Launching a New Food Product or Dietary Supplement in the United States: Industrial, Regulatory, and Nutritional Considerations

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Abstract

Launching a new food/dietary supplement into the US market can be a confusing process to those unfamiliar with the food industry. Industry capability and product specifications are initial determinants of whether a candidate product can be manufactured in a reproducible manner and whether pilot production can be brought up to the market scale. Regulatory issues determine how a product can be produced and marketed; the primary federal institutions involved in regulations are the US Department of Agriculture, the Food and Drug Administration, and the Federal Trade Commission. A primary distinction is made between food and drugs, and no product may enter the food market if it is in part or whole a drug. Product safety is a major concern, and myriad regulations govern the determination of safety. New foods/dietary supplements are often marketed by health claims or structure/function claims, and there are specific regulations pertaining to claims. Not understanding the regulatory issues involved in developing a new product or failing to comply with associated regulations can have legal and financial repercussions.

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INTRODUCTION

Diet is a major factor in many of the chronic diseases plaguing the US population, including heart disease, cancer, and diabetes, and dietary choices play a central role in the alarming rise in obesity, which also is implicated in chronic disease (21). The Dietary Guidelines for Americans issued by the US government (60) provide general information on dietary patterns to promote health, but they do not provide specifics on foods and dietary components that fit within that plan. Because only approximately one-fourth of the food consumed by Americans is minimally processed (14), the food industry plays a central role in dietary choices in the United States.

Many manufacturers and individuals have ideas for new and potentially healthful food products, but navigating a successful product into the marketplace presents many hurdles. Large food manufacturers have extensive legal, marketing, and production counsel to guide new product development, but small establishments are unlikely to have such resources. The following article provides an overview of the process and describes the hurdles that can be expected.

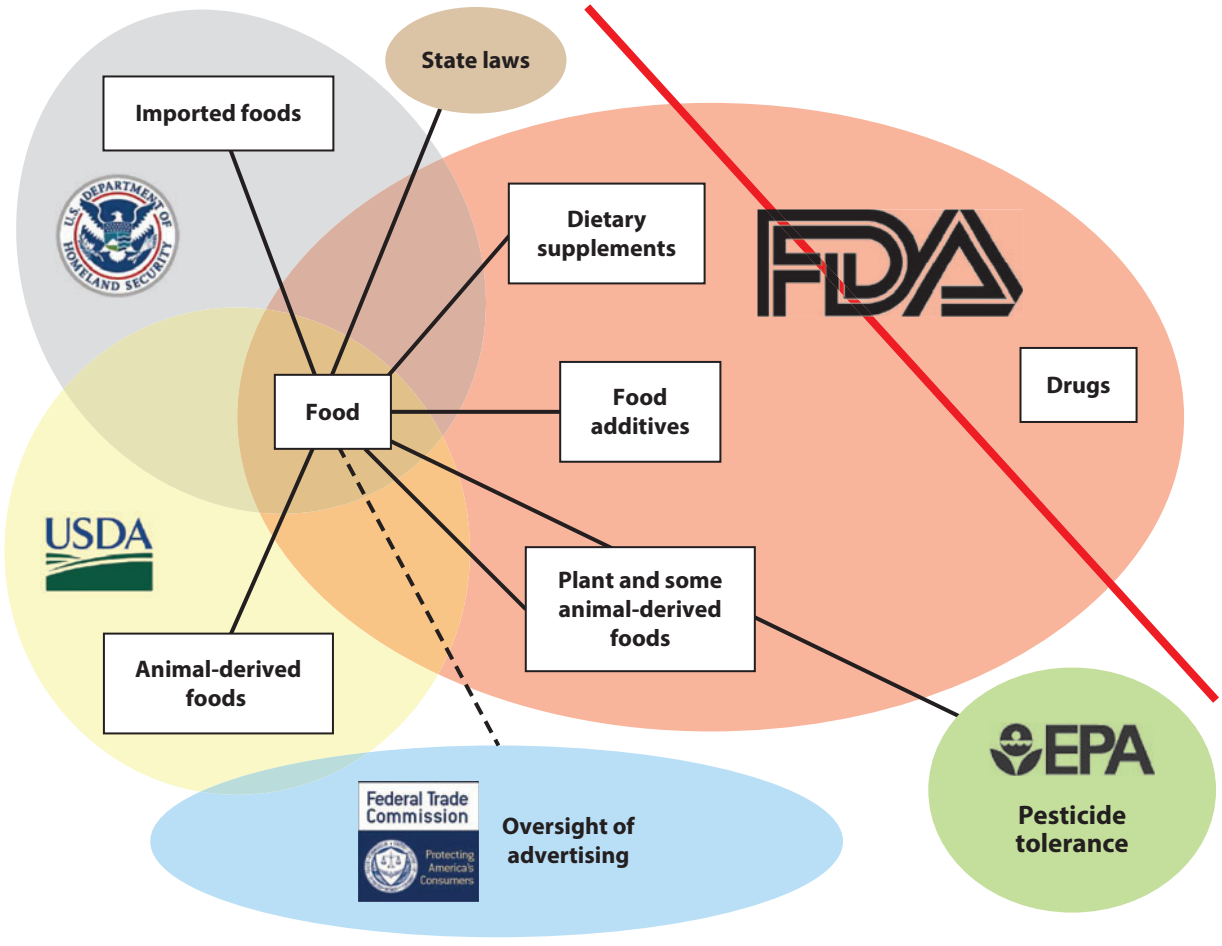

Figure 1

An overview of food regulation in the United States. The agencies involved include the Customs and Border Protection Service within the Department of Homeland Security, Department of Agriculture, Environmental Protection Agency, Federal Trade Commission, and Food and Drug Administration.

Legal Basis for Food Regulation in the United States

Food and dietary supplement products in the United States are regulated by multiple government agencies (50) (**Figure 1**) that work together to assure that domestic and imported food is pure and wholesome, safe to eat, and correctly labeled. The lead agencies are the Food and Drug Administration (FDA), through its Center for Food Safety and Applied Nutrition (CFSAN) (74); the United States Department of Agriculture (USDA), through the Food Safety and Inspection Service (FSIS) (64); and the Animal and Plant Health Inspection Service of the USDA (APHIS), which issues permits for the importation of certain fresh foods (15).

Other agencies also may become involved in food oversight. For example, the Environmental Protection Agency (EPA) regulates pesticide tolerances for food and issues standards for drinking water (67), and the US Customs and Border Protection works closely with the FDA to assure that

imported products meet all domestic standards (59). The US Federal Trade Commission (FTC) regulates advertising, and a 2006 FTC Act (71) prohibits "unfair or deceptive acts or practices" as well as "any false advertisement" that is "misleading in a material respect." The FTC and FDA work together to ensure that the spirit of FDA claims regulations are adhered to in all forms of advertisement other than food labels (69).

The American Food Industry

The American food industry is one of the country's largest manufacturing sectors, accounting for 10% or more of all manufacturing output; the total value of output increased 27% between 1997 ($422 billion) and 2006 ($538 billion) (88). In 2010, there were between 30,000 and 31,000 food manufacturing firms in the United States, with 34,000 establishments. Although the majority of food products are manufactured by large firms, the majority of firms and establishments (~22,000) have fewer than 20 employees (57). It is impossible to characterize all small firms, but it is likely that they have less access to the sophisticated technical and legal resources needed to successfully launch new and compliant food products.

The number of new food product introductions has maintained a steady trend upward from 9,653 in 1992 to 21,528 in 2010 (62). Specialty tags or claims are an important part of many food products. Health and convenience claims have comprised 8 of the top 10 claims every year since 2001 and currently account for approximately one-third of all new claims. In 2010, 25,640 new product claims were launched, and "natural" was the top claim; others included high vitamins/minerals, gluten free, no preservatives, organic, and low/no fat. Most claims are regulated by US agencies. The most popular tags include private label (75% increase since 2006) and store brands (200% increase since 2009) (61).

