile acids into bile salts, and are also better able to synthesise taurine in the body[8]. However, American Cocker Spaniel dogs may be predisposed to taurine deficiencies leading to the heart disease dilated cardiomyopathy[8]. Because of their limited ability to synthesise taurine, cats have a greater requirement for dietary intake of taurine than do dogs. Consequently, commercial feline diets are supplemented with taurine to achieve levels of approximately 1,000 parts per million (1g of taurine/kg of dry food) [8] (Table 2; see also

Part II). Cats fed homemade diets or cereal-based canine diets are at significant risk of taurine deficiency[8].

Arginine is an essential amino acid that cannot be synthesised by cats or dogs and so must be obtained in the diet[8]. Arginine is required for the elimination of toxic nitrogenous wastes from the body which, if allowed to accumulate, can cause neurological dysfunction and death[8]. Thus, adequate arginine levels are ensured in commercial diets (Table 2; see also Part II). Increased dietary arginine has also been shown to improve the quality of life, and increase survival times, of dogs undergoing chemotherapy and radiation treatment for cancer when combined with a diet high in omega-3 fatty acids[8].

Nutraceutical	Benefits	In Commercial Diet
L-carnitine	Prevention of fatty liver during weight loss in cats, maintenance of lean body mass during weight loss in dogs, replacement in carnitine-deficient dogs.	Yes
Taurine	Essential amino acid for normal function of the retina, the reproductive system and the heart.	Yes
Arginine	Essential amino acid required for the elimination of toxic nitrogenous wastes from the body.	Yes

Table 2. Bioactives associated with optimum health and their availability in commercial diets.

Nutraceutical/Bioactive	Meat Source	Yield
Glucosamine	Bovine tracheal cartilage	Could not be determined
Chondroitin sulphate (70% grade)	Bovine tracheal cartilage (Mollusc shells)	0.3g/100g
Pentosan polysulphate	Could not be determined (Synthetically produced)	Could not be determined
L-carnitine	Skeletal muscle and cardiac muscle	0.019-0.21g/100g
Taurine	Bile, muscle, liver and brain	15-44g/100g
Arginine	Skeletal muscle, liver, heart, thymus and kidney	0.9-1.8mg/100g

Table 3. Meat sources of the most significant nutraceuticals and bioactives.

Part II: Veterinary Prescription Diets Containing Nutraceuticals

Prescription diets are animal foods that are manufactured specifically for the nutritional management of a medical condition and, as such, are only available through veterinarians. The prescription diets summarised in this section are all produced by Hill's, which has secured a major portion of the Australian premium pet food market. The values given for the different food components are listed as "content as fed", simply meaning that per 100g of that particular food,

including water and dry matter content, a given percentage of that 100g consists of protein, fat, carbohydrates and the like.

Canine Diets

Canine b/d

Management of: behavioural disorders associated with brain aging.

Nutraceuticals: carnitine, omega-3 fatty acids, beta-carotene and selenium.

Content as fed: protein (chicken) 17.4%, fat 14.2%, carbohydrates 51.9% and carnitine 275 ppm, (omega-3 fatty acids, beta-carotene and selenium: values not given).

Canine h/d

Management of: heart disease.

Nutraceuticals: carnitine and taurine.

Content as fed: protein (chicken) 16.5%, fat 18.7%, carbohydrates 50.4%, carnitine 227 ppm and taurine 0.12%.

Canine j/d

Management of: osteoarthritis.

Nutraceuticals: carnitine, omega-3 fatty acids, glucosamine and chondroitin sulphate.

Content as fed: protein (chicken) 18.5%, fat 13.2%, carbohydrates 46.9%, carnitine 323 ppm and omega-3 fatty acids 0.94%, (glucosamine and chondroitin sulphate: values not given).

Canine k/d

Management of: kidney disease.

Nutraceuticals: omega-3 fatty acids.

Content as fed: protein (chicken) 13.4%, fat 17.6%, carbohydrates 56.5% and omega-3 fatty acids 1.40%.

Canine l/d

Management of: liver disease.

Nutraceuticals: carnitine.

Content as fed: protein (egg) 16.3%, fat 22.3%, carbohydrates 46.9% and carnitine 279 ppm.

Canine n/d (currently unavailable in Australia)

Management of: cancer.

Nutraceuticals: arginine, omega-3 fatty acids.

Content as fed: protein (liver, chicken) 11.1%, fat 9.7%, carbohydrates 5.8%, arginine 0.86%, omega-3 fatty acids 2.13%.

Canine r/d

Management of: obesity.

Nutraceuticals: carnitine.

Content as fed: protein (chicken) 22.8%, fat 7.9%, carbohydrates 34.5% and carnitine 279 ppm.

Canine u/d

Management of: calcium oxalate, urate and cystine uroliths.

Nutraceuticals: carnitine, omega-3 fatty acids and taurine.

Content as fed: protein (egg) 9.3%, fat 19.0%, carbohydrates 59.6%, carnitine 278 ppm, omega-3 fatty acids 0.68% and taurine 0.10%.

Canine w/d

Management of: weight control and fibre-responsive diseases such as diabetes, colitis, diarrhoea and constipation.

Nutraceuticals: carnitine.

Content as fed: protein (chicken) 17.2%, fat 8.1%, carbohydrates 44.7% and carnitine 270 ppm.

Canine z/d

Management of: food allergy and intolerance, general allergic disease.

Nutraceuticals: omega-3 fatty acids and omega-6 fatty acids.

Content as fed: protein (chicken) 18.9%, fat 12.0%, carbohydrates 51.3%, (omega-3 and omega-6 fatty acids: values not given).

Feline Diets

Feline k/d

Management of: kidney disease.

Nutraceuticals: omega-3 fatty acids, taurine.

Content as fed: protein (chicken) 26.2%, fat 20.6%, carbohydrates 40.4%, omega-3 fatty acids 0.20% and taurine 0.15%.

Feline l/d

Management of: liver disease.

Nutraceuticals: carnitine, taurine, arginine.

Content as fed: protein (chicken) 29.4%, fat 21.5%, carbohydrates 34.6%, carnitine 929 ppm, taurine 0.49% and arginine 1.83%. Arginine is added to this diet for liver disease because the

liver is the organ responsible for the processing of nitrogenous wastes, and so additional arginine may be beneficial in helping a diseased liver perform this function.

Feline m/d

Management of: obesity and diabetes mellitus.

Nutraceuticals: carnitine, taurine.

Content as fed: protein (chicken) 48.9%, fat 20.7%, carbohydrates 14.6%, carnitine 521 ppm and taurine 0.28%.

Feline w/d

Management of: weight control and fibre-responsive diseases such as diabetes mellitus, colitis, diarrhoea and constipation.

Nutraceuticals: carnitine, taurine.

