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Scientific and Regulatory Aspects of Nutraceutical Products in the United States

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ABSTRACT

Within the past decade, the so-called health food industry has experienced a tremendous growth such that these products are commonplace in most community pharmacies within the United States. These products have since been defined, by those in the industry, as nutraceuticals. Passage of the Nutrition Labeling and Education Act of 1990 and the Dietary Supplement Health and Education Act of 1994 has had a significant impact on the information available to the consumers to enable them to make educated decisions when "self-medicating" with this class of products. This paper is an attempt to summarize the current state of scientific and regulatory issues that are relevant to nutraceutical products.

INTRODUCTION

As the baby boomers come of age, more and more people are becoming intrigued with the notion of improving their health with "nutraceuticals." Herbal products, glandular extracts, and nutritional "performance enhancers" are no longer confined to health food stores. They are becoming an increasingly common item in nearly all pharmacies across the country. A survey conducted by the American Pharmaceutical Association estimates that more than 80% of hospital and community pharmacies in the United States carry some natural products (1). Indeed, several references that deal primarily with "natural" products can be found among those on the pharmacist's shelf. In particular, *Facts and Comparisons*, long a mainstay reference in community and hospital pharmacies, has recently started distributing a separate volume of monographs entitled *The Review of Natural Products*, and *The Handbook of Nonprescription Drugs* now contains a complete chapter devoted to "herbs and phytomedicinals" (2).

In the United States, the federal Food and Drug Administration (FDA) has made several attempts either to regulate these products as drugs or to remove them from the market, each time being met with a significant response from an indignant public, first in the form of the Vitamins and Minerals Act of 1976 and then with the passing of the Dietary Supplement Health and Education

Act (DSHEA) of 1994. The Vitamin and Minerals Act of 1976 prevents the FDA from regulating dietary supplements as drugs, and the DSHEA limits the action of the FDA such that the agency can only remove dietary supplements from the market if they are misbranded or if they are proven unsafe through clinical evidence obtained by the agency.

Government organizations such as the National Institutes of Health's (NIH's) Office of Alternative of Medicine and Office of Dietary Supplements and the National Cancer Institute's (NCI's) Chemoprevention Program of the Division of Cancer Prevention and Control have been established to address the merits of this rapidly expanding market. In addition, private organizations involved in the field of nutraceuticals, such as the American Nutraceutical Association, the Foundation for Innovative Medicine, the American Herbal Products Association, and the Council for Responsible Nutrition have been growing in number during this decade, and the *Journal of Nutraceuticals, Functional and Medical Foods* published its inaugural issue in January 1997.

Recognizing the increased growth in, consumer desire for, and interest in nutraceutical products, this paper attempts to summarize both the regulatory and scientific issues relating to this industry.

DEFINITIONS

Before discussing some of the scientific and regulatory issues surrounding the field of nutraceuticals, it is useful to set forth several definitions related to this topic. Figure 1 categorizes nutritional products in an effort to make more sense of these terms. It is important to note that two of the terms most commonly found in the nutraceutical literature, "nutraceutical" and "functional food," are not recognized by the FDA.

Nutraceutical

Certainly, the first, and perhaps most difficult, concept to define is nutraceutical itself. The term *nutraceutical* was apparently first used in a 1991 white paper written by Stephen DeFelice, "The Nutraceutical Initiative: A Proposal for Economic and Regulatory Reform" (3). In this paper, DeFelice defined a nutraceutical as "any object that may be considered a food or a part of food and provides medical or health benefits, including the prevention and treatment of disease." It has since been defined by Canada's Health Protection Bureau (HPB) and others as "a product produced from food but sold in pills, powders (potions) and other medicinal forms not generally associated with food and demonstrated to have a physiological benefit or provide protection against chronic disease" (4). These two definitions are at odds when one considers that DeFelice's definition can be applied to nearly anything that is orally ingested and is not a drug, while the HPB's definition specifically limits the term to traditional oral dosage forms. Within the context of this paper, nutraceuticals encompass nutritional products that provide benefits, beyond the intake of nutrients, to the consumer.

Functional Foods

Functional food is another buzzword frequently found in literature related to nutraceuticals. Some identify functional foods as a subclass of nutraceuticals, while others, such as the HPB, consider functional foods to be a completely separate class of products. In their position paper, the American Dietetic Association (ADA) defines functional foods as "any modified food or food ingredient that may provide a health benefit beyond the traditional nutrients it contains" (5); the fact that it is "modified" implies processing of the food beyond its natural state. The HPB, however, considers a functional food to be "similar in appearance to conventional foods, [it] is consumed as part of a usual diet, and has demonstrated physiological benefits and/or reduces the risk of chronic diseases beyond basic nutritional functions" (4). A similar definition established by the University of Illinois Functional Foods for Health Program is that a functional food "refers to foods that, by virtue of physiologically active components, provide benefits beyond basic nutrition and may prevent disease or promote health" (6). The last two definitions differ from the ADA's in that they do not require the food to be modified.

Foods for Special Dietary Uses and Medical Foods

Foods for special dietary uses (FSDU) and medical foods may be classified by some as functional foods. FSDU and medical foods are broadly defined as enteral products designed to meet the specific dietary needs of certain subsets of the population. Both of these terms are discussed in much greater detail in the section of this paper on regulatory issues. In addition, other terms such as disease claim, health claim, and structure/function claim are defined in that section.

