An Introduction to the Clinical Use of Nutraceutical and Botanical Therapies in Small Animal Practice

Part One: The Basics of Nutraceutical and Botanical Compounds

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Herbs and nutraceuticals are becoming used more commonly by clients for their pets. As a result, veterinarians need to know about these novel remedies in order to evaluate their impact on their patients. Additionally, veterinarians need to be able to advise their clients in the safe and judicious use of herbs and nutraceuticals for their animals. The following information will help you as a veterinarian understand better these botanicals and nutraceuticals and their potential benefit or detriment to your patients.

The complex constituents of herbal remedies allows them to have a broad range of therapeutic actions. Thus, effective herbal dosage regimens usually are not as precise as those for pharmaceutical medicines. Patient response time to many natural remedies may take days or weeks to become evident, making it much more difficult on the part of the practitioner to judge the effectiveness of the therapeutic protocol chosen for that patient. Natural remedies also may be more difficult to administer. Most veterinarians do not know how to evaluate an herbal product for potency, quality and safety, much less therapeutic effectiveness.

Clinical success with a patient involves more than just knowing the nature of the disease. Practical considerations concerning the therapeutics for a patient are as important as any other portion of that patient’s medical workup. One could have the most effective therapeutic regimen for a patient, but if one is unable to administer it adequately, the patient will not benefit. A practitioner may know what herb to use for a given condition, but when they go ahead and purchase this herb from a supplier, it doesn’t work. Was the therapeutic choice of that specific herb wrong, or is there another reason for the failure of the herbal therapy such as lack of patient compliance or inadequate potency of the herbal formula?

Not all herbs or herbal formulas are created the same. The same herb, supplied by different suppliers can have entirely different potencies or biological effects. How can a practitioner effectively predict clinical outcomes without standardization of content and potency of natural medicines?

The History Of Botanical Medicine

Although no direct evidence exists explaining how humans and animals initially learned which plants were safe to use as foods or for healing, there is anthropological evidence that supports the premise that plants have been used by humans for themselves and for their animals since the dawn of humanity 60,000 years ago. (1) The Roman herbalist Pliny wrote in the first century AD of the discovery of the medical uses of plants by animals such as swallows, dogs and deer as having been influential in teaching humans which plants to select.

Research in the field of zoopharmacognosy (the study of animals’ recognition and utilization of wild plants) demonstrated that elephants, monkeys, bison, pigs, civets, jackals, tigers, bears, wild dogs, rhinoceros, mole rats and desert gerbils use plants as medicines. (10)
Physicians in the US studied and relied on plant “drugs” as primary medicines through the 1930’s. Up until the 1930’s, medical schools in the US taught basic plant taxonomy, pharmacognosy and medicinal plant therapeutics. Physicians routinely used plant drugs as their primary medicines. In fact, the word “drug” is derived from a word for the root of a plant. In 1870 the US Pharmacopoeia listed 638 herbs in its publication. By 1990 there were only 58 listed. (2) Some of these plants fell out of use due to their weakness or toxicity, however the majority of clinically useful plants were replaced by pharmaceuticals which could be patented, thereby capable of generating larger profits, as well as supporting the increased industrialization and materialism of contemporary conventional medicine. (3)

Herbal medicine is a vibrantly alive discipline that is being used actively in many cultures throughout the world today. There is no question that botanical preparations can have a beneficial or therapeutic effect. The World Health Organization estimates that 80% of the world’s population relies on herbs for their primary health care needs. In France and Germany it has been estimated that 30-40% of all medical doctors rely on herbal preparations as their primary medicines. (4)

**How Herbs Work**

Botanical compounds (herbs) have a variety of ways they can effect biological systems. Herbs are complex compounds which can contain mixtures of amino acids, proteins and peptides, vitamins, minerals, carbohydrates, polysaccharides, fats and oils, as well as a number of biologically active compounds like alkaloids, saponins, sterols, volatile oils and other “phytochemicals”. There are nine classes of these biologically active phytochemicals that will be detailed in the next section. (5)

