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**OFFICE OF
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**DIETARY SUPPLEMENTS:
STRUCTURE/FUNCTION CLAIMS
FAIL TO MEET FEDERAL
REQUIREMENTS**



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DIETARY SUPPLEMENTS: STRUCTURE/FUNCTION CLAIMS FAIL TO MEET FEDERAL REQUIREMENTS, OEI-01-11-00210

WHY WE DID THIS STUDY

The Government Accountability Office and public interest groups have raised concerns about a specific type of claim—called a structure/function claim—that manufacturers may use on dietary supplement labels. Manufacturers have used these claims to promote health benefits of their products. Stakeholders have urged the Food and Drug Administration (FDA) to strengthen oversight of these claims because they are potentially misleading and may lack scientific support. FDA lacks authority to review or approve these claims before products enter the market. Manufacturers must have competent and reliable scientific evidence to show that claims are truthful and not misleading, but they do not have to submit the substantiation to FDA, and FDA has only voluntary standards for it. A manufacturer must notify FDA when it uses structure/function claims, and a product label must include a disclaimer stating that FDA has not reviewed the claim and that the product is not intended to diagnose, treat, cure, or prevent any disease.

HOW WE DID THIS STUDY

We analyzed structure/function claims for a purposive sample of 127 dietary supplements marketed for weight loss or immune system support. We reviewed the claims to determine the extent to which they complied with FDA regulations. We reviewed substantiation provided by manufacturers to describe the quantity and nature of the evidence. We also assessed the accuracy and completeness of notification letters that manufacturers must submit to FDA for their structure/function claims.

WHAT WE FOUND

Overall, substantiation documents for the sampled supplements were inconsistent with FDA guidance on competent and reliable scientific evidence. FDA could not readily determine whether manufacturers had submitted the required notification for their claims. Seven percent of the supplements lacked the required disclaimer, and 20 percent included prohibited disease claims on their labels. These results raise questions about the extent to which structure/function claims are truthful and not misleading.

WHAT WE RECOMMEND

We recommend that FDA seek explicit statutory authority to review substantiation for structure/function claims to determine whether they are truthful and not misleading. We recommend that FDA improve the notification system for these claims to make it more organized, complete, and accurate. We also recommend that FDA expand market surveillance to enforce the use of disclaimers for structure/function claims and to detect disease claims. In its comments on the draft report, FDA did not explicitly concur with our first recommendation, but said it would consider it. FDA concurred with our second and third recommendations.

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OBJECTIVES

1. To determine the extent and nature of structure/function claims on selected weight loss and immune support dietary supplement labels.
2. To assess the extent to which documentation used to substantiate structure/function claims on selected weight loss and immune support supplement labels was consistent with Food and Drug Administration (FDA) guidance.
3. To determine the extent to which structure/function claims on selected weight loss and immune support dietary supplements complied with FDA regulations related to notification and disclaimers.
4. To determine the extent to which selected weight loss and immune support dietary supplement labels included prohibited disease claims.

BACKGROUND

In the United States, dietary supplements are a \$20 billion-per-year industry and are used by 80 percent of adults for a wide range of purposes.¹ Products for weight loss or immune system support represent some of the fastest growing segments of the dietary supplement market.^{2, 3} Previous Office of Inspector General (OIG) and Government Accountability Office (GAO) reports highlighted problems with dietary supplement labels and the claims used to market supplements.^{4, 5} GAO and public interest groups have raised concerns about a specific type of claim—called a structure/function claim—that manufacturers may use on dietary supplement labels.^{6, 7, 8} In recent years, manufacturers have

¹ Natural Products Foundation, *What is the Current Economic Contribution of the Dietary Supplement Industry to the U.S. Economy?* Accessed at www.naturalproductsfoundation.org on May 31, 2010.

² GAO, *Dietary Supplements for Weight Loss: Limited Federal Oversight Has Focused More on Marketing than on Safety*, GAO-02-985T, July 2002.

³ Nutraceuticals World, *Getting Ahead of the Curve: Immunity*, October 1, 2010. Accessed at www.nutraceuticalsworld.com on March 16, 2012.

⁴ OIG, *Dietary Supplement Labels: Key Elements*, OEI-01-01-00120, March 2003; and *Dietary Supplement Labels: An Assessment*, OEI-01-01-00121, March 2003.

⁵ GAO, *Dietary Supplements: Examples of Deceptive or Questionable Marketing Practices and Potentially Dangerous Advice*, GAO-10-662T, May 25, 2010; and *Dietary Supplements: FDA Should Take Further Actions to Improve Oversight and Consumer Understanding*, GAO-09-250, January 2009.

⁶ GAO, *Food Labeling: FDA Needs to Reassess Its Approach to Protecting Consumers from False or Misleading Claims*, GAO-11-102, January 2011.

⁷ Center for Science in the Public Interest, *Food Label Trickery: New Claims On Foods Can Mislead & Confuse*, May 30, 2003. Accessed at www.cspinet.org on March 19, 2012.

⁸ Public Citizen, *Reduction In Cancer Risk Claim for Antioxidant Vitamins Rejected by the Food and Drug Administration*, July 2001. Accessed at www.citizen.org on March 19, 2012.

increasingly used structure/function claims, which do not require preapproval by FDA, to promote the health benefits of their products.⁹ Stakeholders have urged FDA to strengthen its oversight of structure/function claims because such claims are potentially misleading to consumers and may lack scientific support.¹⁰ Critics of structure/function claims have asserted that the claims imply that the supplement will prevent or treat disease or dysfunction, which is prohibited for dietary supplements.^{11, 12, 13, 14}

Dietary Supplements

The Dietary Supplement Health and Education Act (DSHEA) of 1994, an amendment to the Federal Food, Drug, and Cosmetic Act, defines a dietary supplement as, in part, a product that is ingested by mouth to supplement the diet and contains one or more of the following ingredients:

- a vitamin;
- a mineral;
- an herb or other botanical;
- an amino acid;
- a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or
- a concentrate, a metabolite, a constituent, or an extract.¹⁵

DSHEA does not require manufacturers to submit dietary supplements to FDA for safety testing or approval prior to sale.¹⁶ As a result, FDA has no comprehensive list of dietary supplements on the market. Dietary supplement manufacturers must ensure that their products are safe, that

⁹ GAO, *Food Labeling: FDA Needs to Reassess Its Approach to Protecting Consumers from False or Misleading Claims*, GAO-11-102, January 2011.

