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SUPPLEMENT

Scientific substantiation of claims in the USA: focus on functional foods

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Abstract Although functional foods are currently regulated the same as conventional foods by the US Food and Drug Administration (FDA) there is some concern that they should not be. One concern is whether functional foods can/should carry the same type of health and nutrition labeling claims as conventional foods. For example, the type of nutrient content claim that describes a level of the nutrient such as "good or excellent source" presents a problem for functional foods since these claims relate back to a standard value for nutrients (the daily value or DV). At this time the bioactive or functional components in a functional food do not have daily values so they could not take advantage of this type of claim. Structure/function claims are also at issue since they are required to relate to the food's attributes of taste, aroma, and nutritive value, rather than attributes of functionality (which would pertain to functional foods). There appear to be three categories of issues concerning the regulation of functional foods: safety; efficacy; and their effect on the overall diet. Since bioactive components can be synthesized or extracted and concentrated, the concern is that the amounts of these substances in functional foods might reach levels which are actually injurious to health or they may negate beneficial effects of substances in the same food. Most people/organizations consider that functional foods need to document their functionality. This means that unlike conventional foods, all functional foods, by definition, would have to apply for a health claim. Finally, the long term overarching concern is what will be the impact of a functional food-driven market on overall health. It is of interest to see how the regulatory environment for functional foods evolves in the next few years and what impact that environment has on the future of these foods.

Keywords Functional foods · Efficacy/safety · Heath claims · USA

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Introduction

There is no FDA regulatory policy specific to functional foods. Rather they are regulated under the same framework as conventional foods. Whether or not there should be a separate policy for functional foods was the subject of an FDA sponsored public hearing held December 5, 2006 and a request for comments on Conventional Foods Being Marketed as "functional foods" [5]. The FDA Hearing and request for comments was, in part, a response to a number of key reports on functional foods including "Improvements Needed in Overseeing the Safety of Dietary Supplements and 'functional foods'" from the General Accounting Office (GAO) [17]; an Institute for Food Technologists (IFT) report titled "Functional Foods: Opportunities and Challenges" [13]; a report from the Functional Foods Committee of the International Life Sciences Institute (ILSI) [14]; and a citizen petition from the Center for Science in the Public Interest (CSPI) [1].

FDA does not have a formal definition of a functional food, but for the purposes of its public hearing it adopted the definition used in the IFT report, which is "food and food components that provide a health benefit beyond basic

nutrition…" [13]. If a product makes a statement on the food label that is related to health and nutrition, that statement is subject to regulation or enforcement discretion by FDA. One could argue that functional foods, by their very name, are implying a health claim or a structure/function claim and as the GAO report stated, FDA should "ensure that functional foods provide the functions that they claim" [17]. This report will focus on the types of health related statements that might pertain to functional foods; how these statements are evaluated by FDA; and the major issues involved in determining whether functional foods should be considered differently from conventional foods and supplements.

Types of health related statements that might pertain to functional foods

There are generally four types of claims related to health and nutrition in labeling including dietary guidance; nutrient content claims; structure/function claims, and health claims [8]. Each type of claim will be discussed below together with its potential relationship to functional foods.

Dietary Guidance [2] Dietary Guidance statements cannot contain information linking a food or substance to a disease or health related condition (those are Health Claims). Instead, dietary guidance statements focus on general patterns of food intake to promote health. They most often refer to a category of foods such as fruits and vegetables. They can be made without FDA review or authorization. It is difficult to conceive of a functional food making a dietary guidance statement.

Nutrient content claims [3] A nutrient content claim may describe the level of a nutrient or dietary substance. If a claim describes the level of a nutrient as being high or low or a "good source" then it needs to conform to the criteria for that specific nutrient content claim. Most nutrient content claims are compared to a standard for that nutrient (the daily value or DV). For example, the DV for dietary fiber is 25 g/day and a good source is considered 10% of that value (2.5 g) whereas an excellent source is 20% of that value (5 g/day). Of interest, and the subject of considerable controversy, is that there are no daily values for foods or functional components in foods. This means, for example, that there is no daily value for "whole grain." Although a food label can state the amount of whole grain in a product it cannot indicate that it is a good or excellent source of whole grain. The same would hold true for the bioactive components of functional foods (except for traditional nutrients) in part because there is no DV for these substances. Thus nutrients in conventional foods but not bioactive compounds in functional foods may make these types of nutrient content claims in which values are compared to a standard.

