Regulation of Functional Foods and Nutraceuticals: A Global Perspective
Edited by Clare M. Hasler

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1 The Impact of Regulations on the Business of Nutraceuticals in the United States: Yesterday, Today, and Tomorrow

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More than a decade has passed since the term **nutraceuticals** was coined by Dr. Stephen DeFelice (1991), founder of the Foundation for Innovation in Medicine. His original definition was very broad:

> A nutraceutical is any substance considered a food or part of a food which provides medical or health benefits including the prevention or treatment of disease and include isolated nutrients, dietary supplements, diets and dietary plans, genetically engineered foods, herbal products and processed foods such as cereals soups and beverages.

These products represented distinctly different types of businesses and markets. For example, isolated nutrients such as vitamins were a distinct segment of the specialty and fine chemicals business with defined end-use markets including animal feeds, human food, cosmetics, and parenteral and enteral solutions, and pharmaceuticals. Diets included product lines such as formulated meal replacements for weight loss or general nutritional supplementation, and dietary plans are a part of the weight loss services business, which guides consumers who join these programs to change their eating habits. Genetically engineered foods were primarily herbicide-resistant soy and other agricultural commodities sold to growers. At the time, herbs were legally considered as something used to season and flavor food; any claims suggesting a use for disease treatment made them an unapproved drug in the United States and many European countries.

Despite disagreement and confusion over the definition, the term **nutraceuticals** captured the spirit of products at the food/drug interface: "Let food be thy medicine." Nutraceuticals could be derived from food and used for medicinal reasons. For example, the beta glucan component of oat bran is recognized by the scientific and U.S. regulatory community as being responsible for lowering elevated blood cholesterol levels (FDA, 2002). Certain dairy peptides, some of which have a mechanism of action similar to ACE inhibiting drugs, have demonstrated a powerful capacity to lower moderately elevated blood pressure at only milligram levels of intake (Seppo et al., 2003; Hata et al., 1996).

A decade beyond its first appearance in the food technology and marketing vocabulary, **nutraceuticals** still has no agreed upon definition or regulatory standing. The emerging world of nutritional products, including nutraceuticals (however defined), took on a life, language, and segmentation of its own, catapulted by a grass-roots consumer curiosity in alternative food and medicines. By 1990, consumers began to experiment in increasing numbers with herbs, vitamins, and other supplements, natural and health foods, and eventually with mainstream food products marketed for unique health benefits. About the time

of the passage of the Dietary Supplement Health and Education Act (DSHEA) in 1994, the nutritional products industry was growing by double digits. In only a few years, industry publications, syndicated store-level tracking services, and consumer research companies sprang up to monitor product introductions, company activities, product movement through mainstream and emerging distribution channels, and trends and attitudes of the health-conscious consumers; they also provided thoughtful industry analysis. Today, the *Nutrition Business Journal* (NBJ, New Hope Natural Media, a division of Penton Media, Inc., San Diego) is the industry's lead paid-subscription publication monitoring the financial performance of nutritional products and the activities of their manufacturers. *Nutraceuticals World* and *Nutritional Outlook* are among several trade journals that report on new science, technologies, and market activities. NBJ uses **nutraceuticals** as an umbrella term for anything sold at retail (outside of OTC medications) that is consumed primarily or partially for health reasons. SPINS, a San Francisco–based market research firm, works in conjunction with AC Neilsen to track consumer purchases of natural foods and other health and wellness products through their primary retail channels. These include natural food, health food, and mainstream grocery stores and supermarkets, drug stores, and mass merchandisers. Market-research companies, including HealthFocus International (Atlanta, GA) and The Hartman Group (Bellevue, WA) specialize in the demographics, consumer attitudes, and purchasing patterns of the new consumer segment that spends heavily on food and health-oriented products outside mainstream channels. The Freedonia Group (Cleveland, OH) occasionally reports on the business outlook for nutraceutical chemicals, such as herbal and nonherbal extracts, vitamins and minerals, and healthful food ingredients utilized for their health benefits such as soy, fiber, probiotics, and highly polyunsaturated fatty acids. This latter approach to a market definition is similar to that proposed in the first market-outlook report on the topic (Wrick, 1994) prior to the passage of DSHEA. There, nutraceuticals were defined as the bioactive substance in food agricultural commodities (both plant and animal) that showed demonstrable health benefits beyond satisfying the basic nutritional functions of growth, tissue repair, and energy for daily living. This definition had the advantage of allowing the nutraceutical, or "bioactive," to be discussed as a separate, chemically identifiable substance (or family or combination of substances) that could be isolated or extracted from the tissues in which it naturally occurred or even synthesized. It could then be commercialized through the appropriate regulatory pathway as a component of food, as a dietary supplement, or even as a drug. The definition allowed for relatively easy market analysis, making nutraceuticals the raw material that could be followed down the chain to the end users.

However, the marketplace ignored the conundrum over a definition and cautiously wove a path between communicating the messages implied by the emerging science and the regulatory framework governing product claims for foods and drugs. In the United States and many other countries, the claims made for a product determine its status as a food or a drug. The emerging science of food phytochemicals as a potentially safer means to cure, treat, or prevent disease meant their commercialization in the United States under drug law with its associated high development costs, now estimated at an average of $802 million, up from $318 million in 1980 (Tufts, 2002). This barrier to market entry led to the passage of DSHEA, spurred on by a small but zealous industry group convinced that many of the products it wanted to sell for treating or preventing health problems were safe based on their history of use in the Far East and other countries.

Despite the lack of regulatory standing or a universally agreed upon definition, the term

nutraceuticals is still the subject of market research reports and is occasionally interchanged with some or all of the product segments in what is now known and accepted as the nutrition industry. NBJ, launched in 1995, was the first publication to systematically monitor the activities, trends, and financial performance, mergers, and acquisitions of the industry whose products were purchased for nutrition and health reasons, as distinct from mainstream food products purchased to satisfy hunger, taste, and family tradition. Today, NBJ's definition of the nutrition industry includes dietary supplements (pills, powders, tablets, tonics, extracts, and supplemental beverages), meal replacements, functional foods, natural/organic foods, sports and performance foods and beverages, and, more recently, natural personal care (NBJ, 2002a, b, c; 2003a, b).

In an attempt to bring focus to this update, this chapter reviews the nutritional product segments utilizing nutraceutical actives in the U.S. marketplace today, including dietary supplements and functional foods. These categories are defined as the consumer products that utilize nutrients, specialized food components, or other naturally occurring chemicals (or mixtures of chemicals) as components of pills and tablets and as ingredients in foods intended to provide a health benefit beyond basic nutrition. Dietary supplements and functional foods comprise about 66 percent of the $62.9 billion U.S. nutrition industry and capitalize on the health benefits of added food ingredients, naturally occurring food components, or dietary ingredients they contain (see Table 1.1, Definitions).

Table 1.1. Definitions

Dietary ingredient—A substance used in a dietary supplement, which, by law is defined as 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, a constituent, extract, or combination of these ingredients. (Source: paraphrased from Food and Drug Law Institute Series (1995) Compilation of Food and Drug Laws, Volume 1. Federal Food, Drug, and Cosmetic Act, Chapter 2, Definitions. Section 201[321].

Dietary supplement—A dietary supplement is a product (other than tobacco) that is intended to supplement the diet and that bears or contains one or more specified dietary ingredients (see definition that follows). It is intended for ingestion in tablet, capsule, powder, softgel, gelcap, or liquid form. It may not be represented for use as a conventional food or as the sole item of a meal or diet; and it must be labeled as a "dietary supplement." (Source: paraphrased from Food and Drug Law Institute Series (1995) Compilation of Food and Drug Laws, Volume 1. Federal Food, Drug, and Cosmetic Act, Chapter 2, Definitions. Section 201[321].

DSHEA—The Dietary Supplement Health and Education Act (DSHEA) was passed by Congress in 1994 and amended the Food, Drug, and Cosmetic Act to authorize the creation of a separate regulatory category for dietary supplements distinct from foods and drugs. DSHEA provided broad definition and guidance for what dietary supplements are, how they should and should not be marketed, what they can contain and what form they might take, and how they are to be regulated. (See preceding definition of dietary supplement.)

Food ingredient or additive—All foods in the United States must be made from ingredients that are Generally Recognized As Safe (GRAS) according to FDA regulatory critera, or which have been approved by the FDA following an agency review of a submitted food additive petition. The petition must present appropriate data demonstrating that the additive is safe for human consumption at the levels at which they are expected to be used in human food.

Functional Food—A food that provides a health or performance benefit beyond providing basic nutritional value. Some examples include products fortified with certain nutrients or phytonutrients, such as fortified cereals, breads, sports drinks, bars, and fortified snack foods, baby foods, and more. **Functional Foods** is primarily a marketing term and there is no regulatory definition for it. These foods are subject to all food regulations regarding their composition and claims. (*continued*)

Table 1.1. Definitions *(Cont.)*

GRAS (Generally Recognized As Safe)—General recognition of safety of food ingredients and additives may be based only on the views of experts qualified to evaluate the safety of substances added directly (or indirectly) to food. Today, FDA has developed specific procedures that industry must follow to establish GRAS status for new ingredients or additives. The process includes a review by a qualified expert panel of all available data on the product's safety for human consumption, and agreement by the panel that the product is safe.

Health claim—A claim for a food or supplement product that describes the relationship between a food substance and a disease or health-related condition. To secure a health claim, clinical evidence substantiating the relationship to FDA's satisfaction must be presented to the agency as part of a formal petition process. Most health claims describe a reduction in disease risk with use of the food substance to distinguish the claim from those allowed only for drugs (that is, ". . . cures, treats, mitigates, or prevents a disease.") Currently, health claims are subject to an evidence-based ranking system (A = highest; D = lowest) as a means to provide FDA's assessment of how well the publicly available scientific evidence supports the claim. Unqualified health claims are those with clinical substantiation that meets FDA's significant scientific agreement (SSA) standard, and are awarded the highest ranking of "A." Qualified health claims are those that have less substantiating data than required for SSA, and they are ranked from "B" to "D." A "D" rank will indicate that FDA concludes that there is little scientific evidence to support the claim, and this statement must be made on package labeling if the claim is used.

Natural foods—Foods derived from "natural" as opposed to chemically synthesized ingredients. Producers of natural foods strive to use ingredients and raw materials that have not been exposed to pesticides, and avoid preservatives and "synthetic ingredients" whenever possible. There is no legal or commercial standard that defines the term **natural**.

Nutraceutical—Consumer products (foods or dietary supplements) that utilize nutrients, specialized food components (phytonutrients), or other naturally occurring chemicals (or mixtures of chemicals) as ingredients intended to provide a health benefit beyond basic nutrition. (Source: NBJ Functional Foods Report, 2002c).

Organic food—Foods derived from farms and growers who embrace certain principles of sustainable farm management, pesticide and fertilizer use, and the humane treatment of animals. Federal laws now set standards for growing, certifying, and labeling organic foods.

Phytonutrients—Plant food components other than macronutrients, vitamins, or minerals that have some scientific data supporting a health benefit for humans. Examples include antioxidants from grape seed extract, lycopene (the red pigment in tomatoes), or sitostanol ester, the plant sterol derivative from vegetable oils that lower cholesterol at low levels of intake. Phytonutrients can be used as either dietary ingredients in dietary supplements or food ingredients in Functional Foods as long as they meet the appropriate FDA regulatory requirements.

