Nerac White Paper

Bringing Functional Foods to Market: FDA's Regulatory Mandate Drives the Process

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Introduction

Bringing a new functional food product to market is a potentially complex process with many decision points driven by the US Food and Drug Administration's (FDA) regulatory mandate. There is no single definition for functional foods, also known as nutraceuticals. They may encompass a range of products and uses, including dietary supplements, medical foods food additives or drugs. Careful consideration of the potential market for a product must be weighed against the time and expense necessary to determine the exact status of a product under the laws and regulations administered by the FDA. The regulatory status of a product is quite often the basis for the marketing of that product, so every possible consideration should be given to assure scientifically sound and legally defensible claims made for the functionality of the product.

This report outlines the requirements for each potential option and the relevant advantages and drawbacks of each pathway. It is intended to provide valuable background information on regulatory compliance, specific types of claims and key product categories.

Overview of Regulation

New chemical and biological substances intended for use in humans are subject to regulation by the FDA unless specifically exempted. As discussed more fully below, many substances, when used as intended, may potentially be regulated by the FDA as food additives, dietary supplements, medical foods or drugs. The designation depends in large part on **claims** for effects of the product when administered to humans.

Regulation as a **food additive** is contingent on establishing that a substance, when used as intended, is Generally Recognized as Safe (GRAS) by a panel of suitably qualified experts, or on successful submission of a Food Additive Petition. The major drawback of this approach for dietary supplements (nutraceuticals) is that the substance must also exert a technical effect on the food to which it is added. Another drawback is that the Food Additive Petition process is lengthy and expensive. It often requires investment of millions to support safety testing that can take months to complete, followed by lengthy evaluation periods by the FDA.

Another possible approach involves the designation of a substance as a **medical food**. In this case, a GRAS determination is necessary, and the substance can only be administered at a hospital, clinic or long-term-care facility under the supervision of a physician. GRAS determinations are generally accomplished in a matter of months, involving only the review of existing peer reviewed data. Typical investments are on the order of $20,000 to $50,000. The substance must also be a nutrient as defined by the FDA in order to be considered a medical food.

Regulation of a substance as a **dietary supplement** requires a suitable GRAS designation if the substance is not already a recognized food ingredient or botanical, as well as adequate data supporting a structure-function claim, for example, "promotes kidney health." The permitted claim language precludes a claim

such as "treats uremia." Developing scientifically sound and legally defensible structure-function claims is the most cost effective route to market, requiring only FDA notification and an investment of under $5000.

The Investigational New Drug-New Drug Application (IND-NDA) approach is recommended by the FDA for substances for which therapeutic or diagnostic claims will be made. If successful, this will lead to its designation as a **drug**, and the ability to make "treatment" claims. The IND-NDA process is lengthy (on the order of ten years), and expensive (in the range of tens to hundreds of millions of dollars).

Since it is our practice to deliver cost-effective, actionable advice, we begin with the simplest approach, and progress in cost and complexity from structure-function claim to new drug application.

Structure-Function Claims

Structure-function claims differ from health claims and qualified health claims in that the FDA need only be notified that they are being made prior to marketing the product. The FDA exercises "enforcement discretion" for structure-function claims. Thus, claims may or may not be subject to agency review, and any such review occurs only after the product is on the market. Given the potential for agency review, it is prudent to have literature support for structure-function claims prior to marketing a dietary supplement or functional food product. The key requirement of a structure-function claim is that it cannot purport to act as a "drug" as defined by the Federal Food, Drug and Cosmetic Act (FFDCA), thus it may not claim to treat, cure or diagnose a disease. Structure-function claims may be made for dietary supplements *per se*, and for functional ingredients added to or otherwise components of a consumer food product.

Nutrient Content Claims

Nutrient content claims are specifically regulated by the FDA and familiar to most consumers in the form of the "Nutrient Facts" box on all packaged food. These include such items as caloric and fat content, vitamins, minerals, fiber, sugar, protein and other specific parameters. Nutritional contents are also regulated by the FDA in a relative sense in the form of claims such as "low fat," "high fiber," "reduced calorie," and the like. All of these relative claims have explicit definitions under the rules and regulations mandated by the FDA.