Before modern chemistry was able to define the actual chemicals found in plants, herbal actions were described by qualities of the herb based on its physical properties, and its general effect on a biological system. Herbs are described as having taste, temperature, and direction. Thus an herb that tastes bitter, and has a downward direction, could be useful for nausea or vomiting. It is known from practical experience that the bitter taste of an herb stimulates normal gastric emptying, and the downward direction keeps the stomach from “UP” chucking its contents via vomition, and instead moves its contents “downward” which is its normal direction to move digesta. Some herbs are diaphoretic, which means they induce sweating, whereas other herbs are cholegogues, which means they stimulate the contraction of the gall bladder and the release of bile into the duodenum. There are many descriptive names such as these listed in texts of herbal medicine which were used (and still are used) in traditional herbal medicine.

In modern times, herbal medicine has incorporated the science of pharmacology and pharmacognosy into isolating and describing the active ingredients that make up an herbal medicine. Now, many herbal medicine practitioners use more of an indication-based system of prescribing. Ethnobotanical systems match the properties of the herbs and herbal formula with the characteristics of the disease pathology and the symptoms of the patient. Traditional Chinese Medicine and Ayurveda are two such Ethnobotanical systems of herbal medicine.

Prior to the time when pharmaceutical technology gained the technical ability to synthesize drugs *de novo*, most pharmaceuticals could trace their origins to plant materials...
from which they were extracted and then modified. For instance, modern aspirin, acetylsalicylic acid, is derived from salicin, an extract of the inner bark of the white willow tree (Salix alba) or from a plant known as meadowsweet (Filipendula ulmaria). It is interesting to note that in traditional ethnobotanical medicine white willow bark and meadowsweet were used to treat stomach ulcers! The pharmaceutically acetylated form of salicin, on the other hand, is known to cause stomach ulcers. This is one example that traditional herbalists use to explain why they prefer to use the whole plant versus its pharmaceutical extract.

Pharmaceutical herbal extracts are used similarly to their “cousins”, the pharmaceutical drugs. Specific indications for use are based on basic or applied research, and dosages are derived from research or clinical studies. These herbal extracts have drug-like effects.

Herbal extracts will often find themselves described as similar to “Biological Response Modifiers” (BRM). This category of drug action orchestrates activity to enhance the stress-response system, immune system or detoxification system functions. One example of a BRM is silymarin. Studies demonstrate that this flavonoid complex is capable of improving Phase II liver detoxification enzyme systems. Another example is the derivative of the bark of the Western Larch tree, polysaccharides that are called arabinogalactans. These complex polysaccharides can improve Natural Killer T cell function. (9)

**Herb-Drug Interactions and Side-Effects**

Pharmaceutical extracts of herbs may have the ability to reinforce the action of medication the patient may be on. This is not a bad thing, in fact, using herbal supplements may allow a reduction in pharmaceutical drug dosage without a reduction in clinical effectiveness. For instance, Licorice root and fatty acids from fish oil (EPA/DHA) can enhance the effect of cortisone, thus requiring a lower dose of glucocorticoid to produce the same effect.

By enhancing their primary effect, we can potentially reduce the drug-induced side-effects by needing less drug dosage to produce the desired effect. Alternatively, herbs can be used to directly reduce drug side-effects. For example, using silymarin along with prednisone, phenobarbital, or carprofen can reduce these medications’ potential toxicity to the liver.

By definition, herbs have effects. Side-effects are the effects not desired in the patient, and main effects are the effects desired for that patient. With some drugs, such as minoxidil (Rogaine™), was originally a poor quality blood pressure medication. However, it was found that it also had the side-effect of growing hair where it had previously been thinned. This side-effect has become a very lucrative main effect. Another pharmaceutical, Viagra™ (sildenafil) was originally developed as a blood pressure medication until its side effect was discovered, and then it was marketed for erectile dysfunction. Interestingly enough, sildenafil is now being recommended for use in dogs to treat pulmonary hypertension.

Most commonly, an herb will interact with a drug (or visa versa) due to its interference with hepatic detoxification. For instance, it is known that ketoconazole reduces the rate of Phase One liver detoxification systems. Thus, if you have a drug with
a narrow margin of safety, you may not want to use ketoconazole concurrently, due to its slowing of the breakdown of the toxic drug, thus prolonging its potential toxicity. Conversely, if you have a relatively harmless yet very expensive drug like cyclosporine, using ketoconazole concurrently can prolong the serum half life of this drug, thus allowing for more cost effective dosing.

