Regulation of Nutraceuticals and Functional Foods

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2.1 INTRODUCTION

While the numerous sources of market data are not always in absolute agreement on market size, projections, and opportunities, they have been unified on the continued growth, interest, and general potential of the nutraceutical and functional food market. The notion that foods contain bioactive nutrients that can have immediate and long-term benefits is intriguing and aligns with the words of Hippocrates thousands of years ago—"Let food be thy medicine." However, how information is communicated overlaps several industry components, including marketing, quality assurance/control, regulatory, and legal.

As outline in Chapter 1, targeting specific intact foods is the focus of building a nutrient-rich dietary platform, the list of nutraceutical endowed foods is overwhelming. Often, the concentration, isolation, and/or extraction of key foods or nutrients garners the most attention. Once the consumable nutritional offering delivery form transitions to pills, concentrated liquids, or powders packaged up and labeled, they become dietary supplements. While the nutritional information for conventional food is expressed on the Nutrition Facts panel, the nutrition offering in dietary supplements is captured in a Supplement Facts panel. Specific rules and regulations apply to dietary supplements and functional foods, as outlined by one or more federal entities like the Food & Drug Administration (FDA) in the United States. Most of the remaining chapter will provide an overview of some of the key regulatory aspects in the functional food and dietary supplement marketplace.
2.2 FOOD & DRUG ADMINISTRATION, FOOD, VS DIETARY SUPPLEMENTS

2.2.1 HISTORY OF THE FOOD & DRUG ADMINISTRATION AND DIETARY SUPPLEMENTS

In the United States, the FDA oversees a vast number of activities and products, including foods (other than meat and poultry), human and animal drugs, and cosmetics.\(^1\) What began in 1862 as the Division of Chemistry (a single chemist in the U.S. Department of Agriculture) has evolved into the FDA as it exists today under the Department of Health and Human Services.\(^1\) The first regulation, the Pure Food and Drugs Act, was signed by President Theodore Roosevelt in 1906 and prohibited misbranded and adulterated food and drugs in interstate commerce.\(^2\) Although the Pure Food and Drugs Act was a significant step in the right direction, gaps existed in the commodities it covered, many hazardous consumer products remained on the market, and many products were not covered by the Act at all.\(^2\)

President Franklin Roosevelt was elected in 1930 at a time when journalists and consumer protection organizations were pushing for Congress to replace the 1906 law.\(^3\) The catalyst for change came following the death of over 100 people, including many children, in 1937.\(^3\) Elixir Sulfanilamide was an untested new sulfa drug that was marketed by a Tennessee drug company.\(^3\) The solvent in Elixir Sulfanilamide was a chemical analogue of antifreeze, a highly toxic chemical used in motor vehicles, which can be fatal if consumed.\(^3\) On June 25, 1938, President Franklin Roosevelt signed the Food, Drug, and Cosmetic Act (FDCA), which created tighter controls over drugs and food, included new consumer protection provisions, and gave the government greater enforcement ability.\(^4\) The FDCA, as amended, continues to be in force to this day.\(^4\)

Prior to 1994, dietary supplements could only be marketed and labeled the same way as “conventional foods.” This meant that the ingredients in dietary supplements had to be “generally recognized as safe” (GRAS) or specifically covered by a food additive regulation.\(^5\) During this time, dietary supplement claims were governed by the same standard as foods. As a result, claims made about a dietary supplement’s effect on the healthy structure or function of the body typically caused these supplements to be considered a misbranded or unapproved new drug by the FDA.\(^5\)

The law was clearly not working from an industry perspective. Thus, the dietary supplement industry lobbied Congress to amend the FDCA as it pertained to dietary supplements.\(^6\) In 1994, Congress passed the Dietary Supplement Health and Education Act (DSHEA).\(^4\) Although still classifying dietary supplements as a “food” under the FDCA, DSHEA established a clearer and more practical regulatory framework for the regulation of dietary supplements. Among other things, DSHEA created a legal definition for “dietary supplements” and “dietary ingredients,” established specific labeling requirements, and authorized the FDA to establish current Good Manufacturing Practices (cGMP) regulations for supplements.\(^7\)

2.2.2 DIETARY SUPPLEMENT HEALTH AND EDUCATION ACT

In October 1994, President Clinton signed DSHEA into law. The statute was enacted amid claims that the FDA was distorting the then-existing provisions of the FDCA to improperly deprive the public of safe and popular dietary supplement products.