¹⁰ Ibid.

¹¹ Center for Science in the Public Interest, *FDA Needs Authority To See Evidence on Structure/Function Claims, Says GAO*, January 14, 2011. Accessed at www.cspinet.org on March 23, 2012.

¹² USA Today, *Many Food Label Claims May Mislead Rather Than Inform*, January 31, 2011. Accessed at www.usatoday.com on March 23, 2012.

¹³ P. Wilde, *GAO: FDA Lacks the Power It Needs to Address Structure /Function Claims*, January 15, 2011. Accessed at www.usfoodpolicy.blogspot.com on March 23, 2012.

¹⁴ 21 U.S.C. § 343(r)(6).

¹⁵ P.L. 103-417 § 3 (codified at 21 U.S.C. § 321(ff)(1)).

¹⁶ The law does consider a dietary supplement product containing a “new dietary ingredient,” which is any dietary ingredient not marketed in the United States prior to 1994, as adulterated unless it meets one of two statutory requirements: the supplement must contain only dietary ingredients that have been present in the food supply, or there must be a history of use or other evidence of safety establishing that the dietary ingredient will reasonably be expected to be safe. 21 U.S.C. § 350b.

they have evidence to substantiate structure/function claims, and that product labels are truthful and not misleading.¹⁷

FDA is responsible for ensuring that dietary supplements marketed to U.S. consumers are safe. FDA does this by monitoring adverse event reports and consumer complaints, searching the Internet for supplements that do not comply with regulations, conducting onsite inspections of manufacturers' facilities or imported shipments of supplements, and reviewing new dietary ingredient notifications.¹⁸ FDA does not conduct surveillance of dietary supplements sold in retail establishments; however, it does conduct limited surveillance of supplements sold on the Internet.

Claims on Dietary Supplement Labeling

FDA's Center for Food Safety and Applied Nutrition has primary responsibility for overseeing claims made on dietary supplement labeling.¹⁹ Among the most commonly used claims on dietary supplement labels are nutrient content claims, health claims, and structure/function claims. FDA regulates each of these types of claims differently.²⁰

Nutrient content claims describe the level of a nutrient in a dietary supplement or other food (e.g., "200 mg of folic acid," "low fat," or "high fiber").²¹ Health claims describe a relationship between a food or food component (including a dietary supplement ingredient) and reduced risk of a disease or health-related condition. "Adequate calcium throughout life, as part of a well-balanced diet, may reduce the risk of osteoporosis" is an example of a health claim.²² FDA reviews petitions for nutrient content claims and health claims and either authorizes or denies them depending on the amount of supporting scientific evidence.^{23, 24} Generally, nutrient

¹⁷ 21 U.S.C. § 343(a)(1); 21 U.S.C. § 343(r)(6)(B); 21 U.S.C. § 342(f).

¹⁸ 21 U.S.C. § 350b.

¹⁹ "Label" means a display of written, printed, or graphic matter upon the container, 21 U.S.C. § 321(k); "labeling" means all labels and other written, printed, or graphic matter upon the product or any of its containers, wrappers, or accompanying promotional material, 21 U.S.C. § 321(l). See also 21 CFR § 1.3. FDA may take enforcement action against claims made on Web sites as well as claims printed on the supplement package.

²⁰ In addition, dietary supplements may bear claims that do not fall into a defined category as long as the claim is truthful and not misleading.

²¹ 21 CFR § 101.13(b); mg=milligrams.

²² 21 CFR § 101.14(a)(1).

²³ FDA has authorized 12 health claims by regulation, none of which relates to weight loss or immune support.

²⁴ Qualified health claims, which are also permitted by FDA, are health claims that do not meet the evidentiary standard for an FDA-authorized health claim (see 21 U.S.C. § 343(r)(3)(B)(i)), but are supported by credible evidence and include a disclaimer or other qualifying language to prevent the claims from being misleading.

content claims or health claims not explicitly authorized by FDA are prohibited.

Structure/Function Claims

In general, structure/function claims describe the role of a dietary supplement in the structure and function of human bodies, but the claims may not explicitly or implicitly claim to prevent, treat, mitigate, cure, or diagnose a disease.²⁵ A structure/function claim may also:

- claim a benefit related to a classical nutrient deficiency disease (e.g., scurvy) and disclose the prevalence of such disease in the United States,
- characterize the documented mechanism by which a nutrient or dietary ingredient acts to maintain such structure or function, or
- describe general well-being from consumption of a nutrient or dietary ingredient.²⁶

For example, a supplement may claim that it “curbs appetite to help with weight loss,” but it may not claim to “aid weight loss to treat obesity” because obesity is a disease. Similarly, a supplement may claim to “support immunity,” but may not claim to “boost the immune system against colds and flu” because the latter references specific diseases. Although FDA has issued regulations and published guidance describing the difference between structure/function claims and disease claims, it acknowledges the challenge of distinguishing between the two.²⁷

DSHEA requires manufacturers to meet three requirements for placing a structure/function claim on a supplement label: (1) substantiation that the claim is truthful and not misleading, (2) notification to FDA within 30 days of marketing the supplement with the claim, and (3) a disclaimer on the supplement label.²⁸

Substantiation of Structure/Function Claims. Manufacturers must have substantiation for the structure/function claims on their products’ labels to ensure that they are truthful and not misleading. In any legal proceeding concerning structure/function claims, FDA must prove that the claim is

²⁵ 21 U.S.C. § 343(r)(6); 21 CFR § 101.93(f)-(g); FDA, *Structure/Function Claims, Small Entity Compliance Guide*, January 9, 2002. Accessed at www.fda.gov on February 13, 2012.