Content as fed: protein (chicken) 35.9%, fat 9.0%, carbohydrates 34.4%, carnitine 459 ppm and taurine 0.20%.

Feline z/d

Management of: allergic disease.

Nutraceuticals: omega-3 fatty acids, omega-6 fatty acids, taurine.

Content as fed: protein (chicken) 37.0%, fat 15.9%, carbohydrates 32.7%, omega-3 fatty acids 0.61%, omega-6 fatty acids 5.30% and taurine 0.21%.

Part III: Human Diseases and Associated Nutraceutical Use

Consumer interest in nutraceuticals is growing rapidly in the United States, Europe, Australia and Asia. In the United States alone, it is estimated that US$75 billion is spent annually on nutraceuticals and vitamin supplements for human use[9]. Approximately 60% of Americans utilise some form of supplement to enhance their sense of well-being, prevent illness, or on the advice of their physician[9]. The most significant use of nutraceuticals in human medicine, as in veterinary medicine, is for the treatment of osteoarthritis with glucosamine and chondroitin sulphate[10]. To a much lesser degree, nutraceuticals have been utilised as adjunct therapies in the management of hypertension[11], cardiac disease[12], ulcerative colitis[13], asthma and atopic dermatitis[14,15], and cancer[16,17,18].

Osteoarthritis

Osteoarthritis is an inflammatory disease of the joints that progresses over time to cause bone remodelling and destruction of the articular cartilage. Glucosamine and chondroitin sulphate are essential components of joint articular cartilage. In human patients with osteoarthritis, oral administration of glucosamine resulted in a decrease in joint pain and swelling[10]. A common NSAID used in the treatment of osteoarthritis is ibuprofen[10]. In clinical trials comparing the efficacy of glucosamine with ibuprofen, the improvement in clinical signs was rapid in patients treated with ibuprofen but no further improvement was observed beyond 2 weeks after the commencement of treatment; however, patients treated with glucosamine showed a more gradual improvement in clinical signs that was progressive throughout the entire 8 weeks of the trial[10]. Furthermore, improvement persisted up to 2 months after the cessation of treatment[10].

Hypertension

A key strategy in the management of hypertension is to lower blood pressure by decreasing blood volume. This is achieved by down regulating the production of angiotensin converting enzyme (ACE) through the use of ACE inhibitors. Japanese researchers have identified a nutraceutical ACE inhibitor that can be derived from tuna protein[11].

Cardiac Disease

Elevated cholesterol levels in the blood are associated with the deposition of plaque material in the main vessels of the heart. These plaques cause a narrowing of the lumen of the vessels which, in turn, places extra strain on the heart resulting in progressive cardiac disease. A product from the yeast *Monascus purpureus,* marketed as Cholestin™, has been shown to decrease plasma cholesterol levels by approximately 20%, thus reducing the risk of heart disease[12].

Nitric oxide is a potent effector of blood vessel dilation, and is produced by the body from the amino acid arginine. Clinical trials in which patients with heart disease were treated with arginine showed a significant decrease in patient angina pain and an increase in exercise duration[12].

Ulcerative Colitis

Patients with ulcerative colitis have marked inflammation and ulceration of the colon. When patients were treated with germinated barley foodstuff (GBF), derived from the aleurone layer and scutellum fractions of malt, inflammation of the colonic mucosa was significantly reduced[13]. GBF appears to exert its effects by increasing the concentration of butyrate in the colon[13]. Butyrate is the primary nutrient utilised by cells of the colonic mucosa and also has an anti-inflammatory effect by inhibiting the production of inflammatory mediators such as interleukins 6 and 8[13].

Asthma and Atopic Dermatitis

Although the omega-3 fatty acids are routinely used in veterinary medicine for the control of allergic skin diseases, their use in human medicine for similar conditions is less significant. In humans, as in animals, supplementation of the diet with omega-3 fatty acids results in a decrease in the production of the inflammatory mediators associated with allergic disease; however, these effects are minimal in people in whom the allergic disease is chronic[14]. In contrast, Dunston and colleagues (2003) found a decrease in atopic dermatitis in 1 year old infants whose mothers had taken omega-3 fatty acid supplements during pregnancy. Although there was no difference between treatment and control groups in the frequency of atopic dermatitis, infants exposed to the omega-3 fatty acids *in utero* had less severe atopy[15].

Cancer

Active hexose correlated compound (AHCC) is a mixture of polysaccharides, amino acids, lipids and minerals derived from mycelia of several species of Basidiomycete mushrooms[16]. In mice inoculated with melanoma and lymphoma tumour cells, treatment with AHCC delayed tumour development and reduced tumour size compared with controls[16].

Another factor with potential anti-tumourogenic properties is genestein, which is isolated from soybeans. Genestein is a phyto-oestrogen that *in vitro* inhibits the expression of genes that are involved in tumourogenesis[17].

Omega-3 fatty acids have been purported to have a role as adjuncts in human cancer therapy and as cancer preventatives. However, in a recent review by MacLean and colleagues (2006) the effects of omega-3 fatty acids in preventing breast, colorectal and lung cancer appear to be inconclusive. In fact, consumption of omega-3 fatty acids may be correlated with an increased risk of breast and colorectal cancer[18].

Part IV: Nutraceutical and Bioactive Products Purchased By Consumers

Although the prescription of nutraceuticals by medical practitioners for the management of specific diseases is limited, the self-prescribed use of nutraceuticals and vitamin and mineral supplements by consumers is a multi-billion dollar industry worldwide. The following is a table (Table 4) listing the most commonly available nutraceuticals and bioactives in Australia and the U.S.A., focusing on those products which may be derived from animal sources.

Nutraceutical or Bioactive	Purported Benefits
5-hydroxytryptophan	Decreases stress and anxiety.
Aspartic acid	Assists digestion, helps decrease fatigue, involved in the