DSHEA defines a “dietary supplement” as a product that is intended to supplement the diet and contains one or more “dietary ingredients.” By definition, the “dietary ingredients” in these products may include vitamins; minerals; herbs or other botanicals; amino acids; dietary substances for use by man to supplement the diet by increasing the total dietary intake; and substances such as enzymes, organ tissues, and glandular extracts. Further, dietary ingredients may also include extracts, metabolites, or concentrates of those substances. Vitamins, minerals, and amino acids are defined by their ability to provide nutrients to the human body.\(^8\) For this reason, FDA has stated that synthetic versions of vitamins, minerals, and amino acids are considered “dietary ingredients” under DSHEA.\(^8\) On the other hand, herbs and botanicals are defined by their state of matter and not by their ability to provide nutrients to the human body. They include plants, algae, fungi, their exudates...
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(secretions), and their physical parts. FDA has stated that synthetic copies of herbs and botanicals are not considered “dietary ingredients” because these substances have never been part of the herb or botanical in the first place. However, a recent decision by the United States Court of Appeals for the Eleventh Circuit holds contrary to FDA’s long-held position regarding synthetic botanicals. In United States of America v. Undetermined Quantities of All Articles of Finished and In-Process Foods, raw ingredients (bulk powders, bulk capsules), with any lot number, size, or type container, whether labeled, et al, the Court stated “If a product is indeed a dietary supplement because it contains a qualifying dietary ingredients – including, for example, an herb or other botanical – a manufacturer may take the dietary ingredient from nature or produce if artificially.” This is a major decision, as the FDA has sent numerous warning letters to companies claiming that the ingredients contained in the company’s products render the product adulterated because the ingredient is a synthetic botanical. What will happen with this new determination remains to be seen.

The most often confused aspect of the definition of a dietary ingredient is the phrase “a dietary substance for use by man to supplement the diet by increasing the total dietary intake.” Does this give the green light for anything to be a dietary ingredient because it can increase the dietary intake above zero? No; because the term “dietary substance” is not defined in the FDCA or other regulation, FDA interprets it according to its common, usual meaning. Based on the common, usual meaning of the terms contained in the phrase, FDA interprets this subsection to mean “food and food components that humans eat as part of their usual diet.” FDA makes clear that one cannot increase the “total dietary intake” of something that is not part of the human diet in the first place.

Dietary supplements may be found in many forms, such as tablets, capsules, softgels, gelcaps, liquids, or powders, but may only be intended for oral ingestion. Dietary supplements cannot be marketed or promoted for sublingual, intranasal, transdermal, injectable, or any other route of administration except oral ingestion. For this reason, a dietary supplement that states on its label, “place drops under the tongue” (suggesting absorption through the mucosa) would be considered misbranded by the FDA. However, a dietary supplement that states on its label “place drops under the tongue and swallow” (suggesting absorption through the gastrointestinal tract) would likely be an acceptable method of delivery for a dietary supplement.

A supplement can be found in other forms, including those that mirror “conventional foods” such as a bar or shake, as long as the information on its label does not represent the product as a conventional food or a sole item of a meal or diet. Whichever form the dietary supplement takes, the labeling and marketing must make clear that the product is not intended to be a meal by itself or used to replace a meal. One of the best examples of this is in the form of a bar. Protein bars can be found in almost every grocery store, supplement shop, and even convenience stores across America. What makes one bar a supplement while another is a food? Certainly, there are several factors that go into this determination, such as whether it is labeled with a Supplement Facts panel or a Nutrition Facts Panel and which ingredients are used. However, for the purposes of the definition of a dietary supplement under DSHEA, the determination of whether the bar is a food or a supplement comes down to the intended use of the product. If the bar is intended to be eaten in place of a meal or as a snack in between meals, then that bar is a conventional food and should be labeled accordingly. If the bar is intended to be consumed to provide an extra source of protein to the diet and is not marketed to be eaten in place of a meal, then the bar would be a supplement.