Although the profits of food manufacturers and retailers are in line with other American industries, individual products may have a low rate of return and a low probability of success. In the second quarter of 2013, the average return for all US industry was 16.3% of stockholder equity, whereas the average for food was 14.2% and the average for grocery stores was 16% (41, 58). The average profit per dollar of sales for nondurable goods manufacturing was 9.0%, whereas the average for all food was 5.2%. The profit per dollar of sales is highly dependent on the size of the company (58).

New food products face a dynamic and changing market. Changes, primarily since 1996, have been a result of mergers, acquisitions, and internal growth among grocery retailers and wholesalers and have coincided with changes in consumer preferences and an increasing acceptance of packaged and branded items and store brands (31). Grocery stores and supermarkets dominated food retail for many years; in 1997, they had 72% of total market share. However, warehouse clubs and supercenters have seen a massive increase in grocery sales in recent years, claiming 22.5% of total market share in 2012; grocery store/supermarket shares dropped dramatically, but the trend has since leveled off (43). A few companies dominate grocery sales: in 2012, the top companies were Wal-Mart Stores Inc. ($118,725,880,000); Kroger Co. ($61,128,860,000), Safeway ($35,504,060,000), and SuperValu Inc. ($28,229,188,000) (42). The changing landscape of retail grocery outlets is just one factor contributing to the high risk of launching new food products. Scholarly studies suggest that the failure rates of new grocery products are approximately 50% (7), whereas unsubstantiated reports from business periodicals estimate failure rates in the United States at approximately 90% (35). Regardless of the exact rate, it is clear that failure is a strong possibility for even the best-conceived and -executed products and that careful consideration of all factors is essential to improve the chance of success (11).

REGULATION OF FOOD PRODUCTS

Overview

The US Federal Food, Drug, and Cosmetic (FD&C) Act is the statutory basis for the FDA to make regulations intended to assure that foods are pure and wholesome, free of poisonous or deleterious substances, and safe to eat (85). The FD&C Act describes the conditions under which a food is considered to contain a poisonous or deleterious substance (i.e., be adulterated). The initial 1938 FD&C Act did not require the safety of food ingredients be established prior to their use in foods, and consequently there was no federal authority to deter introduction of unsafe ingredients into the food supply. The FDA needed to prove that a food ingredient had caused harm before acting to remove it from the food supply. This process was changed by the 1958 Food Additives Amendment, which established a premarket approval process for food additives and included a provision that an authorizing regulation for the use must be in effect (e.g., an FDA food additive regulation).

Food Additives

Safety, with respect to food additives, means a reasonable certainty that the food additive is not harmful under the intended conditions of use (16). The food additive safety standard is "reasonable" certainty rather than "absolute" certainty of no harm. Factors considered in determining reasonable certainty include the probable level of consumption of the substance (the Estimated Daily Intake), the cumulative exposure to the additive, and the margin of safety generally recognized as appropriate for the nature of the adverse effects. The amount of an ingredient reasonably certain to be safe (the Acceptable Daily Intake) is calculated by multiplying the highest intake level that does not result in the potential adverse effects by an appropriate safety factor. As safety testing is done with animals, the safety factor attempts to account for differences between animals and humans and differences in sensitivity among humans. Food additive regulations typically specify the types of foods in which a food additive may be used, and maximum levels of use, to ensure that the Estimated Daily Intake will be below the Acceptable Daily Intake.

Anyone can petition the FDA to amend the food additive regulation to allow for the use of a new food additive. In its decision, the FDA takes into consideration the specific biological properties of the substance and the adequacy of the methods employed to demonstrate safety. The information required to demonstrate the safety for a proposed use varies with differences in biological properties and level of consumption for the proposed use; guidelines are described in *Guidance for Industry and Other Stakeholders: Toxicological Principles for the Safety Assessment of Food Ingredients* (*Redbook 2000*) (78).

Food Substances Generally Recognized as Safe

The 1958 Food Additives Amendment defined a food additive as "any substance the intended use of which results, or may reasonably be expected to result, directly or indirectly, in its becoming a component of or otherwise affecting the characteristics of any food," if such substance is not generally recognized to be safe under the conditions of its intended use [see section 201 of the FD&C Act (85)]. Because of the large number of food ingredients with a history of recognized safety already in use, the 1958 Food Additives Amendment made a distinction between food ingredients generally recognized as safe (GRAS) and new food ingredients that would be regulated

as food additives (90). The GRAS food ingredient uses were excluded from the premarket FDA regulation process required for food additives.

The criterion for a food ingredient to be GRAS is a common acceptance among qualified experts about the safety of the substance under the intended conditions of its use. The common knowledge of safety can be based on a history of safe use prior to 1958 or on the scientific procedures and safety standard used to establish that a food additive use is safe. The common knowledge aspect of GRAS compels that only publicly available (i.e., published) scientific evidence is considered in GRAS evaluations. GRAS refers to how an ingredient is being used in a food, and, as an example, an ingredient whose use is GRAS as a flavor may not be GRAS for other uses.

Following the 1958 Food Additive Amendment, the FDA compiled an initial list of GRAS food ingredients that was based on nominations from the food industry; this list has been codified in Title 21, Code of Federal Regulations (CFR) Part 182 (18). Because of the large number of ingredients submitted to the FDA, there was little review of ingredients on the initial list. In 1969, the FDA removed cyclamates from the GRAS list because they were implicated in the formation of bladder tumors in rats. A reexamination of all ingredients on the initial GRAS list was then ordered by President Nixon. When the GRAS list safety review affirmed the use of an ingredient to be safe, the ingredient was migrated from the initial GRAS list to a new affirmed GRAS list (21 CFR 184) (18). The GRAS safety review was prioritized, but interest in reviewing the lower-priority ingredients eventually waned, and the review was not completed. As a result, two lists now exist in FDA regulations—both the 21 CFR 182 initial GRAS list and the 21 CFR 184 affirmed GRAS list.

Multiple lists are used to determine the approval status of an ingredient. Everything Added to Food in the United States (EAFUS) is the FDA list of over 3,000 ingredients commonly added directly to food; not all ingredients on the list have been affirmed as safe by the FDA (84). The FDA GRAS Notice Inventory contains information about GRAS notices filed since 1998, and if the FDA has responded to a GRAS notice, it also contains the text of the response (91). A list of substances approved for use as flavors is maintained by the Flavor and Extract Manufacturing Association (FEMA) (22). It should be noted that FEMA GRAS substances (including many natural extracts) are for flavoring only and not for physiologic effects; that is, a FEMA designation of a plant extract as GRAS cannot be used as the basis for putting the same extract into a food or beverage for "functional" characteristics.

Several options exist for securing approved regulatory status of a new ingredient. One option is to petition the FDA for designation of a new food additive, but such a procedure may take years and involves public comment, which may invite negative comments from competitors. A second option is to self-determine the product as GRAS and then notify the FDA (a shorter path that does not require public comment); however, information substantiating safety must be publicly available (the standard of safety is the same for a GRAS product and a food additive), which may make it more difficult to protect intellectual property associated with the ingredient. In addition, if a GRAS notice is submitted to the FDA and then withdrawn, a notice of withdrawal is left on the GRAS Notice Inventory, and other companies may interpret the withdrawal as an indication that there was insufficient evidence of safety for the product. A third alternative is to determine the ingredient as GRAS and not notify the FDA, but it may be very difficult to sell such a product to reputable food companies.

Medical Foods

Some food developers target new products to individuals at risk for certain diseases and label the new products as medical foods. Medical food labels may bear disease-related information, in addition to authorized health claims, without causing the product to be regulated as a drug. The

statutory definition of medical food, which originated in the 1983 Orphan Drug Act (47), is "A food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation."

The purpose for defining "medical food" within the Orphan Drug Act was to make dietary therapies, along with drugs, eligible for research grants to defray the costs of developing medical foods for rare diseases. A rare disease within the context of medical foods is any disease or condition that occurs so infrequently in the United States that there is no reasonable expectation that a medical food for such disease or condition will be developed without the assistance of the Orphan Drug Act incentives. Although the Orphan Drug Act added economic incentives for orphan drug development to the drug sections of the FD&C Act, it did not add medical foods as a regulatory category of food.

