Regulatory Frameworks for Functional Foods and Dietary Supplements
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An understanding of the legal and regulatory requirements for foods, including dietary supplements and so-called functional foods, helps to focus attention on the special challenges that exist, which range from safety determinations to claim substantiation and consumer understanding. This article provides an overview of the Food and Drug Administration’s regulatory framework for these products; it also highlights issues that are emerging and will require consideration and dialog.

Key words: regulations, foods, dietary supplements

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Introduction
Reference is often made to dietary supplements and “functional foods” without an understanding of the regulatory frameworks under which they are marketed and the legislative provisions for their safety and effectiveness. Some would argue that the growing interest in so-called functional foods is a direct result of the increased marketing of dietary supplements. Both are regulated as foods rather than drugs, but from a regulatory perspective, they are different entities. There is some overlap between regulations for these products, but there are differences in pre-marketing versus post-marketing responsibilities for their safety and in provisions for claims and label statements. At times, these differences can have significant practical consequences or little practical consequences, but in any case do have the potential to confuse consumers.

Background
From a regulatory perspective, dietary supplements are defined by law1 as products that, among other things, are intended to supplement the diet and contain one or more of the following “dietary ingredients”: vitamins, minerals, herbs or other botanicals, amino acids, or other dietary substances for use by man to supplement the diet by increasing the total dietary intake, or concentrates, metabolites, constituents, extracts, or combinations of these ingredients. The term functional foods has no legal definition, however, and they are not recognized as a unique regulatory product category by the Food and Drug Administration (FDA). The concept of functional foods may have originated primarily as a marketing term, although researchers have paid considerable attention to them. Various attempts to define functional foods2,3 usually include reference to the activity of enhancing or augmenting a food to result in a health benefit of some type.

As a practical matter, functional food products are regulated by FDA as conventional foods and therefore come under the general provisions of the Federal Food, Drug and Cosmetic Act4 (the Act) that apply to all foods. Dietary supplements are also governed under many of the same provisions of the Act, but as a result of amendments passed by Congress in 1994, known collectively as the Dietary Supplement Health and Education Act (DSHEA),1 dietary supplements also are subject to specific provisions that do not apply to conventional foods and hence functional foods. The Congressional intent underlying DSHEA was twofold: (1) to facilitate consumer access to safe dietary supplements and (2) to specify FDA’s authority to remove unsafe products from the market. Since the passage of DSHEA, the dietary supplement industry has grown and a wide variety of products are available; these products range from the more traditional vitamin and mineral tablets to an increasing number of botanical substances in numerous forms. They are found for sale in gas stations, gyms, shopping malls, and retail stores, and can be purchased via the Internet. This makes dietary supplements readily available not only to adults, but to children and adoles-

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cents as well. While many of these changes appear to be consistent with the expectations and intent of DSHEA, they nevertheless present new regulatory challenges, most notably how to ensure that products on the market are safe under the post-market regulatory framework provided by DSHEA, and that their claims and the conditions of use for these products are appropriate.

Safety
In the current regulatory scheme, establishing safety is the threshold issue for both conventional foods (including functional foods) and dietary supplements. This is because under the Act, food products of any kind cannot be marketed unless they are considered to be safe. For foods, the model for safety has not traditionally been based on a consideration of risk versus benefit, as would be the case for drugs in which the interests in treating or curing disease conditions are balanced against the risk to a patient. Rather, regardless of the level of effectiveness, food products must be safe according to their applicable statutory safety standards. The increased focus on dietary supplements has resulted in an emerging dialog as to whether products such as these should in fact be regulated on a risk-versus-benefit paradigm; at this point in time the dialog continues.

Specific Provisions
Prior to 1994, all foods, including dietary supplements and what might have been functional foods, were subject to the same standard of safety. The ingredients for foods were either Generally Recognized as Safe (GRAS) for their intended use or, if not GRAS, were required to undergo a pre-marketing review process to determine their safety as a food additive. That is, the ingredients were either determined by FDA or independently by the manufacturers to be GRAS, or the ingredient was considered to be a new ingredient and the manufacturer submitted relevant safety data as part of a food additive petition. In the case of food additive petitions, the review process and data requirements are spelled out by regulation and in various guidance documents. Furthermore, the agency has recommended approaches for manufacturers in making self-determinations of GRAS, which typically involves expert review boards convened by manufacturers.