Structure/Function Claim—Structure/function claims are used for dietary supplements and occasionally for food products. Most structure/function claims describe the role that a nutrient or dietary ingredient has on the structure or function of the body, for example, "calcium builds strong bones." If a dietary supplement label includes a structure/function claim, it must, by law, have a disclaimer that states: "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."

Why discuss the marketplace in a volume on food regulations? Quite simply, the U.S. regulatory structure governing foods and drugs has been a powerful force defining the industries that manufacture the products regulated by the FDA. Our regulatory framework has directly or indirectly shaped the structure, key success factors, barriers to entry, rules of competition, and manufacturing operations for conventional foods, various nutritional products, and pharmaceuticals. Figure 1.1 summarizes the statutory or regulatory definitions of the products FDA regulates, and Figure 1.2 shows how these product categories and their attendant regulations have ultimately shaped the boundaries around industries and the scope of their product offerings. Nutraceuticals cut across most of the categories

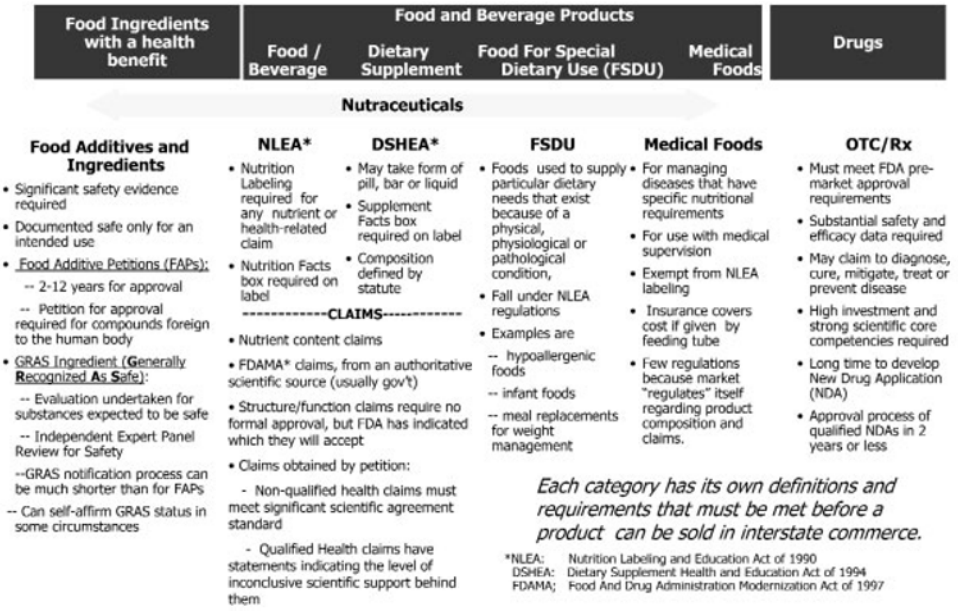

Figure 1.1. U.S. Food, Drug, and Cosmetic Act and its regulations define the product categories for the delivery of health benefits to the American consumer. "Nutraceuticals" cuts across several of these.

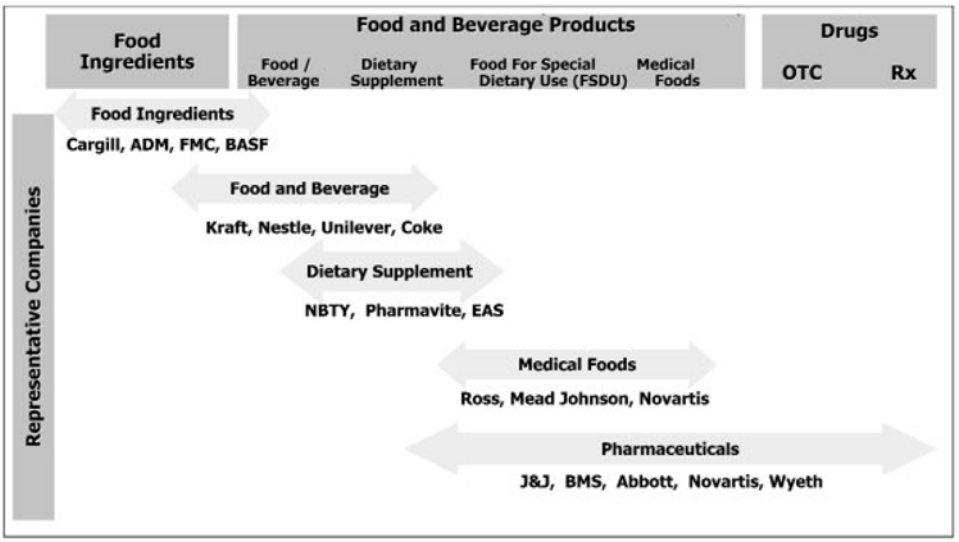

Figure 1.2. Representative global companies in the U.S. nutritional products business. The categories of products created by federal law and regulation for foods and drugs are the single biggest determinant of the industrial and market structures now in place in U.S. nutritional products businesses.

shown. Laws and regulations have been a primary influence on how the companies within each sector have evolved their core competencies, their industry culture, how each markets their products, and the customer segments they serve. Regulations directly shape the cost of entry into a particular market and define the nature of product communications among companies, customers, and end users. The evolution of the U.S. dietary supplement and functional foods markets is interesting in this context.

Dietary Supplements

Background and Market Overview

For decades, dietary supplements were primarily multivitamin/mineral preparations marketed by pharmaceutical manufacturers who built respected brand names that remain today, such as Centrum® (Wyeth), One-A-Day® (Bayer) and Theragran® (Bristol-Meyers Squibb). However, the winds of change began to whisper in the late 1980s as peer-reviewed nutrition research began to show medicinal or disease preventive effects of foods such as berries, garlic, onion and other fruits and vegetables, oats, psyllium, flax and other grains, and certain vitamins or their biological precursors. Around the same time, the National Cancer Institute began research on food phytochemicals and cancer prevention. As China opened its doors to the world following centuries of isolation, Westerners learned of an entirely different approach to health care. The most populous country on earth had not only evolved health care traditions involving acupuncture, herbs, and barefoot doctors but also appeared to be free from many of the chronic diseases that haunted the United States and Europe. Media coverage of these developments combined with growing disenchantment with the escalating costs and perceived insensitivity of health care in the United States and other Western countries made consumer attitudes ripe for alternatives to conventional therapies.

The purveyors of dietary supplements in the growing health-food channel emerged as a segment clearly distinct from the food and pharmaceutical industries in its mission, core competencies, and culture. The segment rapidly took on new, creative products that often did not pass FDA scrutiny when the agency took a close look at the level of substantiation that manufacturers provided for their product claims and, in some instances, data supporting product safety. The fact that the claimed health benefits of many products had been accepted as folklore for centuries in various Asian countries and cultures passed no muster with the agency's regulations, which required safety and efficacy testing by Western scientific methods. Despite periodic market withdrawals of products the FDA judged as unapproved food additives or unapproved drugs, pills and tablets of single-source vitamins, minerals, herbs, and plant extracts had established a significant and very loyal consumer following by the early 1990s. New consumers came to the market because of a growing curiosity about alternative medicines, an increasing suspicion of pharmaceutical products and their side effects, and a growing disenchantment with the U.S. health care system. The latter began as consumers and health care professionals alike began perceiving the industry as an ever more complicated, bureaucratic, indifferent third-party payment system that covered less and less of medical costs. By the mid-1990s as the baby boomers were entering their fifth decade of life, a sizable consumer segment was ripe for a change from what the medical establishment had to offer.

The passage of the DSHEA gave birth to a regulatory environment that provided a legal

definition, and therefore credibility, to the fledgling, fragmented, but growing dietary supplement industry, driven by a passionate belief in the health value of its products. The DSHEA was a culmination of efforts by relatively small firms who, unlike larger food and pharmaceutical companies, had nothing to lose and everything to gain by changing the Food, Drug, and Cosmetic Act to their favor. Their goal was to create opportunity for the industry that, until then, could not legally introduce products to market with meaningful claims about their role in health and disease unless the industry invested the time and money into the food additive or drug approval process for claim substantiation. The Act broke down regulatory barriers to market entry by creating a separate class of dietary ingredients distinctly different from food additives and drugs (refer to Table 1.1.).

The new law did not require manufacturers to submit a dossier of preclinical and clinical studies demonstrating product safety or efficacy. Dietary supplements, including vitamins, minerals, herbs, and some specialty products had already grown to almost $5 billion in sales by 1993, primarily through the health and natural foods channels. Natural food stores were growing in number and capturing new consumers interested in health and wellness, organic foods, and beautifully merchandized displays of higher-quality fresh produce, fish, imported cheeses, fancy baked goods, and fresh-prepared foods than could be found in many mainstream supermarkets. Supplement companies seeking to bring alternative therapies to upscale, health-conscious consumers began the joyride of double-digit growth as the industry sought consumer support for the federal legislation during 1993-1994. Congressional passage of DSHEA was virtually assured by the grassroots letter-writing campaign spearheaded at health and natural food stores by the National Nutritional Foods Association, the industry association for health food retailers. At retail outlets nationwide, consumers signed form letters to their representatives in Congress in response to the (unfounded) fear that the FDA was about to cut off consumer access to their favorite products. Congress received more mail and phone calls on this matter than on any of the national issues of the day combined, including NAFTA (the North American Free Trade Agreement), health care reform, and the war in Bosnia. The dietary supplement sales and annual growth rates are shown in Table 1.2. NBJ forecasts a growth rate of about 4 percent for supplements overall from 2004–2008, with vitamins growing at about 3 percent, herbals at 0 percent, minerals at 4 percent, and specialty products in excess of 9 percent during the same period (NBJ, 2004).