	production of energy from glucose.
Biotin	Strengthens hair and nails, supports healthy skin.
Branched chain amino acids	Assists muscle recovery and supports lean muscle growth.
Co-enzyme Q10	Antioxidant, boosts energy production, protects against heart disease.
Colostrum	Promotes muscle growth, acts as a general growth stimulant.
Conjugated linoleic acid	Decreases body fat, regulates inflammatory response, decreases incidence of asthma.
Creatinine	Boosts energy production, supports muscle maintenance.
Cysteine	Antioxidant, aids in fat metabolism and in the treatment of ulcers.
Dihydroepiandrostenedione (DHEA)	Decreases mood swings, stress and fatigue, increases energy production.
Dimethylaminoethanol	Produced by the human brain. Thought to increase brain activity.
Folate	Decreases birth defects of the brain and spinal cord, promotes healing of tissues.
Gamma-aminobutyric acid (GABA)	Increases brain function, induces better sleep and promotes weight management.
Glucosamine & chondroitin	Improves joint mobility, decreases joint swelling and inflammation, slows cartilage destruction.
Glutamine	Increases immune function, assists brain function, promotes muscle recovery.
(Human) growth hormone	Helps boost energy levels.
Histidine	Decreases stress, promotes muscle growth.
Inosine	Involved in energy production, wound healing and in the prevention of heart disease.
Inositol	Involved in energy production and fat metabolism, decreases cholesterol and acts to promote health of the liver and nervous system.
L-alanine	Assists liver function and induces rehydration.
L-arginine	Removal of ammonia, boosts immune system, decreases blood pressure.
L-carnitine	Required for fatty acid transportation and energy production, encourages fat loss, protects against heart disease.
Lecithin	Promotes healthy skin and hair.
L-lysine	Decreases growth of viruses, promotes bone growth and tissue repair, decreases fatigue.
L-ornithine	Promotes healing, immune function, increased muscle mass and decreased fat.
L-phenylalanine	Elevates mood, decreases appetite, enhances memory and learning.
L-proline	Involved in energy production and collagen synthesis, and increases bone density.
Magnesium	Required for normal muscular and nerve function.
Melatonin	Prevents insomnia, strengthens immune system, decreases incidence of free radicals.
Methylsulphonylmethane	A source of bioavailable sulphur which is essential for normal cell structure and function. Often combined with glucosamine and chondroitin sulphate.
Nicotinamide adenine dinucleotide (NADH)	An essential component in the production of energy by cells. Thought to enhance feelings of strength and energy.
Pyruvate	Accelerates fat loss by increasing cellular respiration.
S-adenosyl-L-methionine (SAMe)	Decreases nervous tension, stress and anxiety.

Selenium	Antioxidant.
Serine	Increases iron absorption, improves memory and concentration.
Sheep placenta	Antiaging effects, revitalises skin, boosts the immune system.
Taurine	Decreases cholesterol and fat absorption, assists memory, decreases anxiety and controls epileptic seizures, important for retinal health.
Threonine	Increases energy production, boosts the immune system, promotes fat metabolism, is required for normal growth of skin, bone and muscle.
Trimethylglycine (betaine)	Decreases the risk of stroke, heart attack and dementia.
Tyrosine	Required for the production of thyroid hormones which are involved in regulating cellular metabolism.
Valine	Supports muscle growth, prevents tissue breakdown, is a component of the myelin sheath surrounding nerves.
Vitamin A (retinol)	Antioxidant, important for vision and the health of skin and mucous membranes.
Vitamin B1 (thiamine)	Required for the breakdown of glucose to form energy. Plays a role in the regulation of memory, mood and concentration.
Vitamin B12	Required for the production of red blood cells and the health and function of the heart and blood vessels.
Vitamin B2 (riboflavin)	Promotes healthy eyes and may decrease inflammation of the eyes.
Vitamin B3 (niacin)	Required for the maintenance of the peripheral circulation.
Vitamin B5	Involved in the production of neurotransmitters and adrenal hormones, and in the metabolism of fats, proteins and carbohydrates.
Vitamin B6	Involved in the production of prostaglandins, haemoglobin, red blood cells and neurotransmitters.
Vitamin C (ascorbic acid)	Antioxidant, promotes wound healing and decreases the effects of the common cold and allergic reactions.
Vitamin E	Antioxidant, promotes heart health.

Table 4. Commonly available nutraceuticals and bioactives in Australia and the USA.

Conclusion

The most commonly used nutraceuticals in veterinary medicine are glucosamine, chondroitin sulphate, pentosan polysulphate and the omega-3 fatty acids. Many of the prescription diets manufactured by the major supplier of veterinary diets in Australia include these nutraceuticals. Carnitine has been suggested to play a role in the prevention of lipid deposition in the livers of obese cats undergoing rapid weight loss[8] and in the maintenance of lean body mass during weight loss in dogs (J. Rand pers. comm.); curiously, it is an ingredient in the majority of the Hill's canine and feline diets, and not just those diets aimed at managing weight loss. Although the use of nutraceuticals has been embraced by consumers world-wide, their prescribed use by medical practitioners is considerably more limited. Currently, the only nutraceuticals in human medicine that are consistently recognised as having any significant benefits are glucosamine and chondroitin sulphate for the management of osteoarthritis.

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Section III: Nutraceuticals and Bioactives in Pet Foods Available in Australia, U.S.A. and Japan

In general, nutraceuticals are more commonly added to premium and veterinary diets rather than standard grocery-line diets. The predominant brands of premium and veterinary pet foods available in Australia are Hill's Prescription Diets, Eukanuba Veterinary Diets, Iam's, Royal Canin Veterinary Diets, Waltham Veterinary Diets and the Australian-owned Advance. Similarly, in North America, Hill's, Eukanuba, Iam's, Royal Canin and Waltham occupy significant shares of the pet food market, in addition to Nestlé Purina Veterinary Diets and Pedigree Veterinary Diets. In Japan, Hill's, Pedigree and Nestlé Purina are the most popular Western brands, in addition to Japanese brands Nippon Pet Food, Nisshin Pet Food and Unicharm Pet Care.

The previously identified 5 most prevalent nutraceuticals and bioactives in veterinary medicine, namely glycosaminoglycans, omega-3 fatty acids, carnitine, taurine and arginine, are present in most premium pet foods. Ingredients that are unique to a specific brand include green-lipped mussel powder, chromium tripicolinate, green tea polyphenols, tyrosine, lycopene and slippery elm.

Introduction

This report lists the nutraceutical and bioactive contents of the major premium pet foods available in Australia, the U.S.A. and Japan. We have concentrated on premium and veterinary diets because it is in the formulation of these diets, rather than the supermarket diets, that the majority of pet nutrition research is focused, and so it is these foods that contain the highest proportions of nutraceuticals and bioactive substances. In Australia, the predominant brands are Hill's Prescription Diets, Eukanuba Veterinary Diets, Iam's, Royal Canin Veterinary Diets, Waltham Veterinary Diets and the Australian-owned Advance. Similarly, Hill's, Eukanuba, Iam's, Royal Canin and Waltham occupy significant shares of the North American pet food market, in addition to Purina Veterinary Diets and Pedigree Veterinary Diets[1]. Japanese consumers also favour Hill's, Pedigree and Purina, in addition to Japanese brands Nippon Pet Food, Nisshin Pet Food and Unicharm Pet Care[2, 3].

The following tables list the nutraceutical and bioactive ingredients in the premium canine and feline foods marketed in Australia, the U.S.A. and Japan. Unfortunately, it was not possible to obtain information regarding the nutraceutical content of the Japanese-produced pet foods since all of the material is written in Japanese without English translations. The values given are on an "as fed" basis for dry foods. Where "na" is listed, the ingredient is present in the food but the amount is not provided by the manufacturer for reasons of confidentiality.