Just like conventional foods, functional foods are subject to the requirements mentioned above. Dietary supplement ingredients were exempted from the food additive provisions in 1994 by a provision of DSHEA. Dietary supplement manufacturers are instead required to determine on their own that the dietary ingredients present no significant or unreasonable risk for consumers as marketed. Under DSHEA, the government does not take part in the pre-marketing safety determinations for most dietary supplements, which are the responsibility of the manufacturer, nor does FDA have authority to oversee safety testing. While it would be possible for the government to set guidance for manufacturers to follow voluntarily, appropriate criteria for dietary supplement safety are still in the stage of evolution. The government is responsible for removing unsafe products from the market, however, should such products be sold. Whereas FDA makes efforts to stay abreast of emerging issues surrounding the safety of dietary supplement ingredients, its activities have been primarily post-marketing.

There are provisions for so-called new dietary ingredients (i.e., dietary supplement ingredients not marketed prior to October 1994), however, that are designed to alert FDA to the fact that a manufacturer intends to market a new ingredient. Manufacturers who intend to market dietary supplements containing “new dietary ingredients” must submit notifications to FDA that contain the information that the manufacturer relied upon to make its determination that its product will reasonably be expected to be safe. These notifications must be submitted to FDA 75 days before the manufacturer intends to sell the ingredient. Within this timeframe, the agency has the opportunity to object to the marketing of the product. With the recent upsurge in interest in marketing new ingredients, FDA must turn its attention to outlining proper procedures and criteria for this process.

While FDA has had considerable history with the principles of GRAS and with food additive review, and therefore can articulate approaches to determining the safety of substances for conventional food under this paradigm, the situation for dietary supplements and their safety standard (i.e., significant or unreasonable risk) is still evolving. Federally generated guidelines for dietary supplement safety determinations do not exist and are not required specifically by statute. Some dietary supplement trade associations and related organizations have volunteered to fill the void by counseling their individual member companies concerning safety, and certainly a number of companies have acted responsibly in this area. Nonetheless, there is an active debate as to whether FDA has sufficient authority to provide for the safety of these substances.

Dietary Supplement Ingredients versus Conventional Foods
As part of its regulatory oversight, FDA has paid attention to the addition of dietary supplement ingredients, notably herbs and botanicals, to conventional foods. Because safety and other provisions for the active ingredients in dietary supplements are governed differently than those for ingredients added to conventional foods, the agency wishes is concerned that when dietary supplement ingredients are added to conventional foods, they meet the appropriate safety standards for conven-
tional foods, meaning that they are GRAS for their intended use or are approved food additives. Ensuring that ingredients added to conventional foods meet the standards for additions to conventional foods means that functional foods—when they become “functional”—through the addition of an ingredient—cannot simply be a product of adding a dietary supplement ingredient to a conventional food without ensuring that the ingredient is safe for use in foods. In short, functional foods are conventional foods and must meet all the specific provisions for conventional foods. The primary goal for FDA, as well as for manufacturers, should be to keep pace with the growing interest in this area while at the same time gaining a sufficient knowledge base to provide for the safety of these products. This is especially important because conventional foods are generally consumed by a wide range of age groups and in a manner generally different than dietary supplements.

**Challenges to Providing for Safety**

For both functional foods and dietary supplements there are new and special challenges related to safety determinations. The substances commonly marketed are often biologically active and can interact readily both within the body and with other consumed substances such as drugs. Considerations for safety must therefore take into account a variety of safety endpoints. The determination of safety is affected by conditions of use in which, to paraphrase an old adage, one man’s dose can be another’s poison. Data on the history of use of some of these substances is not useful or relevant when the substances in question are processed, mixed, concentrated, formulated, and used in ways different from those that provide the basis for assurances of low risk based on historic use. In addition, there is simply a dearth of published data on the safety, and even effectiveness, of many of the ingredients now categorized as dietary supplements or identified as potential candidates to develop as functional foods. The largely post-marketing nature of the regulatory system for dietary supplements means that there is considerable reliance on the voluntary reporting of adverse events to signal safety concerns. Adverse events for functional foods would also be signaled voluntarily. Questions as to how best to interpret and use these data exist and need attention.