Industry Participants

The leading dietary supplement companies are shown in Table 1.3. The companies listed sell pills, tablets, gelcaps, and similar dosing formats. Firms whose main businesses are liquid meal replacements (for use in weight management, diabetes, tube feeding, or general nutritional replenishment) are not included. Table 1.4 shows the highly fragmented nature of U.S. nutritional product companies. There are few leaders and many smaller firms vying for a piece of market share. Some consumer pharmaceutical companies have experimented with herbals and specialty supplements. These companies include Wyeth, with its Centrum® vitamin line, with line extensions with added herbs or phytochemicals, such as added lutein for eye health and soy isoflavones in its product targeted for women. Johnson & Johnson's Personal Products Company has an isoflavone supplement for menopausal women in its Healthy Woman line. McNeil Nutritionals, the newest operating company of J&J and that began in 2001, purchased Viactiv® Calcium Chews from Mead Johnson that

Table 1.2. Dietary supplement sales and growth rates, 1994–2002

Product Category	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	Forecast 2002–05
Vitamins	3,870	4,250	4,720	5,320	5,620	5,900	5,970	6,025	6,179	6,648	
Growth(%)		9.8	11.1	12.7	5.6	4.9	1.2	0.8	2.6	7.6	2–4
Herbs/Botanicals	2,020	2,470	2,990	3,520	3,960	4,070	4,260	4,397	4,276	4,197	
Growth(%)		22.3	21.1	17.7	12.5	2.8	4.7	3.2	–2.7	–1.8	0–1
Minerals	690	800	890	1,020	1,140	1,290	1,350	1,392	1,527	1,765	
Growth(%)		15.9	11.3	14.6	11.8	13.2	4.6	3.1	9.7	15.6	4–6
Specialty/Other	540	710	860	990	1,210	1,730	2,020	2,230	2,374	2,715	
Growth(%)		31.5	21.1	15.1	22.2	42.9	12.1	10.4	6.5	14.4	5–7
Supplements Total	7,120	8,230	9,460	10,850	11,930	12,990	13,600	14,044	14,356	15,325	
Growth(%)		15.6	14.9	14.7	10.0	8.9	4.7	3.3	2.2	6.7	3–5

Table 1.3. Leading U.S. supplement companies, 2003 (marketers of pills, tablets, and capsules)

Company	$ Million Wholesale Supplement Revenues
NBTY	690
Leiner Health Products*	490
Wyeth	480
Pharmavite*	320
Experimental and Applied Science (EAS)	240
Bayer Corporation	170
Weider Nutrition Group	160
Perrigo*	140
TwinLab Corporation	140
Nutraceutical International	120
Natural Organics (Nature's Plus)	110
GNC Manufacturing	110
Metabolife International	110
Goen Group (TrimSpa)	110
Country Life	100

Source: Compiled from *Nutrition Business Journal,* 2004a
*Companies with a substantial portion of revenues from contract manufacturing, multilevel marketing, or private labeling for retailers

Table 1.4. Universe of U.S. dietary supplement companies in 2003

	Total # of Companies	Revenues ($ Million)	% of Market
Greater than $100 Million	21	4,613	46
$20 Million−$99 Million	72	3,299	33
Less than $20 Million	793	2,028	20
	886	**9,940**	**100**

Source: *Nutrition Business Journal,* 2004a

same year, and a rejuvenated marketing program had a significant impact on sales in 2002 and 2003. Pfizer's Warner Lambert division introduced Quanterra™, an herbal supplement line that was discontinued when sales did not live up to expectations. Bayer's One-A-Day® continues to market line extensions with several herbs and phytochemicals, such as One-A-Day Weightsmart, a multivitamin supplement with added tea catechins from green tea extract, specifically, epigallocatechin gallate (EGCG), which has some data supporting an increase in metabolic rate.

The Products

The products considered here include dietary supplements sold primarily as pills, tablets, capsules, gelcaps, powders, or liquid extracts taken for overall general health and nutri-

tional well-being or for the prevention, delay, or management of chronic disease or its symptoms. These segments include vitamins, herbs/botanicals, minerals, and specialty supplements—the latter being a "catch-all" for products that don't easily fit into the other categories. As can be seen in Table 1.2, the industry's double-digit growth trend declined and started to rebound in 2003. Herbs and botanicals plummeted to single digits and have shown a negative growth rate for the past two years. In general, negative publicity about the effectiveness and labeling accuracy of various herbal products reflected poorly on the entire category. Vitamin usage dropped to pre-DSHEA levels in 2002 but jumped to over 7 percent in 2003. Minerals, supported largely by calcium supplements, have fared considerably better, with 2003 growth in double digits. The specialty category also remains strong, because it is often driven by media coverage of clinical studies reporting product benefits. However, the explosive growth rates of some products (anywhere from 50–200 percent growth over several years) that occurred between 1995–1999 are not likely to be seen again. Examples of specialty supplements, a niche category typically led by blockbuster products that often have wide fluctuations in sales from year to year, include enzymes, hormones, probiotic products, homeopathic remedies, and animal-derived products, to name a few, and often target a specific health condition. Table 1.5 shows individual specialty supplements with the highest sales in 2003. Table 1.6 shows the 2002 rate of growth for condition-specific specialty products in the primary channels in which they are sold. Other channels through which dietary supplements are purchased include multilevel marketers, mail order, and the Internet. Health care practitioners, primarily chiropractors, are an emerging channel through which less than 10 percent of products move. Physicians are generally expected to be slow to enter this channel because the vast majority do not sell products to their patients as part of their practice. Their recommendation level for some dietary supplement products may increase significantly with creative industry outreach programs or compelling efficacy and safety data showing value relative to OTC and prescription medications. Sales growth in the health care channel was strong in 2003, at 8 percent (NBJ, 2004b), but the product volume moving through it is still small.

Table 1.5. Leading products in the $2.39 billion specialty supplement market, 2003

Product	$ Million	% change	% Total Category
Glucosamine/chondroitin	739	9	26.4
Homeopathic remedies	453	13	16.2
CoQ_{10}	258	22	9.2
Plant oils	203	32	7.3
Fish/animal oils	192	43	6.9
Probiotics	177	11	6.3
Digestive enzymes	131	24	4.7
MSM	115	4	4.1
SAMe	92	19	3.3
Bee products	77	13	2.7
Others	355	9	12.7
Total	2,791	15	

Source: *Nutrition Business Journal,* 2004a (adapted)

Table 1.6. Condition-specific dietary supplement sales, 2002(a)

Condition	Overall Growth (%)	Channel Sales	
		Natural Foods (%)	FDM(b) (%)
Arthritis	2.8	9.8	90.2
Eye health	54.6	24.2	75.8
High blood pressure	17.6	11.9	88.1
High cholesterol	17.5	33.3	66.7
Joint health	−1.6	9.1	90.9
Migraine	22.3	38.7	61.3
Osteoporosis	7.4	10.7	89.3
Weight loss	4.7	2.9	97.1
Yeast infections	16.7	53.4	46.6

Source: *Nutrition Business Journal,* 2003c

(a) Data represent growth and channel sales for dietary supplements in pill and tablet form, weight loss beverage products, and natural personal care products
(b) Food, Drug and Mass Merchandisers (excluding Wal-Mart)

Industry Issues and Barriers to Growth

The U.S. dietary supplement industry as defined here now stands at over $15 billion (USD). It faces some serious but potentially resolvable barriers to growth that derive from the current laws and regulations that govern the industry and from noncompliance with some regulations on the part of a small segment of companies.

Like a growing baby, the industry rapidly doubled its size, but is now squarely in adolescence and facing adulthood with all the associated growing pains and tough decisions about the future. Falling growth rates, consolidation, and declining prices signal the maturation of virtually any industry; however, few believed that industry adulthood would arrive so quickly. Some of the reasons for this rapid maturity go beyond the recessionary economic conditions that began in 2000 and are rooted in its own history and culture.

The classic adage "Be careful what you wish for because you just might get it" applies in spades to dietary supplements. The regulatory barriers that prevented growth in the late 1980s and early 1990s gave way with the passage of DSHEA, but not without unanticipated consequences associated with newfound marketplace freedom. When the industry took off, companies found that some of the basics of doing business in consumer products and substantiating claims were still problematic. Some of these problems are discussed next.

Product Claim Regulations Hamper Effective Marketing

A successful marketing program for any product must establish sufficient awareness and interest to initiate consumer trial, and the product must deliver on consumer expectations to generate repeat purchase. Restrictions on product claims under DSHEA effectively undermined the development of successful marketing and promotional programs based on clear communication of product benefits. The ability to communicate scientifically documented product benefits remains a challenge for the industry, which was initially limited

to "structure/function claims" by regulation. Structure/function claims allow statements describing how a product affects the structure or function of the (healthy) body; however, the allowed claims are often too broad or too cryptic for meaningful communication to consumers and health professionals. Regardless of the level of recognized scientific support behind a dietary ingredient, claims that promote a product's role in disease management or treatment remain the purview of approved pharmaceuticals. Supplement (and food) companies have the option of filing a health claim petition with FDA's Center for Food Safety and Applied Nutrition (CFSAN) for either an unqualified or qualified health claim. An unqualified health claim would allow a phrase such as "may reduce the risk of (relevant chronic disease)" on package labels; however, this claim must be accompanied by clinical data to satisfy FDA's significant scientific agreement standard. Most supplement firms lack the core competencies and the funds to invest in a comprehensive clinical program to meet this standard. Qualified health claims are a new option for companies to consider. Their purpose is to allow communication of emerging scientific information about food components and disease that has not yet reached the agency's significant scientific agreement standard. As described later in this chapter, these claims are currently of limited marketing value.

In the absence of an approved health claim petition, a product that is effective in lowering serum cholesterol is limited to phrases allowed for in structure/function claims, such as "promotes heart health" or "helps the circulatory system" on package labeling. Similarly, products associated with data demonstrating effectiveness against hypertension are currently limited to phrases such as "reduces blood pressure already within the normal range." Articulating scientifically documented benefits in an accurate message that consumers understand usually establishes the product as an unapproved drug. These communication challenges undermine the industry's ability to effectively brand product lines and develop effective marketing strategies that can be backed with significant advertising and promotion dollars. The exception has been for products with nutrients long accepted by consumers as beneficial, such as calcium supplements for bone health. Nonetheless, some industry participants are willing to risk product claims that do not fall within the letter of the regulations, betting that FDA's severely restrained enforcement resources and focus on food safety and bioterrorism will keep the agency looking the other way.

The challenges of communicating product benefits to consumers through product labeling means that this information has typically been communicated through public relations programs and the media. However, what the media giveth it may also taketh away. The positive media reports of scientifically supported health benefits that prevailed in the early years and helped drive product sales have been overshadowed by recent mainstream news reports on issues of quality, safety, efficacy, and other regulatory infractions by the less responsible industry participants.

Resolution of the marketing challenges will be time consuming, expensive, or both for dietary supplement companies. In theory, one approach is to invest in unqualified health claim development for the supplements that have efficacy data for the well-documented, diet-related chronic diseases, such as heart disease, hypertension, and diabetes. This approach requires that a dietary ingredient first qualifies for as Generally Recognized As Safe (GRAS) according to FDA procedures and then substantiates its health benefit claims through adequately controlled clinical trials. However, no dietary supplement company has ever chosen this route as part of its development strategy, and few are likely to do so be-

cause of the cost and nonproprietary nature of the claim. Another approach is to continue to hammer away at FDA by taking it to court when an appropriate case can be made so that claim restrictions may be loosened. This pathway can have unpredictable results, however. The outcome of the *Pearson v. Shalala* case was in the industry's favor in that CFSAN was charged by the court to establish a means to communicate that there is **not** significant scientific agreement behind a diet/disease relationship. Unfortunately, the qualified claims the agency proposed as an outcome of the *Pearson* case (Table 1.7) are very unwieldy and of questionable value from a marketing standpoint. The FDA rationale behind qualified health claims is described later in this chapter.

