COMMENTS TO PROPOSED RULE:

Current Good Manufacturing Practice in Manufacturing, Packing or Holding Dietary Ingredients and Dietary Supplements

DOCKET NO. 96N-0417

Presented to:

Dockets Management Branch
Food and Drug Administration

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April 24, 2003

We are encouraged by the Food and Drug Administration's March 7, 2003 announcement on "action to help consumers get accurately labeled and unadulterated dietary supplements by proposing a new regulation to require current good manufacturing practices (CGMPs) in their manufacturing, packing and holding." We commend the Agency for proposing a rule that will provide greater protection of public health and offer conditional support of Current Good Manufacturing Practice in Manufacturing, Packing or Holding Dietary Ingredients and Dietary Supplements.

We agree that it is vital to support consumer desire to take greater control and responsibility for better health. This eagerness to "take charge" can lead to earlier diagnosis of disease and prompt medical treatment. This self-directed interest must be matched with the manufacturers commitment to provide accurate information and high-quality product production to ensure proper purity, strength and composition – regardless of source (prescription, over-the-counter or dietary supplement).

Alternative health remedies have their attraction; however, not all dietary supplements have identical benefit and risk. For this reason, we ask the Agency to consider closer oversight on the sale of non-prescription or dietary supplement niacin products, and create classes of review to correspond to public safety needs. Additionally, we suggest that the proposed three-year rule be accelerated in cases where public health is a recognized concern.

To this end, we offer our "conditional" support to the Proposed Rule, and ask that you consider the following information toward establishing these essential standards in the final Rule.

1. The evidence suggests that the unrestricted use of dietary supplement niacin constitutes an increasing risk to the consumer and, in select cases, may lead to health risk. For this reason, we urge the Food and Drug Administration to continue to closely watch over companies manufacturing and distributing dietary supplement niacin products.

    - In "Illnesses and Injuries Associated with the Use of Selected Dietary Supplements," published in 1993 by the Agency, dietary supplement niacin is noted in the report as having been associated with severe adverse reactions, including "gastrointestinal distress (burning pain, nausea, vomiting, bloating, cramping and diarrhea) and mild to severe liver damage. (Exhibit 1) Less common, but more serious (in some cases life-threatening) reactions include liver damage." It is noted in the report that these are cases where the consumer is not under the care of a physician or may have independently switched from one dietary supplement to another.

    - The vast majority of dietary supplement niacin users take these products at high doses (between 250-1000 mg per day) well above the recommended daily dietary intake of 18-21 mg. (Note: Exhibit 1 often refers to dietary supplement products as "over-the-counter" or OTC niacin products; this designation is for ease-of-use only, we are fully aware that these products technically are dietary supplements and have not been approved as "OTC" drugs.) In light of the data it is evident that without oversight consumers can purchase niacin from a health food or grocery store in doses almost 30 times greater than the Upper Intake Level considered safe by the Institute of Medicine of the National Academy of Sciences. Therefore, the ability of dietary-supplement companies to offer single dosage forms of sustained-release niacin in strengths that exceed the recommended daily dietary intake of 18-21 mg. per day (e.g., 250 mg, 500 mg, or 750 mg per dosage unit) on a non-prescription basis is counter to the intended objective of using these products as dietary supplements.

- As these dietary supplement products are marketed in higher strengths, consumers have access to quantities and combinations of non-prescription niacin products that are potentially harmful. These products are offered in numerous doses and formulations; the risk of inadvertently taking harmful doses is high. Consumers, bypassing physician oversight, who switch from one dietary supplement niacin formulation to another have increased risk. Knowledgeable of the inherent health risk, FDA has for almost 10 years publicly acknowledged the potential for liver toxicity with these dietary supplement products, especially when switching between immediate- and slow-release dietary-supplement niacin formulations.