Finally, DSHEA provides two sections about what a dietary supplement does, and does not, include. First, DSHEA states that a dietary supplement does include “an article that is approved as a new drug … certified as an antibiotic … or licensed as a biologic” if the article was marked as a dietary supplement or as a food prior to such approval, certification, or license. A perfect example of this is in the case of fish oil. Fish oil supplements have been marketed and sold in the United States for centuries, long before the passage of DSHEA. In the early 2000s, Reliant Pharmaceuticals developed a highly purified, chemically altered version of omega-3-acid ethyl esters that was put through the FDA drug approval process. The FDA-approved prescription fish oil Lovaza was sold by GlaxoSmithKline for the treatment of very high triglycerides. Because omega-3 fish oils were
marketed and sold as dietary supplements prior to Lovaza’s approval as a drug, they are still able to be legally marketed and sold as dietary supplements notwithstanding the new drug approval. The same is true for other products that were marketed and sold as dietary supplements prior to their approval as drugs—vitamin D is available as a dietary supplement and as a prescription drug called Drisdol.

Second, this section of DSHEA explains that a dietary supplement does not include “an article authorized for investigation as a new drug, antibiotic, or biological for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public” if the article was not marketed as a dietary supplement or food prior to such authorization. This means that if a pharmaceutical company conducts substantial clinical investigations for a substance, and the public is made aware of these investigations (typically through press releases from the company), then that substance cannot be a dietary supplement unless it was marketed as such prior to the investigations. This is one of the major obstacles being faced by companies that are selling cannabidiol (CBD) as a dietary supplement. The pharmaceutical company GW Pharmaceuticals began conducting substantial clinical investigations that were made public on its CBD drug Epidiolex in 2007. FDA has opined that CBD was not sold as a dietary supplement prior to GW Pharmaceuticals’ clinical investigations, and as a result is not a legal dietary supplement. Companies that market and sell CBD argue that CBD was sold as a dietary supplement prior to GW Pharmaceutical’s clinical investigations; however, at this point, FDA has expressed that there has not been evidence to validate the truth of that argument.

Contrary to widespread mainstream media claims, DSHEA did not leave the industry unregulated. The dietary supplement industry is in fact regulated by the FDA as a direct result of DSHEA. The law ensures the authority of the FDA to provide legitimate protections for the public health. In addition to the FDA, the Federal Trade Commission (FTC) has jurisdiction over the marketing claims that dietary supplement manufacturers or companies make about their products. The FDA and FTC operate in a cooperative fashion to regulate the dietary supplement industry. In this respect, the extent to which information is shared and jurisdiction between these two entities overlaps with regard to the marketing and advertising of dietary supplements continues to increase.

### 2.3 NUTRITION PRODUCT LABELING

#### 2.3.1 Nutritional Labeling and Education Act

The Nutritional Labeling and Education Act (NLEA) of 1990 amended the FDCA to give the FDA authority to require nutrition labeling on most food packages, including dietary supplements. DSHEA further expanded on this in part by defining the term “dietary supplement” but also by requiring specific labeling requirements for dietary supplements. The labeling requirements for both foods and dietary supplements can be found in 21 C.F.R. 101.

Labeling accuracy is important, and claims regarding nutrient levels must meet certain guidelines. In the U.S., the FDA classifies nutrients that are declared on Nutrient Facts and Supplement Facts as Class I or II as follows:

- **Class I Nutrients**—Nutrients that are specifically added to food (e.g., fortified food) to increase its nutritional value or formulated as part of a dietary supplement. These nutrients include added vitamins, minerals, and fiber, as well as nutraceutical nutrients such as amino acids (e.g., taurine, citrulline, caffeine, plant extracts, etc.). Class I nutrients must be present at 100% or more of the value declared on the label all the way to the end of a product’s expiration date. Class I nutrients would include vitamins and minerals added to a breakfast cereal as well as nutrients formulated into a multivitamin/mineral supplement. In addition, if a specific nutrient is called out in the Statement of Identity on the front of the package (e.g., protein powder or protein bar), then the protein listed in the Nutrition Facts panel
becomes a Class I nutrient. The same is true if a product makes a nutrient content claim somewhere on the package/label (e.g., “10 grams of protein”) in a food not commonly assumed to deliver that nutrient in significant amounts: then in this case protein could be classified as a Class I nutrient as well.