Table 1.7. Qualified health claims permitted for U.S. foods and dietary supplements

1. Selenium and Cancer Risk (eligible for dietary supplements containing selenium)
   Selenium may reduce the risk of certain cancers. Some scientific evidence suggests that consumption of selenium may reduce the risk of certain forms of cancer. However, FDA has determined that this evidence is limited and not conclusive.
   or,
   Selenium may produce anticarcinogenic effects in the body. Some scientific evidence suggests that consumption of selenium may produce anticarcinogenic effects in the body. However, FDA has determined that this evidence is limited and not conclusive.
2. Antioxidant Vitamins and Cancer (eligible for dietary supplements containing Vitamin E and/or Vitamin C)
   Some scientific evidence suggests that consumption of antioxidant vitamins may reduce the risk of certain forms of cancer. However, FDA has determined that this evidence is limited and not conclusive.
   or,
   Some scientific evidence suggests that consumption of antioxidant vitamins may reduce the risk of certain forms of cancer. However FDA does not endorse this claim because this evidence is limited and not conclusive.
   or,
   FDA has determined that although some scientific evidence suggests that consumption of antioxidant vitamins may reduce the risk of certain forms of cancer, this evidence is limited and not conclusive.
3. Nuts and Heart Disease (eligible for the following whole or chopped nuts that are raw, blanched, roasted, salted and/or lightly coated and/or flavored, for which any fat or carbohydrate added must meet the definition of an insignificant amount [§101.9 (f) (1)]: almonds, hazelnuts, peanuts, pecans, some pine nuts, pistachio nuts and walnuts, or other nuts listed in the petition as long as they do not exceed 4 grams saturated fat per 50 grams
   Walnuts:
   Supportive but not conclusive research shows that eating 1.5 ounces per day of walnuts as part of a diet low in saturated fat and cholesterol may reduce the risk of heart disease. See nutrition information for fat content.
   or,
   Scientific evidence suggests but does not prove that eating 1.5 ounces per day of most nuts, such as walnuts, as part of a diet low in saturated fat and cholesterol may reduce the risk of heart disease. See nutrition information for fat content.
4. Omega-3 Fatty acids and Coronary Heart Disease (eligible for dietary supplements containing omega-3 long chain polyunsaturated fatty acids eicosapentaenoic acid (EPA) and/or docosahexaenoic acid (DHA).
   Consumption of omega-3 fatty acids may reduce the risk of coronary heart disease. FDA evaluated the data and determined that although there is scientific evidence supporting the claim, the evidence is not conclusive.

(*continued*)

Table 1.7. Qualified health claims permitted for U.S. foods and dietary supplements (*Cont.*)

5. B Vitamins and Vascular Disease (eligible for dietary supplements containing vitamins B6, B12, and/or folic acid)
   As a part of a well-balanced diet that is low in saturated fat and cholesterol, Folic Acid, Vitamin B6 and Vitamin B12 may reduce the risk of vascular disease. FDA evaluated the above claim and found that, although it is known that diets low in saturated fat and cholesterol reduce the risk of heart disease and other vascular diseases, the evidence in support of the above claim is inconclusive.
7. Phosphatidylserine and Cognitive Dysfunction and Dementia (eligible for dietary supplements for soy-derived phosphatidylserine)
   Consumption of phosphatidylserine may reduce the risk of dementia in the elderly. Very limited and preliminary scientific research suggests that phosphatidylserine may reduce the risk of dementia in the elderly. FDA concludes that there is little scientific evidence supporting this claim.
   or,
   Consumption of phosphatidylserine may reduce the risk of cognitive dysfunction in the elderly. Very limited and preliminary scientific research suggests that phosphatidylserine may reduce the risk of cognitive dysfunction in the elderly. FDA concludes that there is little scientific evidence supporting this claim.
8. 0.8 mg Folic Acid and Neural Tube Birth Defects (dietary supplements containing folic acid)
   0.8 mg folic acid in a dietary supplement is more effective in reducing the risk of neural tube defects than a lower amount in foods in common form. FDA does not endorse this claim. Public health authorities recommend that women consume 0.4 mg. folic acid daily from fortified foods or dietary supplements or both to reduce the risk of neural tube defects.

Source: FDA (2002b), Summary of Qualified Health Claims Permitted, http://www.cfsan.fda.gov/~dms/qhc-sum.html

Product Quality Problems in the Industry Persist

The early double-digit growth of the supplement industry put pressure on consistent sourcing of raw materials, especially those in herbal products and specialty supplements, for which reliable sources of supply were still being established. The high growth rates enticed foreign suppliers who were not familiar with U.S. standards for product certification or regulatory requirements for labeling. Negative media coverage increased as independent laboratories began testing products to see whether they delivered what package labels promised. One California firm made headlines because some of the raw materials it obtained from China were found to contain undeclared prescription drug ingredients. Though some of these product shortfalls could arise from irresponsible companies trying to cut costs, a very real problem is the absence of validated analytical methods for use in manufacturing controls and finished product testing to assure that label claims, and therefore consumer expectations, are met. In contrast to pharmaceuticals, for which active compound(s) are identified and methods of analysis for finished formulated products are established before a product is approved and marketed, dietary supplements have no similar regulatory requirement. Natural products are some of the most complex matrices found in the world of analytical chemistry. Sometimes they contain thousands of phytochemicals in one plant, which may vary in composition and quantity depending on season and soil. Analytical methods developed to confirm the identity of incoming raw materials often cannot be applied to finished products to confirm dosages (or serving sizes, in the regulatory language of dietary supplements) against label claims. This is especially true of combination products for which other botanicals or excipients and binders are used as part of for-

mulations that may interfere with marker compound analysis. Consumer confidence will return when negative media reports cease and become a distant memory so that they no longer influence purchase decisions.

FDA's strained resources have prohibited the level of DSHEA enforcement that responsible companies would like to see. Companies will have to address their own quality issues internally, and the industry must agree on how to police those members whose misdeeds tarnish its image.

More Rigorous Clinical Substantiation to Support Product Claims for Many Dietary Ingredients Is Needed

Different segments of the supplement industry face different challenges in clinically substantiating product benefits. The biological behavior and nutritional value of vitamins and minerals have been studied for decades, ever since analytical methods were established to synthesize or process pure compounds of a consistent molecular identity for further study in animals and humans. The National Academy of Sciences' Institute of Medicine continues its 60-year program of periodic comprehensive and systematic scientific reviews of the known science behind recommended nutrients. This organization establishes recommended amounts as well as upper limits of intake that should not be exceeded for the healthy, noninstitutionalized members of the U.S. population as a whole (Food and Nutrition Board, 1998–2000). For more than a decade, a growing focus in the nutrition science community has been the epidemiology of nutrient (or phytonutrient) intake and its relationship to chronic disease. Frequent studies have related nutrient intake at multiples of the levels satisfying established nutritional standards to disease prevention or reduction in disease risk. Though inadequate for drawing firm conclusions about metabolic responses by individuals, these studies are often compelling to consumers who follow the media reports about their results.

Herbal, botanical, and some specialty supplement products face different hurdles for clinical substantiation of benefits. The analytical challenges discussed previously that create difficulties in confirming finished product composition also create problems in clinical study design. The absence of a standard chemical fingerprint for a particular active or group of actives means that different investigators may administer products that have the same name and taxonomy but different compositions. Lack of standard preparations for clinical testing is one of the major factors contributing to conflicting outcomes of human studies investigating herbal products and ingredients used in specialty supplements. It is an area of investigation in some of the National Institutes of Health (NIH)–funded Botanical Centers (Table 1.8). The pharmaceutical industry sought to overcome these same challenges decades ago in the search for a plant's active constituent that had a recognized chemical identity and fingerprint. The active could be synthesized in pure form to be free of the inert or other undesirable components that co-existed in the plant tissue. The ability to measure physiologic potency in terms of a pure chemical entity, whose composition and manufacture could be controlled, was one of the key reasons that administering a purified active was advantageous in the first place (NBJ, 2002a; Foster and Tyler, 2000). The enthusiastic and passionate purveyors of herbal and botanical supplements unknowingly inherited these scientific challenges with their newfound marketplace freedom under DSHEA. The responsible companies are trying to resolve these problems; however, well-designed clinical trials for many herbs and botanicals await standardized methods to vali-

Table 1.8. NIH botanical research centers

Center and Principal Investigator	Funding	Research Focus/Project Description
UCLA Center for Dietary Supplements Research: Botanicals. David Heber, MD, PhD.	$1.5 million/yr for 5 years from ODS and NCCAM	Chinese **red yeast rice** and heart disease, **green tea extract** and **soy** for effect on tumor inhibition, and **St. John's Wort** and depression.
University of Illinois at Chicago: NIH Center for Dietary Supplements Research in Women's Health. Norman Farnsworth, PhD.	$1.5 million/yr for 5 yrs from ODS, NCCAM, Office of Women's Health, and NIGMS (General Medical Sciences)	Botanicals (approximately 10) and Women's Health, especially menopause. Projects include: Standardization of botanical preparations, bioassay development for estrogenic agents, *in vitro* and *in vivo* studies of absorption, metabolism and toxicity, and clinical evaluation.
The Arizona Center for Phytomedicine Research at Tuscon. Barbara Timmerman, PhD.	$1.5 million/yr for 5 yrs from ODS, NCCAM	For the botanicals **ginger, tumeric** and **boswellia**, considered to have antiinflammatory (including antiarthritic) properties: (1) chemistry, MOA, (2) bioavailability, (3) pharmacokinetics, pharmacodynamics in humans.
Purdue University and the University of Alabama at Birmingham. Botanicals Research Center for Age Related Diseases. Connie M. Weaver, PhD.	$1.5 million/yr for 5 yrs from ODS, NCCAM	Age-related diseases and disorders (including osteoporosis, cancer, cardiovascular disease and loss of cognitive function). (1) **grape polyphenols** and neuroprotection; inflammation, (2) **tea catechins** and cancer, (3) **soy isoflavones** and bone resorption in post-menopausal women.
University of Missouri Center for Phytonutrient & Phytochemical Studies. Dennis Lubahn, PhD.	$6 million over 5 yrs from NIEHS	Molecular mechanisms for several phytonutrients. (1) phytonutrients and prostate tumor progression, (2) **phytoestrogens** and immunity in animals, (3) **plant polyphenols** and neuroprotection and, (4) botanical identification and characterization.
University of Iowa and Iowa State University. Center for Dietary Supplement Research. Diane F. Birt, PhD.	$6 million over 5 yrs from ODS, NCCAM, NIEHS, and other NIH Institutes	Health effects of **echinacea** and **St. John's Wort.**

Source: compiled from www.nih.gov

date plant species and analytical methods to establish a quantitative chemical fingerprint for the preparations under study. This standardization has been achieved or is in progress for some botanicals, animal tissues, and other specialty dietary ingredients such as St. John's Wort, shark cartilage, gingko biloba, glucosamine and chondroitin sulfate, tea extracts, ginger, tumeric, boswellia, grape polyphenols, soy isoflavones, and echinacea. Some of these are under investigation at the six botanical research centers awarded to several universities through competitive grants funded by NIH's National Center for Complementary and Alternative Medicine (NCCAM) and the Office of Dietary Supplements (ODS), as shown in Table 1.8.

The major U.S. pharmaceutical companies that are participants in the dietary supplement industry avoided many of these problems by marketing carefully selected actives with well-understood chemistry (or microbial species identification in the case of probiotic products) and some clinical data supporting their safety and efficacy. Firms such as Wyeth and Bayer with established vitamin supplement brands created line extensions with added specialty ingredients that these companies reviewed for safety and efficacy. Their strong medical science core competency and established marketing expertise will allow these firms to pick and choose selected dietary ingredients that resonate with consumers while minimizing any risk of product liability because of safety issues.