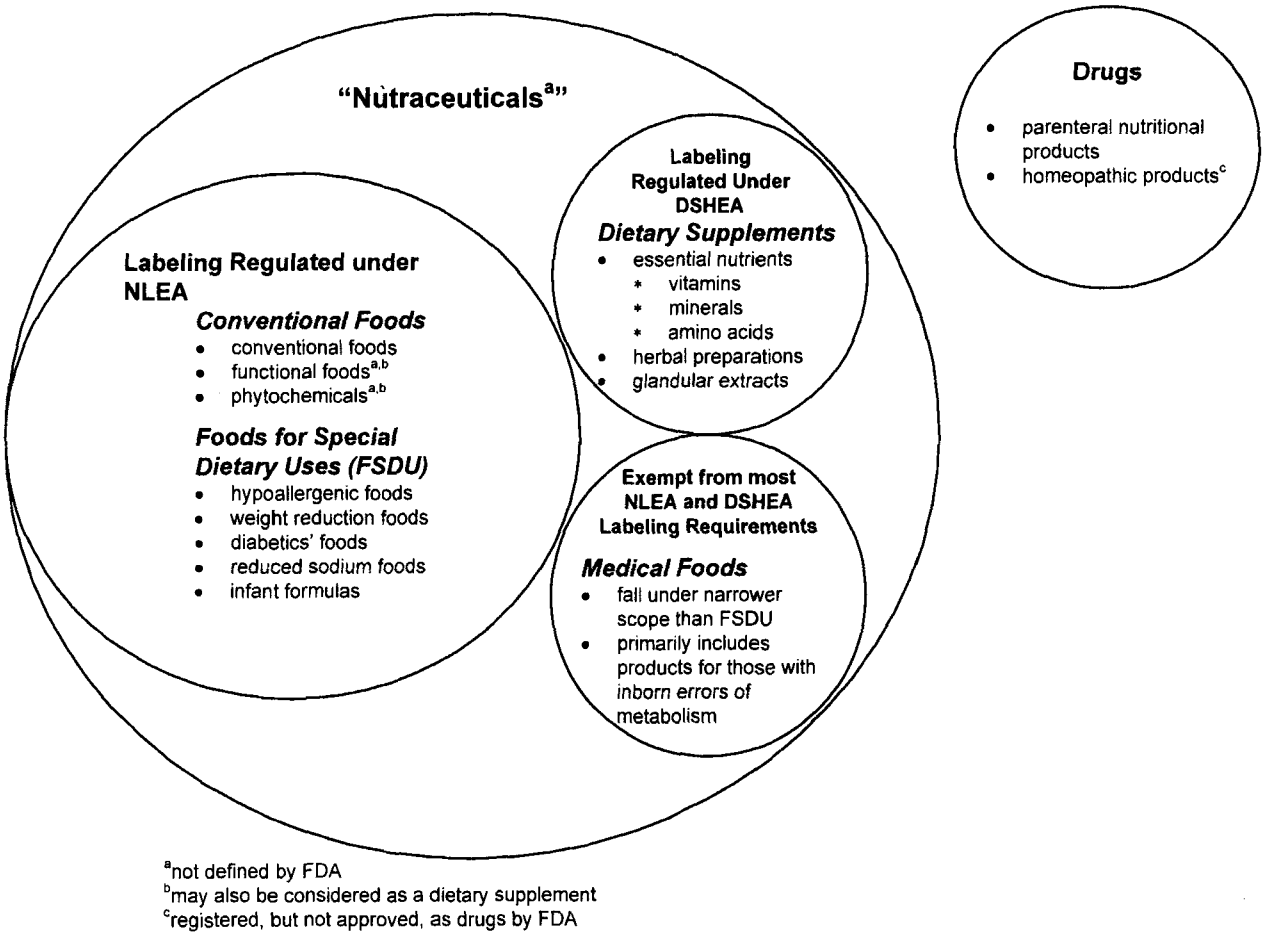

Figure 1. Categorization of nutritional products. (Adapted from Ref. 58.)

Dietary Supplements

Dietary supplements are defined in Section 201(ff) of the Food, Drug, and Cosmetic (FD&C) Act and are discussed, at length, in the Regulatory Issues section of this paper. Dietary supplements can include nutrients, botanicals, and glandular extracts and are generally marketed as either liquid or solid oral dosage forms. The FDA has expanded this definition so that, under certain circumstances, dietary supplements may be in the form of conventional foods.

Nutrients

Nutrients include vitamins, minerals, and amino acids. Essential nutrients are defined as "substances that must be provided in small quantities from the environment because either they cannot be synthesized de novo in human beings or their rate of synthesis is inadequate for the maintenance of health" (7), with vitamins being organic nutrients and minerals inorganic.

The amino acid, L-tryptophan was formerly marketed as a sleep aid in the United States. The FDA, however, removed this product from the market in 1990 after its use was correlated with more than 1000 cases of eosinophilia myalgia syndrome (EMS).

Botanicals

Tyler and Foster define herbal products as "botanicals used to treat disease states, often of a chronic nature, or to attain or maintain a condition of improved health" and categorizes phytomedicinals as a subclass of herbal products that are "preparations made by extracting herbs with various solvents" (2). Similarly, Lowe and Ku define

phytotherapy as "the use of plants or plant extracts for medicinal purposes" (8).

Glandular Extracts

Glandular extracts found in the United States include dehydroepiandrosterone (DHEA) and melatonin. DHEA and melatonin either can be extracted from animal sources or can be produced synthetically. Given the detection of transmissible spongiform encephalopathies (TSE) in materials derived from animals, one is wise to choose synthetic products over those extracted from animals. In particular, melatonin is extracted from the pineal gland of the brain, TSE's target organ.

Homeopathic Products

Homeopathic products are often confused with other herbal products. Although the FDA does not approve homeopathic products, they are registered as drugs with the agency. The discipline of homeopathy is somewhat analogous to the subcutaneous administration of allergens to treat allergies and relies on the tenet that substances that cause a set of symptoms in large amounts can be used, in much smaller quantities, to alleviate those same symptoms. In addition, homeopathic products are not meant to be used until the symptoms abate; they rely on the body's natural homeostatic mechanisms to "kick in" once the healing process has been initiated.

RESEARCH RELATED ISSUES

Clinical studies and research concerning nutraceutical products varies greatly in terms of the quality of work performed and the general conclusions that can be drawn. Many studies are well thought out and meet high scientific standards. Others, unfortunately, are poorly designed and executed and proffer unsubstantiated conclusions.

Nutrients

Listed in Table 1 are common nutrients and their associated health benefits. Some feel that these nutrients may provide much more than nutritional support. Therefore, as mandated by the DSHEA, the NIH has established the Office of Dietary Supplements to "explore the potential role of supplements and their value in preventing chronic disease."

When reading literature relating to supplementation of nutrients, it is important to bear in mind that many, including the ADA, regard dietary intake as the best means of ingesting nutrients as it is unknown whether supplementation provides the same benefits as dietary intake

Table 1

Common Nutrients and Their Associated Health Benefits

Nutrient	Health Benefits
Fat-Soluble vitamins	
Vitamin A	Antioxidant, essential for growth and development; maintains healthy vision, skin, and mucous membranes; may aid in the prevention and treatment of certain cancers and in the treatment of certain skin disorders (note: the body converts beta carotene into Vitamin A)
Vitamin D (calciferol)	Essential for formation of bones and teeth; helps the body absorb and use calcium
Vitamin E (tocopherol)	Antioxidant; helps form blood cells, muscles, and lung and nerve tissue; boosts the immune system
Vitamin K	Essential for blood clotting
Water-soluble vitamins	
Ascorbic acid (vitamin C)	Antioxidant; necessary for healthy bones, teeth, and skin; helps in wound healing; may prevent common cold and attenuate its symptoms should a cold occur
Thiamine (vitamin B1)	Helps convert food into energy; essential in neurologic function
Riboflavin (vitamin B2)	Helps in energy production and other chemical processes in the body; helps maintain healthy eyes, skin, and nerve function
Niacin (vitamin B3)	Helps convert food into energy; helps maintain proper brain function
Pyridoxine (vitamin B6)	Helps produce essentials proteins; helps convert protein into energy
Cyanocobalamin (vitamin B12)	Helps produce the genetic material of cells; helps with formation of red blood cells and maintenance of central nervous system; helps make amino acids; involved in metabolism of fat, protein, and carbohydrates