- **Class II Nutrients**—Nutrients that are naturally occurring in an intact/near intact food (e.g., fruits, vegetables, oatmeal) or recipe foods (e.g., baked goods, peanut butter) can vary in concentration for reasons that cannot be controlled or predicted easily. Examples would be vitamin C in picked oranges or calcium in whole milk. Class II nutrients must be present at 80% or more of the value declared on the label.

- **Third Group Nutrients**—In addition, specific nutrients of health-related interest are grouped together as a “third group,” which cannot exceed 120% of label claim. Third group nutrients include calories, sugars, total fat, saturated fat, cholesterol, and sodium.

Five statements are required on the containers and packages of both dietary supplements and foods. These statements include: (1) the statement of identity; (2) the net quantity of contents; (3) the nutrition labeling; (4) the ingredient list; and (5) the name and place of business of the manufacturer, packer, or distributor.\(^{14}\) The statement of identity is the name of the dietary supplement or food product and must be placed on the principal display panel (the panel that faces the consumer). The statement of identity of a food, including dietary supplements, is the name specified by federal law or regulation, or the common or usual name of the food.\(^{15}\) For dietary supplements, the regulations specify that the statement of identity must include the term “dietary supplement”; however, the word “dietary” may be replaced with a description of the type of dietary ingredients in the product.\(^{15}\) For example, the statement of identity can be “protein supplement,” in the case of a protein powder that is marketed and sold as a dietary supplement.

The net quantity of contents statement is located on the principal display panel and informs consumers of the amount of product that is in the container or package.\(^{16}\) The net quantity of contents statement can be expressed in weight, measure, numerical count, or a combination of numerical count and weight or measure.\(^{16}\) When expressed in weight or measure, the net quantity of contents statement must specify both metric and U.S. Customary System terms, with the U.S. terms listed first and the metric terms listed parenthetically.\(^{16}\) In the case of a dietary supplement marketed in the form of tablets, the net quantity of contents can be stated as the number of pills in the container (e.g., 60 tablets). In the case of a powdered dietary supplement, the net quantity of contents can be stated as the weight of the powder in the container (e.g., 3 LB [1.36 KG]).

The nutrition label for a dietary supplement is called a “Supplement Facts” panel, while the nutrition label for conventional foods is called a “Nutrition Facts” panel.\(^{17}\) There are specific differences between a Supplement Facts panel and a Nutrition Facts panel. The key difference is that the Nutrition Facts panel for conventional foods cannot list nutrients for which the FDA has not determined a Recommended Daily Value (RDV), while the Supplement Facts panel for dietary supplements must list these nutrients. For example, while red meat contains creatine, the Nutrition Facts panel of a steak cannot list the amount of creatine it contains. A post-workout recovery powder that contains creatine as an active ingredient within the product would list the amount of creatine in the Supplement Facts panel.

The ingredient list for dietary supplements and conventional foods is located directly underneath the Supplement or Nutrition Facts panel. The major difference between the ingredient labeling of dietary supplements as compared to conventional foods is that sources of dietary ingredients may be listed within the “Supplement Facts” panel itself.\(^{18}\) For example, in a dietary supplement containing calcium, calcium (as calcium carbonate) can be listed directly in the Supplement Facts panel. When listed in this manner, “calcium carbonate” would not be listed in the ingredient list. On the other hand, conventional foods are not permitted to list the source ingredients in the “Nutrition Facts” panel. Instead, conventional foods list all the ingredients contained in the product in the ingredient list underneath the Nutrition Facts panel.
Finally, the name and place of business of the manufacturer, packer, or distributor must be placed on the principal display panel or the information panel (the panel to the right of the principal display panel). When the food or dietary supplement is not manufactured by the person, or company, whose name appears on the label, the name must be qualified by a phrase that reveals the connection between the person and the food or supplement. This could be stated as, “Manufactured for John’s Supplements,” “Distributed by John’s Supplements,” or another phrase that expresses the facts. The statement of the place of business includes the street address, city, state, and ZIP code, except that the street address can be omitted if it is shown in a current city directory or telephone directory.