²⁶ 21 U.S.C. § 343(r)(6)(A); see also 21 CFR § 101.93.

²⁷ 21 CFR § 101.93(f)-(g); FDA, *Structure/Function Claims, Small Entity Compliance Guide*, January 9, 2002. Accessed at www.fda.gov on February 13, 2012.

²⁸ 21 U.S.C. § 343(r)(6).

false or misleading.²⁹ However, DSHEA does not require manufacturers to submit the substantiation to FDA to determine its adequacy, and FDA may not compel manufacturers to produce substantiation upon request. Therefore, FDA has limited authority to enforce the substantiation requirement.

FDA has published guidance on the extent and nature of substantiation that manufacturers should have to comply with the law.³⁰ In general, FDA recommends that evidence be derived primarily from human studies that use widely accepted scientific methods. The guidance also lists types of background information—such as in vitro or animal studies, meta-analyses, and review articles—that manufacturers may use to substantiate claims. However, the guidance notes that background information, when used alone, may not be adequate to substantiate claims.³¹

FDA uses a standard of “competent and reliable scientific evidence” for substantiation. To meet this standard, FDA recommends that manufacturers consider the following when substantiating structure/function claims:

- The relationship of the evidence to the claim. The evidence should demonstrate a direct effect of the supplement on a structure or function of the body in a population similar to that which will be consuming the product. The evidence should test either the product itself or an amount and potency of the active ingredients that are similar to the product.
- The totality of the evidence. Manufacturers should consider the total body of evidence—both favorable and unfavorable—in determining whether it is adequate to substantiate a claim. If evidence conflicts or shows inconsistent results, it will raise questions about whether a structure/function claim is substantiated.
- The quality of the evidence. Manufacturers must consider the scientific quality of studies used to substantiate claims. FDA considers human studies that are randomized, double-blind,

²⁹ An enforcement action against a dietary supplement based on an unsubstantiated structure/function claim could be brought under certain provisions of the Federal Food, Drug and Cosmetic Act, such as 21 U.S.C. §§343(a)(1) and 343(r)(6) and 21 U.S.C. §§ 331, 332, and/or 334.

³⁰ FDA, *Guidance for Industry: Substantiation for Dietary Supplement Claims Made Under Section 403(r) (6) of the Federal Food, Drug, and Cosmetic Act*, December 2008. Accessed at www.fda.gov on February 17, 2012. Following FDA’s guidance on substantiation is recommended, but not required.

³¹ FDA guidance lists seven types of documentation that would be considered background information: animal studies, in vitro studies, testimonials or anecdotal evidence, meta-analyses, review articles, comments and letters to the editor, and product monographs.

parallel group, placebo-controlled trials that focus on a representative population to be the “gold standard” for substantiation. Manufacturers may use other human or nonhuman studies to substantiate claims, but should consider factors in the studies’ methods that may affect the results.

- The meaning of the claim(s) being made. Manufacturers should have substantiation for each possible interpretation of a structure/function claim. For example, a supplement may claim to “promote weight loss.” If the manufacturer’s evidence is a study showing that the supplement’s main ingredient temporarily increases metabolism, but not showing actual weight loss, then the manufacturer has not accounted for the meaning of the claim in its substantiation.³²

Notification to FDA. Dietary supplement manufacturers must notify FDA of any structure/function claims no later than 30 days after first introducing a product into the market. The notification must include the name and address of the manufacturer, the text of the claim, the name of the ingredient for which the claim is being made, and the name of the dietary supplement. In the notification, the manufacturer must attest that it has substantiation that the claim is truthful and not misleading. The notification must be signed by a person who can certify the accuracy and completeness of the information.³³

FDA reviews each notification to ensure it meets the definition of a structure/function claim. If it does not, FDA sends a letter to the manufacturer notifying it that the claim is not in compliance and follows up as needed. FDA keeps copies of all notifications on file.³⁴

Disclaimer. All structure/function claims must be accompanied by the following mandatory disclaimer: “This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.”³⁵

Prohibition on disease claims

Dietary supplements may not include disease claims on their labels or in other labeling. A disease claim is defined as a claim that mentions or implies the mitigation, treatment, diagnosis, prevention, or cure of a

³² FDA, *Substantiation for Dietary Supplement Claims Made Under Section 403(r) (6) of the Federal Food, Drug, and Cosmetic Act*, December 2008. Accessed at www.fda.gov on February 17, 2012.

³³ 21 CFR § 101.93(a)(2).

³⁴ The number of manufacturers that do not submit structure/function claims to FDA is unknown.

³⁵ 21 CFR § 101.93(c)(1).

disease or its symptoms.³⁶ For example, a dietary supplement may not claim that it “prevents or treats cancer,” “reduces pain associated with arthritis,” or “relieves bronchospasms” (which would imply treatment of a disease because bronchospasms are a symptom of asthma). A product that assists in the diagnosis, mitigation, treatment, cure, or prevention of a disease is considered a drug under the Federal Food, Drug, and Cosmetic Act.³⁷

If FDA learns that the label of a product marketed as a dietary supplement contains a disease claim, it treats the product as an unapproved drug and may take enforcement action against the manufacturer or distributor. Actions include issuing a warning letter, seizing the product, seeking criminal prosecution, or prohibiting the sale of the product through an injunction.³⁸

Companion Report on Dietary Supplements

This report is being issued in conjunction with another OIG evaluation report entitled *Dietary Supplements: Companies May Be Difficult To Locate in an Emergency* (OEI-01-11-00211). Both reports are based on the same sample of dietary supplements.