- Consumers, eager to take care of their health, make purchasing decisions based on less than clear information that includes terms such as "safe" and "effective" and "physician recommended" or "clinically proven." Products labeled as "slow-release" or "rapid-dissolving" without further qualification. Almost none of the information provided by dietary supplement companies discloses potential safety issues and risks to be considered including the absence of appropriate information about flushing and/or liver toxicity.

2. Standards for quality, purity, and potency for purposes of manufacture also do not exist for dietary-supplement niacin products. A recently conducted analytical study conducted by the University of Washington, Department of Medicine, Division of Metabolism (by C.D. Meyers, M. Carr and J.D. Brunzell) titled "Over-the-Counter 'Flush-Free' Niacin Preparations Contain No Free Nicotinic Acid, and Are More Expensive than Plain Niacin Tablets," clearly demonstrates that irregularities in strength, purity and composition of dietary supplement niacin products are common – reinforcing the need for the Proposed Rule. (Exhibit 2)

   - After purchasing and analyzing 14 of these dietary supplements niacins that were all marked as plain or crystalline niacin it was found that none of the products sold as "flush-free" contained any measurable levels of free nicotinic acid. In fact, several of the "flush-free" dietary supplement niacin products could only be partially dissolved, despite attempts to vary the solvent.

   - The study authors determined that all of the "'over-the-counter' 'flush-free' niacin preparations contain essentially no free nicotinic acid, and are likely to have no beneficial hypolipidemic effects." People selecting to take these non-physician supervised products are either at side-effect risk for strength variation or clinical risk due to a misconception that their nutritional behaviors, leading to unchecked cholesterol, are "under control" due to accessing a dietary supplement niacin. It is possible that these same consumers are at greater risk for a significant coronary event.

   The summary of the Proposed Rule states, "the proposed rule would establish the minimum cGMPs necessary to ensure that, if you engage in activities related to manufacturing, packaging, or holding dietary ingredients or dietary supplements, you do so in a manner that will not adulterate and misbrand such dietary ingredients or dietary supplements." The above quoted study is evidence that manufacturers of dietary supplement niacin products are providing products that are adulterated or misbranded and do not adhere to normally accepted standards of manufacture.

3. Our support for the Proposed Rule is conditional based on the apparent need for timely consumer information and safety actions. The Agency has been clear for almost a decade on its concerns regarding dietary supplement niacin. We agree on this course of action; however, urge earlier intervention on categories of dietary supplements recognized by the Agency as associated with potential public health risks. Dietary supplement niacin has stood out as a classic concern. On March 7, 2003, the Agency selected to use dietary supplement niacin as an example in its press release announcing the publication of the Proposed Rule in the Federal Register (FDA Proposes Labeling and Manufacturing Standards for All Dietary Supplements).

   - It is possible that patients taking a prescription niacin product under physician oversight (immediate-release Niacor® and extended-release forms such as Niaspan® are approved for use on a prescription basis for the treatment of cholesterol disorders) will be confused by language in the Agency's press release referring to the "recalled niacin product." Unintentionally, this

phrasing may lead to patients discontinuing prescription therapy without consulting with their physician.

- According to the American Heart Association, one of the major challenges in treating high cholesterol remains diagnosis and patient compliance. We will do our utmost to support professional and patient organizations toward the early detection of cholesterol disorders. Under Agency guidelines we also market two "niacin-related" prescription products for the treatment of this disease. We ask for the Agency's consideration in terming "niacin product" as " a dietary supplement niacin product" to avoid any confusion going forward.

We look forward to learning more about your thoughts and assessment of this important public health issue. If data on prescription niacin will help your efforts, please do not hesitate to contact this office.

Your consideration of these data and observations are greatly appreciated.

U. S. Food and Drug Administration
Center for Food Safety and Applied Nutrition
1993

Exhibit 1

Illnesses and Injuries Associated With the Use of Selected Dietary Supplements

This list of selected dietary supplements associated with serious safety problems is found in the section entitled "Illnesses and Injuries Associated With the Use of Selected Dietary Supplements" of an out-of-print 1993 FDA document "Unsubstantiated Claims and Documented Health Hazards in the Dietary Supplement Marketplace."