Moreover, a key aspect of any regulatory framework is the ability of the responsible agency to conduct effective and timely enforcement of the existing rules. As part of the process to implement the 1994 DSHEA, FDA developed The Dietary Supplement Strategic Plan, which was published in January 2000. The goal of the program is, “By the year 2010, to have a science-based regulatory program that fully implements DSHEA, thereby providing consumers with a high level of confidence in the safety, composition, and labeling of dietary supplement products.” Among other things, the Plan set out FDA’s enforcement priorities, with safety issues as the top priority. The enforcement section of the Plan includes activities devoted to improving FDA’s internal capacity in the enforcement area, but also identifies the need to work closely with the Federal Trade Commission (FTC) to address issues of fraud and consumer deception. Recently, this component of FDA’s role has been revitalized with enhanced activities to take enforcement actions against fraudulent claims. Nonetheless, enforcement requires resources, including the availability of review staff, legal counsel, and a field staff. In the area of dietary supplements, and increasingly in the area of functional foods, such resources have been very limited.

**Label Claims**

**Product Boundaries**

Under the Act, it is the intended use of the product rather than the specific chemical or other makeup of the product that determines into which regulatory category the product falls. A product intended to diagnose, treat, prevent, cure, or mitigate a disease is regarded by FDA as a drug, regardless of the ingredient’s derivation. In turn, the claims—or the nature of the claimed effect—that manufacturers make about their products determine how their product is reviewed and regulated by FDA. Advertising is primarily regulated by the FTC, and that agency does not make such distinctions for it purposes. However, FDA can use advertising to establish the intended use of the product or ingredient.

For both functional foods and dietary supplements, there are essentially two types of claims that capture most of the attention, putting aside the nutrient content claim (e.g., high in calcium, low in sodium). One type is a health claim, which focuses on the potential to reduce the risk of disease within the context of the total daily diet. The second type of claim is a structure/function claim that specifies the effect of a consumed substance on an aspect of the structure or function of the human body. By definition, such claims are not about disease endpoints. Any claim that specifies or implies treating, preventing, curing, or mitigating a disease results in the product being considered a drug.

Historically, based on case law, structure/function claims for conventional foods (and therefore functional foods) have been required to reflect food-like effects. With the advent of the 1994 DSHEA, dietary supplements continued to be allowed to make labeling claims about food-like effects, but were given additional provisions allowing them to also bear claims about non-food-like effects. These 1994 provisions also specified that the dietary supplement manufacturer must use the standard label 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\(^7\)) when a structure/function claim is used in labeling and that, within 30 days of marketing a product with a structure/function claim, the manufacturer submit a notice to FDA specifying the wording of the claim. FDA has often taken the opportunity to let manufacturers know that their submitted claims inappropriately imply disease treatment and therefore cannot be used.

Non-food-like claims for dietary supplements mark an important distinction between dietary supplements and functional foods. These provisions have, inevitably, put some pressure on the interest to define a food-like effect, particularly if the boundaries between the product categories are to be maintained. Not surprisingly, such a definition has proved to be elusive and problematic. Recent attempts have focused on articulating what is nutritive value given the historic precedent set in a 1983 court case (known as Nutrilab v. Schweiker\(^6\)) in which the court determined that a product is a food if it is consumed primarily for taste, aroma, or nutritive value. FDA has provided only general definitions; it has suggested that nutritive value is not necessarily limited to classic Recommended Dietary Allowance nutrients and is likely more broad.\(^7\) Without specific definitions, however, it is difficult to clarify boundaries between functional food claims and dietary supplement claims.