The FDA explains its thinking regarding the restrictions to marketing medical foods in its medical foods guidance document (87). The FDA considers the medical foods category to be narrowly constrained. Outside of medical foods that have been developed for dietary management of rare diseases, the FDA has considered most products marketed as medical foods not to qualify as medical foods. In a number of situations, the FDA has sent Warning Letters to firms marketing products labeled as medical foods to inform them that their products are illegal because (*a*) the product does not meet the statutory definition of a "medical food" and thus is mislabeled and (*b*) the product is an unapproved new drug because it is intended to be used to treat or mitigate a disease.

Dietary Supplements

Dietary supplements represent another route by which a substance can be marketed, although not as a conventional food. The 1994 Dietary Supplement Health and Education Act (DSHEA) (49) defined a dietary supplement as a product taken by mouth that contains a "dietary ingredient" intended to supplement the diet. DSHEA defined the term dietary ingredient as one or more of the following substances: (*a*) a vitamin, (*b*) a mineral, (*c*) an herb or other botanical, (*d*) an amino acid, (*e*) a dietary substance for use by man to supplement the diet by increasing the total dietary intake, or (*f*) a concentrate, metabolite, constituent, or extract of one of the above categories. A "new dietary ingredient" (NDI) is a substance that meets the above definition for a dietary ingredient and was not sold in the United States as a dietary supplement before October 15, 1994 (the date the DSHEA was enacted). "Pre-DSHEA ingredient" is the term commonly used to mean a dietary ingredient that had been sold in the United States as a dietary supplement prior to October 15, 1994.

Supplement manufacturers are responsible for ensuring that their dietary supplement products are safe before they are marketed. There is no provision in the DSHEA for the FDA to review or approve dietary ingredients before they are used in dietary supplements. Conventional food ingredients are deemed to be unsafe if there is no premarket safety determination (either through a food additive regulation or a GRAS determination). However, the FDA must show that a dietary supplement presents an unreasonable risk of illness or injury before acting to remove it from the market for being unsafe. Premarket notification of an NDI is required; the manufacturer of an NDI-containing dietary supplement is required by law to submit to the FDA, at least 75 days prior to marketing the supplement, a notification informing the FDA of the basis by which the manufacturer has concluded that use of the NDI will reasonably be expected to be safe in the dietary supplement [Section 413 FD&C Act (85)]. Pre-DSHEA ingredients are not subject to the NDI notification requirement. Although dietary supplement manufacturers are responsible

for ensuring that all NDIs and pre-DSHEA dietary ingredients they use are reasonably expected to be safe, it is generally perceived that the pre-DSHEA dietary ingredients have been grandfathered as safe and thus they typically are used without any deliberative evaluation of their safety. Also exempt from the NDI notification requirement are ingredients that have been used as articles for food (rather than as dietary supplements) in the same chemical form as that of the dietary ingredient.

New Dietary Ingredient Notification

There is no authoritative grandfathered list of dietary ingredients marketed in the United States prior to October 15, 1994. Lists compiled by supplement industry groups are available, but these lists have not been independently verified and include vaguely described ingredients. The FDA does not accept inclusion of an ingredient on these lists as proof that an ingredient is not an NDI. Each supplement manufacturer is responsible for establishing that its dietary ingredients are NDIs and that they comply with the NDI notification requirements. Differences exist between the supplement industry and the FDA in what is perceived to be an NDI and what evidence is needed to establish an NDI's safety. The FDA believes NDI notifications to be an important preventive control to ensure that consumers are not exposed to unnecessary public health risks from new ingredients with unknown safety profiles. However, the number of NDI notifications that have been submitted to the FDA is low relative to the large number of new dietary supplement products introduced each year.

The Food Safety Modernization Act (88) was signed into law in 2011 and instructed the FDA to publish guidance that clarifies (*a*) when a dietary ingredient is an NDI, (*b*) when the supplement manufacturer should submit an NDI notification to the FDA, (*c*) the evidence needed to document the safety of an NDI, and (*d*) methods for establishing the identity of an NDI. In the summer of 2011, the FDA published a draft of their guidance to clarify the FDA's expectations on NDI notification issues (83). The topics discussed in the draft NDI guidance included (*a*) determining whether an NDI notification is necessary, (*b*) procedures for submitting an NDI notification, and (*c*) what to include in an NDI notification. Public comment was invited on the draft's content, and a large number of comments were submitted. The FDA eventually will replace the draft NDI notification guidance with a final version that takes into consideration the public comments. At that time, it can be expected that the FDA will place an increased emphasis on compliance with the NDI notification requirement. Independent of the guidance, the statute requires that firms submit NDI notifications for products containing NDIs.

Reporting of Adverse Events

The Dietary Supplement and Nonprescription Drug Consumer Protection Act in 2006 provided that firms must submit serious adverse event reports to the agency within 15 business days (see **http://www.fda.gov/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdcact/significantamendmentstothefdcact/ucm148035.htm**). Supplement companies receive adverse event reports through the address or telephone number they provide on the supplement product label. A serious adverse event is defined as one or more of the following patient outcomes: death, a life-threatening experience, hospitalization, a persistent or significant disability or incapacity, a congenital anomaly or birth defect, or a medical intervention to prevent one of the above situations. The FDA evaluates the serious adverse event reports it receives for evidence that particular dietary supplement products have caused illness or injury and should be considered unsafe.

When a dietary supplement safety issue becomes known through postmarket reporting of adverse events, the FDA can investigate and take steps to remove unsafe products from the market. However, the FDA must undertake a series of lengthy scientific and legal steps in order to ban a dietary supplement ingredient. To date, the only dietary ingredient that has been banned because of an unreasonable risk of illness or injury is ephedrine alkaloids (21 CFR 119.1; see **http://www.gpo.gov/fdsys/pkg/CFR-2011-title21-vol2/pdf/CFR-2011-title21-vol2-sec119-1.pdf**). The statutory process required to ban the use of ephedrine in dietary supplements required many years, during which marketing of the supplements continued.

Because of the time and resources required to ban a dietary ingredient, the FDA often relies on more expedient paths to remove known unsafe dietary ingredients from the market. 1,3-Dimethylamylamine (DMAA) is a substance that had, until recently, been used as a "natural" stimulant in supplements. The FDA received many postmarket adverse event reports that linked ingestion of DMAA to psychiatric disorders, heart problems, nervous system disorders, and death. DMAA had been claimed to be a botanical constituent and as such met the statutory definition for a dietary ingredient. However, the FDA found no reliable science indicating DMAA exists naturally in plants and determined that DMAA thus is not a dietary ingredient. In 2012, FDA began sending Warning Letters to supplement companies marketing DMAA-containing products, advising them that DMAA-containing products marketed as dietary supplements are illegal and must be taken off the market. If a company that receives such a Warning Letter from the FDA does not voluntarily remove its products, the FDA can seize the product from the market or obtain an injunction to prevent the company from manufacturing and distributing illegal supplement products.

Food Regulation by the USDA

The USDA has jurisdiction over meat (cattle, sheep, swine, goats, and equine species), poultry (chickens, turkeys, ducks, geese, and guineas), and egg products. Regulation of food products by the USDA is found in 9 CFR chapters 1–3 (**http://www.fsis.usda.gov/wps/portal/information**). The FSIS is the primary agency that a food scientist will potentially interact with because it regulates—with some exceptions—products that contain more than 3% meat or 2% poultry. Authority for the FSIS is provided by the Federal Meat Inspection Act of 1906 (44), the Poultry Products Inspection Act of 1957 (45), and the Egg Products Inspection Act of 1970 (46). For food scientists, perhaps the biggest difference between the FSIS and the FDA is the requirement for premarket approval of all labels. Information regarding labels and label approval is available on the FSIS website (65). The FSIS website also maintains information on substances approved for use with meat and poultry products (62).