METHODOLOGY

Scope

This study analyzed the structure/function claims on a purposive sample of 127 dietary supplements marketed for weight loss or immune system support in retail stores and on the Internet. All of the supplements in our sample had one or more structure/function claims on their labels. We reviewed the structure/function claims to determine the extent to which they complied with FDA regulations. We also reviewed substantiation documents submitted by dietary supplement manufacturers to describe the quantity and nature of the evidence. We did not test the scientific validity of the substantiation, nor did we determine whether the documents were adequate to substantiate the claims. For the supplements in our sample, we also assessed the accuracy and completeness of notification letters that manufacturers must submit to FDA for their structure/function claims. Our findings from this evaluation are limited to the weight loss and immune support supplements in our sample.

³⁶ 21 U.S.C. § 343(r)(6); 21 CFR § 101.93(g).

³⁷ 21 U.S.C. § 321(g)(1)(B).

³⁸ 21 U.S.C. § 332; 21 U.S.C. § 333; 21 U.S.C. § 334.

Data Collection and Analysis

We focused on two types of supplements—immune support supplements and weight loss supplements—after consulting with FDA. Our sample included 67 immune support supplements and 60 weight loss supplements. We purchased 67 of the supplements from retail stores and 60 from Internet sites.

Supplements Purchased From Retail Stores. To purchase supplements from retail stores, we selected five major cities to achieve a wide regional distribution: New York, Chicago, Dallas, Los Angeles, and Seattle. Within each city, we purchased a minimum of 12 unique supplements from a mix of small and large pharmacies, supermarkets, and supplement retailers. We did not seek supplements that appeared to violate FDA regulations, but rather we sought to purchase a variety of weight loss and immune support supplements with a variety of structure/function claims on their labels.

Supplements Purchased From the Internet. To select supplements from Internet sources, we created a set of search terms related to weight loss or immune support. Using three major search engines, we searched the Internet with these terms. We selected sites and products with the goal of purchasing as many different brands of supplements as possible.

Review of Structure/Function Claims and Disease Claims on Supplement Labels. We reviewed the structure/function claims on the labels and labeling of sampled supplements to determine the extent to which they included disease claims.³⁹ We also reviewed labels and labeling for the required disclaimer.

Review of Notification Letters for Structure/Function Claims. To determine the extent to which structure/function claims are on file at FDA, we asked FDA to retrieve notification letters using a list of the 127 sampled supplements and the companies that make them. We analyzed the letters to determine the extent to which they included required information (e.g., manufacturer contact information, notice that the manufacturer has substantiation for the claim). We also compared the claims on the product with those in the letters to determine whether they matched.

Manufacturers' Substantiation of Structure/Function Claims. We requested substantiation from manufacturers for 119 of the supplements in

³⁹ 21 CFR § 1.3. "Labeling" includes any text or graphics on Web sites where the supplements are sold. FDA may take enforcement action against claims made on Web sites as well as claims printed on the actual product package. We reviewed structure/function claims on Web sites for supplements purchased from the Internet.

our sample. We dropped 8 supplements from our original sample of 127 either because the manufacturers were outside the United States or because we could not reach them by telephone or mail. We asked manufacturers to submit documentation that substantiated the structure/function claims on their products.

We requested the substantiation by mail and followed up by telephone or email when necessary. We made three attempts to contact each manufacturer.

We received 1,624 substantiation documents from 66 manufacturers, representing 72 (61 percent) of the 119 supplements for which we requested substantiation.

From each substantiation document, we abstracted key pieces of information, such as what type of document it was (e.g., human study, review article, product monograph), whether it included the name of the supplement, and which structure/function claim it was intended to support. For human studies, we also noted the methods and population studied and the results of the studies and noted whether they clearly stated support for the structure/function claims. We did not assess factors such as statistical power, selection biases, or limitations. (For additional descriptive statistics, see Appendix A.)

Limitations

Because no comprehensive list of dietary supplements or manufacturers exists, the universe of supplements and manufacturers is unknown. Therefore, we were unable to select a random sample of supplements and we do not generalize our findings beyond the products in our review.

We did not determine whether manufacturers submitted notifications for structure/function claims to FDA within 30 days of marketing their supplements because FDA lacks information on when supplements enter the retail market.

Manufacturers were not required to respond to our requests for substantiation of their structure/function claims. Therefore, any substantiation we received may not be representative of substantiation in general.

Through guidance documents, FDA outlines the amount, type, and quality of evidence it believes is necessary to substantiate a claim. When reviewing substantiation documents, we focused on human studies because FDA recommends them as the primary basis for structure/function claims. We did not assess background documents (e.g., in vitro studies, animal studies) against FDA guidance on competent and reliable scientific evidence because the nature and methods of the studies varied widely.

We also did not determine whether manufacturers adequately substantiated their structure/function claims because this would require a full scientific review, which was beyond the scope of this evaluation. Instead, we described the substantiation documents and compared them with FDA guidance.

Standards

This study was conducted in accordance with the *Quality Standards for Inspection and Evaluation* issued by the Council of the Inspectors General on Integrity and Efficiency.

FINDINGS

Supplements had multiple structure/function claims that stated various health benefits

The 127 supplements in our sample had a total of 378 structure/function claims, ranging from 1 to 12 per supplement. The median number of structure/function claims per supplement was three. Structure/function claims related to weight loss generally focused on reducing or burning body fat, increasing metabolism, suppressing appetite, or overall weight reduction. Claims related to immune support varied, focusing on free radicals or antioxidant properties, increasing antibody production, or supporting general immune function. See Table 1 for examples.