Hill's Prescription Diets

Carnitine: Carnitine has been suggested to play a role in the maintenance of lean body mass during weight loss in dogs (J. Rand pers. comm.), and in the treatment of dilated cardiomyopathy in L-carnitine-deficient dogs[4]. In cats, the addition of increased levels of carnitine to the diet has been shown to prevent lipid accumulation in the liver of cats undergoing rapid weight loss[4]. Furthermore, obese cats on a weight reducing diet and supplemented with L-carnitine lose weight more rapidly, and retain a greater proportion of muscle mass, compared to cats not receiving L-carnitine[5].

Taurine: Taurine is an essential amino acid that is routinely added to commercial diets to prevent deficiencies[4]. In particular, cats and Cocker Spaniel dogs may be predisposed to taurine deficiency[4].

Arginine: Arginine is an essential amino acid that cannot be synthesised by cats or dogs and so must be obtained in the diet[4]. Arginine is required for the elimination of toxic nitrogenous wastes from the body which, if allowed to accumulate, can cause neurological dysfunction and death[4]. Furthermore, when combined with the omega-3 fatty acids, arginine has been shown to improve the quality of life and increase survival times of dogs undergoing treatment for cancer[4].

Glucosamine, Chondroitin Sulphate: Glucosamine and chondroitin sulphate are routinely used by veterinarians to alleviate the pain and cartilage destruction associated with osteoarthritis[6, 7, 8].

Omega-3 Fatty Acids: The omega-3 fatty acids – docosahexaenoic acid and eicosapentaenoic acid – are potent inhibitors of inflammation[9].

Omega-6 Fatty Acids: The omega-6 fatty acids are plant-derived essential fatty acids that mammals cannot synthesise - thus they must be supplied in the diet, usually as vegetable oils[4]. Omega-6 fatty acids are the precursors for a range of inflammatory mediators; thus, by altering the ratios of the various omega-6 fatty acids and the ratio with omega-3 fatty acids, it is possible to decrease the production of those particular omega-6 fatty acids that are directly involved in the inflammatory process[4].

Canine

Diet	Carnitine	Taurine	Arginine	Omega-3	Omega-6	Glucosamine	Chondroitin
b/d: Brain Aging	275 ppm			na			
h/d: Heart Disease	227 ppm	0.12%					
j/d: Osteoarthritis	323 ppm			0.94%	2.96%	980mg/kg	674mg/kg
k/d: Kidney Disease				1.40%			
l/d: Liver Disease	279 ppm						
n/d: Cancer*			0.86%	2.13%			
r/d: Obesity	279 ppm						
u/d: Uroliths	278 ppm	0.10%		0.68%			
w/d: Weight Control	270 ppm						
z/d: Allergic Disease				0.38%	2.95%		

The values given are on an "as fed" basis for dry foods. The exception is n/d which is only available as a canned food and so values given are on an "as fed" basis for 100g of wet food.
* Currently not available in Australia.

Feline

Diet	Carnitine	Taurine	Omega-3	Omega-6
k/d: Kidney Disease		0.15%	0.20%	
l/d: Liver Disease	929 ppm	0.49%		
m/d: Obesity, Diabetes mellitus	521 ppm	0.28%		
w/d: Weight Control	459 ppm	0.20%		
z/d: Allergic Disease		0.21%	0.61%	5.30%

The values given are on an "as fed" basis for dry foods.

Waltham Veterinary Diets

Vitamin E: Vitamin E is an antioxidant that is synthesised only by plants and is an essential component of the diet[4].

Green-lipped Mussel Powder: The green-lipped mussel (*Perna canaliculus*) is a source of chondroitin sulphate and the omega-3 fatty acid eicosatetraenoic acid[10].

Canine

Diet	Taurine	Omega-3	Vitamin E	Green-lipped Mussel Powder
Digestive Tract Support	0.16%		0.022%	
Sensitivity Control	0.17%		0.030%	
Hepatic Support	0.189%		0.030%	
Renal Support	0.22%	na	0.027%	
Mobility Support	0.20%		0.047%	0.3%
Weight Management	0.16%		0.020%	
Urinary Tract Support	0.16%		0.070%	
Glucomodulation (Diabetes)	0.17%		0.019%	

The values given are on an "as fed" basis for dry foods.

Feline

Diet	Taurine	Vitamin E
Sensitivity Control	0.23%	0.040%
Renal Support	0.28%	0.027%
Weight Management	0.16%	0.030%
Urinary Tract Support	0.23%	0.030%

The values given are on an "as fed" basis for dry foods.

Eukanuba Veterinary Diets

Chromium tripicolinate: Chromium tripicolinate is a mineral used to maintain normal glucose metabolism by potentiating the activity of insulin[4].

Canine

Diet	***Carnitine***	***Omega-3***	***Omega-6***	***Glucosamine***	***Chondroitin***	***Vitamin E***	***Chromium Tripicolinate***
Response FP (allergies)		0.24%	1.20%				
Low Residue		0.27%	1.35%				
Restricted Calorie	40mg/kg	0.20%	1.15%				250µg/kg
Weight Control	40mg/kg	0.25%	1.25%				
Joint Health	40mg/kg	0.30%	1.50%	475mg/kg	45mg/kg		
Senior Plus	40mg/kg	0.25%	1.25%	475mg/kg	45mg/kg	140IU/kg	
Renal Disease		0.35%	1.75%				
Maximum Calorie		0.65%	3.25%				

The values given are on an "as fed" basis for dry foods.

Feline

Diet	***Carnitine***	***Taurine***	***Omega-3***	***Omega-6***	***Chromium Tripicolinate***

Response LB (allergies)		0.07%	0.21%	1.05%	
Low Residue		0.13%	0.22%	1.10%	
Restricted Calorie	80mg/kg	0.12%	0.18%	0.90%	500µg/kg
Weight Control	80mg/kg	0.21%	0.23%	1.15%	500µg/kg
Renal Disease		0.15%	0.65%	3.30%	
Maximum Calorie		0.10%	0.22%	1.10%	

The values given are on an "as fed" basis for dry foods.

Iams

Canine

Diet	Carnitine	Omega-3	Omega-6	Glucosamine	Vitamin E
Chunks		0.25%	2.5%		
Large Breed		0.23%	2.3%	350mg/kg	
Lamb & Rice		0.20%	2.0%		
Weight Control	30mg/kg	0.20%	2.0%		
Weight Control Large Breed	30mg/kg	0.20%	2.0%	350mg/kg	
Active Maturity	30mg/kg	0.20%	2.0%		140IU/kg
Active Maturity Large Breed	30mg/kg	0.20%	2.0%	350mg/kg	140IU/kg

The values given are on an "as fed" basis for dry foods.