While the five statements above are mandatory for all foods, including dietary supplements, there are additional statements that may be required depending on certain circumstances. As explained below, for dietary supplements, the “FDA Disclaimer” is required if the product bears any “structure function claims” on its label. This disclaimer must be placed in a box either immediately adjacent to the claim with no “intervening material,” or elsewhere on the same panel or page that bears the statement. If the disclaimer is placed on another panel, it must be linked by a symbol (such as an asterisk) that refers to the disclaimer. For foods and dietary supplements that contain a “major food allergen,” the package or container must disclose the presence of the major food allergen. The Food Allergen Labeling and Consumer Protection Act of 2004 (FALCPA) requires that food labels must clearly identify the food source names of any ingredients that are one of the major food allergens. The eight major food allergens designated by FALCPA are milk, eggs, fish, crustacean shellfish, tree nuts, peanuts, wheat, and soybeans. Contrary to what is typically seen on food labels, the statute does not require a company to provide a warning about possible cross-contamination. This means that statements about a product being produced on “shared equipment” or “in a facility that also manufactures nuts” are not required.

### 2.3.2 Marketing Claims

According to the 1990 Nutrition Labeling and Education Act, the FDA can review and approve health claims (claims describing the relationship between a food substance and a reduced risk of a disease or health-related condition) for dietary ingredients and foods. However, since the law was passed, the FDA has only approved a few health claims. The delay in reviewing health claims of dietary supplement ingredients resulted in a lawsuit, <i>Pearson v. Shalala</i>, filed in 1995. After years of litigation, in 1999, the U.S. Court of Appeals for the District of Columbia Circuit ruled that qualified health claims may be made about dietary supplements with approval by the FDA, as long as the statements are truthful and based on adequate science. Supplement or food companies wishing to make health claims or qualified health claims about supplements can submit research evidence to the FDA for review.

The FTC also regulates the supplement industry, specifically in regard to truth in advertising. Unsubstantiated claims invite enforcement by the FTC (along with the FDA, state district attorney offices, groups like the Better Business Bureau, and plaintiff’s lawyers who file class action lawsuits). The FTC has typically applied a substantiation standard of “competent and reliable scientific evidence” to claims about the benefits and safety of dietary supplements. FTC case law defines “competent and reliable scientific evidence” as “tests, analyses, research, studies, or other evidence based on the expertise of professionals in the relevant area, that has been conducted and evaluated in an objective manner by persons qualified to do so, using procedures generally accepted in the profession to yield accurate and reliable results.” The FTC has claimed that this involves providing at least two clinical trials showing efficacy of the actual product, within a population of subjects relevant to the target market, supporting the structure/function claims that are made. While the exact requirements are still evolving, the FTC has acted against several supplement companies for misleading advertisements and/or structure/function claims.
2.3.3 Structure Function and Benefit Claims

In the United States, dietary supplements are classified as food products, not drugs, and there is generally no mandate to register products with the FDA or obtain FDA approval before producing or selling supplements to consumers. However, if a dietary supplement manufacturer makes claims about their product, the company must submit the claims to FDA within 30 days of marketing the product. Compare this, for example, with Canada, where under the Natural Health Product (NHP) Regulations enacted in 2004, supplements must be reviewed, approved, and registered with Health Canada. The rationale for the U.S. model is based on a presumed long history of safe use; hence, there is no need to require additional safety data.

DSHEA also requires supplement marketers to include on any label displaying structure/function claims (i.e., claims that the product affects the structure or function of the body) the mandatory FDA disclaimer “This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.” Opponents of dietary supplements often cite this statement as evidence that the FDA does not review or approve dietary supplements. However, most dietary ingredients have been “grandfathered in” as DSHEA-compliant ingredients due to a long history of safe use, and those products containing new ingredients must generally be submitted by a notification to the FDA for a safety review prior to being brought to market.

2.4 Manufacturing and Ingredients

2.4.1 Good Manufacturing Practices

When DSHEA was passed in 1994, it contained a provision requiring that the FDA establish and enforce current Good Manufacturing Practices (cGMPs) for dietary supplements. However, it was not until 2007 that the cGMPs were finally approved, and not until 2010 that the cGMPs applied across the industry, to large and small companies alike. The adherence to cGMPs has helped protect against contamination issues and should serve to improve consumer confidence in dietary supplements. The market improved as companies became compliant with cGMPs, as these regulations imposed more stringent requirements such as Vendor Certification, Document Control Procedures, and Identity Testing. These compliance criteria addressed the problems that had damaged the reputation of the industry with a focus on quality control, record keeping, and documentation.