Table 1 Continued

Nutrient	Health Benefits
Folic acid[a] (pteroylglutamic acid, folacin)	Necessary to produce the genetic materials of cells; essential in first 3 months of pregnancy for preventing birth defects; helps in red blood cell formation; protects against heart disease
Panthothenic acid (in B = complex family)	Aids in synthesis of cholesterol, steriods, and fatty acids; crucial for intraneuronal synthesis of acetylcholine
Minerals	
Calcium	Essential for building bones and teeth and maintaining bone strength; important in muscle function
Iron	Helps in energy production; helps to carry oxygen in the bloodstream and to transfer oxygen to muscles
Magnesium	Essential for healthy nerve and muscle function and bone formation; may help prevent premenstrual syndrome (PMS)
Phosphorus	Essential for building strong bones and teeth; helps in formation of genetic material; helps in energy production and storage
Trace elements	
Choromium	Works with insulin to convert carbohydrates and fat into energy
Cobalt	Essential component of vitamin B12, but ingested cobalt is metabolized in vivo to form the B12 coenzymes
Copper	Essential for makeing hemoglobin and collagen; essential for healthy functioning of the heart; helps in energy production; helps in absorption of iron from digestive tract
Flourine	Presumably makes enamel resistant to erosive action of acids produced by bacteria in the oral cavity
Iodine	Essential for proper functioning of the thyroid
Manganese	Required for glucose utilization, synthesis of the mucopolysaccharides of cartilage, biosynthesis of steriods
Molybdenum	May function as an enzyme cofactor
Nickel	Involved in specific metalloenzymes
Selenium	Antioxidant; essential for healthy functioning of the heart muscle
Silicone	Functions in the development and maintenance of connective tissue
Tin	May be involved in growth and reproductive functions
Vanadium	May be involved in functions related to growth and reproduction
Zinc	Essential for cell reproduction, normal growth and development in children, wound healing, and production of sperm and the male hormone testosterone
Vitamin-like compounds	
Biotin (vitamin H)	Member of B-complex group of vitamins; required for various metabolic functions
L-Carnitine	Oxidation of fatty acids, promotion of certain organic acid excretions, and enhancement of the rate of oxidative phosphorylation
Choline	Lipotropic agents; they have been used to treat fatty liver and disturbed fat metabolism
Essential fatty acids (vitamin F)	Involved in proper development of various membranes and the synthesis of prostaglandins, leukotrienes, and various hydroxy fatty acids
Inositol	Necessary for amino acid transport and movement of potassium and sodium; lipotropic agent
Laetrile (amygdalin, vitamin B17)	No vitamin activity; no nutritional or therapeutic value; no approved medical use
Pangamic acid (vitamin B15)	No nutritional or therapeutic value
Taurine (aminoethanesulfonate)	Aids in retinal photoreceptor activity, bile acid conjugation, white blood cell antioxidant activity, CNS neuromodulation, platelet aggregation, cardiac contractility, sperm motility, growth, and insulin activity

Source: Adapted from Refs. 52 and 53.

[a] Many bakery products are now fortified with folic acid.

(4). For example, by striving to eat foods that are rich in vitamin C, one is probably deriving additional benefits that are not necessarily related to the vitamin C content alone.

The antioxidants, vitamins A, C, and E, are among the most commonly known nutrients (note that beta carotene ingested as a food component is metabolically converted to vitamin). Many potential benefits have been attributed to antioxidant use in the form of dietary intake or supplementation (9–13). Antioxidants, in general, may be useful in the prevention of cancer and cerebrovascular disease (9). Supplementation with vitamin C may be beneficial in the management of asthma patients (10), and high dietary intake of vitamin E may prevent Parkinson's disease (11). Moreover, researchers have recently determined that the oxidized form of vitamin C, dehydroascorbic acid, readily crosses the blood brain barrier (12). These findings have implications for increasing the uptake of antioxidants in the central nervous system (CNS); thus, some feel that this has the potential for improving the treatment of Alzheimer's disease.

The combination of vitamin E, C, and beta carotene has been useful in reducing low density lipoprotein (LDL) oxidation and subsequent atherosclerosis (13). Researchers Jialal and Fuller speculate that all three of these substances work synergistically, in slightly different ways, to prevent oxidation of LDL in the following manner:

1. Vitamin C scavenges aqueous radicals and regenerates alpha-tocopherol from the tocopheroxyl radical species;
2. Vitamin E, in the form of alpha-tocopherol protects polyunsaturated fatty acids within the LDL particle, reduces platelet adhesion and inhibits smooth muscle cell proliferation and protein kinase C activity; and
3. Beta carotene provides reserve antioxidant activity, especially in the arterial wall where low partial pressures of oxygen are found. (13)

Other substances, such as beta carotene, selenium, and pycnogenol, are considered to be antioxidants. However, as there are currently no recommended daily allowances (RDAs) for these compounds, products containing these compounds cannot be labeled "high in antioxidants" (14).

Those genetically predisposed to pancreatic cancer have low serum levels of selenium; thus, it is assumed that supplementation with selenium may help to prevent this condition (15,16). Selenium has also been evaluated for its potential use by those suffering from asthma and skin cancer; results have been inconclusive (10,17). In vitro, pycnogenol has been found to be a potent superoxide anion and hydrogen peroxide scavenger, yet little, if any, clinical data currently exist (18).

Not all activities attributed to supplementation are positive; some are generally inconclusive, and others are negative. In a double-blind trial of more than 22,000 healthy males who received 50 mg of beta carotene every other day over the course of 12 years, it was determined that supplementation with beta carotene produced neither benefit nor harm in terms of the incidence of malignant neoplasms, cardiovascular disease, or death from all causes (19). More disturbingly, in a double-blind, placebo-controlled trial of more than 18,000 people that was designed to demonstrate the benefits of beta carotene and vitamin A supplementation in those at risk for the development of lung cancer (i.e., smokers or those exposed to asbestos), it was found that supplementation may have actually resulted in an increased incidence of lung cancer, death from lung cancer, and cardiovascular disease in this population (20). In addition, some studies indicate that supplementation with selenium may induce, rather than prevent, pancreatic cancer (21), and vitamin A at superphysiological levels is a well-known teratogen.

Herbal Products

Table 2 provides a list of some of the more commonly known herbal extracts. The Office of Alternative Medicine at the NIH currently studies and disseminates information about the following herbal products: echinacea, ginger rhizome, ginkgo biloba extract, ginseng root, wild chrysanthemum flower, witch hazel, yellowdock, and traditional nutritional supplements. In addition, many of the extracts listed in this table are commonly used in Germany in a fashion similar to the use of over-the-counter (OTC) products in the United States. For instance, it is estimated that up to 90% of all benign prostatic hyperplasia (BPH) cases in Germany are treated with herbal products (8).

Herbal extracts, including beta-sitosterols (found in saw palmetto berry, SPB), cernilton (pollen extract), and *Pygeum africum* (African plum) have been clinically evaluated for use in the treatment of BPH (8,22). However, as is the case in many clinical studies of nutraceutical products, interpretation of the results are confounded by the inability to determine the quality of the material evaluated and the poor study design, including lack of placebo control or comparator and insufficient study duration.

St. John's wort extract, often touted as "herbal Prozac," has been the object of much debate throughout the

Western world and is thought to function as a serotonin reuptake inhibitor. Studies conducted in Europe have found St. John's wort to be effective in the treatment of depression (23,24), and a meta-analysis of 23 randomized trials of more than 1500 patients found it to be better than placebo and similar in effect to standard antidepressants, most commonly amitriptyline (25). However, as may be the case with many products derived from natural origin, St. John's wort contains at least 10 constituents that may contribute to its pharmacological effect, and the ability to extract the appropriate constituents in the appropriate amounts consistently is difficult (26).

In an effort to generate substantive clinical data in the United States, the NIH's Office of Alternative Medicine, in conjunction with the National Institute of Mental Health, initiated a study of St. John's wort in October 1997. In this study, patients receive (1) a uniform dose of St. John's wort, (2) a placebo, or (3) a selective serotonin reuptake inhibitor. In the press release announcing the launching of this study, an NIH official stated that it "will be the first rigorous clinical trial of the herb that will be large enough and long enough to fully assess whether it produces a therapeutic effect." This statement reflects many of the problems associated with the current state of knowledge of nutraceutical products.

Another common herbal treatment is the use of echinacea for the prevention and treatment of colds and flu. A series of five placebo-controlled studies evaluating the use of echinacea produced mixed results, which the authors attribute to either the use of healthy volunteers, rather than patients, or the use of extracts that were not standardized or chemically defined monopreparations (27). Aside from the inability to have a standardized source of echinacea, some patients have suffered from echinacea-associated anaphylaxis (28).