Feline

Diet	Carnitine	Taurine	Omega-3	Omega-6	Vitamin E
Original		0.15%	0.23%	2.30%	
Hairball		0.15%	0.23%	2.30%	
Ocean Fish & Rice		0.15%	0.23%	2.30%	
Lamb & Rice		0.15%	0.23%	2.30%	
Weight Control	80mg/kg	0.13%	0.20%	2.00%	
Active Maturity		0.15%	0.23%	2.30%	250IU/kg

The values given are on an "as fed" basis for dry foods.

Royal Canin Veterinary Diets

Green tea polyphenols (GTP): Green tea polyphenols are thought to have bactericidal properties and to prevent the adhesion of plaque to teeth[11].

Tyrosine: Tyrosine is an amino acid synthesised by the body, and which is required for normal coat colour[4].

Arginine: Arginine is an essential amino acid that cannot be synthesised by cats or dogs and so must be obtained in the diet[4]. Arginine is required for the elimination of toxic nitrogenous wastes from the body[4].

Green-lipped Mussel Powder (GMP): The green-lipped mussel (*Perna canaliculus*) is a source of chondroitin sulphate and the omega-3 fatty acid eicosatetraenoic acid[10].

Canine

Diet	Carnitine	Taurine	Omega-3	Omega-6	Glucosamine & Chondroitin	GMP	GTP	Tyrosine	Arginine
Dental			0.8%		100mg/kg		na	na	
Development			0.8%						
Cardiac	830mg/kg	0.2%	0.8%						2.15%
Hepatic LS			0.8%						
Hifactor Formula	na								
Hypo-allergenic			0.8%						
Mobility Support			0.73%			na			
Skin Support		0.3%	na						

GMP: Green-lipped mussel powder; GTP: Green tea polyphenols.

The values given are on an "as fed" basis for dry foods.

Feline

Diet	Carnitine	Omega-3	Omega-6	Glucosamine & Chondroitin	Tyrosine
Dental		0.54%			na
Development		na	na		
Diabetic	50mg/kg				
Hifactor Formula (obesity)	na				
Hypoallergenic		0.9%			
Mature	50mg/kg	na		500mg/kg	na
Weight Formula	50mg/kg				

The values given are on an "as fed" basis for dry foods.

Advance

Lycopene: Lycopene is an antioxidant that is found in red-coloured plants and fruits such as tomatoes[4].

Slippery elm: Slippery elm is purported to help prevent the formation of hairballs in cats[12].

Canine

Diet	Taurine	Lycopene	Green-lipped Mussel Powder
Chicken	na	na	
Turkey & Rice	na	na	
Energy	na	na	na
Light	na	na	
Senior Dog	na	na	na

The values given are on an "as fed" basis for dry foods.

Feline

Diet	Taurine	Lycopene	Slippery Elm	Omega-3
Chicken	na	na	na	na
Fish	na	na	na	na
Light	na	na	na	na
Senior Cat	na	na	na	na

The values given are on an "as fed" basis for dry foods.

Nestlé Purina Veterinary Diets

Canine

Diet	Carnitine	Taurine	Omega-3	Omega-6	Vitamin E
Cardiovascular	50mg/kg	0.08%			
Diabetes, Colitis			na	na	
Gastroenteric			0.16%	1.87%	
Hypoallergenic			na	na	
Limited Antigen			1.10%	1.10%	116IU/kg
Kidney Function			0.27%	2.51%	

The values given are on an "as fed" basis for dry foods.

Feline

Diet	Carnitine	Taurine	Omega-3	Omega-6	Vitamin E
Cardiovascular	100mg/kg	0.09%			
Diabetes		0.19%	0.36%	2.02%	100IU/kg
Gastroenteric		0.12%	0.28%	1.38%	
Kidney Function		0.17%	0.29%	1.87%	

The values given are on an "as fed" basis for dry foods.

Pedigree Veterinary Diets

Neither the printed dietary information for Pedigree Veterinary Diets, nor the Pedigree website[13], list nutraceuticals or bioactives as being present in their products. Canine diets include: Low Sodium, High Fibre, Hepatic Support, Selected Protein, Low Calorie, Low Phosphorus and Low Fat. Feline diets include: Low Calorie, Low Phosphorus, Selected Protein and Low pH Control.

Conclusion

The 5 most prevalent nutraceuticals and bioactives in veterinary medicine, as discussed in reports 1 and 2, namely glycosaminoglycans, omega-3 fatty acids, carnitine, taurine and arginine, are well represented in premium pet foods. Ingredients that are unique to a specific brand include green-lipped mussel powder, chromium tripicolinate, green tea polyphenols, tyrosine, lycopene and slippery elm.

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Section IV: Potential Yields of Nutraceuticals and Opportunities For Collaboration With Existing Companies

The most abundant source of carnitine is skeletal muscle and heart; however, Hill's uses a synthetic form of carnitine in their diets. Skeletal muscle, liver, heart, thymus and kidney are all significant sources of arginine. Taurine is currently extracted from bovine gall; however liver, heart and skeletal muscle are also thought to be rich sources of taurine. Both Hill's and Advance use synthetic forms of taurine in their diets. Chondroitin sulphate and glucosamine can both be obtained from bovine trachea; however, Hill's and Eukanuba both use poultry meal as their source of chondroitin sulphate and glucosamine, while Advance uses glucosamine extracted from mussel shells. Pentosan polysulphate is commercially produced via synthetic processes.

Attempts to identify companies within Australia that extract nutraceuticals from the raw materials and supply to the pet food industry were unsuccessful due to issues of confidentiality. Nutrition companies are not willing to divulge their suppliers.

Part I: Sources and Yields of the Top 5 Pet Food Nutraceuticals

Nutraceutical	Commercial Source	Yield	Potential Alternative Source
Carnitine	Skeletal muscle (sheep)[1, 2]	209 mg/100g[1] 168 mg/100g[2]	
	Skeletal muscle (cattle)[2]	62 mg/100g[2]	
	Heart (sheep)[2]	59 mg/100g[2]	
	Heart (cattle)[1, 2]	125 mg/100g[1] 19 mg/100g[2]	
Taurine	Gall (cattle)[1]	15 g/L[1]	Liver, heart, CNS, skeletal muscle[4]
Arginine	Skeletal muscle (sheep)[2]	1.8 mg/100g[2]	
	Skeletal muscle (cattle)[1,2]	1 mg/100g[1] 1.4 mg/100g[2]	
	Skeletal muscle (pig)[2]	1.2 mg/100g[2]	
	Liver (sheep)[2]	1.1 mg/100g[2]	
	Heart, thymus (cattle)[1], liver (cattle)[2]	1 mg/100g[1] 1.1 mg/100g[2]	
	Kidney (sheep)[2]	0.9 mg/100g[2]	
	Kidney (cattle)[2]	0.9 mg/100g[2]	
Glucosamine	Trachea (cattle)[5]	na	
Chondroitin sulphate	Trachea (cattle)[1]	0.3 g/100g[1]	
Pentosan polysulphate	Synthetically produced[1,3]	-	Trachea