However, it does appear that some within the industry continue to struggle with compliance. In fiscal year 2017, it was reported that approximately 23.48% of the FDA’s 656 total cGMP inspections resulted in citations for failing to establish specifications for the identity, purity, strength, and composition of dietary supplements. Further, 18.47% of those inspected were cited for failing to establish and/or follow written procedures for quality control operations. Undoubtedly, relying on certificates of analysis from the raw material supplier without further testing, or failing to conduct identity testing of a finished product, can result in the creation of a product that fails to contain the proper amounts of ingredients it should, or contains something it should not contain, such as synthetic chemicals or even pharmaceutical drugs. All members of the industry need to ensure compliance with cGMPs.

2.4.2 New Dietary Ingredients

Recognizing that new and untested dietary supplement products may pose unknown health issues, DSHEA distinguishes between products containing dietary ingredients that were already on the market and products containing new dietary ingredients (NDIs) that were not marketed prior to the enactment of the law. A “new dietary ingredient” is defined as a dietary ingredient that was not marketed in the United States before October 15, 1994. DSHEA grants the FDA greater control over
supplements containing NDIs. A product containing an NDI is deemed adulterated and subject to FDA enforcement sanctions unless it meets one of two exemption criteria: Either (1) the supplement in question contains “only dietary ingredients which have been present in the food supply as an article used for food in a form in which the food has not been chemically altered”; or (2) there is a “history of use or other evidence of safety” provided by the manufacturer or distributor to the FDA at least 75 days before introducing the product into interstate commerce. The first criterion was silent in the law as to how and by whom presence in the food supply as food articles without chemical alteration is to be established. The second criterion—applicable only to new dietary ingredients that have not been present in the food supply—requires manufacturers and distributors of the product to take certain actions. Those actions include submitting, at least 75 days before the product is introduced into interstate commerce, information that is the basis on which a product containing the new dietary ingredient is “reasonably expected to be safe.” That information would include: (1) the name of the new dietary ingredient and, if it is an herb or botanical, the Latin binomial name; (2) a description of the dietary supplement that contains the new dietary ingredient, including (a) the level of the new dietary ingredient in the product, (b) conditions of use of the product stated in the labeling, or if no conditions of use are stated, the ordinary conditions of use, and (c) a history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, is reasonably expected to be safe.

In July 2011, the FDA released a Draft Guidance for Industry, entitled “Dietary Supplements: New Dietary Ingredient Notifications and Related Issues.” While a guidance does not carry the authority or the enforceability of a law or regulation, the FDA’s NDI draft guidance represented the agency’s current thinking on the topic. The guidance prompted great controversy, and FDA agreed to issue a revised draft guidance to address some of the issues raised by industry. In August 2016, FDA released a revised Draft Guidance that replaced the 2011 Draft Guidance. The purpose of the 2016 Draft Guidance was to help manufacturers and distributors decide whether to submit a premarket safety notification to FDA, help prepare NDI notifications in a manner that allows FDA to review and respond more efficiently and quickly, and improve the quality of NDI notifications. The 2016 Draft Guidance has been criticized by industry and trade associations for its lack of clarity and other problems. Some of these issues include the lack of clarity regarding pre-DSHEA (grandfathered) ingredients and FDA requiring an NDI notification even if another manufacturer has submitted a notification for the same NDI.

The lack of clarity surrounding the “new” Draft Guidance has led to many NDI notifications being rejected by FDA for lack of safety data and other issues. Other companies have opted to utilize the “Self-Affirmed GRAS” route in order to “bypass” the NDI notification process. Self-Affirmed GRAS is a process in which a company engages a team of scientific experts to evaluate the safety of their ingredient. There is no requirement that the safety dossier be submitted to FDA, but it is retained by the company as an internal document that may be relied upon if the ingredient is challenged by the FDA. The FDA has expressed its concern with this practice and does not encourage dietary supplement manufacturers to use Self-Affirmed GRAS to avoid submitting NDI notifications. In any event, the likelihood of another revised Draft Guidance from the FDA becoming available in the future is high, and possibly more enforcement actions taken against companies that market an NDI without submitting a notification.