Products marketed as "dietary supplements" include a diverse range of products, from traditional nutrients, such as vitamins or minerals, to such substances as high-potency free amino acids, botanicals, enzymes, animal extracts, and bioflavanoids that often have no scientifically recognized role in nutrition.

There is currently no systematic evaluation of the safety of products marketed as dietary supplements. Dietary supplements routinely enter the marketplace without undergoing a safety review by FDA. Published studies on the safety of these products are extremely sparse. There is no systematic collection and review of adverse reaction reports for dietary supplements, as there is for drugs, and physicians rarely seek information about their patients' use of dietary supplements. Despite the lack of any system for gaining information about the risks of dietary supplements, an increased number of reports of adverse reactions to dietary supplement products has recently been recognized. Because of concern about these products, FDA has, in the last year, initiated an effort to collect and evaluate existing studies and case reports on safety problems associated with dietary supplements. As a result of that effort, FDA has begun to identify dietary supplements for which serious adverse reactions have been documented. A list of selected dietary supplements associated with serious safety problems follows. This list is not intended to include all hazardous ingredients in dietary supplements.

I. Herbals

Herbal and other botanical ingredients of dietary supplements include processed or unprocessed plant parts (bark, leaves, flowers, fruits, and stems), as well as extracts and essential oils. They are available in a variety of forms, including water infusions (teas), powders, tablets, capsules, and elixirs, and may be marketed as single substances or in combination with other materials, such as vitamins, minerals, amino acids, and non-nutrient ingredients. Although data on the availability, consumer use, and health effects of herbals are very limited, some herbal ingredients have been associated with serious adverse health effects.

A. Chaparral (*Larrea tridentata*)

Chaparral, commonly called the creosote bush, is a desert shrub with a long history of use as a traditional medicine by Native Americans. Chaparral is marketed as a tea, as well as in tablet, capsule, and concentrated extract form, and has been promoted as a natural antioxidant "blood purifier," cancer cure, and acne treatment. At least six cases (five in the United States and one in Canada) of acute non-

viral hepatitis (rapidly developing liver damage) have been associated with the consumption of chaparral as a dietary supplement. Additional cases have been reported and are under investigation. In the majority of the cases reported thus far, the injury to the liver resolves over time, after discontinuation of the product. In at least two patients, however, there is evidence that chaparral consumption caused irreversible liver damage. One patient suffered terminal liver failure requiring liver transplant.

Most of these cases are associated with the consumption of single ingredient chaparral capsules or tablets; however, a few of the more recent cases appear to be associated with consumption of multi-ingredient products (capsules, tablets or teas) that contain chaparral as one ingredient. Chemical analyses have identified no contaminants in the products associated with the cases of hepatitis. Products from at least four different distributors and from at least two different sources have been implicated thus far.

After FDA's health warning, many distributors of chaparral products voluntarily removed the products from the market in December of 1992. Some chaparral products remain on the market, however, and other distributors who removed their products from the market are seeking to clarify the status of these products.

B. Comfrey (*Symphytum officinale* (common comfrey), *S. asperum* (prickly comfrey), *S. X uplandicum* (Russian comfrey))

Preparations of comfrey, a fast-growing leafy plant, are widely sold in the United States as teas, tablets, capsules, tinctures, medicinal poultices, and lotions. Since 1985, at least seven cases of hepatic veno-occlusive disease--obstruction of blood flow from the liver with potential scarring (cirrhosis)--including one death, have been associated with the use of commercially available oral comfrey products.