Part II: Top 5 Nutraceutical Content in Premium Pet Foods Marketed in Australia

Hill's Prescription Diets

Canine

Diet	Carnitine	Taurine	Arginine	Glucosamine	Chondroitin
b/d: Brain Aging	27.5 mg/100g				
h/d: Heart Disease	22.7 mg/100g	120 mg/100g			
j/d: Osteoarthritis	32.3 mg/100g			98 mg/100g	67.4 mg/100g
l/d: Liver Disease	27.9 mg/100g				
n/d: Cancer*			860mg/100g		
r/d: Obesity	27.9 mg/100g				
u/d: Uroliths	27.8 mg/100g	100 mg/100g			
w/d: Weight Control	27.0 mg/100g				

The values given are on an "as fed" basis for dry foods: that is, xmg of a given nutraceutical are present in each 100g of dry food. The exception is n/d which is only available as a canned food and so values given are on an "as fed" basis for 100g of wet food.

** Currently not available in Australia.*

Feline

Diet	Carnitine	Taurine
k/d: Kidney Disease		150 mg/100g
l/d: Liver Disease	92.9 mg/100g	490 mg/100g
m/d: Obesity, Diabetes mellitus	52.1 mg/100g	280 mg/100g
w/d: Weight Control	45.9 mg/100g	200 mg/100g
z/d: Allergic Disease		210 mg/100g

The values given are on an "as fed" basis for dry foods: that is, xmg of a given nutraceutical are present in each 100g of dry food.

Waltham Veterinary Diets

Canine

Diet	Taurine
Digestive Tract Support	160 mg/100g
Sensitivity Control	170 mg/100g
Hepatic Support	189 mg/100g
Renal Support	220 mg/100g
Mobility Support	200 mg/100g
Weight Management	160 mg/100g
Urinary Tract Support	160 mg/100g
Glucomodulation (Diabetes)	170 mg/100g

The values given are on an "as fed" basis for dry foods: that is, xmg of a given nutraceutical are present in each 100g of dry food.

Feline

Diet	Taurine
Sensitivity Control	230 mg/100g
Renal Support	280 mg/100g
Weight Management	160 mg/100g
Urinary Tract Support	230 mg/100g

The values given are on an "as fed" basis for dry foods: that is, xmg of a given nutraceutical are present in each 100g of dry food.

Eukanuba Veterinary Diets

Canine

Diet	Carnitine	Glucosamine	Chondroitin
Restricted Calorie	4 mg/100g		
Weight Control	4 mg/100g		
Joint Health	4 mg/100g	47.5 mg/100g	4.5 mg/100g
Senior Plus	4 mg/100g	47.5 mg/100g	4.5 mg/100g

The values given are on an "as fed" basis for dry foods: that is, xmg of a given nutraceutical are present in each 100g of dry food.

Feline

Diet	Carnitine	Taurine
Response LB (allergies)		70 mg/100g
Low Residue		130 mg/100g
Restricted Calorie	8 mg/100g	120 mg/100g
Weight Control	8 mg/100g	210 mg/100g
Renal Disease		150 mg/100g
Maximum Calorie		100 mg/100g

The values given are on an "as fed" basis for dry foods: that is, xmg of a given nutraceutical are present in each 100g of dry food.

Iams

Canine

Diet	Carnitine	Glucosamine
Large Breed		35 mg/100kg
Weight Control	3 mg/100g	
Weight Control Large Breed	3 mg/100g	35 mg/100kg
Active Maturity	3 mg/100g	
Active Maturity Large Breed	3 mg/100g	35 mg/100kg

The values given are on an “as fed” basis for dry foods: that is, xmg of a given nutraceutical are present in each 100g of dry food.

Feline

Diet	Carnitine	Taurine
Original		150 mg/100g
Hairball		150 mg/100g
Ocean Fish & Rice		150 mg/100g
Lamb & Rice		150 mg/100g
Weight Control	8 mg/100g	130 mg/100g
Active Maturity		150 mg/100g

The values given are on an "as fed" basis for dry foods: that is, xmg of a given nutraceutical are present in each 100g of dry food.

Royal Canin Veterinary Diets

Canine

Diet	Carnitine	Taurine	Glucosamine & Chondroitin	Arginine
Dental			10 mg/100g	
Cardiac	83 mg/100g	200 mg/100g		2.15 g/100g
Hifactor Formula (obesity)	na			
Skin Support		300 mg/100g		

The values given are on an "as fed" basis for dry foods: that is, xmg of a given nutraceutical are present in each 100g of dry food.

Feline

Diet	Carnitine	Taurine	Glucosamine & Chondroitin	Arginine
Diabetic	5 mg/100g	230mg/100g		2.45g/100g
Hifactor Formula (obesity)	na	230mg/100g		1.9g/100g
Mature	5 mg/100g	60mg/100g	50 mg/100g	440mg/100g
Renal		200mg/100g		1.1g/100g
Weight Formula	5 mg/100g	350mg/100g		2.01g/100g

The values given are on an "as fed" basis for dry foods: that is, xmg of a given nutraceutical are present in each 100g of dry food.

Advance

Canine

Diet	Taurine
Chicken	na
Turkey & Rice	na
Energy	na
Light	na
Senior Dog	na

The values given are on an “as fed” basis for dry foods: that is, xmg of a given nutraceutical are present in each 100g of dry food.

Feline

Diet	Taurine
Chicken	na
Fish	na
Light	na
Senior Cat	na

The values given are on an “as fed” basis for dry foods: that is, xmg of a given nutraceutical are present in each 100g of dry food.

Nestlé Purina Veterinary Diets

Canine

Diet	Carnitine	Taurine
Cardiovascular	5 mg/100g	80 mg/100g

The values given are on an “as fed” basis for dry foods: that is, xmg of a given nutraceutical are present in each 100g of dry food.

Feline

Diet	Carnitine	Taurine
Cardiovascular	10 mg/100g	90 mg/100g
Diabetes		190 mg/100g
Gastroenteric		120 mg/100g
Kidney Function		170 mg/100g

The values given are on an “as fed” basis for dry foods: that is, xmg of a given nutraceutical are present in each 100g of dry food.

Part III: Sources of Nutraceuticals Included in Pet Foods

Hill's Prescription Diets

Carnitine: is added as a synthetic purified product.

Arginine: red meat used to manufacture the pet food is the sole source of arginine.