Structure/function claims [7] These claims describe the role of substances that affect the normal structure or function in humans. The example that is frequently provided is "calcium builds strong bones." Conventional foods and functional foods may not be viewed the same way with respect to structure/function claims. For example, for a food to bear a structure/function claim or a health claim the claim is required to be related to the food's attributes of taste, aroma, and nutritive value. If the claim is not based on the product's "food" attributes it may be classified as a drug. Although "nutritive value" has been rather broadly interpreted by FDA, the IFT report argues that this approach is too restrictive and does not allow for claims based on the food providing a functional or physiological effect [13]. This appears to place a functional food in a hybrid category with some characteristics of food and some characteristics of drugs.

Health claims [4] One outcome of the way that FDA exercises its oversight on health claims is that it allows foods (including dietary supplements) to bear certain science-backed claims about reducing disease risk in their labeling without being regulated as drugs. All health claims must be about reducing the risk of a disease or health-related condition, not treating, mitigating, or curing diseases. If statements are made about treating a disease they are considered drugs, not foods. FDA exercises its oversight on health claims in three ways. (1) FDA issues a regulation for claims which involve significant scientific agreement (SSA). If the strength of the relationship between the substance and decreased risk of a disease reaches the level of significant scientific agreement (SSA), The Nutrition Labeling and Education Act of 1990 (NLEA) [16] provides for the FDA to issue regulations authorizing health claims. Guidance for Industry on the significant scientific agreement standard is available online [11]. (2) FDA prohibits or modifies, by regulation, a health claim that is submitted based on an authoritative statement from a scientific body of the US government or the National Academy of Sciences. See guidance for this at [6]. (3) FDA issues a letter of enforcement discretion for qualified health claims. For information on qualified health claims for which FDA has issued a letter of enforcement discretion, see [10]. The evaluation process is the same for conventional foods and functional foods. Letters of enforcement discretion lay out agency thinking and criteria for health claim evaluation. They are available on the FDA CFSAN website at [10].

How health claims are evaluated by FDA

A new "guidance for Industry titled "evidence-based review system for the scientific evaluation of health claims" has recently been released by FDA [9]. This draft guidance represents the agency's current thinking on the scientific evaluation process for health claims. Although evidence-based reviews differ from each other, they all have certain aspects in common. These include: definition of the question/statement; collection of all relevant studies; evaluation of the type of study (randomized clinical trial versus observational study); evaluation of the quality of the study; and a rating of the strength of the entire body of evidence. The initial question is very important since it sets the criteria for the type of evidence that is pertinent. Typically the question takes the form of "Does substance '*x*' reduce the risk of disease '*y*' in (name the population). To answer that question requires defining the substance, defining the disease, and defining the target population. Relevant studies must test "substance *X*" rather than a mixture. For example, if the question is "Does eating fish reduce the risk of coronary heart disease"? then the appropriate studies would be on fish intake; if the question were "Do omega 3 fatty acids reduce the risk of coronary heart disease"? then the studies considered should deal with intake of omega 3 fatty acids. Relevant studies would concentrate on those done in humans in non-diseased populations. Animal studies, in vitro studies, review articles and meta analyses would be used as background information but not as part of the evidence based review with few exceptions. What constitutes a "non-diseased population" is not entirely clear. For example, in the US, 2/3 of the adult population is overweight or obese. Are overweight or obese individuals considered a healthy non-diseased population? Similarly, many individuals have some degree of insulin resistance; as individuals age, hypertension is more the norm than an example of a "diseased population." If a case can be made, based on the evidence, that a disease progression is part of a continuum and that those individuals to the greater disease progression end of the continuum react to diet in the same way as do those further to the left on the continuum then data from individuals with hypertension or elevated cholesterol or a higher than desirable body mass index may be considered in the evidence-based review with an appropriate explanation.