For those wishing to try herbal products, Tyler recommends that the following caveats be followed (7):

1. Only purchase products from a reputable manufacturer as many of these products are misbranded and do not contain the contents claimed on the label;
2. Check that the product contains standardized extracts;
3. Be aware that products containing several herbal ingredients are not, in general, able to provide sufficient quantities of each to ensure therapeutic effect;
4. Never consume herbal products if pregnant or nursing (note that young children in general should not consume these products)
5. Those experiencing serious health problems should always check with their physician prior to use.

In addition, the FDA issued published proposed rules regarding the sale of ephedra, also known as the Chinese herb Ma Huang, a potent CNS stimulant (29). In their proposal, the FDA considers products adulterated if a single dose/serving contains more than 8 mg of ephedrine alkaloids. The FDA has also pulled "herbal fen-phen" products and cholestin off the market.

Functional Foods, Foods for Special Dietary Uses, and Medical Foods

Presumably, any food for which there exists an approved health claim can be regarded as a functional food. Table 3 lists those health claims that are currently approved by the FDA. In addition, as cited in the Definitions section, medical foods and FSDU may be regarded by some as functional foods as they are foods that provide health benefits.

In the early 1980s, the NCI's Chemoprevention Program of the Division of Cancer Prevention and Control was established to study the merits of numerous foods and food components for their applicability in preventing and treating cancer. Wargovich reviewed the types of anticancer activity of some of these foods, and a summary of these results is provided in Table 4 (30).

In addition to the health claims listed in Table 3, researchers have found that minimally refined grains may reduce the incidence of diabetes (31) and may be beneficial in the prevention of gastrointestinal cancers (32). Other common foods that may have potential therapeutic value include edible mushrooms. For example, several species of edible mushrooms have been attributed with immunomodulatory, lipid-lowering, and antimicrobial properties (33).

Dietary regimens have also been developed to manage a variety of diseases. For instance, prepackaged, nutritionally balanced meals that meet the recommendations of national health organizations improved multiple risk factors for patients with cardiovascular disease and increased patient compliance with dietary restrictions (34). Treatment of epilepsy via a ketogenic diet that is high in fat and low in protein has been evaluated (35). Researchers initially proposed this therapy based on the observation that seizures often cease in patients who fast.

In the same vein, a high-carbohydrate drink, PMS Escape, has been developed to treat symptoms associated

Table 2

Common Herbal and Phytochemical Products

Compound	Reported Activity/Use
Digestive system disorders	
Chamomile (*Matricaria recutita* L.)	Oral: anti-inflammatory, spasmyolitic, antimicrobial Topical: wound-healing, anti-inflammatory, antimicrobial
Ginger (*Zingiber officinale* Rosc.)	Carminative, antiemetic, cholagogue, positive inotrophic; treatment of dizziness (note: USP patient pamphlet available; information currently under study and disseminated by NIH's Office of Alternative Medicine)
Licorice (*Glycyrrhiza glabra* L., *Glycyrrhiza uralensis* Fisch.)	Expectorant, secretolytic; treatment of peptic ulcers
Milk thistle (*Silybum marianum* L.)	Prophylaxis and treatment of chronic hepatoxicity
Peppermint (*Mentha* × *piperita* L.)[b]	Leaf: carminative, cholerectic Oil: reduces symptoms of irritable bowel syndrome (IBS)
Plantago seed, psyllium seed (*Plantago arenaria* Waldst., *Plantago arenaria* Kit., *Platago ovata*)[c]	Carthartic
Senna (*Cassia acutifolia* Del., *Cassia angustifolia* Vahl., *Senna alexandrina* Mill.)	Cathartic
Kidney, Urinary Tract and Prostate Disorders	
Beaberry (*Arctostaphylos uva-ursi* L., Spreng. [Ericacaeae])	Antibacterial for urinary tract infection (UTI), diuretic
Cranberry (*Vaccinium macrocarpon* Ait.)	Bacteriostatic for treatment of UTIs
Goldenrod (*Solidago virgaurea* L., *Solidago serotina* Ait., *Solidago canadensis* L.)	Prophylaxis and treatment of urinary calculi and kidney stones
Saw palmetto (*Serenoa repens* [Batr.])	Antiandronergic, anti-inflammatory; treat symptoms of benign prostatic hyperplasia (BPH)
Performance and endurance enhancers	
Echinacea (*Echinacea purpurea* L. Moench., *Echinacea angustifolia* DC, *Echinacea pallida* Nutt. Nutt.)	Oral: immunostimulatant; treatment of cold and fle symptoms (information currently under study and disseminated by NIH's Office of Alternative Medicine) Topical: treatment of hard-to-heal wounds, eczema, burns, psoriasis, herpes, herpes simplex, etc.
Eleuthero (*Eleutherococcus senticosus* Rupr. & Maxim., Maxim)	Adaptogen
Ginseng (*Panax ginseng* C.A. Meyer, *Panax quinquefolius* L.)	Adaptogen (information currently under study and disseminated by NIH's Office of Alternative Medicine)
Nervous system disorders	
Feverfew (*Tanacetum parthenium* L.)	Treatment of headaches, fever, and menstrual problems; prophylactic to reduce frequency, severity, and duration of migraine headaches
St. John's wort (*Hypericum perforatum*) L.)	Anxiolytic, anti-inflammatory, antidepressant, monoamine oxidase inhibitor (note: NIH study under way)
Valerian (*Valeriana officinalis* L.)	Spasmolytic, mild sedative, sleep aid (note: USP patient pamphlet available)
Willow bark (*Salix alba* L., *Salix fragilis* L., *Salix daphnoides* Villars, *Salix pentandra* L.)	Anti-inflammatory, analgesic, antipyretic, astringent; treatment of rheumatic and arthritic conditions, mild headache, and gout
Metabolic and endocrine disorders	
Black cohosh (*Cimicifuga racemosa* L. Nutt.)	Emmenagogue; treatment of premenstrual discomfort and dysmenorrhea
Black currant seed oil (*Ribes nigrum* L.)	Dietary supplementation of linoleic acid; treatment of atopic eczema
Borage seed oil (*Borago officinalis* L.)	Dietary supplementation of linoleic acid; treatment of atopic eczema