Taurine: is added as a synthetic purified product.

Glucosamine: is supplied as poultry meal and by-products.

Chondroitin: is supplied as poultry meal and by-products.

Advance

Carnitine: red meat used to manufacture the pet food is the sole source of carnitine.

Arginine: red meat used to manufacture the pet food is the sole source of arginine.

Taurine: red meat and poultry used to manufacture the pet food contribute the majority of the taurine requirement; however, if there is a deficit in taurine content in the final product, synthetic taurine is added.

Glucosamine: is derived from mussel shells, since this is more cost-effective than cartilage-derived glucosamine.

Nestlé Purina Veterinary Diets

Nestlé Purina include bone meal and red meat by-products in their pet foods and these are the sole sources of the nutraceuticals.

Eukanuba and Iams

Carnitine: is added as a naturally-derived purified product if required.

Taurine: is added as a naturally-derived purified product.

Glucosamine: is supplied as poultry meal.

Chondroitin: is supplied as poultry meal.

Part IV: Opportunities For Collaboration With Existing Companies

The aim of this part of Milestone 4 was to identify companies that extract nutraceuticals from the raw source material and to identify any areas that can be targeted by MLA to improve the supply or demand of meat-derived nutraceuticals. To this end, we contacted the following Australia-based companies which produce nutraceuticals or products that contain nutraceuticals:

a) *Nature Vet Pty Ltd:* produces Pentosan Equine, Pentosan 100 and Cosequin, which contain pentosan polysulphate, glucosamine and chondroitin sulphate. In speaking with a representative of the company we were told that the source of their nutraceutical ingredients was confidential. Phone: 1800 624 174. E-mail: naturevet@bigpond.com

b) *Bio Concepts Pty Ltd:* produce a range of nutraceutical products for human consumption. They were able to provide information on the range of nutraceuticals available, but were not willing to comment on their supplier/s. Phone: 07 3868 0699. E-mail: info@bioconcepts.com.au. Web address: www.bioconcepts.com.au

c) *Waltham:* produce Advance and Optimum pet foods in Australia, using Australian ingredients where possible. In speaking with Mr. Neil Thorneycroft we were informed that Waltham uses a trader to source the nutraceutical ingredients for their pet foods. This trader may purchase nutraceuticals from Australia or the USA. The identity of this trader is confidential; however, Mr. Thorneycroft offered to speak with his superior and will contact us if this information becomes available. Further attempts to contact Mr. Thorneycroft were not successful: he did not reply to an e-mail or messages left on his mobile phone.

d) Other individuals contacted on the recommendation of Antoine Valterio include Jane Hales at MLA (jhales@mla.com.au) and Chris McDowell (chrism@wecon.com.au). Mr. McDowell's response was as follows: "We are currently handling some of the products you mention of various origins but so far we have not fully researched the Australian availability. I do not know of any producers making these products aside from the contacts you will have from the Antoine's MLA seminars. When in the future we do have more information on these we would be pleased to share some information with you".

e) The major producers of premium pet foods such as Waltham Veterinary Diets, Hill's, Eukanuba/Iams, Royal Canin, and Nestle Purina produce their products overseas and then export them to Australia. The following are contact details for these companies in Europe and USA:

i/ Waltham:
Helen Munday (Head of Research): helen.munday@eu.effem.com
Peter Markwell (Research and Development): peter.markwell@eu.effem.com
ii/ Royal Canin
Vince Biourge: biourge@royal-canin.fr
iii/ Iams/Eukanuba
Greg Sunvold (Senior Research and Development and patents): sunvold.gd@pg.com
Beth Flickinger (Research and Development): flickinger.ea@pg.com
iv/ Hill's
Tim Allen: tim_allen@hillspet.com
v/ Nestle Purina
Mark Roos (Director, Super Premium Product Technology Centre):
mark.roos@rdmo.nestle.com

Ignacio Boixeda (European Veterinary Manager): ignacio.boixeda@purina.nestle.com

Jill Cline: Jill.Cline@rdmo.nestle.com

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Section V: Investigation of Regulatory Requirements Involved With the Production of Nutraceuticals For Inclusion Into Pet Foods

In Australia, pet foods and their ingredients require registration with the Australian Pesticides and Veterinary Medicines Authority (APVMA) if the food is considered therapeutic, rather than nutritional, by claiming to "prevent, treat, alleviate or cure" disease. If therapeutic claims are not made, registration is not required.

In the USA, both the Food and Drug Administration (FDA) and the Association of American Feed Control Officials (AAFCO) are involved in the regulation of pet foods and their ingredients. In a similar situation to that in Australia, pet foods do not require registration as drugs so long as the labelling of the food does not make therapeutic claims.

Within the European Union, only those food additives that have been scientifically evaluated by the European Food Safety Authority and listed on the Community Register For Feed Additives can be included in pet foods and marketed. To date, carnitine, taurine, omega-3 fatty acids and omega-6 fatty acids are listed on the register.

Australia

The Australian Pesticides and Veterinary Medicines Authority (APVMA) is the government body that oversees the registration of substances that qualify as "veterinary chemical products" [1]. A veterinary chemical product (as defined in the AgVet Codes) is a substance, or mixture of substances, that is administered, applied or fed to an animal as a way of directly, or indirectly:
(a) "preventing, diagnosing, curing or alleviating a disease or condition in the animal or an infestation of the animal by a pest; or
(b) curing or alleviating an injury suffered by the animal; or
(c) modifying the physiology of the animal:
    (i) so as to alter its natural development, productivity, quality or reproductive capacity; or
    (ii) so as to make it more manageable; or
(d) modifying the effect of another veterinary chemical product"[1].

With respect to pet foods, registration is only required if the pet food is considered therapeutic[1]. A therapeutic pet food is one which:
• "is to be used or intended to be used, under veterinary supervision; and/or
• has been formulated, or is represented to provide a beneficial component in the prevention, treatment, alleviation, cure or recovery of a specific condition i.e. it meets the definition of a veterinary chemical product" [1]. The example given by the APVMA is as follows: "a pet food label

making the claim '…. a calcium-rich diet prevents, treats, alleviates or cures the progression, of osteoporosis…..' would require registration with the APVMA as it is a product that is represented as preventing, treating, alleviating or curing the disease osteoporosis" [1].

Vitamins, minerals and other nutrients added to pet foods only require registration with the APVMA if they qualify as a veterinary chemical product as described above[1]. However, where these nutrients are considered to have a therapeutic effect, rather than a strictly nutritional effect, they may require registration with the APVMA[1].