Transplant surgeons used to recommend to their patients on cyclosporine that they drink 8 oz of grapefruit juice with each dose of cyclosporine, because grapefruit juice contains a bioflavonoid known as naringinen. Naringinen has the same effect as ketoconazole on Phase One liver detoxification, but is not potentially liver toxic as is naringinen. (8) (11)

Nine Categories Of Biologically Active Organic Chemicals Commonly Occurring In Natural Compounds (6)

1. **Complex Polysaccharides**: Starches, gums, pectins. E.g.: Inulin, psyllium.

2. **Glycosides**: Compounds that yield one or more sugars among the products of hydrolysis. Play an important role in the life of the plant; involved in its regulatory, protective and sanitary functions. E.g.: Digitalis, *cascara sagrada*.

3. **Lipids**: Esters of long chain fatty acids and alcohols, fats, oils and waxes, prostaglandins. Function as food storage for the plant, used as emollients, or for their specific properties such as castor oil.

4. **Terpenoids**: AKA: terpenes. Divided into isoprene (C5H8) units. Monoterpenoids=two units; Sesquiterpenoids=3 units, Diterpenoids=4 units, Triterpenoids=6 units, tetraterpenoids=eight units and are also known as carotenoids. Widely distributed in nature. Found in insect phermones and defense secretions. E.g.: Vitamin E, Vitamin K, camphor, menthol, thymol, chamomile, valerian, taxol.

5. **Steroids and Sterols**: Any compound containing a cyclopentanoperhydrophenanthrene nucleus. Wide diversity of biological activity: Reproduction, development, anti-inflammatory, anabolic, Vitamin D precursors, cholesterol. E.g.: Cardiac glycosides such as digitalis and oleander, bile acids, wild yam.

6. **Phenylpropanoids**: Non-nitrogen containing phenolic compounds derived from phenylalanine or tyrosine. Also known as plant phenolics. Represented by the flavonoids, lignans, coumarins and tannins. E.g.: Methyl salicylate, salicin, vanillin, proanthocyanidins, milk thistle, rutin, witch hazel.

7. **Alkaloids**: Organic nitrogenous compounds with a limited distribution in nature, not a homogenous group. Have potent physiological effects on mammals. E.g.: Atropine, morphine, quinine, vincristine, ergot, nicotine, goldenseal, ipecac, curare, physostigmine.

8. **Proteins and Peptides**: Enzymes and hormones. E.g.: Papain, bromelain, ficin.

9. **Saponins**: Specialized glycosides that form a soap-like lather when shaken with water. The steroideal saponins mimic the activity of the female sex hormones; the triterpenoid saponins mimic ACTH, immune modulatory, anti-inflammatory activity (7)
Botanical and Nutraceuticals Defined

Botanical compounds (herbs) have a variety of ways they can effect biological systems. Herbs are complex compounds consisting of amino acids, proteins and peptides, vitamins, minerals, carbohydrates, polysaccharides, fats and oils, as well as a number of biologically active compounds like alkaloids, saponins, sterols, volatile oils and other “phytochemicals”. There are nine classes of these biologically active phytochemicals that have been described in the pharmacognosy literature, and which have been listed above.

Herbs create their effects in biological systems by providing nutrients that can influence health, or from providing phytochemicals that have a direct or indirect biological effect on the animal at the cellular level. Often the effects of the herbs on biological systems is the result of the concerted effect of multiple phytochemicals in the herb combined with the nutritive effect of the herb. When a multiple herbal formulation is being used, the result response is very complex based on the multiple effects of the multiple constituents of the multiple ingredients in the formulation. Multiple herbals contain mixtures of 2 to 25 different herbs in the same formula, designed to produce a cohesive effect in the patient.

Nutraceuticals have been defined as: Compounds that are neither nutrients nor pharmaceuticals that play a “non-nutrient” role in normalizing health and overcoming disease.