Health Claims and Qualified Health Claims

Health claims and qualified health claims require pre-market notification of and review by the FDA. The data requirements are rigorous, and most dietary supplement and functional food manufacturers rely on the FDA's list of previously approved claims for certain ingredients, unless potential market factors support undertaking an effort to seek new approval from the agency. These claims appear in the following table:

Figure 1 – FDA-Approved Health Claims and Qualified Health Claims

Health Claim		Qualified Health Claim	
Calcium, Vitamin D	Osteoporosis	**Tomatoes**	Certain cancers
Dietary Lipids	Cancer	**Calcium**	Colorectal cancer
Sat. Fat, Cholesterol	Heart risk	**Green tea**	Cancer
Non-cariogenic carbohydrate sweeteners	Dental caries (cavities)	**Monounsaturated fatty acids from olive oil**	Heart disease
Fiber	Cancer	**Selenium**	Cancer
Folic acid	Neural tube defects	**Antioxidant vitamins**	Cancer
Fruits and vegetables	Cancer	**Omega-3 fatty acids**	Heart disease
Soluble fiber	Heart risk	**Nuts**	Heart disease
Sodium	Hypertension	**B-vitamins**	Vascular disease
Soy protein	Heart risk	**Corn, canola oil**	Heart disease
Stannols/Sterols	Heart risk	**Phosphatidylserine**	Cognitive function
		Chromium picolinate	Diabetes
		Calcium	Hypertension

Source: USFDA

Dietary Supplements

The *Dietary Supplement Health and Education Acts of 1994* (DSHEA) defines a dietary supplement as "a product taken by mouth that contains a dietary ingredient intended to supplement the diet." The Federal Food, Drug and Cosmetic Act (FFDCA) distinguish between conventional food (or beverages) and dietary supplements in that, among other requirements, dietary supplements are "not represented for use as conventional food or as a sole item of a meal or diet."[1]

The FDA offers further guidance regarding the composition of dietary supplements; they must be one or any combination of the following:

- 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 dietary intake (e.g., enzymes or tissues from organs or glands), or
- A concentrate, metabolite, constituent or extract.

[1] DSHEA

These ingredients, as well as the liquid used for their delivery (e.g., water, fruit juice and milk), must have appropriate status as direct food additives or GRAS substances under the laws and regulations administered by the FDA. Additionally, dietary supplement manufacturers must register themselves pursuant to the *Bioterrorism Act of 2002*, and their products must be manufactured pursuant to current Good Manufacturing Practices (cGMP) to assure their identity, purity, quality, strength and composition.

The distinguishing features of dietary supplements are the claims made on the product labels. As we have pointed out above, there are four types of claims, health claims, qualified health claims, structure-function claims and nutritional claims, all are regulated by the FDA, and all point out various health benefits of consuming certain constituent components of the dietary supplement product.

GRAS Status

A key component of the FDA's regulatory approach to all food and drugs is the concept of GRAS, or General Recognition of Safety. A GRAS determination means that a substance is generally recognized as safe among experts qualified by scientific training and experience to evaluate its safety under the conditions of its intended use, and further, that the substance is **exempt from regulation by the FDA**. Experts comprising the GRAS panel evaluate peer-reviewed publications and other information to reach consensus on each substance submitted for review. Additional exclusions from FDA regulation as a food additive are made for:

- Pesticides or chemical residues on raw agricultural commodities,
- Pesticide chemicals *per se*,
- Color additives, or
- Substances used in accordance with a sanction or approval granted prior to the enactment of *Public Law 85-929* (enacted Sept. 6, 1958), the *Poultry Products Inspection Act,*[1] and the *Meat Inspection Act of March 4, 1907*.[2]

Food Additive

Any substance that is reasonably expected to become a component of food is a food additive, subject to pre-market approval by the FDA, unless the substance is GRAS under the conditions of its intended use, or meets one of the other exclusions from the food additive definition.[3] Any food additive that is

[1] 21 USC 451 *et seq*

[2] 34 Stat. 1260, as amended and extended (21 USC 71 *et seq*)

[3] §201 of the FFDCA

intended to have a technical effect in food must conform to the terms of a regulation prescribing its use or to an exemption for investigational use. Otherwise, the additive is deemed unsafe,[1] and any food containing an unsafe additive is deemed adulterated.[2]

Technical Effect

In general, a presumptive food additive must exert a technical in the food of which it is a component. A number of technical effects for which added substances may be used, such as antimicrobial agents, humectants, flavoring agents, surface-active agents, stabilizers and thickeners, are defined in 21 CFR 170.3(o). A substance added to food might have legitimate technical effects in food other than that intended; however, the quantity of the substance added to food shall not exceed the amount reasonably required to accomplish its intended technical effect(s) in the food. [3]