A creative outcome of DSHEA was a mandate for the creation of an Office of Dietary Supplements (ODS) within the NIH to study dietary ingredients. DSHEA framers recognized that scientific stature would be needed for their products and that without patent protection, their margins would not be sufficient over the long term to support expensive scientific investigations. This means that U.S. tax dollars support a sizable portion of the research on dietary ingredients used in dietary supplements. Only a few firms invest in clinical trials, and their objective is usually to substantiate marketing and advertising claims rather than to understand the fundamental aspects of biological behavior.

The ODS resides in the program offices of the NIH Director, under the Office of Disease Prevention. As are its sister program offices, the ODS is responsible for developing research initiatives and for supporting, funding, and coordinating research activities through the 27 institutes and seven centers within NIH. ODS was established in 1995 with the specific mission to support research, evaluate scientific information, and publicize research results on dietary supplements. It also supports conferences and workshops on scientific topics relevant to dietary ingredients and their usage. ODS does not have the authority to directly fund investigator–initiated research grant applications; it can, however, co-fund research either through contracts or by funding grants or awards to investigators in conjunction with the other NIH institutes and centers.

In 1998, Congress authorized the formation of the National Center of Complementary and Alternative Medicine (NCCAM) within NIH to support research, train researchers, and disseminate information to health professionals and the public about complementary and alternative medicine.

The establishment of ODS and NCCAM, combined with the aggressive growth of supplement use, served as a catalyst for scientific investigation of numerous vitamins, minerals, herbs and botanicals, and other dietary ingredients in relation to various disorders. Though investigations are funded and conducted through NIH, a large, prestigious, and highly credible venue, investigators will design their research to expand the knowledge base about these substances, and findings may not necessarily support a marketing claim that the industry wishes to make for its products. Industry will have little to no influence

on how results are communicated. Science has shown mild support for the efficacy of some supplements, but results for other studies under way may test the passionately held health-related beliefs of some industry segments and their loyal consumer following. Recent examples of products that did not prove efficacious in clinical trials were St. John's Wort for major depression (Hypericum Depression Trial Study Group, 2002; Shelton et al., 2001) and ginkgo biloba for memory in adults without cognitive impairment (Solomon et al., 2002). During the first quarter of 2003, NCCAM authorized a $4 million, four-year, 300-participant study to determine St John's Wort's effectiveness in mild depression. The multicenter trial will be conducted at Massachusetts General Hospital in Boston, Cedars-Sinai Medical Center in Los Angeles, and the University of Pittsburgh Medical School.

Marketers in the glucosamine/chondroitin sulfate category, a $739 million business for dietary supplement and cosmetic applications in 2003 (NBJ, 2004b), are likely waiting for the results of the study under way by the National Institute of Arthritis, Musculoskeletal and Skin Diseases (NIAMS). This trial is investigating the role of these compounds in the prevention and treatment of osteoarthritis (OA) of the knee. The $14 million Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT) study of more than 1,500 adults with OA is being coordinated by the University of Utah School of Medicine. Results are expected in 2005.

Overall, NIH financial support for research on dietary supplements is substantial. Programs encompass a wide variety of dietary ingredients, so few are under investigation in great depth. Approximately $98 million was awarded in 1999 and $117 million in 2000 according to the ODS. Independent estimates prepared from government and state databases that track funding from ODS and NCAAM suggest that these funding levels were surpassed in subsequent years.

Business and Economic Issues Increased as Industry Growth Declined

DSHEA eliminated the major technical and regulatory barriers to market entry for companies wishing to market dietary supplement products. The post DSHEA era saw a rush of companies to the market because in contrast to food additives and drugs, dietary supplements had no FDA pre-market review mandated for safety and structure/function claim substantiation. In only 10 years, an industry of almost 900 supplement companies is doing business in the United States. Almost 800 of them command less than $20 million in annual revenues (Table 1.4). With growth having reached a plateau in 2001-2002, industry fragmentation led to consolidation followed by an impressive 6 percent overall industry growth in 2003.

Price wars led to price declines, lower profit margins, and the search for alternative markets for dietary ingredients. Though many dietary ingredient suppliers now look to the food industry as an outlet for their products, many firms seek outside scientific and regulatory counsel for establishing GRAS status for their products. Larger firms in the food ingredient and pharmaceutical business that are well recognized for skills in scientific and regulatory affairs have succeeded in establishing GRAS status for some dietary ingredients such as plant sterols and stanols or their esters (McNeil Consumer Healthcare, Cargill, ADM, Novartis Consumer Health), milk-derived lactoferrin (DMV International) lutein and lutein esters (Roche/Kemin Foods, and Cognis Corporation, respectively) and lycopene (Roche, BASF).

When many companies market similar products, as occurs in the dietary supplement in-

dustry, the result can be downward pressure on prices. Average gross margins for dietary supplements are now about 40–45 percent, not unlike those of the food industry. In addition, some products that have short life cycles curtail industry growth as manufacturers respond to the latest trend, which often lasts only a few years. The business dynamic and associated economics is not conducive to investment in clinical trials, analytical method development programs, or thoughtfully designed, long-term marketing programs backed by significant advertising and promotional support.

As more dietary ingredients qualify for use in food products, the growth of functional foods should slowly increase. However, establishing GRAS status, successfully formulating ingredients into food products that meet consumer expectations for taste and texture, and securing broad retail distribution will take far more time than some dietary ingredient suppliers are used to. In addition, claim substantiation remains problematic for the benefits these ingredients provide because preparing a successful health claim petition, especially for an unqualified health claim, requires a significant investment of money and time.

Not Enough Consumers Embrace the Regular Use of Supplements

Industry estimates of heavy supplement users generally fall between 35–40 percent, and the occasional and rare users number around a third of the U.S. population. National surveys of supplement use typically take a snapshot-in-time approach, concluding that anywhere from 55 to 75 percent of the U.S. population takes a vitamin or other dietary supplement. Most consumers, however, do not do this regularly, and regular use of multiple products is what sustains the supplement industry. For many, supplement use is a discretionary decision rather than one considered essential for health. The recent economic downturn has shown that the business is vulnerable to these consumer attitudes. According to SPINS (2002), supplements in the food/drug/mass market channel averaged about $12–14 for a 30-day supply in 2001-2002, though some cost as much as $60. Despite the dramatic increase in supplement distribution over the past five years, many consumers doubt that supplements are either necessary or effective. A number of factors may further discourage the large segment of occasional users who could drive the business forward. These factors include the lack of new and intriguing products, inconsistent quality, reports of serious safety problems (including deaths in some ephedra and androstenedione users), a lack of medical endorsement for herbal and specialty products, and press coverage contradicting product claims. There are some bright notes for the industry, however. The American Medical Association now recommends the use of a multivitamin and mineral supplement for the American population at large because our lifestyle changes in recent years have compromised our nutrient intake. On the business front, industry consolidation creates larger companies with more sizable marketing budgets, making airwave and print advertising communication options to consumers. Federal Trade Commission (FTC) rules on claim substantiation differ somewhat from those of FDA, which potentially creates new opportunities for companies to bring new users into the category once a base of clinical data to support claims is established.

The Outlook for Dietary Supplements

As the industry adjusts to slower growth rates, its future depends on successful policing of the companies whose activities generate negative publicity that reflects on all members. In

2004, some members of Congress and key regulators have brought DSHEA under attack following the ban on ephedra alkyloid use in dietary supplements. S-722 is a bill imposing a premarket approval process on some dietary supplements introduced by Senator Richard Durban (D-IL) in 2003. A related piece of legislation was introduced in the House (HR-3377) and is co-sponsored by Susan Davis (D-CA), Henry Waxman (D-CA), and John Dingell (D-MI), who have been critics of the industry in the past. More bills at the national level are expected that may even go so far as to call for DSHEA's repeal or at least some strong modification. The industry is seeking support among its membership to preserve DSHEA as it is through outreach, education, and lobbying of Congress to pressure FDA for more rigorous enforcement of companies who are noncompliant with existing laws and regulations. Many responsible companies, especially the pharmaceutical companies and their suppliers with established, branded supplement products, are usually above the fray. But for those seeking bigger growth and marketplace stature in mainstream channels, the internal issues described will have to be addressed in their business plans and rectified over the near term.

Functional Foods in the United States

Background and Market Overview

As is nutraceuticals, **functional foods** is a marketing term whose definitions have ebbed and flowed over the years. The U.S. Institute of Medicine of the National Academy of Sciences has put forward a definition for functional foods that appears to satisfy marketers as well as nutritionists and food scientists. Simply put, Functional Foods are those in which the concentrations of one or more ingredients have been manipulated or modified to enhance their contribution to a healthful diet (American Dietetic Association, 1999). In practice, a small but growing segment of the retail U.S. food industry is comprised of foods for health or improved physical performance. Sometimes these products are made with added nutrients or phytochemicals. Alternatively, some are promoted for a new health benefit attributable to a food component that has always been present. Perhaps the most salient example is cranberry juice, in which the proanthocyanidins naturally present in the cranberry fruit have been shown to prevent urinary tract infections by inhibiting bacterial adhesion to the urinary tract wall and therefore the cellular reproduction needed for infection to occur. Clearly the new science has supported the old conventional wisdom about this beverage.

These products are now generally accepted as functional foods and are distinct from those that have been enriched with added nutrients for the public health purpose of preventing nutrient deficiencies in the population. These latter examples include iodine in salt, B vitamins and iron in certain cereals, pasta, and flours, or vitamin D in milk. Few of these products are available today without enrichment to meet government standards.

The large, mature food industry serves as a backdrop to the comparatively spritely little segment that comprises functional foods. This segment grew slightly in excess of 7 percent in 2003 to $21.9 billion compared to the $518 billion mainstream food industry's 3 percent growth. The retail value of organic foods was about $10.4 billion in 2003, an increase of over 20 percent from 2002 (NBJ, 2004b). The organic and natural food segments have been the source of many functional food acquisitions by mainstream food companies. Despite the slow growth rates, the food industry is highly competitive, with thin-

to-modest margins along the value chain from agricultural commodities to retail food products. Compared to the natural/organic and dietary supplement industries, the mainstream food industry culture can be characterized as risk averse and seeking a harmonious rather than confrontational relationship with its regulators. Against this cultural landscape, larger companies have positioned their products for health benefits much more conservatively, generally with stronger scientific and regulatory support than those in the dietary supplement industry. In the early 1990s the food industry did not take seriously the small companies who took risks with product claims lacking scientific rigor. As a result, mainstream food companies and their industry associations were caught by surprise by DSHEA's passage. However, the growth of nutritional products in general since the 1994 legislation became law has caught the food industry's attention in a big way.

Traditional food industry messages on health and nutrition have centered on the fact that a balanced diet includes a wide variety of foods, including sweets and snacks, all consumed in moderation. For the most part, this nutrition education philosophy has historically served industry participants well, assuring consumers and the manufacturers of all foods, including salty snacks, carbonated beverages, dessert products, and confectionery that these products had a place in the American diet. When consumer interest in low-fat foods materialized during the early 1990s, many companies offered low- or reduced-fat alternatives. Intensive industry efforts reduced the fat content of processed foods wherever it was possible through ingredient substitution and new ingredient technology development, though there has been general agreement that taste qualities were often compromised. The meat and meat-processing industry provided substantially leaner products at retail through traditional breeding techniques, modified animal diets, and increased trimming of visible fat. These efforts not only addressed consumer demand but also helped to exceed the specific objectives to the industry made in 1990 by the U.S. Department of Health and Human Services' "Healthy People 2010" initiative. The assigned food industry target to increase the availability of reduced-fat processed foods was achieved in substantially fewer than five years (National Center for Health Statistics, 2001).