USA

The Food and Drug Administration (FDA)

The Food and Drug Administration (FDA) is the body responsible for the regulation of human and animal foods, drugs and food additives[2, 3]. Within the FDA, the Center for Veterinary Medicine (CVM) is specifically responsible for the regulation of veterinary drugs, medicated feeds, food additives and feed ingredients[2, 3]. Pet foods and their ingredients do not require FDA approval in order to be marketed[2, 3]. However, "they must be made with ingredients that are 'generally recognized as safe' (GRAS) or ingredients that are approved food and colour additives. If scientific data show that an ingredient or additive presents a health risk to animals, CVM can prohibit or modify its use in pet food" [2]. The CVM reviews the data available on a given ingredient to their satisfaction that the ingredient is safe and can be "manufactured consistently to meet product specifications" [2, 3].

The FDA has strict guidelines on the labelling of pet foods, especially as regards therapeutic claims. The following is taken from the FDA's web site[2] and concerns the labelling of pet foods that contain therapeutic ingredients:

"Statements that a product can treat, prevent or reduce the risk of a disease are considered drug claims and are not allowed on pet food. CVM also disallows claims such as 'improves skin and coat,' 'prevents dry skin,' and 'hypoallergenic.' Consumers may see phrases such as 'promotes healthy skin' and 'promotes glossy coat.' CVM permits these claims, but any healthy animal that gets adequate nutrition should have these qualities anyway without eating a special food.

Recognizing the close link between diet and disease, CVM does allow certain health-related information on labels to help consumers evaluate pet foods. For example, while a product cannot claim to treat feline lower urinary tract disease, a concern for some cat owners, it may make the claim that the food 'reduces urine pH to help maintain urinary tract health,' provided data generated by the manufacturer and reviewed by CVM support the statement.

CVM permits some dental claims on pet foods. The jaw movement of animals as they chew on certain foods or treats, or some chemicals in foods, can help reduce plaque and tartar, so CVM allows claims such as 'helps control plaque' and 'helps control tartar.' CVM does not allow claims to treat or prevent gingivitis or periodontal disease because these are drug claims.

CVM provides manufacturers some latitude in making health claims regarding a category of food known as veterinary medical foods, which consumers can obtain only through a veterinarian. Manufacturers design these foods to treat a particular disease or condition. Although not regulated as drugs, these foods may carry health information in promotional materials for the veterinarian to help them treat their patients correctly" [2].

Association of American Feed Control Officials (AAFCO)

The Association of American Feed Control Officials (AAFCO) "develops and implements laws, regulations, standards and enforcement policies for regulating the manufacture, distribution and sale of animal feeds" [4]. The CVM and AAFCO work together to determine the safety of pet food ingredients[2]. The CVM gives scientific advice to AAFCO, serves on AAFCO committees and meets with AAFCO's board of directors[2].

European Union

The *European Food Safety Authority (EFSA)* is the regulatory body that oversees the registration of all additives contained in pet foods sold throughout the European Community[5]. Of particular interest to this study are those deemed "Nutritional additives" which includes[5]:

(a) vitamins, pro-vitamins and chemically well-defined substances having similar effect;

(b) compounds of trace elements;

(c) amino acids, their salts and analogues;

(d) urea and its derivatives.

Only those food additives that have been scientifically evaluated by EFSA and listed on the Community Register For Feed Additives can be included in pet foods and marketed[5]. To date, carnitine, taurine, omega-3 fatty acids and omega-6 fatty acids are listed on the register[6].

Pet foods labelled in such a way as to claim that they will prevent, treat or cure a disease are considered medicinal and are thus subject to veterinary legislation[5]. However, foods that are intended to meet the specific nutritional requirements of particular medical conditions are considered "dietetic feeds" and the following legislation applies[5]:

"Council Directive 93/74/EEC: pet food for particular nutritional purposes covers cat and dog food intended for specific health purposes, for example, nutritional management of animals with insufficient renal or liver function. In addition to the general labelling requirements, specific labelling information is provided:

Compulsory Information

- The expression "dietetic" together with the description of the pet food
- Particular nutritional purpose. For each of the particular nutritional purposes defined in Council Directive 94/39/EEC the corresponding [must be given]:
- [An] indication of the essential nutritional characteristics
- labelling declaration
- recommended length of use
- other provisions
- The following particular nutritional uses are listed:
- Support of renal function in case of chronic renal insufficiency
- Dissolution of struvite stones
- Reduction of struvite stone recurrence
- Reduction of urate stone formation
- Reduction of oxalate stone formation
- Reduction of cystine stones formation
- Reduction of ingredient and nutrient intolerances
- Reduction of acute intestinal absorptive disorders
- Compensation for maldigestion
- Support of heart function in [the] case of chronic cardiac insufficiency
- Regulation of glucose supply
- Support of liver function in [the] case of chronic liver insufficiency

- Regulation of lipid metabolism in [the] case of hyperlipidaemia
- Reduction of copper in the liver
- Reduction of excessive body weight
- Nutritional restoration, convalescence
- Support of skin function in [the] case of dermatosis and excessive loss of hair
- The Indication: *"It is recommended that a specialist's (or in some cases veterinarian's) opinion be sought before use".*

Voluntary Information

- A reference to a specific pathological condition if this corresponds to the particular nutritional purpose of the pet food
- The labelling may highlight the presence or low level of certain analytical constituents essential for the description of the pet food. In this case, the minimum or maximum level of the analytical constituent expressed as percentage weight must be indicated in the list of declared analytical constituents".

References

1. www.apvma.gov.au

2. www.fda.gov/cvm

3. www.michigan.gov/documents/FDAsRegulationofPetFood(Benz2000)

4. www.aafco.org

5. http://useu.usmission.gov/agri/petfood.html

6. http://ec.europa.eu/food/food/animalnutrition/feedadditives/comm_register_23052006.pdf

Section VI: Future Directions

Currently, the market availability of nutraceuticals for veterinary use is very small compared with the range of products available for human medicine. However, it is only to be expected that as more people look to nutraceuticals for their own health, they will look for the same options for their pets. Thus, there is significant potential for development in the area of veterinary nutraceuticals and bioactives. Areas of key opportunity include:

- Increasing the production of nutraceuticals that can be derived from red meat
- Identifying novel nutraceuticals and bioactives not currently used for pets

While great potential exists in the identification of novel nutraceuticals and bioactives, this is an expensive process to develop, and is labour-intensive requiring the identification of potential nutraceuticals and bioactives from work performed in other species. Once candidate nutraceuticals or bioactives have been identified, they must be trialled to demonstrate safety and clinical benefit, which can cost anywhere from $100,000 to $350,000 per year. Patenting of ingredients or the macronutritient profile in pet food is commonly used by manufacturers of veterinary diets to protect claims. The ingredients or macronutritient profile may not necessarily be considered novel based on research in other species, for example a low carbohydrate diet for prevention and treatment of feline diabetes, but patents are issued based on company research to support the claim, when there is no other pre-existing claim for this use in the nominated species.

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