Table 2 Continued

Compound	Reported Activity/Use
Chaste tree berry (*Vitex agnus-castus* L.)	Treatment of menstrual disorders
Evening primrose oil (*Oenothera biennis* L.)	Dietary supplementation of linoleic acid; treatment of atopic eczema
Respiratory tract disorders	
Ephedra (*Ephedra sinica* Stapf., *Ephedra intermedia* Schrank., *Ephedra equisetina* Bunge.)	Bronchodilator, vasoconstrictor, reduces bronchial edema, appetite supressant (note: FDA has restricted use of ephedra-containing products)
Horehound (*Marrubium vulgare* L.)	Espectorant, antitussive, cholerectic (note: FDA has declared it ineffective as a nonprescription cough supressant and expectorant)
Slippery elm (*Ulmus rubra* Muhl.)	Mucilaginous demulcent, emmollient, and nutrient; used to sooth irritated mucous membranes or ulcerations of the digestive tract (note: FDA has approved its used as a soothing demulcent for sore throat)
Cardiovascular system disorders	
Garlic (*Allium sativum* L.)	Antibacterial, antifungal, antithrombotic, hypotensive, fibrinolytic, anti-inflammatory, antihyperlipidemic
Ginkgo (*Ginkgo biloba* L.)	Increases vasodilation and peripheral blood flow rate in capillary vessels and end arteries; treatment post-thrombotic syndrome, chronic cerebral vascular insufficiency, short-term memory loss, cognitive disorders secondary to depression, dementia, tinnitus, vertigo (information currently under study and disseminated by NIH's Office of Alternative Medicine)
Grapeseed (*Vitis vinifera* L.)	Antioxidant; treatment of hypoxia from atherosclerosis, inflammation, and cardiac or cerebral infarction
Hawthorn (*Crataegus laevigtata* [Poir] DC.)	Sleep aid; treatment of diminished cardiac performance
Pinebark (*Pinus maritima* Lam.), pycnogenol	Antioxidant; treatment of hypoxia from atherosclerosis, inflammation, and cardiac or cerebral infarction
Disorders of the skin, mucous membranes, and gingiva	
Aloe vera gel (*Aloe vera* L. N.L. Burm.)	Dilates capillaries, anti-inflammatory; emollient and wound-healing properties when applied topically
Goldenseal (*Hydrastis canadensis* L.)	Antimicrobial, astringent, antihemorrhagic; treatment of mucosal inflammation, dyspepsia, and gastritis
Melissa (*Melissa officinalis* L.), lemon balm	Topical antibacterial and antiviral
Tea tree oil (*Melaleuca alternifolia* [Maiden & Betche] Cheel)	Topical bacteriostatic and germicidal
Witch hazel (*Hamamelis virginiana* L., *Hamamelis vernalis* Sarg.)	Topical treatment of local inflammation of skin and mucous membranes; astringent, anti-inflammatory, and local hemostyptic for minor skin injuries, hemorrhoids, and varicose veins (information currently under study and disseminated by NIH's Office of Alternative Medicine)

Source: From Refs. 2 and 54.

Glossary (adapted from Refs. 2 and 57): adaptogen—an agent facilitating resistance to various kinds of stress; antiemetic—a drug that prevents vomiting; carminative—a drug that relieves flatulence and is used to treat gastric discomfort and colic; carthartic—laxative; cholagogue—a drug that stimulates the flow of bile from the gall bladder and bile ducts of the duodenum; cholerectic—an agent that stimulates the secretion of bile by the liver, thereby increasing the flow of bile; diuretic—a drug that increases the volume of urine by promoting the excretion of salts and water from the kidney; emmenagogue—an agent that stimulates menstruation; positive ionotropic—a drug that stimulates heart muscle contractions and causes the heart rate to increase.

[a] Common name (*Latin name*).

[b] As a result of a decision by the FDA Advisory Review of Over-the-Counter Miscellaneous Internal Drug Products, peppermint oil was dropped from nonprescription drug status in 1990.

[c] *Plantago psyllium* L. and *Plantago indica* l. are botanical names with invalid standing, although official in USP XXIII.

Table 3

FDA Approved Health Claims

Component	Claim[a]	Regulatory Citation
Calcium	Reduces risk of osteoporosis	21 CFR 101.72
Low sodium	Reduces risk of high blood pressure	21 CFR 101.74
Low fat	Reduces risk of some cancers	21 CFR 101.73
Low saturated fat and low cholesterol	Reduces risk of coronary heart disease (CHD)	21 CFR 101.75
Fiber-containing grain products, fruits, and vegetables	Reduces risk of some types of cancer	21 CFR 101.76
Fruits, vegetables, grain products that contain fiber (particularly soluble fiber)	Reduces rist of CHD	21 CFR 101.77
Fruit and vegetables containing vitamin A, vitamin C, or dietary fiber	Reduces risk of some types of cancers	21 CFR 101.78
Folate	Reduces woman's risk of having a child with a brain or spinal cord defect	21 CFR 101.79
Dietary sugar alcohol	Does not promote tooth decay	21 CFR 101.80
Soluble fiber from whole oates and psyllium seed	Reduces risk of CHD	21 CFR 101.81

Source: Adapted from Ref. 55.

[a] Additional criteria for use of any claim include the following:

Only information on the value that intake or reduced intake, as part of a total dietary pattern, may have on a disease of health-related condition.

Enables public to understand information provided and significance of information in the context of a total daily diet.

Complete, truthful, and not misleading.

All information in one place without intervening material (reference statement pemitted).

Not represented for infants or toddlers less than 2 years of age.

Uses "may" or "might" to express relationsip between substance and disease.

Does not quantify any degree of risk reduction.

Indicates disease depends on many factors.

Food contains, without fortification, 10% or more of the Daily Value for one of six nutrients (dietary supplements excepted):

Vitamin A	500 IU	Protein	5 g
Calcium	100 mg	Iron	1.8 mg
Vitamin C	6 mg	Fiber	2.5 g

Food contains less than the specified levels of four disqualifying nutrients:

Disqualifying nutrients	Foods	Main Dishes	Meal Products
Fat	13 g	19.5 g	26 g
Saturated fat	4 g	6 g	8 g
Cholesterol	60 mg	90 mg	120 mg
Sodium	480 mg	720 mg	960 mg

with premenstrual syndrome (PMS) (36). Researchers initially found that those patients suffering from severe PMS consumed levels of carbohydrates in the late luteal phase of their menstrual cycle that exceeded levels consumed at other phases (37). The researchers postulated that the surge in carbohydrate intake was an innate form "self-medication" as the carbohydrates are converted into serotonin; recent studies have shown that dietary and pharmacological interventions that increase serotoninergic activity normalize food intake and diminish depressed mood (38).

In addition, Zbar and NiteBite are two products, in the form of bars, that contain sucrose, protein, and uncooked starch in order to provide continuous glucose release to diabetics during the night (39,40). The sucrose is released immediately, while the protein is converted to glucose approximately 2–5 hours after ingestion, and the uncooked starch is converted to glucose 6–8 hours postingestion.

Enteral products such as those listed in Table 5 can be classified by the FDA as conventional food, FSDU, or medical foods (note that, in general, the FDA does not

Table 4

Foods Containing Compounds That May Prevent Cancer

Action	Food Source	Chemopreventive Agent	Tumor Site
Modification of carcinogen activation	Alliums (e.g., garlic and onions)	Alkyl sulfides and disulfides	Esophagus, colon, and lung
	Crucifers (e.g., cauliflower, broccoli, cabbage)	Isothiocyanates	Liver, lung, mammary
	Citrus	Monoterpenes	Mammary, pancreas
	Tumeric	Flavonoids	Colon, skin
	Teas	Polyphenols	Colon, lung, skin
Modulation of carcinogen detoxification	Alliums	Sulfide volatiles, alkylcysteines	Esophagus, colon, and lung
	Crucifers	Isothiocyanates	Liver, lung, mammary
Interception of DNA-reactive species	Green tea	Polyphenol fraction	Colon, lung, skin
	Green tea	Epigallocatechin gallate (EGCG)	Duodenum, skin
	Green tea	Tea infusion	Esophagus, fore-stomach, lung, skin
	Ellagic acid (found in a variety of fruits and nuts)	Polyphenolics	Esophagus
		Curcumin	Skin, mammary, colon, fore-stomach (nonhuman)
Reversal of abnormal proliferation	Citrus	Monoterpenes	General
		Calcium	Colon
		Vitamin A and its precursors and metabolites	General

Source: Adapted from Ref. 30.

consider dietary supplements to be in the form of food; exceptions, however, can be made). As discussed below, many products that are currently marketed as medical foods do not meet the FDA's criteria. Products that provide dietary intake of nutrients to those with inborn metabolic errors can unequivocally be classified as medical foods. Recent research includes formulas with increased palatability or performance for the treatment of carbohydrate-deficient glycoprotein syndrome type I (CGDPS) (41) and phenylketonuria (PKU) (42).