Nutraceuticals are derived from food materials and are either concentrated, like fish oil, or pharmaceutically extracted, like glucosamine. There is a very fine line of distinction, if any, between pharmaceutically-extracted herbal compounds and pharmaceutically-extracted nutraceutical compounds.

Safety Considerations

“Natural” does not necessarily mean safe. For many herbs the difference between effective and toxic is a matter of dosage. Fortunately, except for a few extremely potent plants, the volume of material that needs to be ingested to achieve patient toxicity is usually greater than that which an animal would voluntarily accept. In fact, in most cases, the toxicity is so low that even when administered against the animal’s will, toxicity will not occur.

There always are exceptions and exceptional patients, it is therefore important to continually be vigilant, and consider the potential of toxicity to a specific patient whenever prescribing an herbal formula. In many cases a toxic herb is present only in small amounts as part of a larger formula. Many of the truly effective herbal remedies are made up of combinations of herbs, sometimes as many as 15 or 20 herbs. The actual amount of a single herb ingested thus, is very small.

It is important to be aware that there are species differences with respect to the potential toxicity of plants. Members of the feline species, as a result of their poor Phase II hepatic detoxification enzyme systems are especially sensitive to certain chemicals, such as salicylates.

With some patients, however, even the use of the very safe food-like herbs (such as alfalfa or nettles) can be associated with undesirable side-effects. Diarrhea, appetite loss and lethargy are the most usual complaints following ingestion of herbal preparations.
Occasionally vomiting or urticaria will also be observed. Usually these reactions are unique to that patient’s experience, and may subside with oral tolerance.

Advise your clients to inform you immediately if any unusual reactions are observed, and recommend that they temporarily discontinue the administration of the herbal preparation to determine if in fact it was the causative agent for the response. If it was the agent, then discontinuing its use will allow the reaction to subside.

**Pharmaceutically Standardized Extracts**

Due to the physical-chemistry and organic chemistry constraints inherent in pharmaceutical technology, each plant has a different amount of its active ingredient that can be extracted and concentrated. For instance, Milk Thistle, standardizes to 70-80% flavonoid content. *Boswellia (Boswellia serrata)* standardizes to 95% Boswellic acids. Gingko standardizes to contain 24% ginkgo flavone glycosides. Each herb has a specific standardization value.

Botanical compounds that have been standardized have the advantage of providing a consistent amount of active ingredients. Herbal potency can vary from harvest to harvest, from one grower to another, and from one method of processing and storage to another. Thus, by standardizing the amount of active ingredient in an herb, accurate dosing of the patient is improved and predictable clinical outcomes are more likely.

There are a number of different proprietary pharmaceutical processes that pharmaceutical companies have developed to provide standardization of herbal compounds. When a botanical compound is standardized, it may be standardized to a single ingredient in the herb, or it may be standardized to several ingredients in the herb. In one method of standardization, a company will concentrate one or several “marker” compounds in order to produce a product with higher potency but similar effects to the original whole herb. When a single compound is used as a marker compound, the difference between a botanical and nutraceutical becomes rather indistinct.

There is controversy amongst practitioners of botanical medicine regarding the relative effectiveness of the whole herb compound versus the pharmaceutically-extracted herbal compound when a single marker compound is extracted versus when a group of marker compounds are extracted. Many traditional herbalists believe that the complex interactions of the many constituents of a plant produce a better impact on the patient than the use of a single or multiple extracted ingredients. Some of these traditionalists reject the use of any herbal compound that has undergone pharmaceutical processing. Traditional herbalists believe that the essence and effectiveness of the plant becomes disrupted by this processing.

At the same time, though, because there are a number of factors that influence the potency of a whole herb, such as soil quality, weather conditions, genetic strain of plant, methods of harvesting, storage and preservation, many medical practitioners prefer to use herbal compounds that have been standardized in terms of potency of active ingredients. For a clinician, knowing that an herbal compound has a set potency, allows for more effective dosing.