While claims often drive efforts to outline the boundaries between conventional (and functional) foods and dietary supplements, there is a noteworthy boundary distinction that is not related to claims. Specifically, DSHEA stipulated that dietary supplements may not represent themselves as conventional foods. The legislation allows that dietary supplements can take the form of conventional foods—they can look like cereals and candy bars, for example—but they cannot represent themselves as a conventional food. From a regulatory standpoint, this means that a dietary supplement product in bar form and labeled as a dietary supplement (i.e., using the dietary supplement facts panel rather than the nutrition facts panel) would be acceptable, but if it also bears labeling statements that, for example, represent it as a snack food or as a substitute for a candy bar, then it would be subject to regulation as a conventional food. Similarly, a cereal-type product may be able to be marketed as a dietary supplement if it did not also represent itself as a breakfast food or use the term cereal in its identity labeling.

One message that FDA has directed to the industry in its efforts to specify boundaries between conventional foods and dietary supplements is that, because the regulatory provisions for dietary supplements and conventional/functional foods are not the same, manufacturers should not try to circumvent the existing provisions for conventional/functional foods by adding dietary supple-

\textbf{Effectiveness}

Some special challenges are presented when the basis for substantiating ingredient effectiveness is considered within the context of the regulatory framework. Existing provisions provide that claims about food and supplement ingredients are claims targeted to healthy populations, unlike drug efficacy claims, which target diseased populations. Therefore, food claims—and the research needed to establish them—must be considered in the context of maintaining health or providing a health benefit for a non-diseased population.

This is particularly complicated for structure/function claims. The basis for health claims, that is pre-authorized claims about the relationship between the consumption of a substance and the increased/decreased risk for a disease, can at least generally be measured in a meaningful fashion. On the other hand, attempts to determine effectiveness when the endpoint is a change in the structure or function of the body and when the endpoints are not related to a disease condition appear to be more problematic. There are unanswered questions about the measures to be used for such endpoints as well as the relevance of the observed change from a public health perspective. The existing regulations allow FDA to take action when claims are not truthful or are misleading, but the substantiation approach used by the agency for such claims has been case by case. The situation has been further complicated by the misconception that structure/function claims are merely “emerging” health claims. Since by definition structure/function claims are not about disease, either inferred or implied, emerging data about effects on disease are not relevant to structure/function claims; structure/function claims are rather limited to affecting the structure or function of the body and do not focus on effects related to reducing disease risk but instead on maintenance, support, and health promotion.

There is currently no agreed-upon central body of acceptable approaches for establishing effectiveness of dietary supplement structure/function claims, and under the existing laws, each manufacturer is responsible for the determination. While FDA has signaled its interest in providing guidelines for manufacturers to use in substantiating their structure/function claims, this process will take some time. Some have suggested that identifying and measuring relevant structure/function claim endpoints is a quagmire, characterized by a lack of clarity about claim endpoints and concerns about whether an observed change has any anchor or meaning relative to health. But in today’s world, the work to clarify the substantiation basis is needed and must eventually be incorporated into the regulatory framework. Not only are
research agendas unspecified, questions have been raised by some as to whether claims that report factual findings or outcomes, such as increased levels of circulating zinc, are meaningful either in a health benefit context or to consumers. Clearly, maintaining consumer confidence in the utility of label claims is paramount and must be worked into considerations for substantiation criteria.

The difficulty of these combined tasks suggests that considerable leveraging of resources and expertise is required. It is also a new and emerging area that lacks a track record in terms of research agendas and resource allocation. The best hope is that collaborative partnerships among academia, the regulated industry, and government scientists will be fostered to effectively identify and address these issues.

Conclusion
The appropriate regulatory strategies and related scientific underpinnings for the safety and effectiveness of dietary supplements and so-called functional foods are emerging slowly. Public health policy is both helped and hindered by laws that reflect a patchwork of effort to provide for new and different products; it also suffers from an increasingly better understanding of science, which in turn acts to blur the distinctions not only between foods and drugs, but also between conventional foods and dietary supplements. The next several years will require considerable input from many components of society in order to provide for a system that allows consumers to have access to safe and effective products with meaningful claims. Maintaining consumer confidence in the food supply is a critical component of public health policy.