Comfrey, like a number of other plants (e.g., *Senecio* species), contains pyrrolizidine alkaloids. The toxicity of pyrrolizidine alkaloids to humans is well-documented. Hepatic veno-occlusive disease following ingestion of pyrrolizidine alkaloid-containing products, has been documented repeatedly throughout the world. Hepatic veno-occlusive disease is usually acute and may result in fatal liver failure. In less severe cases, liver disease may progress to a subacute form. Even after apparent recovery, chronic liver disease, including cirrhosis, has been noted. Individuals who ingest small amounts of pyrrolizidine alkaloids for a prolonged period may also be at risk for development of hepatic cirrhosis. The diagnosis of pyrrolizidine alkaloid-induced hepatic veno-occlusive disease is complex, and the condition is probably underdiagnosed.

The degree of injury caused by pyrrolizidine alkaloid-containing plants, like comfrey, is probably influenced by such factors as the age of the user, body mass, gender, and hepatic function, as well the total cumulative dose ingested and the type of exposure (i.e., whether exposure was to leaves or roots, infusions or capsules). Infants in general appear to be particularly susceptible to adverse effects of exposure to pyrrolizidine alkaloids; there are reports of infants developing hepatic veno-occlusive disease following acute exposure of less than one week. Transplacental pyrrolizidine poisoning has been suggested by the occurrence of hepatic disease in the newborn infant of a woman who consumed herbal tea during pregnancy.

Although liver damage is the major documented form of injury to humans from pyrrolizidine alkaloid-containing herbals, animal studies suggest that their toxicity is much broader. Animals exposed to pyrrolizidine alkaloids have developed a wide range of pulmonary, kidney and gastro-intestinal pathologies. Pyrrolizidine alkaloid-containing plants, including comfrey, have also been shown to cause cancer in laboratory animals.

Four countries (the United Kingdom, Australia, Canada, and Germany) have recently restricted the availability of products containing comfrey, and other countries permit use of comfrey only under a physician's prescription.

C. Yohimbe (*Pausinystalia yohimbe*)

Yohimbe is a tree bark containing a variety of pharmacologically active chemicals. It is marketed in a number of products for body building and "enchanced male performance." Serious adverse effects, including renal failure, seizures and death, have been reported to FDA with products containing yohimbe and are currently under investigation.

The major identified alkaloid in yohimbe is yohimbine, a chemical that causes vasodilation, thereby lowering blood pressure. Yohimbine is also a prescription drug in the United States. Side effects are well recognized and may include central nervous system stimulation that causes anxiety attacks. At high doses, yohimbine is a monoamine oxidase (MAO) inhibitor. MAO inhibitors can cause serious adverse effects when taken concomitantly with tyramine-containing foods (e.g., liver, cheeses, red wine) or with over-the-counter (OTC) products containing phenylpropanolamine, such as nasal decongestants and diet aids. Individuals taking yohimbe should be warned to rigorously avoid these foods and OTC products because of the increased likelihood of adverse effects.

Yohimbe should also be avoided by individuals with hypotension (low blood pressure), diabetes, and heart, liver or kidney disease. Symptoms of overdosage include weakness and nervous stimulation followed by paralysis, fatigue, stomach disorders, and ultimately death.

D. Lobelia (*Lobelia inflata*)

Lobelia, also known as Indian tobacco, contains pyridine-derived alkaloids, primarily lobeline. These alkaloids have pharmacological actions similar to, although less potent than, nicotine. There have been several reported cases of adverse reactions associated with consumption of dietary supplements containing lobelia.

Depending on the dose, lobeline can cause either autonomic nervous system stimulation or depression. At low doses, it produces bronchial dilation and increased respiratory rate. Higher doses result in respiratory depression, as well as sweating, rapid heart rate, hypotension, and even coma and death. As little as 50 milligrams of dried herb or a single milliliter of lobelia tincture has caused these reactions.

Because of its similarity to nicotine, lobelia may be dangerous to susceptible populations, including children, pregnant women, and individuals with cardiac disease. Lobelia is nevertheless found in dietary supplement products that are marketed for use by children and infants, pregnant women, and smokers.