2.4.3 INTELLECTUAL PROPERTY AND PATENTS AND NOVEL INGREDIENTS

Companies can develop and pursue patents involving new processing and purification processes if the nutrient has not yet been extracted in a pure form or is not available in large quantities. Reputable raw material manufacturers conduct extensive tests to examine the purity of their raw ingredients. When working on a new ingredient, companies often conduct a series of toxicity studies on the new nutrient once a purified source has been identified. The company would then compile a safety dossier and communicate it to the FDA as a New Dietary Ingredient submission, with the hopes of it being allowed for lawful sale in the United States.
When a powdered formulation is designed, the list of ingredients and raw materials is typically sent to a flavoring house and packaging company to identify the best way to flavor and package the supplement. In the nutrition industry, several main flavoring houses and packaging companies exist who provide these services for supplement companies. Most reputable dietary supplement manufacturers submit their production facilities to inspection from the FDA and adhere to cGMPs, which represent industry standards for good manufacturing of dietary supplements.

2.4.4 **Product Testing Programs**

Some companies also submit their products for independent testing by third-party companies to certify that their products meet label claims. The certification services offered by these companies may include product testing, GMP inspections, ongoing monitoring, and use of branded markings indicating the products comply with inspection standards and screening for contaminants. More recently, companies have subjected their products for testing by third-party companies to inspect for banned or unwanted substances (e.g., Banned Substances Control Group, Informed Choice, NSF International, etc.). These types of tests help ensure dietary supplements made available to athletes do not contain substances banned by the International Olympic Committee, the World Anti-Doping Agency, or other athletic governing bodies (e.g., NFL, NCAA, MLB, NHL, etc.). While third-party testing does not guarantee that a supplement is void of banned substances, the likelihood is reduced. Moreover, consumers can request copies of the results of these tests, and each product that has gone through testing and earned certification can be researched online to help athletes, coaches, and support staff understand which products best meet their needs. In many situations, companies who are not willing to provide copies of test results or certificates of analysis should be viewed with caution, particularly for individuals whose eligibility to participate in athletics and employment might be compromised if a tainted product is consumed.

2.5 **Product Safety**

2.5.1 **Adverse Event Reporting**

In response to growing criticism of the dietary supplement industry, the 109th Congress passed the first mandatory Adverse Event Reporting (AER) legislation for the dietary supplement industry. In December 2006, President Bush signed into law the Dietary Supplement and Nonprescription Drug Consumer Protection Act, which took effect on December 22, 2007. After much debate in Congress and input from the FDA, the American Medical Association (AMA), many of the major supplement trade associations, and a host of others all agreed that the legislation was necessary, and the final version was approved by all. In short, the Act requires that all “serious adverse events” regarding dietary supplements be reported to the Secretary of Health and Human Services. The law strengthened the regulatory structure for dietary supplements and built greater consumer confidence, as consumers have a right to expect that if they report a serious adverse event to a dietary supplement marketer, the FDA will be advised about it.

An adverse event is any health-related event associated with the use of a dietary supplement that is adverse. A serious adverse event is an adverse event which (A) results in (i) death, (ii) a life-threatening experience, (iii) inpatient hospitalization, (iv) a persistent or significant disability or incapacity, or (v) a congenital anomaly or birth defect; or (B) requires, based on reasonable medical judgment, a medical or surgical intervention to prevent an outcome described under subparagraph (A). Once it is determined that a serious adverse event has occurred, the manufacturer, packer, or distributor (responsible person) of a dietary supplement whose name appears on the label of the supplement shall submit to the Secretary of Health and Human Services any report received of the serious adverse event accompanied by a copy of the label on or within the retail packaging of the dietary supplement. The responsible person has 15 business days to submit the report to the FDA after being notified of
the serious adverse event. Following the initial report, the responsible person must submit follow-up reports of new medical information that they receive for 1 year.