CLAIMS FOR FOODS AND DIETARY SUPPLEMENTS

Structure/Function Claims

The FDA has implemented multiple regulations concerning label claims. The FDA issued a final rule on January 6, 2000 (75) defining statements that can be made concerning the effects of a dietary supplement on the structure or function of the body. As part of this rule, criteria were established for determining when a statement about a dietary supplement is a claim to diagnose, cure, mitigate, treat, or prevent disease. The regulation was intended to clarify the types of claims that may be made for dietary supplements without prior review by the FDA and the types of claims that require prior authorization as health claims or approval as drug claims. The DSHEA authorized certain types of claims about uses of dietary supplements that included some claims that formerly would have been reviewed by the FDA before marketing the product. DSHEA added section 403(r)(6)

of the Federal Food, Drug, and Cosmetic Act (79), which allowed dietary supplement labeling to bear a statement that "describes the role of a nutrient or dietary ingredient intended to affect the structure or function in humans," or "characterizes the documented mechanism by which a nutrient or dietary ingredient acts to maintain such structure or function." These statements are referred to as structure/function claims. A manufacturer who wishes to make a structure/function claim [see section 403(r)(6) of FD&C Act (79)] need not obtain prior review of the statement by the FDA. However, the manufacturer must have substantiation that the statement is truthful and not misleading. It must include in a disclaimer for dietary supplements that the FDA has not evaluated the statement. This disclaimer must also state that the product is not intended to "diagnose, treat, cure, or prevent any disease" (75). The manufacturer must also notify the FDA, no later than 30 days after the first marketing of the dietary supplement with a structure/function claim, that such a statement is being made for the product. The FDA did not believe that the final rule violated the First Amendment because it did not prohibit any speech, but the FDA clarified the circumstance under which it would consider a certain type of speech—labeling claims—to be evidence of the intention to use as a product as a drug, absent authorization as a health claim (75).

Section 403(r)(6) of the act requires that a manufacturer of a dietary supplement making a nutritional deficiency, structure/function, or general well-being claim have substantiation that the claim is truthful and not misleading. In December 2008, the FDA issued guidance for industry for substantiation of dietary supplement claims (79). In developing the guidance, the FDA drew upon its own expertise with regard to regulations and case law pertaining to substantiation of various statements that may be made in the labeling of dietary supplements, conventional foods, and drug products; the FTC's experience with its policy on substantiating claims made for dietary supplements in advertising; and recommendations from the Commission on Dietary Supplement Labels. The FDA applied a standard for the substantiation of dietary supplement claims that is consistent with the FTC approach of "competent and reliable scientific evidence." The FTC standard of competent and reliable scientific evidence has been defined in FTC case law [see, e.g., Vital Basics, Inc., C-4107 (Consent April 26, 2004); **http://www.fda.gov/ohrms/dockets/dockets/04d0466/04d-0466-c000006-Exhibit-D-02-Graham-vol2.pdf**]. The guidance document identifies four issues to be addressed in assessing the scientific evidence for the claim: (*a*) the meaning of the claim(s) being made, (*b*) the relationship of the evidence to the claim, (*c*) the quality of the evidence, and (*d*) the totality of the evidence (79). For example, if a dietary supplement manufacturer wants to claim that its product helps maintain blood vessel tone or supports a healthy immune system, then there needs to be a clear understanding of the claim's meaning in order to develop end points that could be measured and replicated in the studies used as the basis for substantiation. The guidance document discusses each of these issues and provides examples (79).

Health Claims and Qualified Health Claims

Health claims were first authorized through the Nutrition Labeling and Education Act of 1990 (NLEA) (48). Prior to the 1990 act, the FDA considered statements about disease made on food labels to be drug claims within the meaning of the act. Health claims establish a causal relationship between a substance (a food or food component) and reduction in the risk of a disease or health-related condition for the general U.S. population or subpopulation (21 CFR 101.14; **http://www.gpo.gov/fdsys/pkg/CFR-2011-title21-vol2/pdf/CFR-2011-title21-vol2-sec101-14.pdf**). Health claims are not about treatment, prevention, cure, or mitigation of a disease because these are drug claims. A health claim is any claim made on the label or in the labeling of a food, including dietary supplements, that expressly or by implication,

including third-party references, written statements (e.g., a brand name that includes a term such as "heart"), symbols (e.g., a heart symbol), or vignettes, characterizes the relationship of any substance to a disease or health-related condition (**http://www.gpo.gov/fdsys/pkg/CFR-2011-title21-vol2/pdf/CFR-2011-title21-vol2-sec101-14.pdf**).

Congress set the standard for scientific evidence for the claim as "significant scientific agreement." The significant scientific agreement standard is reached when it has been determined, on the basis of the "totality of publicly available scientific evidence, including evidence from well-designed studies conducted in a manner that is consistent with generally recognized scientific procedures and principles, that there is significant scientific agreement, among experts qualified by scientific training and experience to evaluate such claims, and that the claim is supported by such evidence" [21 USC 343(r)(3)(B)(i); see **http://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/pdf/USCODE-2010-title21-chap9-subchapIV-sec343-1.pdf**]. The significant scientific agreement standard is intended to be a strong standard that provides a high level of confidence in the validity of a substance-disease relationship. The continuum of scientific discovery extends from emerging evidence to a strong consensus for a relationship. Although there need not be absolute consensus for significant scientific agreement, such agreement means that evidence for the relationship is not likely to be reversed by new and evolving science. The FDA applies this standard equally to conventional foods and dietary supplements. Health claims that meet the significant scientific agreement standard may be found in CFR Title 21 Subpart E of Part 101 (see **http://www.gpo.gov/fdsys/pkg/CFR-2008-title21-vol2/xml/CFR-2008-title21-vol2-part101.xml**).

Several dietary supplement manufacturers challenged the FDA decision to apply the significant scientific agreement standard to dietary supplements. The lawsuit addressed the decision of the FDA not to authorize four dietary supplement health claims because they did not meet the significant scientific agreement standard. In this court case, *Pearson v. Shalala*, 164 F.3d 650, 658 (D.C. Cir. 1999), the District Court ruled for the FDA, but the US Court of Appeals for the District of Columbia Circuit concluded that First Amendment protection of commercial speech does not permit the FDA to prohibit dietary supplement health claims that the agency determined to be potentially misleading unless the agency could also determine that adding a disclaimer to the claim would not eliminate the potential deception. In a subsequent Court case, *Whitaker v. Thompson*, involving the FDA's continued denial of a health claim concerning antioxidant vitamin (vitamins C and E) supplements and the reduced risk of certain cancers, the FDA concluded that a disclaimer could not make this claim nonmisleading because evidence weighed more heavily against than in support of the relationship, and the claim was therefore inherently misleading. The District Court told the FDA that where there was credible evidence for a substance-disease relationship, the claim was only "potentially misleading," and the FDA must permit the claim with a disclaimer in the absence of evidence that consumers would be misled by the qualified claim. Both authorized and qualified health claims are required to be reviewed and evaluated by the FDA prior to use.

The FDA progressed through a series of steps to implement the *Pearson* court decision. In October 2000, the FDA stated its intention to rely on enforcement discretion to provide for qualified health claims for dietary supplements (76). In December 2002, then-FDA Commissioner Dr. Mark McClellan announced a major new initiative, the "Consumer Health Information for Better Nutrition Initiative" (77). This initiative provided for the use of qualified health claims for both conventional human foods and dietary supplements. A regulatory framework for qualified health claims in the labeling of human foods and dietary supplements provided guidance for an interim evidence-based ranking system for scientific data as well as for interim procedures for qualified health claims in the labeling of conventional human food and dietary supplements; the framework also developed a consumer studies research agenda. In January 2009, the FDA issued

a guidance document for industry entitled "Evidence-Based Review System for the Scientific Evaluation of Health Claims" (81). This final guidance document replaced prior versions on this subject. The document describes the evidence-based review system that the FDA uses to evaluate the publicly available scientific evidence for health claims meeting significant scientific agreement or those that are qualified. Ascertaining whether a relationship exists between the substance and the disease or health-related condition is more complex for qualified health claims because the scientific evidence for qualified health claims is uncertain, limited, inconclusive, preliminary, and/or inconsistent. The FDA must determine whether credible evidence supports the claim. If so, the FDA must determine the claim language and the disclaimer for each claim. In addition, the FDA determines what, if any, other factors to apply in connection with its consideration of enforcement discretion. The FDA has conducted consumer studies on ways to communicate different levels of scientific support for substance-disease relationships on product labels (**http://www.fda.gov/OHRMS/dockets/dockets/03N0496/03N-0496-rpt0001.pdf**). Other factors are claims cannot be included on foods that exceed disqualifying levels of total fat, saturated fat, cholesterol, or sodium levels and claims on foods other than dietary supplements that do not contain at least 10% of the nutrition labeling value for one or more of six core nutrients (dietary fiber, protein, vitamin A, vitamin C, calcium, and iron). These same factors apply to claims that meet the significant scientific agreement standard. The FDA has issued several letters of enforcement discretion for qualified health claims (97); the qualifying language represents the most accurate depiction of the scientific evidence for the claim.