Table 1: Examples of Structure/Function Claims From Sampled Dietary Supplements, by Type

Weight Loss Supplement	Immune Support Supplement
"Helps burn fat faster with exercise ... helps stimulate metabolism ... helps support healthy weight maintenance"	"Maintains peak natural killer cell function, supports enhanced cytokine production, promotes optimal T-cell and macrophage activity"
"Controls your appetite and sugar cravings ... burns excess calories for energy ... antioxidants to enhance health and radiance"	"Traps the toxins, free radicals, and metals from your body ... a one-two punch in detoxifying the body, balancing the body's pH, and boosting the immune system"
"Delays the digestion and absorption of carbohydrates ... enjoy many of the foods you love without worrying about the carbohydrates"	"Possesses 3 times more IgG and total immunoglobulins than colostrum and has twice as much cysteine, an important amino acid for maintaining glutathione levels"
"Suppress appetite, reduce weight, increase energy, stimulate metabolic processes"	"Boosts the immune system ... supports breast, prostate, cardiovascular, vision, skin and colon health"

Source: OIG analysis of structure/function claims from sampled dietary supplements, 2011.

Substantiation documents for structure/function claims were not consistent with FDA guidance

Manufacturers are not required to submit substantiation to FDA or OIG for structure/function claims. However, 66 of 104 manufacturers voluntarily submitted substantiation documents in response to our request. We reviewed 1,624 substantiation documents for 72 of the supplements in our sample. The number of substantiation documents per supplement ranged from 1 to 137, with a median of 7.

In contrast to FDA guidance, most substantiation was not derived from human studies. Just over half of the substantiation documents would be

considered background information according to FDA guidance, and 10 percent of the documents appeared to have no significance in supporting structure/function claims.

Of the 34 percent of substantiation documents that were human studies, none met all of FDA's recommendations for competent and reliable evidence

Among the 1,624 substantiation documents that manufacturers submitted, 557 were human studies. Manufacturers of 55 supplements provided at least 1 human study as substantiation for their claims. Although FDA does not specify a minimum number of human studies needed to substantiate a claim, it does recommend that such studies use widely accepted scientific methods.

However, none of the human studies we reviewed met all four of the elements that FDA recommends for competent and reliable scientific evidence: (1) the relationship of the evidence to the claim; (2) the totality of evidence; (3) the quality of the evidence, specifically high-quality human studies; and (4) the meaning of the claim.⁴⁰

Human Studies Rarely Showed a Direct Relationship to the Claims. Only 2 percent of the 557 human studies that we reviewed studied the actual products in our sample, in contrast to FDA guidance. FDA recommends that studies used to substantiate claims “identify a specific dietary supplement or ingredient and serving size and that the conditions of use in the studies are similar to the labeling conditions of the dietary supplement product.” FDA guidance also states that the results of studies that focus on an ingredient in a product (but not the product itself or a similar formulation) are not applicable to the specific dietary supplement product.

The remaining 98 percent of human studies focused on an active ingredient that may have been in a different form, dose, or potency.⁴¹ For example, a weight loss supplement in our sample claimed that the supplement burns fat because it contains green tea extract. A human study supporting this claim involved subjects ingesting brewed green tea rather than the green tea extract formulation used in the supplement. A study of this type does not have a direct relationship to the claim because it

⁴⁰ FDA, *Substantiation for Dietary Supplement Claims Made Under Section 403(r) (6) of the Federal Food, Drug, and Cosmetic Act*, December 2008. Accessed at www.fda.gov on February 17, 2012.

⁴¹ Because many supplement formulations are proprietary, their labels did not always list the form, dose, or potency of the active ingredients. We could be certain of the form, dose, and potency only in the 2 percent of studies that focused on the actual products. These were generally proprietary studies commissioned by the manufacturers. The remaining 98 percent of studies were published in trade or scientific journals.

demonstrates the effect of a green tea in a formulation that is different from that contained in the supplement.

Most Human Studies Did Not Appear To Represent the Totality of Evidence. Among the 557 human studies that manufacturers submitted, 4 percent (20 studies) had results that contradicted the claims of sampled supplements.⁴² FDA guidance recommends that when determining whether a claim is substantiated, manufacturers should consider all available scientific evidence—both favorable and unfavorable—and present the evidence in context.

Interviews with staff at the National Center for Complementary and Alternative Medicine at the National Institutes of Health indicated that a large body of science exists that contradicts existing structure/function claims. Yet, 96 percent of the human studies we received were favorable to the supplements' claims, suggesting that manufacturers either have not considered the body of available scientific evidence, that there is a positive bias in the documents selected to substantiate their claims, or that no such contradictory evidence exists.

Most Human Studies Were Not Consistent With FDA Guidance on Quality. Overall, 85 percent of the 557 human studies we reviewed were not randomized, double-blind, parallel group, placebo-controlled trials. FDA guidance recommends that human intervention studies use these methods because they offer the greatest assessment of a relationship between a dietary supplement and an outcome.

In addition, 49 percent of the human studies were not based on populations similar to those that will be consuming the supplements. FDA guidance recommends that high-quality human studies use representative populations with respect to factors such as age, geographic location, and health status. For example, studies tested a supplement or its active ingredient in elderly women with diabetes. But the effect of a product in an older population with a disease (as opposed to a representative sample of healthy individuals) could not be expected to translate to the general population.

About a Third of Human Studies Were Not Consistent With FDA Guidance on the Meaning of the Claim. One hundred eighty-nine (34 percent) of the 557 human studies we reviewed focused on disease research rather than

⁴² To assess the totality of evidence, we focused on human studies because their methodologies are intended to show a direct effect on humans from a supplement or an ingredient. The other types of substantiation documents varied widely and could not be aggregated.

the meaning of the structure/function claim.⁴³ FDA guidance recommends that when assembling substantiation for claims, manufacturers consider the meaning of the claims they are substantiating, including any implied claims, and tailor the substantiation accordingly. For example, because supplements may not make claims that directly state or imply the treatment of a disease, studies that focus on diseases are inconsistent with FDA guidance. If substantiation documents demonstrate a supplement’s effect on a disease, they raise questions about the implied meaning of the structure/function claims.

Among the substantiation documents, 56 percent would be considered background information according to FDA guidance

According to FDA guidance, information in background documents may provide indirect support or context for structure/function claims, but this information alone may not be sufficient to support the claims. Manufacturers of eight supplements submitted only background information as substantiation. In our review, background documents submitted by manufacturers included in vitro or animal studies, review articles, and other types shown in Table 2. Although manufacturers are free to submit such documentation as part of their substantiation, FDA does not consider these to be primary sources of evidence.