However, even with standardization there is controversy as far as which plant
constituents should be concentrated and standardized. For instance, in the case of extracts of milk thistle (*Silybum marianum*), quite a bit of research has been done on two different extracts of this plant. Silymarin is considered to be the active constituent of the milk thistle plant. It is a flavolignan complex that is made up of four flavolignans: Silibinin (or silibin), Isosilibinin, Silydiadin, and silychristin. Studies have been performed on both silymarin and Silibinin and have found both to be effective in most cases. Some research, though, has found that the other flavolignans found in silymarin, such as Silydiadin and silychristin also have effectiveness. For this reason, this author prefers to use the silymarin complex for his patients who need milk thistle, as it may have a broader spectrum of activity than just the silibinin alone.

**How To Read A Supplement Label To Find Out Information About A Product.**

From the information presented in this paper, it should be obvious that not all commercially acquired herbs and herbal formulas are the same. Even with the same information on the label, the actual contents of the formula may vary.

At this point in time there is no over-riding regulatory agency that strictly controls labeling and content in herbal formulas. For herbal formulas that are specifically for people, there is the DSHEA (Dietary Supplement Health and Education Act) act of 1994 which provides guidelines for standardizing labels. For animals there is no such regulatory overview.

The FDA-CVM (Food and Drug Administration-Center for Veterinary Medicine) had been looking at regulating herbal and nutraceutical supplements for animal use in the late 1990s. In fact, supplements containing glucosamine were about to be removed from the shelves of veterinary hospitals by the FDA-CVM, when a small group of animal supplement manufacturers formed the National Animal Supplement Council (NASC) in order to work with the FDA-CVM to develop standards for safety, uniformity and quality control for what then was a small but rapidly growing animal supplement industry.

The NASC then formed a Scientific Advisory Board to review existing animal supplements, and established a comprehensive set of guidelines which were written into a manual that would provide structure for a regulatory environment that would help to control the quality and consistency of animal supplements of companies that are members of the NASC.

The NASC’s Scientific Advisory Board and Task Force has reviewed over 900 ingredients that are found in supplements and has developed a grading system to evaluate the potential risk of these supplements in healthy, pregnant and lactating animals of dog, cat and horse species. As a result of the overview by an industry watchdog such as the NASC, the FDA-CVM has tasked the NASC to regulate the animal nutraceutical and botanical industry. ([www.NASC.cc](http://www.NASC.cc))

Some regulation is good in the marketplace, as there are companies that do not always have the best interests of their customers in mind, may simply not be knowledgeable of the potential risks associated with herbal compounds, or without oversight manufacturing problems that affect the safety of the animal supplements might not be detected until an unfortunate event occurs.

One of the most powerful aspects of the regulatory environment created by the
NASC is its establishment of an Adverse Event Report (AER) website. Companies that are members of the NASC that have problems reported to them regarding a supplement they manufacture are required to post this information on this website as a condition of their membership in the NASC. Statistics are compiled from the adverse event reports which help to establish levels of risk for supplement ingredients.

The NASC has established a labeling template that members must adhere to when designing labels for their products. This label template very closely follows similar guidelines to the labeling requirements of DSHEA, and the guidelines for the labeling of packaged foods. Adherence to these labeling guidelines and templates increases the uniformity of animal supplement packaging, and also increases the ability of the consumer to understand what is contained inside the labeled bottle. A sample of this label template is reproduced below.

Companies that are members of the NASC will display the NASC logo on their bottles of supplements and will allow the NASC to send inspectors to their manufacturing facilities to ensure that members are in compliance with NASC standards. This is why it is important to recommend supplements that are manufactured by members of the NASC.

**Supplement Selection Guidelines:**

How can a veterinarian select a supplement for their patients and be certain that it contains what is listed on the label, has the guarantee of potency as stated on the label, and that it is free from adulteration? Listed below are 5 recommendations that will assist the veterinarian in the selection of an animal supplement with “integrity”.

1. Buy from an established company that has been in business long enough that if problems were to have arisen, they would have been dealt with already or the company would have gone out of business.

2. Look for the NASC membership of companies you purchase supplements from.

3. Request from the company certificates of analysis regarding the content of the formula, and testing that has been done to measure the level of toxins, microflora and active herbal components in the formula. These tests cost the company money to run, and will ultimately contribute to the increased cost of the supplement, but the peace of mind, and increased clinical effectiveness are worth the cost. Beware of low cost deals that are too good to be true, they probably are.