Petitions for health claims and qualified health claims undergo both a scientific and regulatory review. Claims that meet the significant scientific agreement standard are authorized by regulation and result in a final rule, whereas qualified claims that are supported by credible evidence are issued a letter of enforcement discretion. Qualified health claims do not meet the significant scientific agreement standard and are not authorized by an FDA ruling.

Scientific Evaluation of Health Claims and Qualified Health Claims

The FDA uses an evidence-based review process for evaluating the scientific evidence for health claims and qualified health claims (for an overview of the process, see **Figure 2**). Evidence-based systematic reviews in the field of nutrition have become increasingly common for evaluating the strength of the scientific evidence on a given nutrition-related topic and for identifying research gaps. The FDA's guidance document (81) describes the evidence-based review system that is used to evaluate the publicly available scientific evidence for both authorized and qualified health claims. The intent of the guidance document is to provide a clear description of the process used to review petitions for authorized and qualified health claims. The goal is to ensure an objective, transparent, and rigorous process for reviewing scientific evidence. Most nutrition studies are not designed with the objective of obtaining a health claim. The guidance document is briefly summarized here (for a description, see 20). The substance that is the subject of the claim as defined by regulation can be a food (e.g., tomato) or a food component (e.g., a nutrient such as calcium), irrespective of whether the substance is in a conventional food or a dietary supplement (21 CFR 101.14; **http://www.gpo.gov/fdsys/pkg/CFR-2011-title21-vol2/pdf/CFR-2011-title21-vol2-sec101-14.pdf**). A disease or health-related condition is defined in the regulation as (*a*) damage to an organ, part, structure, or system of the body such that it does not function properly (e.g., coronary heart disease) or (*b*) a state of health leading to such dysfunction (e.g., hypertension) (**http://www.gpo.gov/fdsys/pkg/CFR-2011-title21-vol2/pdf/CFR-2011-title21-vol2-sec101-14.pdf**). Human studies that are publicly available and written information pertaining to the substance-disease relationship are considered. The review of studies is focused primarily on

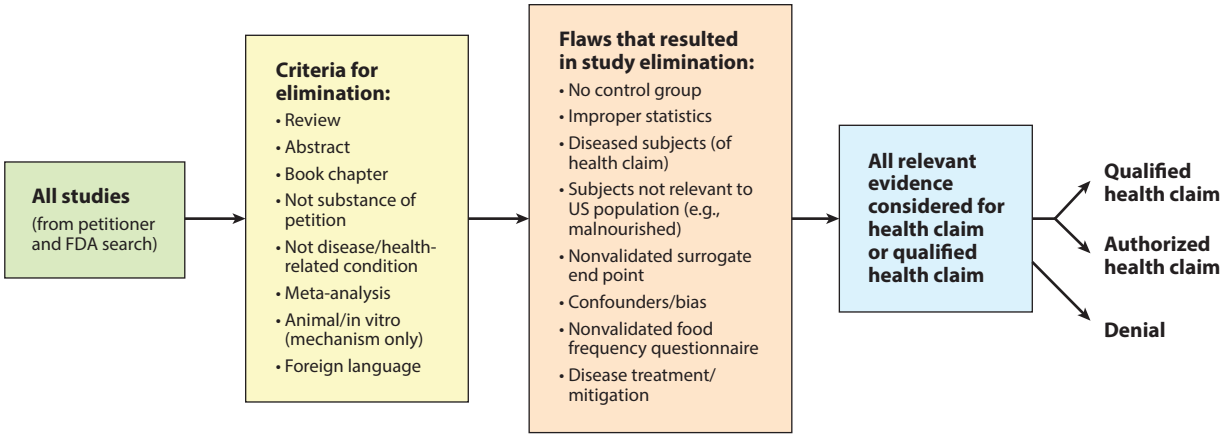

Figure 2

An overview of evidence-based evaluation of studies by the United States Food and Drug Administration (FDA). Adapted with permission from Reference 20.

articles reporting human intervention and observational studies because these studies provide evidence from which scientific conclusions can be drawn about the substance-disease relationship in humans. Randomized controlled studies offer the best assessment of a causal relationship between a substance and a disease because they control for known confounders. Observational studies measure associations between the substance and disease. Known confounders of disease risk need to be collected and adjusted to minimize bias. Many observational studies rely on self-reports of diet; thus, it is important to critically evaluate the method used to assess dietary intake. Estimate of a whole food intake is based on recorded dietary intake methods; thus, a common weakness is the limited ability of these studies to ascertain the actual intake of the substance in the population under investigation. Moreover, if the substance is a food component, the amount of the food component that is present in the individual foods is also estimated. Well-designed observational studies can provide information that is useful in identifying possible associations for testing in intervention studies. Review articles and meta-analyses lack detailed information. Animal and in vitro studies are useful for providing background information regarding the mechanisms that might be involved in any relationship between the substance and disease.

Surrogate end points are risk biomarkers that have been shown to be valid predictors of disease risk and may be used in place of clinical measurements of disease onset in a clinical trial. The FDA has accepted few validated surrogate end points of disease risk. The FDA contracted with the Institute of Medicine to develop a framework for the qualification of evidentiary standards for risk biomarkers and surrogate end points in chronic disease. The committee that was formed recommended a framework consisting of analytical validation, evidentiary qualification, and utilization analysis (29). Human studies are evaluated to determine whether any scientific conclusions can be drawn about the substance-disease relationship. If certain critical elements of a study, such as design, data collection, and data analysis, are seriously flawed, then it is not possible to draw scientific conclusions. It is important that the study population be relevant to the general US population or the population subgroup identified in the proposed health claim. Studies that are not eliminated from review receive a methodological quality rating that is based on several factors such as study design, data collection, quality of statistical analysis, type of outcome measured, and study population characteristics other than relevance to the US population. The totality of scientific evidence is derived from studies in which scientific conclusions can be drawn. In general,

intervention studies provide the strongest evidence for the claimed effect. When the evidence for a substance-disease relationship is credible but does not meet the significant scientific agreement standard, then the proposed claim includes qualifying language that identifies limits of the level of scientific evidence to support the relationship. A comprehensive discussion of the process for reviewing the scientific evidence for authorized and qualified health claim petitions is available in the guidance document (81).

Nutrient Content Claims

Nutrient content claims expressly or implicitly characterize the level (or range) of a nutrient in a food (a nutrient of the type required to be in nutrition labeling as described in 21 CFR 101.9 or 101.36). Examples of expressed nutrient content claims are direct statements such as "low fat," "low sodium," or "contains 100 calories." In contrast, an implied nutrient content claim (21 CFR 101.65) is a claim about a food or ingredient or method of preparation that suggests that the nutrient or ingredient is absent or present in a certain amount (e.g., "high in oat bran") or suggests a food may be useful in maintaining healthy dietary practices and that is made with an explicit claim (e.g., "healthy; contains 3 grams of fat"). Implied claims also include those that claim a food contains or is made with an ingredient that is known to contain a particular nutrient; such claims may be made if the nutrient is "low" in or a "good source" of the nutrient (e.g., "good source of oat bran"). Equivalence claims (e.g., "contains as much vitamin C as an 8-ounce glass of orange juice") are also considered to be implied claims provided both the reference food and labeled food are an equivalent "good source" of a nutrient on a per-serving basis. "Healthy" and related terms are commonly used implied claims on food labels that must meet very specific conditions for use [21 CFR 101.65(d)(2); see **http://www.fda.gov/food/guidanceregulation/guidancedocumentsregulatoryinformation/labelingnutrition/ucm064916.htm**]. A "good source" or "high" claim can be made when a food contains 10–19% or 20% or more of the Daily Value (DV), respectively. Nutrients must have an established DV. If a nutrient does not have an established DV, a claim may be made that specifies only the amount of the nutrient per serving and does not implicitly characterize the level of the nutrient in the product (e.g., "*x* grams of omega-3 fatty acids"). Many more nutrient content claims can be used to describe the food in labeling; these are well characterized in the FDA's *Food Labeling Guide* (80). If a nutrient content claim is not included in the FDA's regulation, it cannot be used without a premarket review.