The functional food concept that began to catch on in the early 1990s ran counter to the trend of reducing the less desirable food components such as sugar and fat. The original concept for functional foods allowed a food product to become a delivery vehicle for a particular health benefit that was distinct from traditional mainstream food commodities and brands (Wrick, 1994) though that definition expanded over the 1990s (Wrick and Shaffer, 2002; NBJ, 2002b). In order to capitalize on rapid growth of new products while also protecting existing brand franchises, major food firms such as Kraft and Nestle acquired functional food brands in the energy bar market (Balance Bar and PowerBar®, respectively).

Despite the interest in the functional food concept, most companies entered the market through acquisition because line extensions for many prepared foods positioned for better health would imply that the flagship brand was nutritionally inferior. Only a few food and beverage companies, who had products already associated with good nutrition, adopted a strategy that included a health positioning for line extensions to current brand franchises. Tropicana Orange Juice (PepsiCo) is one of the most notable examples, with two FDA approved health claims to their credit. Their calcium-fortified citrus juices contain Fruitcal®, the brand name for calcium citrate malate, the acid-soluble form of calcium for which they have an exclusive license from the ingredient's inventor, Procter & Gamble. These products provide similar amounts of calcium to a glass of milk without the chalky

mouth feel or precipitation of calcium salts typically encountered in acidic products. As a result, they qualify for the FDA unqualified health claim that relates calcium intake to the prevention of osteoporosis, though the company has not consistently used the claim as a marketing tool. Tropicana later filed for the first health claim under FDAMA (the Food and Drug Administration Modernization Act). This statute allowed Tropicana to claim that consumption of its citrus juice products could help reduce the risk of hypertension and stroke by virtue of the authoritative statements made by the National Academy of Sciences National Research Council publication, *Diet and Health* (1988). This publication reviewed the well-accepted relationship between increased potassium and low sodium intake and the reduced incidence of high blood pressure and stroke.

Commodity businesses such as poultry and fish began promoting the health benefits of naturally occurring components that scientific reports indicated were important, such as omega−3 fatty acids in fish, or in eggs from hens on special diets. Cancer-fighting phytochemicals in cruciferous vegetables (that is, glucosinolate compounds found naturally in broccoli, broccoli sprouts, Brussels sprouts, and other vegetables) were occasionally touted in promotional materials, as was the FDA health claim that the increased consumption of fruits and vegetables could reduce the risk of certain forms of cancer. Though scientifically accurate, these health messages did not resonate well with many consumers, and few companies used these messages on package labels. More recently, the National Cancer Institute "5-A-Day" program has been used to try to encourage more produce consumption for its vitamin and phytochemical content.

These conservative approaches to communicating health messages relative to the dietary supplement and natural/organic segments, and the industry's history of conflict-avoidance with the FDA, have resulted in a slower, more gradual start of the functional foods category than was achieved with dietary supplements following the passage of DSHEA. But the cautious cultural environment may be just what is needed to sustain a more gradual and prolonged growth curve than that initially achieved for the dietary supplement segment. Clearly, the 7–9 percent growth rates for functional foods during 2001–2003 (NBJ 2002b, 2003b, 2004) began to turn the heads of industry executives toward a serious evaluation of their companies' opportunities in this market. Historical and projected sales for functional foods are shown in Table 1.9.

Table 1.9. Historical and projected sales of functional foods in the U.S.

	1997	1998	1999	2000	2001	2002	2003	2008e
Sales $B	$13.7	14.8	16.1	17.4	18.9	20.5	21.9	29.7
Growth (%)		8.0	8.8	8.0	8.6	9.0	7.7	Est. 6.8%/yr
% of total food industry sales	3.0	3.2	3.4	3.5	3.8	4.0	4.3	Est. 5–6%

Source: *Nutrition Business Journal*, 2002c, 2003a, 2004a estimates

Nutrition Business Journal defines functional foods as follows: Foods fortified with added (nutrients) or concentrated ingredients to a functional level that improves health and/or performance. They also include products marketed for their "inherent" functional qualities. They include some enriched cereals, breads, sports drinks, bars, fortified snack foods, baby foods, prepared meals, and more.

Participants and Products

The first mainstream U.S. food product that could be called a functional food by today's definition was Kellogg's All Bran®, a wheat bran cereal high in fiber and well known for its laxative properties. In 1984, Kellogg pushed the envelope on FDA labeling regulations and, in conjunction with the National Cancer Institute, described the relationship of a high-fiber diet to cancer prevention, based on the epidemiological evidence of the day, on the back of the All Bran package. Kellogg's strategy with All Bran led to the establishment of the health claim regulations we have in place today. Later, the Quaker Oats Company successfully filed a health claim petition for oats and the reduced risk of heart disease, based on accumulated evidence that oat bran (specifically the beta glucan–rich soluble fiber fraction) helped lower serum cholesterol.

Kellogg began a functional foods division in 1996 based on its patented technologies for soluble fiber derived from psyllium seed husk, which was awarded a health claim for reduced heart disease risk. However, this path was later abandoned because product acceptability of the Ensemble product line with psyllium fiber did not pass the critical taste and texture acceptability test with consumers, despite its health benefits of lowered cholesterol. Today, with its acquisition of Loma Linda, Worthington Foods, and Morningstar Farms brands, Kellogg is well positioned to take advantage of the FDA-approved health claim for soy and its role in reducing the risk of heart disease.

Companies participating in the functional food market today vary considerably and include large, mainstream multinationals such as PepsiCo, General Mills, Kellogg, Coca-Cola, and Kraft, who collectively had about a 34 percent share of the $21.9 billion market in 2003. Another 25 branded manufacturers are responsible for more than $100 million each in U.S. functional food sales (NBJ, 2003a). The remaining companies focus primarily on the natural/organic channel, which has served as a testing ground for many nutritional products that have grown over time to a size attractive enough to be acquired by large food companies. An example of one of the relative newcomers to the United States is Red Bull GmbH, which markets, to young adults, beverages with caffeine, taurine, and gluconolactones for energy and alertness. Red Bull® has been marketed for more than 14 years in Europe and is now found in more than 60 countries, from Angola to Yemen. Since its founding in 1992, Ferrulito, Vultaggio & Sons, owners of AriZona brand beverages, have become leaders in the New Age beverage category, which includes flavored teas and fruit-based beverages with added herbs and botanicals; whether the levels provided of these added ingredients deliver any demonstrable health benefit is not clear, however. No health-related claims are made for the products. Clif Bar® was introduced to the United States in 1992 and grew to a $130 million business in 10 years. Clif Bar, Inc. has also launched line extensions, including one with a salty taste rather than the sweet flavors offered by other energy bar products. All products provide high-carbohydrate, low-fat, portable nutrition initially targeted to the physically active who want to be able to eat immediately before, during, or after their sport. These products have evolved to meet the mainstream need for a quick yet satisfying snack or meal replacement when time is not available for breakfast or lunch.

PepsiCo, with its acquisition of Quaker Oats and its Gatorade® brand in 2001 is now the largest functional food company, though its Pepsi beverage franchise and Frito Lay snacks still make up the lion's share of the business. Pepsi's brands associated with health and nutrition or performance include Quaker cereals, Tropicana® and Dole® Juices,

Lipton® teas (which Pepsi distributes for Unilever), Aquafina® bottled water, SoBe® non-carbonated soft drinks, and Gatorade. In addition to the success of the Quaker and Tropicana health-claim positioning, teas that contribute polyphenols and antioxidants to the diet are gently promoted through print media rather than product labeling and advertising. SoBe beverages are either tea- or fruit juice–based and have added caffeine for "mind-blowing energy," or herbal extracts. Gatorade, a 30-year-old functional beverage, replenishes some of the salt lost through perspiration and is well accepted for its hydrating and rapid fluid replenishment during and after exercise. Today, in addition to the athletes to whom the product was originally targeted many years ago, a broad consumer segment has emerged who appreciates the sweet-salty taste, and the brand has a global presence.

General Mills has been very proactive in repositioning long-standing brands such as Cheerios®, which is now promoted for heart health based on oat content. General Mills was responsible for the FDAMA health claim petition that FDA accepted regarding the role of whole-grain foods in reducing the risk of heart disease and certain cancers. Recently, a joint venture between General Mills and Dupont's Protein Technologies International (Dupont/PTI's Solae) launched a new brand, 8th Continent™, a significant entry into the soymilk market. The 8th Continent™ product is formulated with soy protein isolate, which has successfully overcome many (but not all) of the flavor problems that can occur when the crushed whole bean is used in soymilk manufacture. Most soymilks in the marketplace utilize the heart health claim for soy because it appeals to their health-conscious target market. As a result, these soymilks contain at least 6.25 grams of soy protein per serving, which is the qualifying amount required by regulation for use of the claim.

Though soymilks have had the strongest consumer acceptance as reflected in soyfood sales, other soy products are now considered mainstream following acquisitions of their brands by large food companies. Consumers have been exposed to soy as an ingredient in many processed foods for decades. In the late 1960s, soy protein was sold as a hamburger extender when beef prices temporarily skyrocketed. Long before the Solae joint venture between DuPont and PTI was even conceived, PTI built an extensive scientific database of peer-reviewed studies on the health benefits of soy and soy protein, from feeding milk-intolerant or allergic infants to cholesterol reduction in adults. Work in the latter area gradually built the significant scientific agreement in the nutrition and medical science communities required to support its health claim for reduced risk of heart disease. The market for soymilk is forecast to reach $1 billion by 2005. About six firms command more than 70 percent of the market and include White Wave, Hain, Eden Foods, Imagine Foods, Vitasoy USA, and Pacific Foods. General Mills' 8th Continent™ is expected to expand the category and take shares from others. Soy-based meat alternatives are also a significant category. Today's products are meat-free patties that look like hamburgers but have a grilled, meat-like taste. Large multinationals such as Con Agra (Lightlife), Kraft (Boca Burger) and Kellogg (Worthington, Loma Linda) have acquired soy businesses and are now major players.