Table 2: Percentages of Substantiation Documents That Are Background Information for Selected Supplements, by Type

Background Document Type	Weight Loss Supplement (n=280)	Immune Support Supplement (n=621)
In vitro study	13%	32%
Animal study	40%	35%
Reference book	14%	9%
Review article	28%	20%
Product monograph	4%	5%
Meta-analysis	2%	2%
Testimonial/anecdotal	0	0

Source: OIG analysis of dietary supplement manufacturers’ substantiation documents, 2011.
Columns do not sum to 100 percent because some studies used more than one methodology.

⁴³ We counted a study as focusing on a disease when the disease or its major symptoms (e.g., insulin resistance in diabetics) was plainly stated. Other studies may have involved biological processes associated with diseases, but we did not count these in our analysis.

The remaining 10 percent of documents did not qualify as substantiation

Among the substantiation documents we reviewed, 166 did not fall into any of the categories defined in FDA guidance. Manufacturers of nine supplements submitted only this type of documentation as substantiation. For example, one company submitted a 30-year-old handwritten college term paper to substantiate its structure/function claim, while others included articles from trade newsletters; press releases; advertisements; and links to Web pages, such as Wikipedia or an online dictionary. Such extraneous information suggests that some manufacturers may be unfamiliar with FDA guidance on substantiation or that they performed only cursory research to substantiate their claims.

FDA could not readily determine the extent to which manufacturers of sampled supplements had submitted the required notification for their structure/function claims

FDA could retrieve notification letters for only 21 of 127 supplements in our sample. FDA's failure to locate notification letters raises questions about its ability to adequately monitor and enforce manufacturers' compliance with structure/function claim requirements.

FDA lacks a reliable tracking system for notification letters

FDA keeps two versions of notification letters: scanned letters, which are filed in a centralized document management system; and paper copies, which are stored in multiple locations. FDA saves letters in a PDF format that cannot be searched by keyword. As a result, FDA could not locate letters for our sampled supplements using the product name or the manufacturer's name.

As of December 2011, FDA staff told us the agency had letters waiting to be scanned that dated back almost a year. FDA files the paper copies of notification letters chronologically. Therefore, FDA would have had to search thousands of files by hand to locate letters for our sample of supplements.

The majority of notification letters we reviewed were missing required information

Among the 21 letters FDA was able to retrieve, 17 did not contain all the required information. Eleven notification letters contained structure/function claims that did not match those listed on the products' labels. Manufacturers may have submitted other letters to FDA with the correct claims, but FDA could not retrieve them. Only 12 of the 21 letters attested that the companies had substantiation that the claims were truthful and not misleading. Finally, because FDA regulations do not require manufacturers to include in their notifications the date that they first marketed a supplement, FDA cannot verify whether the notification was submitted within 30 days as required. Of the 21 letters we reviewed, only 4 made any reference to the 30-day timeframe and none listed the date that the supplement was first marketed.

Seven percent of supplements in our sample were missing the required disclaimer for structure/function claims

Nine supplements in our sample were missing the required disclaimer on the label (see Table 3). By law, all structure/function claims must be accompanied by the following disclaimer: "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease."⁴⁴ Academic researchers have found that the lack of disclaimers can lead consumers to assume that FDA has reviewed or approved a product.⁴⁵

Table 3: Supplement Labels That Were Missing the Required Disclaimer

Supplement Type (n=127)	Label Missing Required Disclaimer
Immune Support	5
Weight Loss	4

Source: OIG analysis of dietary supplement labels, 2011.

Twenty percent of the supplements in our sample had prohibited disease claims on the labels

The 26 supplements in our sample that had prohibited claims purported to treat diseases, such as influenza, the common cold, herpes, and HIV, while

⁴⁴ 21 U.S.C. § 343(r)(6); 21 CFR § 101.93(c)(1).

⁴⁵ Neal Hooker and Ratapol Teratanavat, "Dissecting Qualified Health Claims: Evidence From Experimental Studies," *Critical Reviews in Food Science and Nutrition*, vol. 48, issue 2, February 2008.

others claimed to reduce cholesterol or prevent diabetes (see Table 4). Pursuant to FDA regulations, dietary supplements may not make explicit or implicit disease claims. If a product marketed as a dietary supplement bears a disease claim, it must be regulated as a drug.⁴⁶ Supplements that make disease claims could mislead consumers into using them as replacements for prescription drugs or other treatments for medical conditions, with potentially dangerous results.

Table 4: Examples of Disease Claims From Labels of Sampled Dietary Supplements

Disease Claim	Implied or Stated Benefit
"Conditions which may benefit from aggressive nutritional support include cancer, HIV/AIDS, MRSA, Chronic Fatigue Syndrome"	Treatment of human immunodeficiency virus, methicillin-resistant Staphylococcus aureus, chronic fatigue syndrome
"To cure cough and chest problems; a cure for every ailment"	Cure of the common cold or other illnesses
"Provides defense against heart diseases, blood pressure, diabetes and other terrible conditions"	Prevention of heart disease, high blood pressure, or diabetes
"Contains natural cancer fighters, boosts immune system, helps prevent colds, flu"	Treatment or prevention of cancer, the common cold, influenza virus

Source: OIG analysis of sampled dietary supplement labels, September 2011.

⁴⁶ 21 CFR § 101.93(f).

CONCLUSION AND RECOMMENDATIONS

Under Federal law, FDA does not test or approve dietary supplements prior to sale. Therefore, consumers rely on a supplement's claims to determine whether the product will provide a desired effect, such as weight loss or immune support. Although supplement manufacturers' use of structure/function claims has grown, FDA's authority to monitor such claims remains limited by law. FDA currently has three main requirements to help ensure that structure/function claims on dietary supplement labels are truthful and not misleading: substantiation to support the claims, which manufacturers must possess but need not submit to FDA; notification to FDA of claims within 30 days of first marketing the supplement with the claim; and a required disclaimer on supplement labels.