The FTC and Oversight of Food Advertising

The NLEA of 1990 and subsequent amendments established FDA regulations applicable only to label information/claims for foods. Statutory authority to regulate advertising continued to reside with the FTC under authority of the FTC Act, Section 5, that prohibits "unfair or deceptive acts or practices," and in the case of food products, sections 12 and 15 of the FTC Act prohibit "any false advertisement" that is "misleading in a material respect" (71). The Federal Food, Drug, and Cosmetic Act prohibits "labeling [that] is false or misleading in any particular"; since 1954, the FDA and FTC have utilized a Memorandum of Understanding to divide regulatory responsibility, with the FDA having primary responsibility for labeling and the FTC having responsibility for other forms of advertising. Although the two agencies have different standards and approaches to enforcement, the FTC has publicly stated that it "has traditionally accorded great weight to FDA's scientific determinations in matters of nutrition and health and will continue to do so," and "it is unlikely that the Commission will take action under. . . the FTC Act regarding nutrient content and health claims if they comply with FDA's regulations" (69).

Given the above framework, the FTC has stated that it "will find an advertisement deceptive. . . and, therefore, unlawful, if it contains a representation or omission of fact that is likely to mislead consumers acting reasonably under the circumstances, and that representation or omission is material" (69). The FTC guidance for manufacturers and marketers notes that a claim can be more than words and can be pictures in proximity to the product. The overall context, information given, and information omitted are all considered in the context of a "consumer acting reasonably under the circumstances." In the case of objective claims, the FTC considers whether valid evidence supports the claim at the time it is made.

Food product developers that intend to advertise health benefits will profit from seeking competent legal counsel and/or reading case histories of FTC actions. Food advertising in particular has been a focus of the FTC, and as many as 100 cases have been prosecuted in the past 10 years. The examples below illustrate the FTC's intent and judicial power.

- The marketers of "Seasilver," a dietary supplement promoted as a cure for a number of diseases, used claims that the FTC said were unsubstantiated. The marketers were hit with an injunction in 2004 that barred further marketing and suspension of a $120 million "avalanche clause" pending payment of a $3 million fine; the marketers did not comply, and a district court ordered the defendants to pay $120 million. The FTC also secured liens against the defendants' assets. The case illustrates that the FTC will pursue "ill-gotten gains," will use "avalanche clauses" to ensure that injunctions are adhered to, and has the power to go after the individual assets of the owner/corporation (70).
- In 2012, the FTC reached an agreement whereby the Clickbooth affiliate network agreed to pay $2 million for deceptive advertising regarding acai berry supplements and weight-loss claims. The case is notable in that product sales were not directly by the company. Instead, a network of affiliate marketers sold products online, and claims were monitored by and even suggested by the parent company (72). Under FTC law, all parties who participate directly or indirectly in the marketing of dietary supplements have a responsibility to make sure claims are adequately supported.
- In 2013, a district court upheld an opinion that the makers of POM Wonderful 100% Pomegranate Juice and POMx supplements used deceptive advertising and did not have adequate support for claims. The FTC action barred the defendants from making any further claims that their products are "effective in the diagnosis, cure, mitigation, treatment, or prevention of any disease," including heart disease, prostate cancer, and erectile dysfunction. The FTC's order in the POM case is notable in that it requires that any future health-related claims made by POM must be supported by "two randomized, well-controlled, human clinical trials." This more specific substantiation requirement is limited to the POM matter but does provide an indication that the FTC's substantiation standard for health-related claims is a rigorous scientific standard, and the agency generally expects quality human clinical studies to support such claims. Also notable is the FTC's requirement that claim substantiation is a process independent of the FDA health claim approval process (73).

NEW FOOD PRODUCTS: FOOD MANUFACTURING CONCERNS

Initial Considerations

Manufacturing concerns provide potential hurdles for new food products, especially those that are designed to deliver ingredients that may promote health. **Figure 3** provides an overview of the process, from initial discovery to consumption by the consumer.

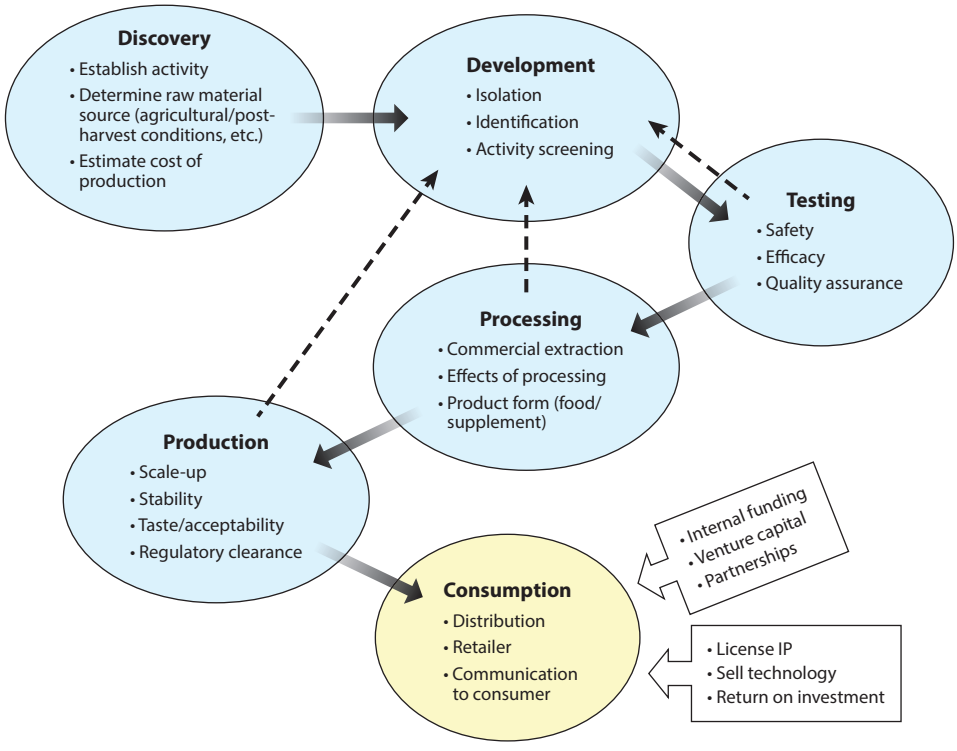

Figure 3

An overview of the process for new food products, from discovery/invention, to production of a food with functional characteristics, and finally to consumption.

An initial determination is of specific benefits to be derived from the product and how these benefits may be communicated to the consumer. As noted, label claims and advertising face certain regulations, so it may not be possible to list potential benefits on the label. Moreover, today's consumers are generally looking for products that provide convenience and some level of short-term gratification (54); thus, long-term benefits may not be attractive to the consumer. Other products may provide advantages for specific subgroups but not necessarily to the general population. For example, one may wish to develop a supplement/food that benefits individuals engaged in physical exercise. Evidence suggests that whey supplements increase muscle mass in athletes engaged in rigorous exercise and strength training (24), and in the shorter term they may reduce muscle soreness and thus allow more frequent intense workout sessions (28). However, such data would not necessarily be applicable to individuals not engaged in rigorous exercise/training.

Unlike for the development of drugs, no established protocol exists for the development of new foods that the manufacturer thinks may have "functional" characteristics ("functional foods" is an industry term with no regulatory definition). Foods need to follow the general FDA guidelines that require them to be safe and to use truthful, and not misleading, labels. Label claims may require a certain level of scientific evidence for approval, but in the absence of claims and given the paucity of human studies associated with most bioactives, it is up to the developer to decide whether there is sufficient scientific evidence to warrant the production of a specialized food or inclusion of a specialized ingredient.