Although many dietary ingredients have been introduced into dietary supplements since October 1994 and have not been submitted to the FDA for a safety review, nutritional supplementation appears generally safe, especially when compared to prescription drugs. While there are over 50,000 dietary supplements registered with the Office of Dietary Supplement’s “Dietary Supplement Label Database,” a 2013 Annual Report (released in 2015) of the American Association of Poison Control Centers revealed zero fatalities occurred due to dietary supplements compared to 1692 deaths due to drugs. A 2015 report by the Centers for Disease Control alarmingly suggests that 2,287,273 emergency room visits were due to prescription drug-related events—dwarfing the 3266 emergency room visits due to dietary supplements (adjusted from 23,000 visits after excluding cases of older adults choking on pills, allergic reactions, unsupervised children consuming too many vitamins, and persons consuming ingredients not defined by DSHEA as a dietary supplement).22

2.5.2 ADULTERATED SUPPLEMENTS

The FDA has various options to protect consumers from unsafe supplements. The Secretary of the Department of Health and Human Services (which falls under the FDA’s oversight) has the power to declare a dangerous supplement to be an “imminent hazard” to public health or safety and immediately suspend sales of the product. The FDA also has the authority to protect consumers from dietary supplements that do not present an imminent hazard to the public but do present certain risks of illness or injury to consumers. The law prohibits introducing adulterated products into interstate commerce. A supplement shall be deemed adulterated if it presents “a significant or unreasonable risk of illness or injury.” The standard does not require proof that consumers have actually been harmed or even that a product will harm anyone. It was under this provision that the FDA concluded that dietary supplements containing ephedra, androstenedione, and 1-3, Dimethylamylamine (DMAA) presented an unreasonable risk. Most recently, the FDA imposed an importation ban on the botanical Mitragyna speciosa, better known as Kratom. In 2016, the FDA issued Import Alert #54-15, which allows for detention without physical examination of dietary supplements and bulk dietary ingredients that are, or contain, Kratom. Criminal penalties are present for a conviction of introducing adulterated supplement products into interstate commerce. While the harms associated with dietary supplements may pale in comparison to those linked to prescription drugs, recent pronouncements from the U.S. Department of Justice confirm that the supplement industry is being watched vigilantly to protect the health and safety of the American public.

2.5.3 A SAFER INDUSTRY AHEAD

As demonstrated, while some argue that the dietary supplement industry is “unregulated” and/or may have suggestions for additional regulation, manufacturers and distributors of dietary supplements must adhere to several federal regulations before a product can go to market. The safety of the dietary supplement industry has also been demonstrated in the relative infrequency in recalls. According to data obtained from the FDA and published in the American Herbal Products Association’s August publication, only 2% of more than 800 recalls initiated in 2019 involved dietary supplements.23 Further, before marketing products, manufacturers must have evidence that their supplements are generally safe to meet all the requirements of DSHEA and other FDA regulations. For this reason, over the last 20 years, many established supplement companies have employed research and development directors who help educate the public about nutrition and exercise, provide input on product development, conduct preliminary research on products and ingredients, and/or assist in coordinating research trials conducted by independent research teams (e.g., university-based researchers or clinical research sites). These companies also consult with marketing and legal teams with the responsibility of ensuring that structure/function claims do not misrepresent the results of research findings. This has increased job
opportunities for sports nutrition specialists as well as enhancing external funding opportunities for research groups interested in exercise and nutrition research.

Although some companies have falsely attributed research on different dietary ingredients or dietary supplements to their own products, suppressed negative research findings, and/or exaggerated results from research studies, the overall trend in the sports nutrition industry has been to develop scientifically sound supplements. This trend toward greater research support is the result of: (1) attempts to honestly and accurately inform the public about results, (2) efforts to obtain data to support the safety and efficacy of products for the FDA and the FTC, and/or (3) endeavors to provide scientific evidence to support advertising claims and increase sales. While the push for more research is due in part to greater scrutiny from the FDA and FTC, it is also in response to an increasingly competitive marketplace where established safety and efficacy attracts more consumer loyalty and helps ensure a longer lifespan for the product in commerce. Companies that adhere to these ethical standards tend to prosper, while those that do not will typically struggle to comply with the FDA and FTC guidelines, which results in a loss of consumer confidence and an early demise for the product.

REFERENCES

1. https://www.fda.gov/AboutFDA/WhatWeDo/History/FOrgsHistory/EvolvingPowers/ucm124403.htm
2. https://www.fda.gov/AboutFDA/Transparency/Basics/ucm214416.htm
3. https://www.fda.gov/AboutFDA/WhatWeDo/History/FOrgsHistory/EvolvingPowers/ucm054826.htm
6. https://www.fda.gov/AboutFDA/WhatWeDo/History/FOrgsHistory/EvolvingPowers/ucm125632.htm