The type of study design is an important consideration in determining the strength of the evidence, and here the concept is to minimize bias. A randomized clinical trial is rated more highly than a prospective cohort study which in turn is rated more highly than a cross sectional observational study. Also important is the appropriate choice of surrogate markers as substitutes for a disease endpoint. Many studies do not have the disease of interest as the endpoint for the study. Instead surrogate markers of that disease are used. The markers must be accepted by FDA and NIH as markers, and justified. For example, an intervention that decreases the level of LDL cholesterol is considered a surrogate marker for decreasing the risk of CHD. If the diet intervention for the study affects the rest of the diet, then a highly rated study would characterize the rest of the diet. For example, a low fat intervention would have to mean that as fat was decreased something else must be increased. That "something else" would have to be defined. Other quality factors include the type of population in which the study is performed. If that population is very different from the one for which the proposed health claim is made, it would not be highly rated. Studies done in populations with substantial evidence of malnutrition, or very different rates of disease, or differences in genetic backgrounds known to affect outcomes would be "downgraded" accordingly. All excellent intervention studies have a control group that does not receive the intervention, not just measurements on groups before and after an intervention with no control group. It is always possible (and sometimes highly likely) that a factor independent of the intervention could cause the outcome, rather than the intervention. Finally, there should be no key differences between the control and test groups (e.g. more smokers in one group vs. the other; differences in age or gender between groups). The study must be long enough to observe the effect being tested, and the food/substance needs to be characterized. Appropriate statistical methods are important. For example, the use of paired *T* tests for multiple endpoints is not accepted. And, for epidemiological studies it is always necessary to control for the known confounders. The final decision on the strength of the evidence between the food or substance and decreased risk of the disease or health related condition is a combination of the overall quality and quantity of the data. The benefit of the intervention and the consistency of the findings are considered. The end result of using an evidence-based review system is a statement linking a substance to a disease/health-related condition with a ranking as to the scientific evidence behind that statement. It should be a clear and transparent demonstration of which research studies were evaluated to provide the ranking combined with evidence tables showing the rigor of the evaluation. Trained scientists should come to similar conclusions using the same data base.

Major issues involved in determining whether functional foods should be considered differently from conventional foods and supplements

Do functional foods need to have their own category? Currently, functional foods are regulated the same as conventional foods with no different requirements. Some

have argued that there is a need for a separate category for functional foods [13]. The major arguments revolve around issues of safety and efficacy, and the effect of a diet high in functional foods on human health.

Safety A manufacturer who wants to add a new additive to a food must first prove that it is safe and that there is a reasonable certainty of no harm under the substance's intended conditions of use [15]. Typically an "additive" for a conventional food is there for its benefit to the food itself (e.g. to prevent oxidation, to aid in emulsification, etc.). With functional foods the "additive" may be there as a concentrated source of a bioactive component at levels higher than typically found in conventional foods. Thus, even though "functional foods" are being considered as conventional foods, they may differ in this regard and the "intended use" could be different also. At what point might we be concerned about an upper level of a functional component? Generally, we are not concerned about eating too much of a substance from a conventional food, but when substances are extracted and concentrated in functional foods this may become an issue at some level. Some argue that we should not have to concern ourselves with "side effects" of our foods and we might have to consider such effects from functional foods. Therefore functional foods should be regulated differently from traditional foods.

Efficacy The beneficial effects of traditional nutrients in conventional foods have been well described as have their interactions. This is not true for most bioactive compounds in functional foods. It is also not known how high amounts of one bioactive component added to a food may affect other nutrients in that food. Nor is there a good literature base on the bioavailability of most functional food ingredients when these substances are added to different types of foods. If a functional component is synthesized or extracted from a plant, for example, does it produce the same physiological response as if it were endogenous to that food?

Overall effect of functional foods on health Currently, FDA states that it "regulates conventional foods being marketed as 'functional foods' under the same regulatory framework as other conventional foods [2]. Perhaps that statement should be modified to explain that conventional foods are not required to have a health claim, but it appears that it would not be possible to market a food as a "functional food" unless there was a claim concerning its function. In addition to having to satisfy all the criteria of a particular type of claim, a functional food would have to meet the qualifying criteria for a product for amounts of fat, saturated fat and sodium, and perhaps for "positive" nutrients, just as a conventional food with a health claim would have to meet. Unless a conventional food bears a health claim it does not need to meet these qualifying criteria. It would also seem that for a food to be called "functional" it would have to contain a reasonable amount of the functional component, just as a conventional food needs to contain a set amount of the substance that is the subject of the claim. Finally, what effect will an increased emphasis on functional foods have on recommendations and consumption patterns of conventional foods? Will a diet of foods fortified with functional ingredients have the same overall benefits to health as consuming a diet high in fruits, vegetables, lean protein sources, low or non-fat dairy products and whole grains as recommended by the Dietary Guidelines [12]? It will be interesting to see how the future of functional foods plays out from a regulatory viewpoint in the next few years, particularly as the EU establishes their regulatory environment. Most important to evaluate will be the effect of the regulations on research, product innovation, and human health.

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