Food Additive Petition

In the event that a GRAS position cannot be reached a Food Additive Petition is required, and the substance is subject to a pre-market evaluation by the FDA. The components of a Food Additive Petition are:

- Identity of the substance
- Manufacturing process
- Specifications for food-grade material
- Stability of the added substance
- Intended technical effect and use
- Methodology for analysis of the added substance in food
- Consumer exposure

[1] §409 of the FFDCA

[2] §402(a)(2)(C) of the FFDCA

[3] 21 CFR 172.5(a)(1), 182.1(b)(1), and 184.1(b)

Medical Food

Additional regulatory structure and the ability to make medical claims are afforded by designation of a product as a medical food. A medical food is marketed for "dietary management of a specific disease or condition." Unlike drugs, neither dietary supplements nor medical foods are subject to pre-market approval by the FDA. There are three key features that distinguish medical foods from dietary supplements: (1) medical foods can be consumed orally or administered enterally, (2) a physician must supervise their use, and (3) it is a virtual certainty that medical food products will be subject to analysis and facility inspection under the FDA's *Medical Foods Program – Import and Domestic* compliance program. By contrast, dietary supplements cannot be administered enterally, physician involvement is not required, and they are not subject to the medical foods compliance program.

The *Orphan Drug Act* defines a medical food as "a food which is formulated to be consumed or administered enterally under the supervision of a physician, and which is intended for the dietary management of a specific disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation." All of a medical food's ingredients must have appropriate status as investigational food additives,[1] direct food additives, or GRAS substances. The FDA offers the following clarification of its requirements for a product to be considered a medical food; it must be:

- Specifically formulated as opposed to naturally occurring;
- A food for oral or tube feeding;
- Labeled for dietary management of a medical disorder, disease or condition; and
- Labeled to be used under medical supervision and obtained primarily from hospitals, clinics, or other medical or long term care facilities.

Medical foods are not subject to health claim and nutrient content labeling requirements under the *Nutrition Labeling and Education Act of 1990* (NLEA), but they are subject to general FDA rulemaking on the matter.[2] The label must contain a statement of identity, quantity of contents, manufacturer, and list of ingredients. The label must also contain notice of any allergens under the *Food Allergen Labeling and Consumer Protection Act of 2004* (FALCPA). Medical foods are subject to cGMP, *Registration of Food Facilities*,[3] and if applicable, the *Low Acid Canned Food* regulations[1] and *Emergency Permit Control* regulations.[2]