The results of our analysis, which is based on 127 dietary supplements, demonstrate the extent to which submitted substantiation of structure/function claims fell short of meeting FDA's recommendations for competent and reliable evidence. In addition, our analysis revealed noncompliance with requirements regarding disclaimers and problems with FDA's notification process. These results raise questions about the extent to which structure/function claims are truthful and not misleading. Finally, our analysis also found that more than one in five supplements in our sample had disease claims, which are prohibited, in addition to structure/function claims.

To improve oversight of structure/function claims, we recommend that FDA take the following steps:

Seek Explicit Statutory Authority To Review Substantiation for Structure/Function Claims To Determine Whether Claims Are Truthful and Not Misleading

To better ensure that structure/function claims are truthful and not misleading as required by DSHEA, FDA requires explicit statutory authority to compel manufacturers to submit substantiation that supports their claims. We defer to FDA concerning the breadth of that authority. FDA could seek legislation requiring approval for all structure/function claims in the labeling of dietary supplements. However, absent dedicated funding to support such an activity, FDA's resource constraints could be prohibitive.

The legislation could require manufacturers to submit for review their substantiation for all structure/function claims upon request by FDA or in circumstances identified by FDA in regulation or guidance. For example, by focusing on supplements that appear to make false or misleading

structure/function claims, FDA could target its resources where major vulnerabilities exist. If FDA obtains explicit statutory authority to review substantiation, its current guidance could form the basis of new regulation. Furthermore, FDA could also develop a protocol by which to assess substantiation.

Improve the Notification System To Make It More Organized, Complete, and Accurate

The current filing system for notification letters does not enable FDA to readily locate information on existing structure/function claims or the manufacturers that submit them. An effective notification system would include:

- An organized and indexed filing system that permits FDA to search for and retrieve notification letters using the name of the supplement and manufacturer.
- Updated guidance that informs manufacturers of the information required in notification letters. FDA's Web site and ongoing communication with the supplement industry could create additional opportunities to provide this information.
- Useful information to be provided, such as the date that manufacturers first marketed the supplement with the claim. Having this date would enable FDA to determine whether manufacturers are complying with the 30-day timeframe for notification and would provide FDA with a more complete view of structure/function claims as they enter the market. This may require FDA to amend its current regulations.

Expand Market Surveillance of Dietary Supplements To Enforce the Use of Disclaimers for Structure/Function Claims and Detect Disease Claims

FDA currently conducts Internet surveillance to detect supplements that are sold online with disease claims or false and misleading claims. FDA could also consider expanding its surveillance to retail establishments to detect disease claims and ensure that manufacturers that make structure/function claims are placing the required disclaimer on their products. FDA may also find additional opportunities to review supplements at industry gatherings, such as trade shows or promotional events.

AGENCY COMMENTS AND OFFICE OF INSPECTOR GENERAL RESPONSE

In its comments on the draft report, FDA did not explicitly concur with our first recommendation, but said it would consider it. FDA concurred with our second and third recommendations.

In addressing our first recommendation to seek explicit statutory authority to review substantiation for structure/function claims, FDA stated that it will consider seeking expanded authority. FDA commented that a manufacturer must have substantiation that a structure/function claim used in the labeling of a supplement is truthful and not misleading. Further, the agency stated that it may ask manufacturers for such substantiation, but these requests are not always granted. We ask that FDA's final management decision clarify the agency's plans for seeking explicit statutory authority to review substantiation.

FDA concurred with our recommendation to improve its notification system for structure/function claims to make it more organized, complete, and accurate. FDA stated that it has initiated a feasibility study to determine whether adapting its existing system would enable it to access all structure/function claim notifications. The agency said it would also assess regulatory changes that would be required to ensure that supplement manufacturers comply with the 30-day notification requirement.

Finally, FDA concurred with our recommendation to expand market surveillance to enforce the use of disclaimers for structure/function claims and to detect disease claims. FDA commented that it will continue to focus primarily on disease claims because they pose the greatest threat to public health, but that it will continue to address situations in which products fail to meet dietary supplement labeling requirements, including the use of structure/function claims without a disclaimer.

For the full text of FDA's comments, see Appendix B.

APPENDIX A ADDITIONAL DESCRIPTIVE STATISTICS

Table A-1: Sampled Supplements, by Supplement Type and Source

Supplement Type	Number in Sample
Immune Support	67
Weight Loss	60
Retail	67
Internet	60
Total	127

Source: Office of Inspector General (OIG) analysis of sampled dietary supplements, September 2011.

Table A-2: Number of Supplements for Which Manufacturers Submitted Substantiation, by Supplement Type and Source

Supplement Type	Manufacturer Submitted Substantiation
Immune Support	39
Weight Loss	33
Retail	42
Internet	30
Total	72

Source: OIG analysis of sampled dietary supplements, September 2011.

Table A-3: Number of Substantiation Documents Received, by Supplement Type

	Weight Loss	Immune Support
Total number of substantiation documents received	667	957
Median (range) number of substantiation documents per supplement	21 (1–54)	21 (1–137)

Source: OIG analysis of sampled dietary supplements, September 2011.

Table A-4: Number of Structure/Function Claims and Substantiation Documents, by Supplement Type

	Weight Loss	Immune Support
Median (range) number of structure/function claims per supplement	3 (1–7)	2 (1–12)
Median (range) number of substantiation documents per structure/function claim	8 (1–137)	6 (1–54)

Source: OIG analysis of substantiation documents submitted by manufacturers of sampled dietary supplements, September 2011.

Table A-5: Median Population of Human Studies Submitted by Manufacturers as Substantiation, by Supplement Type

	Weight Loss	Immune Support
Median population of human studies overall	27	40
Median population of human intervention studies	27	34
Median population of human observational studies	83	267

Source: OIG analysis of substantiation documents submitted by manufacturers of sampled dietary supplements, September 2011.