E. Germander (*Teucrium* genus)

Germander is the common name for a group of plants that are contained in medicinal teas, elixirs and capsules or tablets, either singly or in combination with other herbs, and marketed for the treatment of obesity and to facilitate weight loss.

Since 1986, at least 27 cases of acute nonviral hepatitis (liver disease), including one death, have been associated with the use of commercially available germander products in France. These cases show a clear temporal relationship between ingestion of germander and onset of hepatitis, as well as the resolution of symptoms when the use of germander was stopped. In 12 cases, re-administration of

germander was followed by prompt recurrence of hepatitis. Recovery occurred gradually in most cases, approximately two of six months after withdrawal of germander. Analyses of these cases does not indicate a strong relationship between the dosage or duration of ingestion and the occurrence of hepatitis.

Although the constituent in germander responsible for its hepatic toxicity has not been identified, germander contains several chemicals, including polyphenols, tannins, diterpenoids, and flavonoids.

On the basis of the 27 French hepatitis cases, the French Ministry of Health has forbidden the use of germander in drugs. Its use has been restricted in other countries.

F. Willow Bark (*Salix* species)

Willow bark has long been used for its analgesic (pain killing), antirheumatic, and antipyretic (fever-reducing) properties. Willow bark is widely promoted as an "aspirin-free" analgesic, including in dietary supplement products for children. Because it shares the same chemical properties and the same adverse effects as aspirin, this claim is highly misleading. The "aspirin-free" claim is particularly dangerous on products marketed, without warning labels, for use by children and other aspirin-sensitive individuals.

The pharmacologically active component in willow bark is "salicin," a compound that is converted to salicylic acid by the body after ingestion. Both willow bark and aspirin are salicylates, a class of compounds that work by virtue of their salicylic acid content. Aspirin (acetylsalicylic acid) is also converted to salicylic acid after ingestion.

All salicylates share substantially the same side effects. The major adverse effects include irritation of the gastric mucosa (a particular hazard to individuals with ulcer disease), adverse effects when used during pregnancy (including stillbirth, bleeding, prolonged gestation and labor, and low-birth-weight infants), stroke, and adverse effects in children with fever and dehydration. Children with influenza or chickenpox should avoid salicylates because their use, even in small doses, is associated with development of Reye syndrome, which is characterized by severe, sometimes fatal, liver injury. Salicylate intoxication (headache, dizziness, ringing in ears, difficulty hearing, dimness of vision, confusion, lassitude, drowsiness, sweating, hyperventilation, nausea, vomiting, and central nervous system disturbances in severe cases) may occur as the result of over-medication, or kidney or liver insufficiency. Hypersensitivity, manifested by itching, broncho-spasm and localized swelling (which may be life-threatening), can occur with very small doses of salicylates, and may occur even in those without a prior history of sensitivity to salicylates. Approximately 5 percent of the population is hypersensitive to salicylates.

G. Jin Bu Huan

Jin Bu Huan is a Chinese herbal product whose label claims that it is good for "insomnia due to pain," ulcer, "stomachic ¬sic| neuralgia, pain in shrunken womb after childbirth, nervous insomnia, spasmodic cough, and etc." Jin Bu Huan has been recently reported to be responsible for the poisoning of at least three young children (ages 13 months to 2 2 years), who accidentally ingested this product. The children were hospitalized with rapid-onset, life-threatening bradycardia (very low heart rate), and central nervous system and respiratory depression. One child required intubation (assisted breathing). All three utlimately recovered following intensive medical care.

Although the product label identified the plant source for Jin Bu Huan as *Polygala chinensis*, this appears to be incorrect since preliminary analyses indicate the presence of tetrahydropalmatine (THP), a

chemical not found in *Polygala*. THP is found, however, in high concentrations in plants of certain *Stephania* species. In animals, exposure to THP results in sedation, analgesia, and neuromuscular blockade (paralysis). The symptoms of the three children are consistent with these effects.