4. Be sure that the label contains full disclosure of the contents of the formula, which means that the true weight of each of the components on the formula should be listed specifically; also look for information regarding the amount of standardized herb in the formula. For instance, if a milk thistle formula contains 80% silymarin and the label lists the amount of milk thistle as 100 mg per capsule, standardized to 80% silymarin, then the true content and silymarin potency of the formula is 80 mg of silymarin per capsule. When you are trying to establish an effective dosage it is important that you are giving adequate amount of herb to produce an adequate response.

5. Carefully read the label to see if it contains deceptive information. For instance,
some companies will tell you how much of a given substance in the entire bottle or bag of herb, versus on a per dose basis. This makes the formula look more potent than it is and may result in ineffective treatment results.

6. Buy from companies that provide you with technical data and support for the use of their products.

7. Be sure to inform the company of any perceived side-effects from the use of their products. The NASC has set up an adverse event reporting system on their website to compile adverse events from products manufactured by their member companies.

RESOURCES for FURTHER LEARNING
Veterinary Botanical Medicine Association (www.VBMA.org)
American Holistic Veterinary Medical Association (www.AHVMA.org)
Herb Research Foundation/American Botanical Council (www.herbs.org)
Veterinary Herbal Medicine Textbook (Mosby; edited by Wynn and Fougere, 2007)

CITATIONS

APPENDIX A: NASC Label Template

NASC Label Template for products that do NOT contain Glucosamine, Chondroitin or sources of Glucosamine and Chondroitin

<table>
<thead>
<tr>
<th>Panel A</th>
<th>Panel B</th>
<th>Panel C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product Facts</strong></td>
<td></td>
<td><strong>Product Facts (continued)</strong></td>
</tr>
<tr>
<td><strong>Active Ingredients per (tablet, scoop, ounce [dosage unit]): (list in descending order by weight)</strong></td>
<td>Primary Label to include: Product Brand Name Intended Use (Structure/Function Statement[s]) Company/Brand Logos Etc.</td>
<td><strong>For use in (list species) only.</strong></td>
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<tr>
<td>XXXXXXXXXX .................. xx mg</td>
<td></td>
<td>Recommended (for, to) support (... specific structure/function statement).</td>
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<td>XXXXXXXXXX .................. xx mg</td>
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<tr>
<td>XXXXXXXXXX .................. xx mg</td>
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<td></td>
</tr>
<tr>
<td>Inactive ingredients (list in alphabetical order) - Binders, Fillers, Flavoring, Excipients, Processing Agents, and Preservatives only</td>
<td>Cautions: Safe use in pregnant animals or animals intended for breeding has not been proven. [if applicable]</td>
<td></td>
</tr>
<tr>
<td>XXXXXXX, XXXXXXX, XXXXXXX, XXXXXXX, XXXXXXX, XXXXXXX, XXXXXXX, XXXXXXX, XXXXXXX</td>
<td>If animal’s condition worsens or does not improve, stop product administration and consult your veterinarian.</td>
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</tr>
<tr>
<td></td>
<td>Federal law prohibits the off-label use of this product in ruminants. [Any product containing bovine-sourced ingredients]</td>
<td></td>
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<tr>
<td></td>
<td>An examination from a veterinarian is recommended prior to using this product. [If the product is for a “condition” — See NASC Claims Appendix II for list]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any other Cautions stated in the Ingredient Risk Assessment. REVIEW FOR ALL INGREDIENTS.</td>
<td></td>
</tr>
<tr>
<td><strong>Questions?</strong> List manufacturer name, city, state, phone, website</td>
<td></td>
<td><strong>Directions for Use: (clearly state amount, interval, and duration)</strong></td>
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<tr>
<td></td>
<td><strong>Warnings:</strong> For animal use only. Keep out of the reach of children and animals. In case of accidental overdose, contact a health professional immediately. This product should not be given to animals intended for human consumption. [equine only]</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Net Contents:</strong> (in terms of weight, must list both US &amp; Metric Weight Units), measure, or numerical count)</td>
<td><strong>Lot Number:</strong> (should appear somewhere on the label or container)</td>
</tr>
</tbody>
</table>