Table A-6: Examples of Structure/Function Claims and Disease Claims From Labels of Sampled Supplements

Structure/Function Claim	Disease Claim
"Supports healthy immune function"	"Conditions which may benefit from aggressive nutritional support include cancer, HIV/AIDS, MRSA, Chronic Fatigue Syndrome"
"Increases your body's metabolic rate and decreases your appetite"	"To cure cough and chest problems; a cure for every ailment"
"Promotes fat-burning and weight loss"	"Provides defense against heart diseases, blood pressure, diabetes and other terrible conditions"
"Enhances the growth of beneficial intestinal microflora and stimulates non-specific immune activity"	"Contains natural cancer fighters, boosts immune system, helps prevent colds, flu"

Source: OIG analysis of sampled dietary supplement labels, September 2011.

Table A-7: Supplement Labels That Had Disease Claims

Supplement Type (n=127)	Label Included Disease Claim
Immune Support	17
Weight Loss	11

Source: OIG analysis of dietary supplement labels, 2011.

APPENDIX B

Agency Comments



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Date: August 21, 2012
To: Inspector General
From: Acting Associate Commissioner for Policy and Planning
Subject: FDA's General Comment to OIG Draft Report on Dietary Supplements:
Structure/Function Claims Fail to Meet Federal Requirements

FDA is providing the attached general comments to the Office of Inspector General's draft report entitled, *Dietary Supplements: Structure/Function Claims Fail to Meet Federal Requirements (OEI-01-11-00210)*.

FDA appreciates the opportunity to review and comment on this draft report before it is published.

/S/

David H. Dorsey

Attachment

APPENDIX B (CONTINUED)

The Food and Drug Administration's General Comments to the Office of Inspector General's Draft Report, *Dietary Supplements: Structure/Function Claims Fail to Meet Federal Requirements* (OEI-01-11-00210)

The Food and Drug Administration (FDA or the Agency) appreciates the opportunity to comment on the Office of Inspector General's (OIG) draft report. FDA recognizes the concerns that the OIG report raises about structure/function claims and offers the following responses to OIG's recommendations:

1) Seek Explicit Statutory Authority to Review Substantiation for Structure/Function Claims to Determine Whether Claims Are Truthful and Not Misleading

FDA will consider whether to seek explicit statutory authority to review substantiation for structure/function claims beyond its pre-existing authorities. As noted in the report, under section 403(r)(6) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), a manufacturer must have substantiation that a structure/function claim used in the labeling of a supplement is truthful and not misleading, and must notify FDA of the claim no later than 30 days after the first marketing of the supplement with the claim. FDA can, and does, request that manufacturers voluntarily submit substantiation for structure/function claims, but these requests are not always granted.

FDA agrees with OIG that its document titled, *Guidance for Industry: Substantiation for Dietary Supplement Claims Made Under Section 403(r)(6) of the Federal Food, Drug, and Cosmetic Act*, provides valuable information as to the amount, type, and quality of evidence that FDA recommends a manufacturer have to substantiate a claim under section 403(r)(6) of the FD&C Act.

FDA shares the OIG's concern that certain aspects of the OIG's recommendation could place considerable demands on FDA's resources and appreciates that the OIG is deferring to FDA as to the breadth of any possible new authority.

2) Improve Notification System to Make It More Organized, Complete, and Accurate

FDA concurs with OIG's recommendation to improve the notification system to make it more organized, complete, and accurate. FDA has initiated a feasibility study to determine whether adapting an existing IT system would provide the functionality for FDA to easily access all structure/function claim notifications. If the feasibility study determines that the existing IT system could be adapted for this purpose, and if resources allow, FDA will develop a formal proposal for a claim notification system.

The proposal would include features that could eventually be accessed via the Internet and would provide additional guidance to the industry on what to include in a claim notification. Such a system could also help FDA to "date-stamp" when certain claims first appear in dietary supplement labeling, to the extent that such information is available to FDA. A "date-stamp" in a Web-based notification system could also allow the Agency to determine whether a firm has notified FDA within 30 days after first marketing a dietary supplement with the claim. To require that claim notifications include the date that the supplement was first introduced into interstate commerce with the claim in its labeling, FDA would have to

APPENDIX B (CONTINUED)

amend its current regulations. We will consider amending the regulations as resources and priorities allow.

3) Expand Market Surveillance of Dietary Supplements to Enforce the Use of Disclaimers for Structure/Function Claims and Detect Disease Claims.

FDA concurs with OIG's recommendation to look for additional opportunities to enforce dietary supplement requirements, to the extent that resources allow. FDA's priorities will continue to focus primarily on disease claims because they pose the greatest threat to public health. However, we will continue to address situations in which products fail to meet dietary supplement labeling requirements, including the use of structure/function claims without a disclaimer, as appropriate.

FDA staff currently attend industry gatherings to, among other activities, obtain information about manufacturers' compliance with FDA requirements. We will continue to leverage opportunities we have in that area; however, we do not plan to implement OIG's recommendation to expand surveillance to retail establishments, because we are better able to address violations of the dietary supplement requirements by conducting inspections at dietary supplement manufacturers' facilities.

ACKNOWLEDGMENTS

This report was prepared under the direction of Joyce Greenleaf, Regional Inspector General for Evaluation and Inspections in the Boston regional office, and Russell Hereford, Deputy Regional Inspector General.

Melissa Hafner served as the team leader for this study. Other principal Office of Evaluation and Inspections staff from the Boston regional office who contributed to the report include Tim Chettiath, Alyson Cooper, Jessica Fagnoli, Danielle Fletcher, Maria Maddaloni, and Jesse Valente; other regional office staff who contributed include Maria Balderas and Margarita Rodriguez; central office staff who contributed include Heather Barton, Kevin Farber, and Debra Roush.

Office of Inspector General

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