An additional case of THP toxicity, reported in the Netherlands, appears to be associated with the same product, and is being investigated.

H. Herbal products containing *Stephania* and *Magnolia* species

A Chinese herbal preparation containing *Stephania* and *Magnolia* species that was sold as a weight-loss treatment in Belgium has been implicated recently as a cause of severe kidney injury in at least 48 women. These cases were only discovered by diligent investigations by physicians treating two young women who presented with similar cases of rapidly progressing kidney disease that required renal dialysis. Once it was determined that both these women had used the herbal diet treatment, further investigation of kidney dialysis centers in Belgium found a total of 48 individuals with kidney injury who had used the herbal product.

At the time that a report of these adverse effects was published in February 1993, 18 of the 48 women had terminal kidney failure that will require either kidney transplantation or life-long renal dialysis.

I. Ma huang

Ma huang is one of several names for herbal products containing members of the genus *Ephedra*. There are many common names for these evergreen plants, including squaw tea and Mormon tea. Serious adverse effects, including hypertension (elevated blood pressure), palpitation (rapid heart rate), neurophathy (nerve damage), myopathy (muscle injury), psychosis, stroke, and memory loss, have been reported to FDA with products containing Ma huang as ingredients and are currently under investigation.

The *Ephedras* have been shown to contain various chemical stimulants, including the alkaloids ephedrine, pseudoephedrine and norpseudoephedrine, as well as various tannins and related chemicals. The concentrations of these alkaloids depends upon the particular species of *Ephedra* used. Ephedrine and pseudoephedrine are amphetamine-like chemicals used in OTC and prescription drugs. Many of these stimulants have known serious side effects.

Ma huang is sold in products for weight control, as well as in products that boost energy levels. These products often contain other stimulants, such as caffeine, which may have synergistic effects and increase the potential for adverse effects.

II. Amino Acids

Amino acids are the individual constituent parts of proteins. Consumption of foods containing intact proteins ordinarily provides sufficient amounts of the nine amino acids needed for growth and development in children and for maintenance of health of adults. The safety of amino acids in this form is generally not a concern. When marketed as dietary supplements, amino acids are sold as single compounds, in combinations of two or more amino acids, as components of protein powders, as chelated single compounds, or in chelated mixtures. Amino acids are promoted for a variety of uses, including body-building. Some are promoted for claimed pharmacologic effects.

The Federation of American Societies for Experimental Biology (FASEB) recently conducted an

exhaustive search of available data on amino acids and concluded that there was insufficient information to establish a safe intake level for any amino acids in dietary supplements, and that their safety should not be assumed. FASEB warned that consuming amino acids in dietary supplement form posed potential risks for several subgroups of the general population, including women of childbearing age (especially if pregnant or nursing), infants, children, adolescents, the elderly, individuals with inherited disorders of amino acid metabolism, and individuals with certain diseases.

At least two of the amino acids consumed in dietary supplements have also been associated with serious injuries in healthy adults.

A. L-tryptophan

L-tryptophan is associated with the most serious recent outbreak of illness and death known to be due to consumption of dietary supplements. In 1989, public health officials realized that an epidemic of eosinophilia-myalgia syndrome (EMS) was associated with the ingestion of L-tryptophan in a dietary supplement. EMS is a systemic connective tissue disease characterized by severe muscle pain, an increase in white blood cells, and certain skin and neuromuscular manifestations.

More than 1,500 cases of L-tryptophan-related EMS have been reported to the national Centers for Disease Control and Prevention. At least 38 patients are known to have died. The true incidence of L-tryptophan-related EMS is thought to be much higher. Some of the individuals suffering from L-tryptophan-related EMS have recovered, while other individuals' illnesses have persisted or worsened over time.