Because foods cannot be developed and marketed for the purpose of amelioration or treatment of a disease condition, data showing that a compound will treat a condition such as osteoporosis are of no use in developing or marketing a food product. However, data showing that people who chronically consume a specific compound maintain normal blood pressure better than those who do not may be of value (see section titled Claims for Foods and Dietary Supplements). Clinical data are valuable, although there are many considerations when judging the strength of such evidence (52). In addition, given the expense of well-designed clinical trials, one needs to carefully calculate costs and potential returns. A single clinical trial is highly unlikely to result in a significant scientific agreement health claim, and it will probably not result in an impactful qualified health claim, so it is a judgment call as to whether funds for such a clinical trial are justified. Data from animal and in vitro studies are useful as background information for understanding a mechanism. If literature supports the efficacy of a compound, it may be easier to secure a claim and/or market the compound based on those attributes; however, publicly available data make it harder to protect intellectual property (see section titled Product Protection).

Epidemiologic studies offer different levels of evidence (26). Ecological and case-control studies may provide intriguing indications of a potential effect, but they are of a lower level of certainty compared to prospective studies. Prospective cohort studies provide stronger evidence. It is important that the study population is representative of the target population. Studies done in countries/cultures with very different diets and disease conditions may not be relevant to the general US population. Studies done in subpopulations also should match the target population. For example, a conventional food/dietary supplement shown to benefit high-performing athletes is not relevant to the general population; however, a claim could be tailored toward only high-performing athletes. Properly judging the type and strength of the evidence is important when developing advertising campaigns because the FTC does not have a procedure such as that of the FDA for premarket review of health claims; instead, the FTC relies on the standard of competent and reliable scientific evidence (see section titled The FTC and Oversight of Food Advertising).

The relationship between target consumers and a new product must be clearly defined, with an understanding of how the consumer will benefit and distinct and measurable consumer outcomes (23). Some compounds may provide benefits related to long-term chronic conditions, but a marketer would need to take into account that the consumer might have to wait 25 years to see the benefit of such a product.

Product cost affects consumer appeal. Concentrating specific bioactives from a raw material is expensive; the steps involved in refining, removing solvents, and incorporating the bioactive into a product can increase costs three- to fourfold beyond raw material costs. Wholesalers and distributors add 15% to 20% to the cost, and retailers typically require up to 30%, resulting in a final cost that is 10 to 20 times that of the raw material. Consequently, if a product were to be marketed at a cost of $1.00 per serving/dose, the raw material cost would need to be $0.05 to $0.10 (1, 9).

For a bioactive to be successful, there must be a relationship between efficacy and the intended dose. This can be problematic because only recognized nutrients have established requirements, and data for most bioactives are limited and derived from human studies. Questions to be considered include: Can the effective dose be physically incorporated into the product? For example, if the food product is a beverage, is the bioactive water soluble, or does it require an emulsification system? If delivered in an emulsion, the bioactive must be released and absorbed or modified into a bioavailable metabolite in the gastrointestinal tract. Additional ingredients must not adversely affect the flavor or texture of the final product.

Factors Influencing the Incorporation of Bioactives into a Food Product

Polyphenolic compounds are frequently incorporated into functional products, and special problems associated with them provide examples of challenges faced by the manufacturer. They frequently exhibit bitter or astringent flavors (11, 12, 33); sugars and sweeteners may mask these flavors (34) but may also compromise the healthfulness of the product. Heat processing may cause thermal decomposition (32). Polyphenols tend to be poorly absorbed, and the rate of absorption is not necessarily directly related to the concentrations in the food source (37).

Brownmiller et al. (2) reported that blueberry juices clarified and stored for periods up to six months lost 28% to 30% of total anthocyanins. The matrix containing the anthocyanins was shown to be critical to the extent of loss during heating or other processing (10, 101, 102). Juice tended to be the least stable, and anthocyanin degradation was impacted by pH, oxygen, temperature, and light (4, 55). Improved methods of stabilization could allow development of products with superior bioactivity (40). Pappas & Schaich (39) reported that freezing resulting in the release of more phenolic compounds from the matrix of cranberries, but heat, light, dissolved oxygen, and increased pH and ascorbic acid destabilized color and anthocyanin content. Blackberry products have been reported to lose up to 75% of the anthocyanins as a result of polymerization (25). The degree of damage from processing raises important questions about the value of preparing extracts of antioxidant materials versus the consumption of whole-food ingredients that are rich in these compounds.

Product Protection

When innovative new products are developed, it is important to establish a strategy to prevent competitors from duplicating the new product. New product developers generally hope to find a unique composition of matter or a specific activity from the use of a new material, and if that makes it unique, unexpected, and verifiable, the developer may be able to obtain a patent. Patents involve complex legal issues for which many product developers seek professional advice (for general information on patents, see 98).

The best protection of foods formulated to include natural products is by identification of a unique or unexpected activity. Process patents (describing means of manufacture) are one method of protection, but trade secrets may be better because proving patent infringement may be difficult. If a unique process is used to enrich a specific material, there is potential for claiming a unique composition of matter. Identifying a combination of ingredients that delivers specific benefits frequently does provide potential patent protection, but identifying combinations of ingredients with synergistic activities may provide better protection. Extensive documentation is essential. Documentation needs to be maintained from the beginning using laboratory notebooks, and individual pages should be signed and dated. The public release of any information regarding the product should be carefully evaluated because a simple abstract could be sufficient to rule that the intellectual idea is in the public domain and not subject to patent protection. If a new or unique ingredient is developed and requires an FDA-notified GRAS petition, the process must be reported as part of the petition to the FDA; however, proprietary processing can be marked as confidential and would not be released under the Freedom of Information Act. Thus, trade secret processing would be protected (30).

New products or ingredients must comply with regulations, and those regulations may be a form of product protection. A GRAS or approved food additive substance is based on specific product formulation/composition, and that can be tailored to ensure that the product is unique and thus will receive protection. Unless the composition is identical, the GRAS/food additive status does not apply to a competitor's product (see section titled Food Substances Generally

Recognized as Safe). As another example, many herbal/botanical extracts are produced in parts of the world (including the United States) that are heavily contaminated with substances for which tolerances have been set (e.g., pesticides, heavy metals). If a unique source can be identified that is consistently free of contaminants, then that product will consistently meet standards for sale, whereas the competitor's products may have ongoing problems. For example, ginseng is commonly contaminated with the pesticide quintozen (13), so finding and maintaining a proprietary source of consistently clean ginseng would confer the equivalent of intellectual protection.

Trade secrets can be very effective for maintaining protection. If a product has a unique formulation that is impossible to replicate, then the product is protected, even without legal protection. An example of this protection is the trade secret for the Coca-Cola® formula, which the Coca-Cola Company has held for many years.

Scaling Up Production

Bench-top procedures often require considerable modification to reach manufacturing scale. For example, solvent extraction followed by centrifugation is easily conducted in the laboratory; however, scaling that process up would involve grinding equipment, centrifugation or filtration capability, evaporators, and driers. In addition, the effects of temperature on the stability of the bioactives must be considered (100). Explosion-proof equipment is needed for solvents, and the total capital investment can be substantial. The value of processing by-products should be considered. If by-products are to be disposed of as animal feed, how much revenue will they bring to the operation? Are appropriate facilities located near the projected production site to use the by-product? If the starting material is not a food plant source, the composition of the by-products must be assessed to ensure there are no toxic or undesirable components in the waste. Solvents must be recovered and recycled. Aqueous by-products may be sold wet or dried, but contaminated water may need to be dealt with in a different stream from other wastewater (68).

Product specifications need to be developed, product consistency determined, and lot-to-lot variation assessed and controlled. Even small changes in production may have a very large effect on product variation; e.g., simply moving a grinder from one location to another may change settings, resulting in a coarser or finer grind, which may in turn affect may other specifications of the product. Standards for microbiological safety, authenticity, purity, and identity of ingredients are established for most food ingredients and additives, including food-grade chemicals, flavoring agents, and functional ingredients (6); the US Pharmacopeia (99) provides widely accepted specifications for thousands of ingredients. These specifications are agreed to by the industry and help manufacturers and suppliers distinguish between genuine products and inferior or adulterated products. Standards provide tolerances for normal variations in normal biological materials and minor variation in processing.