REGULATORY ISSUES

Figure 2 illustrates the relationship of the Office of Special Nutritionals to the FDA, and Table 6 provides a list of selected regulatory terms that are relevant to nutraceutical products. The Office of Special Nutritionals deals with products such as dietary supplements and medical foods (note that, depending on the manufacturer's choice of marketing tactics, functional foods may be classified as dietary supplements).

Regulation of Nutraceutical Products in Other Countries

The regulatory framework existing in many parts of Europe currently makes it easier to bring nutraceuticals to market, especially those with a long history of use. This can be attributed to two aspects of these systems: (1) the ability to approve substances under the "doctrine of reasonable certainty" and (2) the reduced cost and time of regulatory approval. The doctrine of reasonable certainty contends that a substance's historical use is a valid way to document safety and efficacy in the absence of scientific evidence to the contrary. Although the FDA has published an Advanced Notice of Proposed Rulemak-

Table 5

Some Currently Marketed Enteral Products

Type of Product	Product	Manufacturer	Indication
Disease-specified formulas	Advera	Ross Products	For dietary management of patients with HIV infection or AIDS
	Glucerna	Ross Products	For patients with abnormal glucose tolerance
	Nepro	Ross Products	For dialyzed patients with renal failure
	Preative	Ross products	For management of metabolically stressed patients
	Pulmocare	Ross products	For pulmonary patients
	Suplena	Ross Products	For dietary management of renal patients prone ot uremia
Inborn errors of metabolism			
	3232A Formula	Mead Johnson Nutritionals	For disaccharidase deficiencies, impaired glucose transport, and intractable diarrhea
	Lofenalac	Mead Johnson Nutritionals	For children with PKU
	Portagen	Mead Johnson Nutritionals	For malabsorptions problems and pancreatic insufficiency
	Pregestimil	Mead Johnson Nutritionals	For fat malabsorption and protien intolerance
Sole source nutritional products	Ensure	Ross Products	Provide enteral nutrition
	Isocal	Bristol-Myers Squibb	Provide enteral nutrition
	Precision	Sandoz	Provide enteral nutrition
	Sustacal	Bristol-Myers Squibb	Provide enteral nutrition
	Vivonex	Norwich Eaton	Provide enteral nutrition
Oral rehydration formulas	Pedialyte	Ross Products	Oral rehydration formula

Source: Adapted from Refs. 48 and 56.

ing (ANPRM), in 1996, seeking industry comment on requirements necessary to approve certain products as OTC drugs based on the doctrine of reasonable certainty, no rules or regulations have been issued to date (43). Thus, this route of approval is currently unavailable in the United States.

In Germany, where herbal products are widely used, the German Federal Health Authority began publishing the Commission E Monographs in 1978. These monographs now contain approximately 400 monographs on natural products, with much of the information derived from historical use. France also allows the marketing of natural products on the basis of historical use. However, in order to derive the benefit of this system, the substance must be licensed by the French Licensing Committee and approved by the French Pharmacopoeia Committee. It should be noted, however, that there are areas of Europe, such as Scandinavia, that view nutraceutical products with much skepticism. In addition, unifying European Union (EU) doctrines may change the regulatory structure for nutraceuticals in Germany and France.

Asian countries such as Japan, China, and India rely on herbal remedies nearly as much as they do conventional medications. In addition, the Japanese regulatory framework allows for the definition, licensing, and approval of functional foods under the Nutrition Approvement Act, which is administered by the Japan Health Food and Nutrition Association.

The Nutrition Labeling and Education and the Dietary Supplement Health and Education Acts

Enacted in 1990, the Nutrition Labeling and Education Act (NLEA) amended the FD&C Act at Section 403(q) to require that almost all foods carry nutrition labeling, and if the labeling contains claims about the level of nutrients that they contain, those claims must be made in accordance with Section 403(r).

As cited in the introduction to this paper, the DSHEA of 1994 was the result of public outcry in response to the FDA's attempt to remove dietary supplements from the

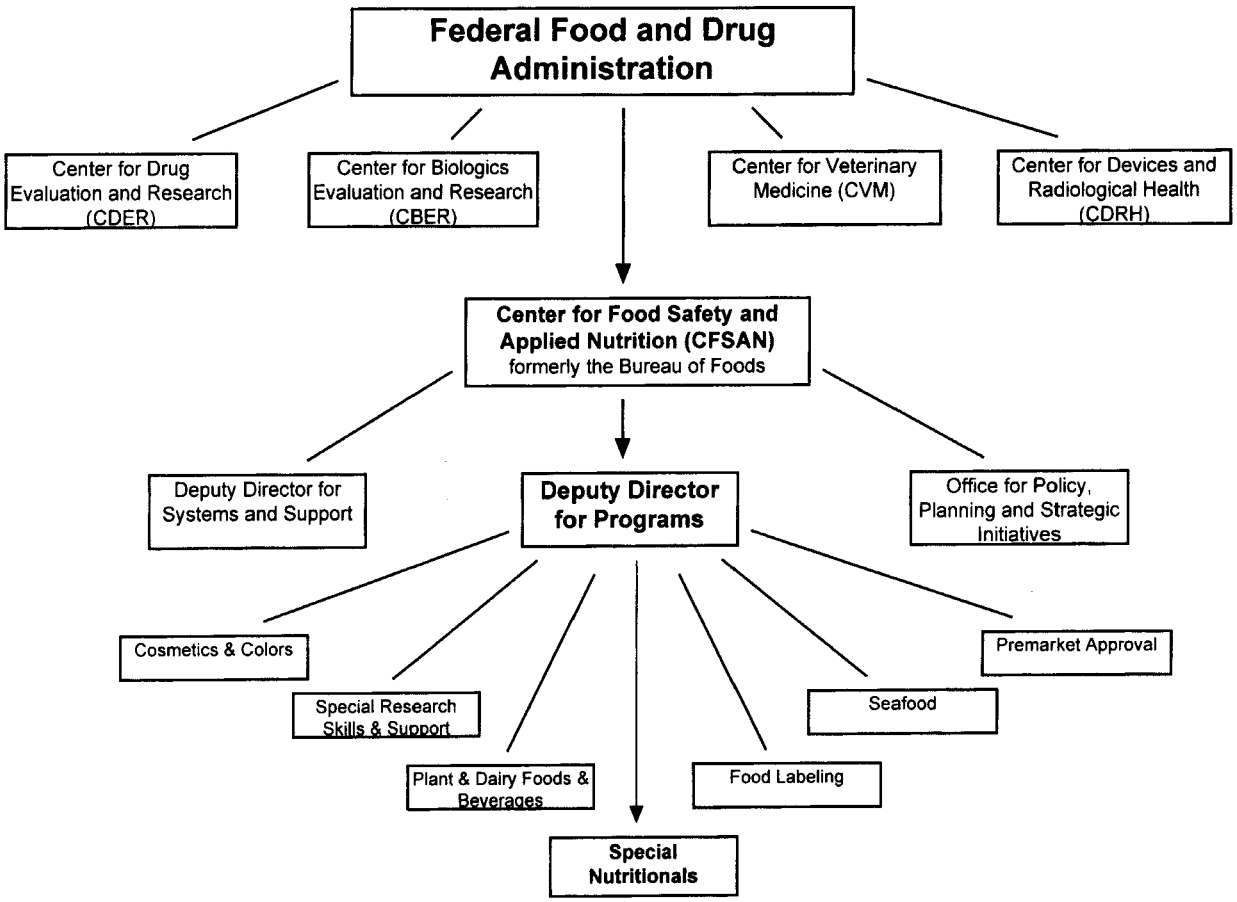

Figure 2. Organization of the Office of Special Nutritionals in the U.S. Federal Food and Drug Administration.