Although initial epidemiologic studies suggested that the illnesses might be due to impurities in an L-tryptophan product from a single Japanese manufacturer, this hypothesis has not been verified, and additional evidence suggests that L-tryptophan itself may cause or contribute to development of EMS. Cases of EMS and related disorders have been found to be associated with ingestion of L-tryptophan from other batches or sources of L-tryptophan. These illnesses have also been associated with the use of L-5-hydroxytryptophan, a compound that is closely related to L-tryptophan, but is not produced using the manufacturing process that created the impurities in the particular Japanese product.

B. Phenylalanine

A number of illnesses, including those similar to the eosinophilia myalgia syndrome (EMS) associated with L-tryptophan consumption, have been reported to FDA in individuals using dietary supplements containing phenylalanine. There are also published reports of scleroderma/scleroderma-like illnesses, which have symptoms similar to EMS, occurring in children with poorly controlled blood phenylalanine levels, as well as in those with phenylketonuria (PKU), a genetic disorder characterized by the inability to metabolize phenylalanine.

III. Vitamins and Minerals

Vitamin and mineral dietary supplements have a long history of use at levels consistent with the Recommended Dietary Allowances (RDA's) or at low multiples of the RDA's, and are generally considered safe at these levels for the general population. Intakes above the RDA, however, vary widely in their potential for adverse effects. Certain vitamins and minerals that are safe when consumed at low levels are toxic at higher doses. The difference between a safe low dose and a toxic higher dose is quite large for some vitamins and minerals and quite small for others.

A. Vitamin A

Vitamin A is found in several forms in dietary supplements. Preformed vitamin A (vitamin A acetate and vitamin A palmitate) has well-recognized toxicity when consumed at levels of 25,000 International Units (IU) per day, or higher. (Beta-carotene does not have the potential for adverse effects that the other forms of vitamin A do, because high intakes of beta-carotene are converted to vitamin A in the body at much lower levels). The RDA for vitamin A is 1,000 retinol equivalents (RE) for men, which is equivalent to 3,300 IU of preformed vitamin A, and 80 percent of these amounts for women.

The adverse effects associated with consumption of vitamin A at 25,000+ IU include severe liver injury (including cirrhosis), bone and cartilage pathologies, elevated intracranial pressure, and birth defects in infants whose mothers consumed vitamin A during pregnancy. Groups especially vulnerable to vitamin A toxicity are children, pregnant women, and those with liver disease caused by a variety of factors, including alcohol, viral hepatitis, and severe protein-energy malnutrition.

There are some studies that suggest vitamin A toxicity has occurred at levels of ingestion below 25,000 IU. In addition, the severity of the injuries that occur at 25,000 IU suggests that substantial, but less severe and less readily recognized, injuries probably occur at somewhat lower intakes. Most experts recommend that vitamin A intake not exceed 10,000 IU for most adults or 8,000 IU for pregnant and nursing women.

B. Vitamin B_6

Neurologic toxicity, including ataxia (alteration in balance) and sensory neuropathy (changes in sensations due to nerve injury), is associated with intake of vitamin B_6 (pyridoxine) supplements at levels above 100 milligrams per day. As little as 50 milligrams per day has caused resumption of symptoms in an individual previously injured by higher intakes. The RDA for vitamin B_6 is 2 milligrams. Vitamin B_6 is marketed in capsules containing dosages in the 100-, 200-, and 500-milligrams range.

C. Niacin (nicotinic acid and nicotinamide)

Niacin taken in high doses is known to cause a wide range of adverse effects. The RDA for niacin is 20 milligrams. Niacin is marketed in dietary supplements at potencies of 250 mg, 400 mg, and 500 mg, in both immediate and slow-release formulations. Daily doses of 500 mg from slow-release formulations, and 750 mg of immediate-release niacin, have been associated with severe adverse reactions, including gastrointestinal distress (burning pain, nausea, vomiting, bloating, cramping, and diarrhea) and mild to severe liver damage. Less common, but more serious (in some cases life-threatening), reactions include liver injury, myopathy (muscle disease), maculopathy of the eyes (injury to the eyes resulting in decreased vision), coagulopathy (increased bleeding problems), cytopenia (decreases in cell types in the blood), hypotensive myocardial ischemia (heart injury caused by too low blood pressure), and metabolic acidosis (increases in the acidity of the blood and urine).