Entry of soy foods into the mainstream grocery channel occurred around the time that FDA published its final rule allowing for the soy/heart disease health claim for products containing 6.25 grams of soy protein per serving. Curiosity and interest in soy had already started in consumers, and the claim became a true driver of soy food sales. Increases in purchases of soy-based foods of more than 20 percent were reported within the first year the claim was used. However, not all products can be reformulated to contain enough soy to qualify for the health claim because of the large amount of soy protein required per serv-

Table 1.10. FDA criteria for the health claim relating soy protein intake to the reduction in risk for heart disease

Soy protein—Must have at least 6.25 grams of soy protein per RACC (Recommended Amount Commonly Consumed).
Low fat—Each serving or RACC must contain less than 3 grams of fat. (Requirements as stated in 21CFR §101.62.) If the product consists of or is derived from whole soybeans and contains no fat in addition to the fat inherently present in the whole soybeans, the 3-gram limit will not apply.
Low saturated fat—A serving or RACC must contain less than 1 gram of saturated fat. The total amount of saturated fat per serving must be no more than 15% of total calories. (Requirements as stated in 21CFR §101.62.)
Low cholesterol—A serving or RACC of food must also contain no more than 20 milligrams (or less) of cholesterol. (Requirements as stated in 21CFR §101.62.)
Note that the eligibility of the food to bear the soy health claim is based on the soy protein per RACC per eating occasion so that 4 eating occasions would provide a total daily intake of 25 grams soy protein. For many foods, but not all, a RACC equates to one serving. After the food qualifies for the health claim, the label statement for the amount of soy protein per serving is based on the actual serving size of the food. Foods currently on the market that are eligible for the health claim include soy-based beverages, tofu, tempeh, and soy-based meat alternatives.
Source: Food and Drug Administration, 1999, Food Labeling: Health Claims; Soy protein and Coronary Heart Disease: Final Rule. *Federal Register* 64(206): 57732–57733

ing as well as other food composition criteria. When the criteria listed in Table 1.10 are met, a product can claim in labeling that "diets low in saturated fat and cholesterol and high in soy protein may reduce the risk of heart disease." The FDA has indicated that 25 grams of soy protein a day (or 4 servings) are needed to positively impact the risk of cardiovascular disease. Soymilk, meat alternatives, and some nutritional bar products can meet the 6.25 grams of protein per serving while meeting the requirements for fat, cholesterol, and sodium content. Other product categories will find formulating to these standards without compromising consumer taste and texture expectations more challenging.

Barriers and Challenges to the Growth of Functional Foods

Today, the functional food industry is poised for growth but faces technical, marketing, intellectual property, and regulatory challenges. The same drivers that helped shape the business environment for nutraceutical products are still in place today; however, incorporating dietary ingredient technologies into food products creates a unique set of challenges.

The Technical Challenges

Not all products can successfully incorporate added nutrients or phytochemicals. Commodity products such as meat, poultry, fish, and eggs can have their composition altered to some extent by the animal's diet, but delivery of truly unique health benefits will probably require genetic engineering, which is not yet accepted by consumers. Should consumer skepticism soften, the future might bring genetic alterations to beef and dairy

cow metabolism to produce increased levels of naturally occurring conjugated linoleic acid (CLA) in meat and milk products. Strong evidence supports the claim that increased levels of dietary CLA in animals help to convert fat tissue to muscle; however, this finding awaits substantiation in humans regarding a role in weight management. Should these benefits be confirmed, CLA will likely be sought after for addition to other food products, if it qualifies as GRAS at the levels needed to deliver health benefits.

Some foods, such as milk, chocolate, and mayonnaise, have government regulations or standards of identity governing product composition that make adding novel ingredients difficult. Unless these standards are revised, adding novel ingredients may require renaming these products to something that implies "imitation" to consumers. The compositional standards for foods such as chocolate have strong economic and labeling implications in world trade, so little incentive exists to change them to incorporate ingredients that appeal to a relatively small consumer segment.

Other indulgent foods, such as ice cream and sweet baked goods, have historically not been candidates for this kind of fortification because consumers want to retain their tradition as a dessert or a special treat, though this may change as consumer attitudes and ingredient technologies evolve. The nutrition bars in the U.S. market have been the creative exception, using confectionery or bakery technology but being positioned as healthful, not too sweet, low in fat, satisfying, and delivering energy and a few added nutrients in a portable, convenient format.

Functional food ingredients may offer formulation challenges as well. Unlike most dietary supplements, which are in the form of pills or tablets, functional foods have the challenge of meeting the taste preferences of target consumer groups. Many functional food ingredients, such as isolated nutrients, phytochemicals, and plant extracts, have inherently unpleasant flavors. When added to foods to meet nutritional requirements, levels of vitamins and some minerals are usually low enough that many undesirable flavor notes or chalky textures are not perceived on the palate, or they can be masked with other ingredients. Higher levels can cause flavor problems over the shelf life of some products. Even if qualifying as GRAS, many herbs, plant extracts, or other phytochemicals that have been found to deliver health benefits have strong, unpleasant flavors or textures. At worst, their flavors cannot be masked or hidden, and at best, their use can cause delays in the food formulation process or increased ingredient costs in order to achieve sensory targets. Modifying ingredients that are complex molecular blends to address sensory problems without compromising health benefits can be a major research undertaking without a guaranteed positive outcome. Resolution of these issues can add significantly to product development time.

The Marketing Challenges

Functional foods have different marketing challenges than those of dietary supplements. Some successful products in the functional food category have capitalized on long-known diet-health relationships for their products or their ingredients, such as calcium and strong bones, carbohydrates and physical energy, and caffeine and alertness. Very little "low-hanging fruit" is left for marketers. Ingredients providing health benefits that may have a complicated educational message require much more careful positioning. The experience with plant sterol– or plant stanol–enriched margarine-like spreads has reinforced the fact that not all consumers with high cholesterol are interested in managing it through diet. And

of those who are, many don't want to use a higher-priced, though good-tasting, spread multiple times a day even if it makes their cholesterol go down. These products developed a small but very loyal consumer following, but mainstream U.S. consumers who might be at risk for heart disease were not necessarily responsive to a product positioning that reminds them of it. Chronic diseases such as hypertension, diabetes, and cardiovascular disease have no demographic boundaries. Identifying the target consumers within a group of people who suffer from a particular disorder usually requires psychographic (for example, attitudinal) segmentation and knowledge of consumer purchasing patterns in order to estimate potential market size. Market research tools exist to do this, though this research is expensive.

To date, marketing a functional food to address a specific medical condition has not proved successful in the eyes of the mainstream food industry. "Food as medicine" appeals to a relatively small consumer segment and will not generate the revenue needed to justify the necessary resources for development or to satisfy shareholder expectations. Large food companies are generally not interested in products with a market potential of less than several hundred million dollars. Industry is now betting that consumers seek positive nutrition in general for overall health and wellness, outside the context of preventing specific diseases. The health benefits of a high protein intake for weight loss as part of a low carbohydrate diet, calcium for strong bones, and dietary fiber and probiotic bacteria for gastrointestinal health are now promoted in a wide variety of functional food categories that are growing at attractive rates. Collectively, these health and wellness products became about as popular as vitamin-fortified products, with a 49 percent and 46 percent share of 2002 functional food sales, respectively (NBJ, 2003b).

The concept of functional foods with key ingredients responsible for a particular health benefit may shift as marketers change their focus from foods for disease management and prevention to the broader message about health and wellness. Ingredients associated with good health but without a link to disease could be used in products marketed to a larger audience. The soy market gives a clue to this trend. That soy is a healthful alternative to meat and dairy protein may be the only message needed to drive consumer sales and for marketers to avoid regulations that can be cumbersome.

The Regulatory Landscape for Nutraceuticals

The regulatory landscape has always had a strong influence on the evolving market for nutraceutical ingredients whether used in foods or supplements, and it will continue to do so for years to come. In the years after DSHEA, when dietary supplement growth was at double-digit rates, very few ingredients were available that had passed regulatory safety requirements for use in food, and insufficient scientific data was available on most to clear the regulatory hurdle of "significant scientific agreement" for health claims. The high costs of building new brands and the need to protect existing ones created downward pressure on functional food development for many processed-food companies. In addition, formulation with some phytochemical actives in foods and beverages presented technical challenges in meeting consumer preferences for taste and texture when the amounts needed to deliver the promised health benefit were used.

A major regulatory distinction exists between the ingredients used for claimed health benefits for foods and for dietary supplements. Any substance added to food, for whatever reason, must meet FDA standards for GRAS status or be an approved food additive, hav-

ing received agency approval via a formal petition to the FDA documenting safety under conditions of intended use. The burden of establishing safety clearly rests with the companies that introduce these ingredients into the food supply. Alternatively, dietary supplement companies are free by federal statute to utilize ingredients that have a different (and controversial) safety standard that does not routinely require a formal FDA premarket scientific review or approval. Dietary ingredients must demonstrate a history of use or other evidence of safety that establishes that they can reasonably be expected to be safe when used as specified by the product label. The burden of proving a dietary ingredient unsafe remains the responsibility of the resource-starved FDA, though this element of the DSHEA statute may be poised for serious reconsideration.

Following DSHEA's passage, it was easy to speculate that the time and expense in establishing GRAS status and meeting the significant scientific agreement standard for a potential health claim could be avoided by putting a dietary supplement product in food form. This strategy was tested in 1998 with McNeil Consumer Healthcare's Benecol® spread and salad dressing lines, which contained the patented and clinically proven cholesterol-lowering ingredient plant stanol esters (sitostanol ester). These products were labeled and positioned as dietary supplements in promotional campaigns to health professionals prior to product launch. Some well-respected attorneys in food and drug law insisted that case law would support this strategy should an FDA court challenge ensue. FDA did intervene with the Benecol launch plan and required that plant stanol esters qualify for GRAS status before the product could enter interstate commerce in the United States. McNeil chose to comply with the FDA's request rather than go to court. Fortunately for McNeil, sufficient scientific backup was already on file so that the notification document supporting GRAS status could be prepared in a matter of weeks. Unilever's Take Control® spread, which also lowered cholesterol using a slightly different patented plant sterol–based ingredient with GRAS status, was introduced to the retail market within weeks of Benecol. Both companies submitted health claim petitions, and FDA granted permission to use a claim for reduced risk of heart disease for products utilizing either plant sterol or plant stanol esters. The strength of the scientific data supporting the health benefit of these ingredients allowed a petition review period of only a few months, one of the fastest on record. Numerous plant sterol–derived ingredients are now available for use; however, products utilizing them represent only about 1 percent of functional food sales (NBJ, 2003a).

Intellectual Property and Regulatory Barriers to Growth

Several barriers to growth for the nutraceutical ingredients used in functional foods and dietary supplements exist. They have centered on intellectual property, claim exclusivity, and federal regulations that may evolve more slowly than the technical and scientific developments in the business environment of the products that are regulated.

There is a dearth of proprietary ingredients or manufacturing technologies that create a clear marketplace advantage for most bioactives derived from plant or animal tissues that offer well documented health benefits and are suitable for use in foods or supplement products. Many bioactives from herbs and plants have been used in folklore and do not qualify for patent protection. Vitamins and mineral preparations have been manufactured for decades and are now priced low enough to be considered commodity ingredients. Any industry know-how, trade secrets, or critical patents with remaining life are held in the hands of companies that have been in the business of nutrient manufacture for a long time.

Though providing a strong technology base, proprietary positioning by means of patented ingredients or manufacturing methods generally have not offered strong marketplace advantages for most dietary or food ingredients used in supplements or foods as they have for pharmaceutical companies. Where patents and licensing agreements exist in the supplement industry, infringements also exist and are costly for smaller companies to fight in court. New chemical forms of traditional nutrients, such as vitamin or mineral chelates, continue to be developed and sometimes patented. However, the majority of supplement companies are too small to defray the cost and often do not have the internal technical expertise to design, manage, and oversee improvements over existing products. Though larger firms could make these investments, anticipated benefits often are not sufficiently attractive to consumers to bring the needed sales or justify the price premium needed to recover clinical costs as well as the strong marketing and communications program needed. An additional disincentive to supplement companies to conducting clinical work is that the trials take a long time to design, conduct, analyze data and draw conclusions, followed by many months of peer review before publication in a respectable, peer-reviewed journal. The timeline from study design to publication is often longer than the product life cycle for some dietary supplement products, though not necessarily for functional foods.