Table 6

Selected Regulatory Terms Used in the Context of Nutracuetical Products

Terms	Regulations	Statutes
Dietary supplement	21 CFR Section 101.9(j)(6)	FD&C Act Section 201 (ff) by DSHEA of 1994
Foods for special dietary uses	21 CFR Part 105	FD&C Act Section 411(c)(3) by the Vitamins and Minerals Amendments of 1976
Medical food	21 CFR Section 101.9(j)(8)	21 U.S. Code Section 360ee(b)(3) by 1988 Amendments to the Orphan Drug Act of 1983; FD&C Act Section 403(r)(5)(A)(iv) by NLEA of 1990
Disease claim	Proposed 21 CFR Section 101.93(g)(2)	Recommended by the CDSL
Health claims	21 CFR Sections 101.14 and 101.70	FD&C Act Section 403(r)(1)(B) by NLEA of 1990
Structure/function claim	Proposed Section 101.93(f)	Permitted for dietary supplements in FD&C Act Section 403(r)(6) by DSHEA of 1994

FD&C = Food, Drug, and Cosmetic; DSHEA = Dietary Supplements Health and Education Act; CDSL = Commission for Drug Supplement Labeling (formation madated by DSHEA of 1994); NLEA = Nutrition Labeling and Education Act.

market. The DSHEA restricts the FDA's authority over herbal products such that the FDA can only remove them from the market if they are either (1) proven to be unsafe through clinical evidence obtained by the agency or (2) misbranded. The removal of cholestin and herbal fen-phen from the market is illustrative of cases in which the FDA was able to take action based on misbranding. The FDA considered both products to be unapproved drugs, cholestin because it contains the drug lovastatin and herbal fen-phen products because they were marketed for the same use as the antiobesity drugs fenfluramine and phentermine, which had recently been pulled from the market. Conversely, the FDA removed the amino acid L-tryptophan, which was marketed as a sleep aid, from the market in 1990 after its use was correlated with more than 1000 cases of EMS.

The DSHEA also contains several provisions that apply only to dietary supplements, including (1) statutory definitions for "dietary supplements" and "dietary ingredients," (2) establishment of a means for ensuring safety, (3) use of claims and nutritional support statements (including the literature associated with the product's use), (4) requirement for ingredient and nutrition labeling, and (5) establishment of CGMPs (current good manufacturing practices) in manufacturing, packaging, and holding. In addition, the law requires the formation of the executive-level Commission on Dietary Supplement Labels (CDSL) and Office of Dietary Supplements within the NIH.

In meeting with the requirements of the DSHEA, on September 23, 1997, the FDA published final rules in the *Federal Register* on labeling of dietary supplements:

- requirements for the identification of dietary supplements (44)
- requirements for nutrition labeling of dietary supplements (44)
- requirements for designation of ingredients contained within dietary supplements (44)
- amendment of nutrient content claims regulations to provide for dietary supplements containing ingredients that do not have Reference Daily Intakes (RDIs) or Daily Reference Values (DRVs) (45)
- requirement that manufacturers notify the FDA within 30 days of marketing a dietary supplement with a new label (46)
- differentiation of premarket approval for new dietary ingredients from premarket approval of new ingredients in foods (47)
- requirements for the use of the terms *high potency* and *antioxidant* (48)

Dietary Supplements

The FD&C Act defines dietary supplements in Section 201(ff). The DSHEA extended the definition of dietary supplements beyond vitamins and minerals and established a formal definition of dietary supplement using the following criteria:

- is a product (other than tobacco) that is intended to supplement the diet that bears or contains one or more of the following dietary ingredients: a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total daily intake, or a concentrate, metabolite, constituent, extract, or combinations of these ingredients.
- is intended for ingestion in pill, capsule, tablet, or liquid form.
- is not represented for use as a conventional food or as the sole item of a meal or diet.
- is labeled as a "dietary supplement."
- includes products such as an approved new drug, certified antibiotic, or licensed biologic that was marketed as a dietary supplement or food before approval, certification, or license (unless the Secretary of Health and Human Services waives this provision).

Foods for Special Dietary Uses

The FDA began regulating products such as those that provide nutrition to patients with inborn errors of metabolism as drugs prior to 1972. In 1972, however, the agency began to regulate these products as FSDU rather than drugs. As discussed in the introduction to this paper, the FD&C Act was amended by the Vitamin and Mineral Amendments of 1976 in order to prevent vitamin and minerals from being regulated as drugs. This amendment provided the statutory definition of "special dietary use" in Section 411(c)(3) of the act as "including, but not limited to" the following:

(A) Supplying a special dietary need that exists by reason of a physical, physiological, pathological, or other condition, including but not limited to the condition of disease, convalescence, pregnancy, lactation, infancy, allergic hypersensitivity to food, underweight, overweight, or the need to control intake of sodium.

(B) Supplying a vitamin, mineral, or other ingredient for use by man to supplement his diet by increasing the total dietary intake.

(C) Supplying a special dietary need by reason of being a food for use as the sole item of the diet.

The five categories of FSDU include (1) hypoallergenic foods, (2) weight-reduction foods, (3) foods for diabetics, (4) reduced-sodium foods, and (5) infant formulas. Subsequent regulations governing FSDU are found in Part 105 of 21 CFR. However, issuance of any regulations under Part 411 of the act is subject to formal rulemaking and evidentiary hearings and thus is cumbersome (48).

Medical Foods

The 1988 Amendments to the Orphan Drug Act of 1983 enacted the statutory definition of medical food in 21 USC 360ee(b)(3) as "a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation."

Although the amendment provided a statutory definition, no further type of information regarding the regulation of such products was offered. Thus, with the passage of the NLEA, the FDA incorporated the statutory definition of medical foods into Section 403(r)(5)(A)(iv) and exempted such products from nutrition labeling and health claim and nutrient content claim requirements applicable to most other foods under Sections 403(q)(5)(A)(iv) and 403(r)(5)(A).

In 1993, the final rule on nutrition labeling incorporated the statutory definition of medical food at 21 CFR 101.9(j)(8). The regulation provides that a food may claim the exemption from nutrition labeling requirements only if it meets the following criteria:

(i) It is a specially formulated and processed product (as opposed to a naturally occurring foodstuff used in its natural state) for the partial or exclusive feeding of a patient by means of oral intake or enteral feeding by tube;

(ii) It is intended for the dietary management of a patient who, because of therapeutic or chronic medical needs, has limited or impaired capacity to ingest, digest, absorb, or metabolize ordinary foodstuffs or certain nutrients, or who has other special medically determined nutrient requirements, the dietary management of which cannot be achieved by the modification of the normal diet alone;

(iii) It provides nutritional support specifically modified for the management of the unique [distinctive to be proposed replacement in next issuance of medical foods regulations] nutrient needs that result from the specific disease or condition, as determined by medical evaluation;

(iv) It is intended to be used under medical supervision; and

(v) It is intended only for a patient receiving active and ongoing medical supervision wherein the patient requires medical care on a recurring basis for, among other things, instructions on the use of the medical food.