Niacin (nicotinic acid) is approved as a prescription drug to lower cholesterol. Many of the observed adverse reactions have occurred when patients have switched to OTC formulations of niacin, and particularly when they have switched from immediate-release formulations to dietary supplements containing slow-release niacin formulations without the knowledge of their physicians.

D. Selenium

Selenium is a mineral found in dietary supplement products. At high doses (approximately 800 to 1,000 micrograms per day), selenium can cause tissue damage, especially in tissues or organs that concentrate the element. The toxicity of selenium depends upon the chemical form of selenium in the ingested supplement and upon the selenium levels in the foods consumed. Human injuries have occurred following ingestion of high doses over a few weeks.

IV. Other Products Marked as Dietary Supplements

A. Germanium

Germanium is a nonessential element. Recently, germanium has been marketed in the form of inorganic germanium salts and novel organogermanium compounds, as a "dietary supplement." These products are promoted for their claimed immunomodulatory effects or as "health-promoting" elixirs. Germanium supplements, when used chronically, have caused nephrotoxicity (kidney injury) and death. Since 1982, there have been 20 reported cases of acute renal failure, including two deaths, attributed to oral intakes of germanium elixirs. In surviving patients, kidney function has improved after discontinuation of germanium, but none of the patients have recovered normal kidney function.

One particular organogermanium compound, an azaspiran organogermanium, has been studied for its potential use as an anticancer drug. Forty percent of the patients in this study experienced transient neurotoxicity (nerve damage), and two patients developed pulmonary toxicity. Because of these side effects, medically supervised administration of this drug with monitoring for toxicity has been recommended for those using germanium chronically.

This document was published in 1993.
For more recent information on Dietary Supplements
See http://www.cfsan.fda.gov/~dms/supplmnt.html

OVER-THE-COUNTER "FLUSH-FREE" NIACIN PREPARATIONS CONTAIN NO FREE NICOTINIC ACID, AND ARE MORE EXPENSIVE THAN PLAIN NIACIN TABLETS. CD Meyers, M Carr, JD Brunzell, Department of Medicine, Division of Metabolism, Endocrinology and Nutrition, University of Washington, Seattle, WA

Exhibit 2

Nicotinic acid is effective in beneficially altering lipoprotein profiles and preventing clinical cardiovascular events, although its use is somewhat limited by the flushing side effect. Many companies produce and market over-the-counter "flush-free" or "no-flush" niacin preparations, but these products are not subject to the rigors of standardization as are prescription drugs. Hyperlipidemic patients may be at risk of purchasing niacin products that contain little nicotinic acid. We purchased fourteen over-the-counter preparations of niacin (500 mg), for the purpose of measuring free nicotinic acid content. Free nicotinic acid levels were obtained using gas chromatographic mass spectrometry. Each of the formulations marketed as plain or crystalline niacin (6/6 products) contained at least 500 mg of free nicotinic acid (average 541 mg). None of the products marketed as "flush-free" niacin (0/8 products) contained any measurable levels of free nicotinic acid. Several of the "flush-free" niacin preparations could only partially be dissolved, despite attempts to vary the solvent (water, methanol, DMSO, ethylacetate, acetonitrile) or the pH (2-10). Furthermore, the average cost of the "flush-free" preparations (18.9 + 0.048 cents per 500mg) was significantly higher than that of plain niacin (6.4 + 0.011 cents per 500 mg, $p < 0.001$). We conclude that many of the over-the-counter "flush-free" niacin preparations contain essentially no free nicotinic acid, and are therefore unlikely to have beneficial hypolipidemic effects. Physicians and patients need to be aware of the potential for wasting resources on these "flush-free" products, and focus on using formulations of niacin that have been proven safe and effective.