The Raisio Group in Finland had a patented technology in the production and use of stanol esters (sitostanol ester) for lowering cholesterol and found tremendous success in its home country when it launched Benecol margarine. In an unfortunate but classic case of underestimating the competitive landscape for the technology in foreign markets, Raisio and its U.S. marketing partner, McNeil Consumer Products (now McNeil Nutritionals), executed a business plan that did not consider the competitive ingredient technologies already patented or in the development pipeline. Raisio's patent protection offered little marketplace advantage because other food phytochemicals also lower serum cholesterol. McNeil's entry into the retail margarine case with national ambitions prompted Unilever to dust off its plant sterols technology, manufacture a comparable product at lower cost and greater profit, and equally share the market space with McNeil. Even if plant stanol esters could be determined to be more effective at lower levels of intake than any other cholesterol-reducing food, ingredient, or drug, FDA regulations would preclude comparative claims. The approved health claim is for a reduction in the risk of heart disease, not for lowering cholesterol by a certain amount.

Current federal statute requires that products making claims for disease treatment or prevention are drugs and can be sold in interstate commerce only when they meet strict premarket approval requirements for safety and efficacy. This remains the case even when abundant and compelling peer-reviewed science supports a role for amelioration or treatment of disease or its symptoms that should support a "truthful and non-misleading" standard in many cases. In addition, there has been no clear route for companies to communicate this science to consumers in an understandable manner in order to drive sales. Further, razor-thin margins in the food and supplement industry discourage investment in preclinical or clinical work in the face of these restraints. Approved health claims for foods and supplements are generic, not exclusive to the petitioner, and may not always reflect what a product actually does, should studies indicate that it is effective in treating or managing disease. Technology development for new ingredients that are sufficiently safe for use in our food supply and could contribute public health benefits against chronic disease will remain curtailed unless some established regulatory barriers are eased.

One possible approach to this dilemma would have the FDA set a regulatory framework

to allow a period of claim exclusivity to the company that invests in the ingredient development, safety testing, and claim substantiation, a model similar to that of the U.S. orphan drug regulations. A fledgling industry group called the Research-based Dietary Ingredient Association (RDIA) was beginning to evaluate workable routes to ultimately propose to FDA. However, this organization never quite achieved the critical mass of industry support and funding required to create a force for change. In addition, the 9/11 terrorist attacks in New York initiated a refocus of FDA's mission and strategy to work with industry to ensure the safety of the U.S. food supply from deliberate attempts to undermine its safety through terrorism.

In light of the new national priorities, legislative or regulatory change designed to foster food and dietary ingredient innovation is getting little if any attention. This absence will likely mean only sporadic development for new nutraceutical ingredients for the foreseeable future. New ingredients that are developed will generally find their way into dietary supplements before functional foods unless the business opportunity is clearly greater for a food application. DHA is one of the n-3 fatty acids with a legacy of clinical research supporting its role in infant retinal and cognitive development. Martek Biosciences developed the methods to produce purified DHA from algal fermentation, made the business decision to seek the support of the infant formula industry worldwide, and proactively sought approval from governments for inclusion in infant formula products. The company's less attractive alternative was to enter the dietary supplement market with its less stable market dynamics. The technical hurdles with the inherent instability of n-3 fatty acids are slowly being overcome, and DHA is now used in many infant formulas internationally.

Recent Developments at the U.S. FDA Liberalize Health Claim Regulations

A major revision to the process for making product claims about diet and health for conventional foods and dietary supplements was initiated in 2002. The revision was based on accumulated experience with product claims in labeling and advertising, and especially the requirements of the 1999 Court of Appeals decision regarding the *Pearson v. Shalala* case. Briefly, the outcome of this ruling mandated that FDA allow qualified health claims on dietary supplements that did not meet the rigorous "significant scientific agreement" standard in place since health claims for foods were first authorized. In practice, this means that a claim can be made for a diet-disease relationship that had not reached significant scientific agreement as long as the consumer is apprised that the data supporting the claim are not yet conclusive.

An FDA guidance document described a process for systematically evaluating and ranking the scientific evidence for a qualified health claim. The ranking system uses an A, B, C, or D grading system. A Grade A claim would meet significant scientific agreement standards for a traditional (now called "unqualified") health claim, and a B Grade would be assigned to those petitions for which good scientific evidence exists supporting the claim but for which the evidence is not entirely conclusive. A C Grade would apply to claims for which the evidence is limited and inconclusive; a D grade would be given to claims with little scientific support.

A petition must be submitted for unqualified and qualified health claims so that FDA can review each potentially qualified claim on a case-by-case basis. Petitions will be accepted for both conventional foods and dietary supplements. Qualified claims will be reviewed according to a new agency policy that will utilize a "weight of the scientific evi-

dence" standard, as has long been used by the (FTC) for claims made in print and airwave media advertising. Petitioners must specifically request a review for a qualified health claim and provide a body of data that is sufficiently scientifically persuasive to demonstrate to expert reviewers that the weight of the evidence supports the proposed claim. The data they provide need not rise to the level of significant scientific agreement.

In evaluating whether claims used in package labeling are truthful and not misleading, FDA will use a "reasonable consumer" standard (as opposed to the "ignorant, unthinking, or credulous consumer"). The reasonable consumer standard is consistent with FTC deception analysis, which means that its use by FDA will contribute to the rationalization of the legal and regulatory environment for food and supplement promotion. This standard also reflects the agency's belief that consumers are active partners in their own health care and behave in health-promoting ways when given health information (FDA, 2002b).

The qualified claims allowed as of September 2003 are listed in Table 1.7, which appears earlier. Each claim listed has some conditions for use that are specific to each. All must meet the health claim requirements of 21 CFR 101.14 except for the significant scientific agreement standard. Other conditions for use include claim placement on the label, package recommendations conforming to the National Academy of Sciences/Institute of Medicine's (NAS/IOM) Tolerable Upper Intake Levels that should not be exceeded, and/or particular product nutrient content specifications. As can be seen in Table 1.7, the allowed claims are not ones that most marketers will immediately embrace. However, as has happened over time with structure/function claims, the specific wording on package labels might be negotiated with the agency on a case-by-case basis. This would inch marketers closer to label-claim strategies to which consumers are more receptive despite the built-in disclaimer regarding inconclusive or lack of scientific support. It will be interesting to see whether the new FDA policy toward claim liberalization will encourage additional clinical research to reach a significant scientific agreement standard for some products, especially foods.

Long-Lasting Drivers That Favor Growth of Functional Foods and Nutraceuticals

There are some industry drivers favoring gradual, long-term growth of functional foods; these factors should provide some patience to consumer product companies that find the longer product development process that some functional foods can take to be frustrating.

For one, consumers in the "baby boom" category now comprise about 27 percent of the U.S. population, and this group, which in general is interested in good health, will be around for a long time. For this group, the food-health connection is already made, though some subsegments may need more convincing of the link between food and disease prevention.

Second, Americans of any age will always eat food for energy and basic nutritional needs. For many, dietary supplements beyond the multivitamin taken for "nutritional insurance" are viewed as expendable. This means that there will likely be a place for food products to be the source of new health benefits. The time pressures of our twenty-first century American lifestyles have led us to become a nation of "grazers" who grab the opportunity to eat when they can, whether while walking to work or riding in a car. Nonetheless, while the supplement industry addresses the marketing challenge of winning over new con-

sumers, most Americans don't yet take supplements regularly, but they all eat food every day.

Third, though some dietary supplements may claim to suppress appetite, supplements in general will never satisfy hunger when someone has gone for extensive periods without eating. Only food can do that.

Functional foods have the potential to be a major growth driver for the food industry; however, the right mix of market research, marketing, science and technology, branding, distribution, pricing, product taste and convenience, and adequate development time before launch has been elusive for the pioneers in the business. Kellogg (Ensemble), Novartis (Aviva line), and McNeil (Benecol) all had mainstream ambitions for a business that appears for now to be destined to start out as a niche. Nonetheless, functional foods might yet become premium brands, even within product segments at or approaching commodity status. Tropicana's brands are a preeminent example. NBJ (2002b) reports that Tropicana's venture into functional foods has brought its citrus beverages to far greater than a $1 billion brand. If Soyatech Inc.'s forecasts are correct, soy food sales will exceed that figure by 2005. A "health and wellness" marketing trend for mainstream foods appears to be under way now that will position products with health benefits as "good-for-you" or "better-for-you" rather than be designed to prevent specific diseases. If successful, this trend will continue to help functional foods become one of the larger-growing segments in the mainstream food industry.

The Future Outlook

Consumer interest in finding real or perceived solutions to health problems outside the traditional Rx and OTC routes will continue to grow as consumers pick up an ever-increasing share of their health care costs and as subsequent activism about quality of health care increases. Continued pressure on physician productivity within managed-care institutions will further compromise the quality of doctor-patient communication. Any further publicity about research studies questioning the claimed benefits of blockbuster pharmaceutical products, as has occurred with hormone replacement therapy (HRT), will continue to shake the confidence of a significant consumer segment that will look for alternatives. A positive outcome of the NIH glucosamine trial, anticipated by about 2005, will help strengthen the credibility of specialty supplements. The dietary supplement industry has some challenging times ahead. It must plan to adjust its businesses to new regulations governing current good manufacturing practices, for which FDA published a proposed set of standards in March of 2003. In addition, the industry must prepare to deal with potential legislative initiatives in Congress, which has the potential to eliminate some of the industry's freedom in selecting products for market in the interest of product safety.

The near-term outlook for functional foods should be brighter as more dietary ingredients begin to qualify for GRAS status and can therefore be used in foods. Time will be required for food or dietary ingredient firms and consumer product companies to establish safety and then substantiate health claims, and the new avenue created for qualified health claims created by FDA in early 2003 may mean increased opportunities for responsible product labeling claims made under standards that are harmonized with those of the FTC.

One might envision a significant, perhaps double-digit growth for functional foods, which now comprise less than 5 percent of retail foods sold in the U.S., if incentives for ingredient technology development, such as claim exclusivity, eventually become part of

the regulatory framework. Such initiatives would lead to a greater search, exploration, and clinical study of potential ingredients with health benefits safe enough for use in foods. One possible scenario could entail the development of food or supplement products that are readily accepted by consumers, show comparable efficacy to some medications in well-designed clinical trials, and are also low enough in cost relative to medications to make managed-care companies begin to take notice. Currently, however neither the FDA nor the pharmaceutical industry is interested in further blurring the lines between foods and drugs, and the managed-care companies are focused on far more near-term industry structure, economic issues, and congressional attitudes toward health care regulation at a national level. But thoughtful and creative pharmaceutical companies could begin the strategy now to identify a bioactive that is safe enough for GRAS status and provides a similar benefit as an established class of pharmaceuticals. These companies have access to and credibility with the medical and scientific community, and they are capable of rapid clinical trial design and execution for building the scientific data and support product claims. A partnership with the right food company would link them to food marketing expertise and manufacturing, and capabilities for nationwide access. The time may be right again for the pharmaceutical companies to revisit functional foods as a strategic option and capitalize on different times and lessons learned.

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