[1] 21 USC 321, 348

[2] 21 CFR 101

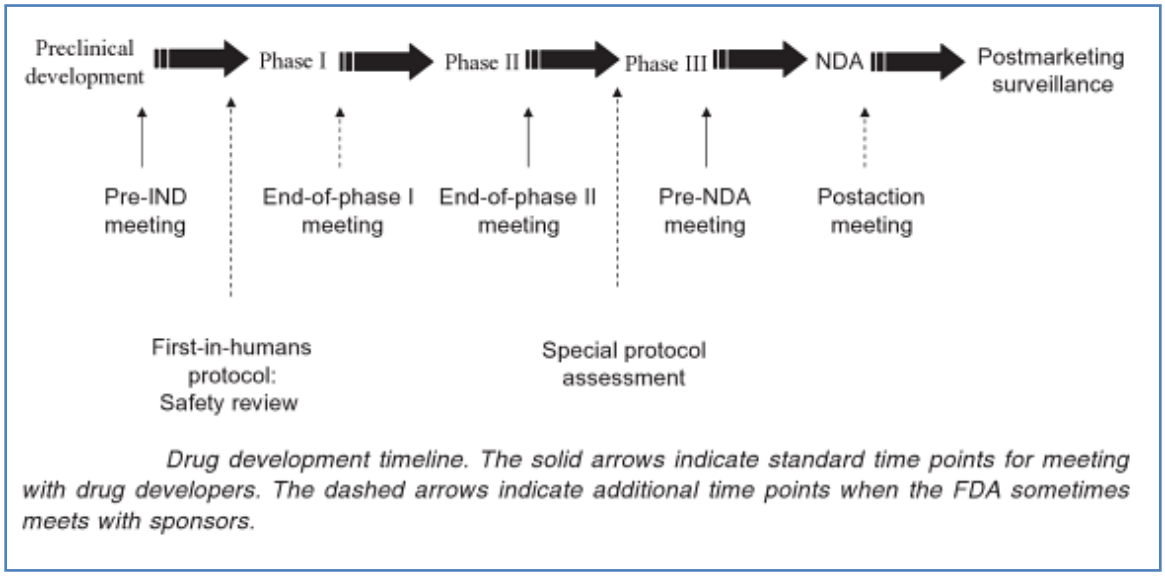
[3] 21 CFR 1

Designation as a Drug

The most lengthy (and costly) path to appropriate regulatory status and market for a functional product or ingredient is designation as a drug.

The FDA website quickly impresses visitors with the complexity and rigor of the current process of bringing a new drug to market. Courses, seminars and textbooks are available describing the details of the process for investigational drug candidates. Entire careers and clinical research companies are built on the preclinical stages of this process alone.

Figure 2 - Drug Development Process



Drug development timeline. The solid arrows indicate standard time points for meeting with drug developers. The dashed arrows indicate additional time points when the FDA sometimes meets with sponsors.

Source: USFDA

[1] 21 CFR 113

[2] 21 CFR 108

New Drug Application (NDA)

As stated on the FDA website, the goals of the NDA are to provide enough information to permit an FDA reviewer to reach the following determinations:

- Whether the drug is safe and effective in its proposed use(s), and whether the benefits outweigh the risks.
- Whether the drug's proposed labeling (package insert) is appropriate.
- Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are sufficient to preserve the drug's identity, strength, quality, and purity.

The NDA is the vehicle through which drug sponsors propose FDA approval of a new pharmaceutical for sale and marketing in the US. The data from animal studies and human clinical trials become incorporated into the NDA. The details of an NDA are equivalent to a drug's entire story, including the results of the animal studies; what happened in clinical trials; the ingredients of the drug; how the drug behaves in the body; and how it is manufactured, processed and packaged.

Conclusion

As this brief overview illustrates, bringing a new product to market, whether it is a dietary supplement, medical food, or food additive is substantively driven by the FDA's regulatory mandate. It is critical to understand the ramifications of the choices for a regulatory pathway: the stakes are high in terms of time and expense. Nerac can assist in navigating the regulatory landscape, providing data-driven, actionable information to support sound business decisions.

About the Analysts

Jeffrey Eberhard, Ph.D.

Jeffrey Eberhard, Ph.D., brings 13 years of industry experience to answering critical technical questions and creating solid business solutions for food, beverage, and pharmaceutical companies. Dr. Eberhard began his career with Morton International Specialty Chemicals (a division of Dow Chemical), where he applied analytical chemistry techniques to support assessments of the safety and efficacy of new chemical products. At Covance Laboratories, he supported regulatory submissions to the FDA and its European counterparts. At Keller and Heckman, Dr. Eberhard advised lawyers, governmental organizations and trade associations on regulatory, legislative, and international affairs regarding chemical and life sciences. At Exponent, he advised industrial clients regarding regulatory and international affairs. Dr. Eberhard spent a year as a patent examiner in the areas of pharmaceutical sciences and medical devices and is knowledgeable in the areas of intellectual property, food science and food packaging, pharmaceuticals, medical devices, polymers, plastics additives, environmental science, analytical chemistry, chromatography, mass spectroscopy, atomic spectroscopy, and occupational and public health.

Credentials
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Irene Zajac

Irene Zajac is a biochemist with a career in the pharmaceutical industry. Ms. Zajac conducts research and provides analysis for Nerac's clients in pharmaceutical, biotechnology, cosmetic and other health sciences. Her technical expertise includes separation techniques, HTS, assay development, protein chemistry, physical biochemistry, toxicology, clinical trials and pharmacovigilance. Clients rely on her research skills in IP and competitive intelligence. Ms. Zajac's lab career focused on aspects of cancer. She was a research scientist in Biometry & Risk Assessment at National Institute of Environmental Health Sciences; in Enzymology and Protein Chemistry at Glaxo; at Argonex Labs, she worked in Immunology toward a vaccine for ovarian cancer. Irene also has experience in clinical trials regulatory and monitoring with PRA International and has led scientific software training classes at Pfizer in the US and abroad. She is an inventor on a 2010 US patent application.

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