The FDA published an ANPRM regarding the regulation of medical foods in the *Federal Register* on November 29, 1996 (49). In its posting, the FDA recognizes that many products claiming to be medical foods do not meet the requirements of being used "under medical supervision" in that they are available to consumers in a variety of places, even in warehouse-type supermarkets. Although the period for submitting comments ended on February 27, 1997, proposed rules have yet to be published.

Medical Foods versus Foods for Special Dietary Uses

The NLEA amendment to the FD&C Act exempted medical foods from many labeling requirements that are applicable to most other foods. It did not, however, exempt FSDU. In the ANPRM for medical foods, the FDA clarified their interpretation of what differentiates medical foods from FSDU. The FDA contends that a product intended to provide the nutritional requirements specific to one disease is a medical food, while a product that addresses nutritional requirements common to several diseases, but not the full range of requirements for any specific disease, are FSDU and must comply with nutrition labeling requirements. Thus, manufacturers obviously prefer marketing an item as a medical food. Strobos (48) outlined the specific advantages of medical food status as

- exemption from requirement for "health claims" in NLEA under regulations issued by FDA in 1993 (21 CFR 101.14(f)(2))
- exemption from requirement for "nutrient content claims" in NLEA under regulations issued by FDA in 1993 (21 CFR 101.13(q)(4)(ii))

- exemption from "nutrition labeling" requirement in NLEA under regulations issued by FDA in 1993 (21 CFR 101.9(j)(8))

Product Claims

On April 28, 1998, the FDA published proposed rules, based on the recommendation of the CDSL, in order to provide clarification of requirements of "structure/function" claims permitted by Section 403(r)(6) of the FD&C Act (50). It also defines disease claims, which are prohibited in labeling of dietary supplements.

Health Claims

Regulations resulting from the passage of the NLEA define health claims at 21 CFR 101.14(a)(1) as "any claim made on the label or in labeling of a food, including a dietary supplement, that expressly or by implication, including 'third party' references, written statements (e.g., a brand name including a term such as 'heart'), symbols (e.g., a heart symbol), or vignettes, characterizes the relationship of any substance to a disease or health-related condition. Implied health claims include those statements, symbols, vignettes, or other forms of communication that suggest, within the context in which they are presented, that a relationship exists between the presence or level of a substance in the food and a disease or health-related condition."

Under Sections 403(r)(3) and 403(r)(4) of the FD&C Act, health claims must be authorized by the FDA prior to use in labeling of foods and dietary supplements. Health claims currently approved by the FDA are provided in Table 3.

Disease Claims

Under their proposed rules, the FDA delineated the types of claims that would cause products to be regulated as a drug (50). These claims are referred to as "disease claims" and under proposed section 101.93(g)(2),

> A statement claims to diagnose, mitigate, treat, cure, or prevent disease if it claims, explicitly or implicitly, that the product:
>
> (i) Has an effect on a specific disease or class of diseases;
> (ii) Has an effect, using scientific or lay terminology, on one or more signs or symptoms that are recognizable to health care professionals or consumers as being characteristic of a specific disease or of a number of different specific diseases;
> (iii) Has an effect on a consequence of a natural state that presents a characteristic set of signs or symptoms recognizable to health care professionals or consumers as constituting an abnormality of the body;
> (iv) Has an effect on disease through one or more of the following factors:
> (A) The name of the product;
> (B) A statement about the formulation of the product, including a claim that the product contains an ingredient that has been regulated by FDA as a drug and is well known to consumers for its use in preventing or treating a disease;
> (C) Citation of the title of a publication or reference, if the title refers to a disease use;
> (D) Use of the term "disease" or "diseased"; or
> (E) Use of pictures, vignettes, symbols, or other means;
> (v) Belongs to a class of products that is intended to diagnose, mitigate, treat, cure, or prevent a disease;
> (vi) Is a substitute for a product that is a therapy for a disease;
> (vii) Augments a particular therapy or drug action;
> (viii) Has a role in the body's response to a disease or to a vector of disease;
> (ix) Treats, prevents, or mitigates adverse events associated with a therapy for a disease and manifested by a characteristic set of signs or symptoms; or
> (x) Otherwise suggests an effect on a disease or diseases.

Structure/Function Claims

Structure/function claims are provided for under Section 403(r)(6) of the FD&C Act (21 U.S.C. 341(r)(6)), amended by the DSHEA, which allows dietary supplement labeling to bear a statement that "describes the role of a nutrient or dietary ingredient intended to affect the structure or function in humans" or that "characterizes the documented mechanism by which a nutrient or dietary ingredient acts to maintain such structure or function." Thus, although disease claims are not permitted by the FD&C Act, manufacturers of dietary supplements can include information in the labeling of their products that does not require regulatory approval prior to use, as is the case with health claims.

Under proposed Section 101.93 (f)(1):

> Dietary supplement labels or labeling may, subject to the requirements of this section, bear statements that describe the role of a nutrient or dietary ingredient intended to affect the structure or function in humans or that characterize the documented mechanism by which a nutrient or dietary ingredient acts to maintain such structure or function, but may not bear statements that are disease claims under paragraph (g) of this section. (50)

Structure/function claims must be accompanied by the following disclaimer: "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease." In addition, the manufacturer must have substantiation that the claim is truthful and not misleading.

Although the FDA is not required to approve labels containing structure/function claims, in accordance with regulations issued on September 23, 1997 (46), at 21 CFR 101.93, the manufacturer must notify the FDA that the claims are being made within 30 days of marketing the dietary statements with such claims.

Regulation of Dietary Supplements as Over-the-Counter Drugs

As previously stated, the DSHEA mandated that an independent agency within the executive branch, known as the CDSL, be established. The mission of the CDSL was to evaluate and make recommendations for the manner in which the FDA should regulate label claims for dietary supplements. The CDSL's Final Report was issued on November 24, 1997, and the FDA released its response to this report in the *Federal Register* on April 28, 1998 (51).

Among their recommendations, the CDSL suggested that some botanicals may qualify as OTC products under existing statutes provided in Section 201(p) of the FD& C Act, which states that a product may avoid "new drug" premarket approval requirements and may be eligible for marketing under an OTC drug monograph if "(1) the product is generally recognized as safe and effective under the conditions for use for which it is labeled; and (2) if the product has been used to a material extent and for a material time under those conditions."

In their response to this recommendation, the FDA referred to the ANPRM, issued on October 3, 1996, in the *Federal Register*, on the "eligibility criteria for considering additional conditions in the Over-the-Counter drug monograph system" (43). The FDA contends that, until the regulations regarding these criteria are issued, it considers that "material extent" and "material time" need to be adequately defined, and it does not regard marketing experience outside the United States to meet conditions of historical use. This could present a significant stumbling block for a large number of botanicals as their long-term marketing experience is not within the United States. However, the agency is developing draft guidance for the dietary supplement industry that outlines the types of data that are necessary to satisfy drug requirements based on existing statutes and regulations.

CONCLUSIONS

The use of nutraceutical products in the United States has been rapidly increasing during this decade, particularly the use of botanical products. The FDA will soon have completed all of the provisions of the NLEA of 1990 and the DSHEA of 1994 to increase the type of information available to the consumer to enabling the consumer to make educated decisions when "self-medicating" with this class of products. In addition, these regulations will ensure that products that are safe and bear truthful information are available to the consumer.

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