Good Manufacturing Practices Guidelines

Production of a finished product requires knowledge of and adherence to a host of guidelines and regulations; this section provides an introduction to these guidelines/regulations. Good manufacturing practices (GMPs) for processed foods are established by the FDA and are available on the FDA website (89); comparable regulations for dietary supplements are available as well (86). The FDA website also publishes many documents (called Guidance for Industry) that provide information on how to interpret and comply with GMPs. For example, the Guidance for Commercial Processors of Acidified and Low-Acid Canned Foods (92) provides guidance on current regulations, including facility registration, and details guidance that is no longer applicable. Guidance

documents established by the FDA are not legally mandated procedures but rather offer advice on how to meet the regulations in the GMPs.

Scale-up production requires adherence to food safety guidelines (74). Hazard analysis and critical control points (HACCP) is a systematic approach to food safety and production. The FDA mandates the approach for seafood and juice, whereas the USDA mandates the approach for meat and poultry; the use of the process in other industries is currently voluntary but is highly encouraged (94). Individual entrepreneurs and small companies are urged to send an individual for training on how to interpret and comply with the FDA guidelines.

Although federal agencies provide the bulk of regulations for food production, individual states may have special regulations for foods sold within the state. An example is California's Proposition 65, which mandates the labeling of any food sold in California that contains a listed toxin at a certain level (38). The current list of chemicals can be found on the California Office of Environmental Health Hazard Assessment website (3).

Special Regulations

The Food Allergen Labeling and Consumer Protection Act of 2004 (93) mandates that all products must declare the presence of any of the following major food allergens: milk, egg, fish, crustacean shellfish, tree nuts, wheat, peanuts, or soybeans. Because no tolerances have been established for any of these items, the manufacturer must either be absolutely certain there is no potential for contamination or must label the product as possibly containing allergens. In practice, the primary means of ensuring no contamination is to maintain dedicated allergen-free production lines in separate facilities and to have absolutely no storage or trafficking of allergens in an allergen-free facility, which can mean attention to details such as maintaining separate truck docking and loading/unloading facilities. A manufacturer should be aware that an allergen contamination that results in serious injury could result in severe civil penalties beyond penalties imposed by the FDA.

Religious dietary laws can be very complex, and an expert should be consulted if product labeling is being considered (for a comprehensive overview, see 51). The term "kosher" originally pertained to proper means of animal slaughter, but today kosher covers all foods fit to eat under Jewish dietary law. Production and processing plants must be inspected and approved by organizations that certify kosher standards and approved products. Halal laws cover foods permitted or fit for Muslims. Many halal food standards, especially those for meats, are similar to those for kosher, and many kosher foods, particularly meat, can be consumed under halal law (19). All religious foods also need to adhere to federal and state guidelines and regulations.

SELENIUM IN FOODS: AN EXAMPLE OF POTENTIAL PROBLEMS IN FUNCTIONAL FOOD DEVELOPMENT

Selenium (Se) is a nutrient/food ingredient of interest to the food and dietary supplement industry, and its history provides an illustration of many of the concepts discussed as well as the pitfalls that may face the food scientist or product developer. Selenium was proven to be nutritionally essential in 1957 (53), and within a few decades a number of researchers working in various areas had established multiple biochemical functions and putative physiologic functions of Se; a Daily Recommended Intake of 55 ug/d for adults was established (56). A large volume of scientific literature has been generated in the area of biomedical and chemical aspects of Se (a PubMed search for the term "selenium" found more than 25,500 articles; a similar search for "selenium" and "human" generated more than 11,000 articles).

Selenium researchers began to focus on cancer following a report that supplementation of 1,312 older subjects with 200 ug/d Se (as selenium-enriched yeast) for 12 years resulted in a 50% decrease in all-cancer mortality (compared to a placebo) and an even greater decrease in prostate cancer (5). Publication of this work resulted in a surge of research in the area of selenium and cancer, including numerous human studies (epidemiologic and clinical trials) (a PubMed search of "selenium" and "cancer" yielded more than 4,000 articles; "selenium," "cancer," and "epidemiology" found 485; and "selenium," "cancer," and "intervention" found 227).

The volume of research and the findings of multiple clinical intervention studies in the United States and elsewhere were the basis on which Wellness Lifestyles, Inc. petitioned the FDA for a health claim in 2002. Despite the volume of work, the FDA determined that the significant scientific agreement standard was not met, and it issued a qualified health claim with the wording, "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" (95). In making its decision, the FDA noted that although five cancer trials were submitted as evidence, only the study of Clark et al. (5) was considered, and the primary end point of that study (skin cancer) did not benefit from Se supplementation. Product designers, marketers, and entrepreneurs may find the letter of enforcement discretion (82) to be informative. The benefit of such a health claim is questionable: A consumer study conducted with Se-enhanced beef labeled as such found that overall, consumers did not prefer the labeled product over an unlabeled product, although the labeling did appeal to some subgroups (27).

The study of Clark et al. (5), as well as additional epidemiologic, clinical, animal, and in vitro evidence suggesting that intakes of Se greater than the requirement lowered the risk of prostate cancer, was the impetus for the Selenium and Vitamin E Cancer Prevention Trial (SELECT), which randomized more than 35,000 men to several arms, including one that supplied participants with 200 ug/d Se as selenomethionine. Originally designed as a 12-year study, the trial was stopped at the interim when Se was found to have no effect (36).

In 2008, the FDA responded to a petition that requested qualified health claims characterizing the relationship between Se from dietary supplements and a reduced risk of site-specific cancers (82). The petition asked the FDA to approve several qualified health claims, including "Selenium may reduce the risk of prostate cancer. Scientific evidence supporting this claim is convincing but not yet conclusive." Although 30 reports were submitted in support of the petition, in 2009 the FDA concluded that the SELECT trial was the only intervention trial that allowed for evaluation of the relationship between Se intake and the risk of a site-specific cancer. On the basis of its evaluation, the FDA used enforcement discretion to allow a claim with the wording, "Two weak studies suggest that selenium intake may reduce the risk of prostate cancer. However, four stronger studies and three weak studies showed no reduction in risk. Based on these studies, FDA concludes that it is highly unlikely that selenium supplements reduce the risk of prostate cancer" (82). The results of the SELECT trial also appear to have impacted the sale of Se for biologics. In 2011, it was reported that sales of Se supplements fell 14%, and the chairman of a biotechnology company that sold such supplements attributed the decline to the negative press created by termination of the SELECT trial (8).

After the revision of the FDA qualified health claim in 2009, the FDA was sued on the basis of First Amendment rights. The settlement, now posted by the FDA on its website, allows claims that include the following: "Selenium may reduce the risk of colorectal cancer. Scientific evidence concerning this claim is inconclusive. Based on its review, FDA does not agree that selenium may reduce the risk of colorectal cancer"; and "Selenium may reduce the risk of prostate cancer. Scientific evidence concerning this claim is inconclusive. Based on its review, FDA does not agree

that selenium may reduce the risk of prostate cancer" (96). Whether the revision of the claims will have a beneficial effect on sales by the dietary supplement industry is yet to be seen.

CONCLUSION

Food scientists and nutritionists may have ideas for conventional foods and dietary supplements that may provide health benefits, but converting such ideas to successful products is a complicated process that requires knowledge of the food industry, legal considerations, and product development. The food industry environment is competitive, and many, if not most, new products will fail. A product may have a competitive advantage if it can claim, either on the label or by advertising, that it has a unique healthful benefit. Label claims are regulated by the US FDA; advertising is regulated by the US FTC. Development of a product requires knowledge of and adherence to various regulations set forth by multiple federal and state agencies. Ingredients are regulated by the FDA and the USDA, and manufacturing conditions are regulated by the same agencies. Individual states may also impose special regulations. Food scientists and product designers are advised to study the history of previous conventional food and dietary supplement products to gain an understanding of the hurdles involved in taking a product from conception to a successful market.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review. The authors are responsible for the content of this article, and the perspectives contained herein may not represent official opinions or positions of any government agency to which the authors are, or have been, affiliated.

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