

IV. Electronic Access

An electronic version of this guidance is available on the Internet at <http://www.fda.gov/ora> under "Compliance References."

Dated: November 2, 2004.

Steve M. Niedelman,
Acting Associate Commissioner for
Regulatory Affairs.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2004D-0466]

Draft Guidance for Industry: Substantiation for Dietary Supplement Claims Made Under Section 403(r)(6) of the Federal Food, Drug, and Cosmetic Act; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a draft guidance entitled "Guidance for Industry: Substantiation for Dietary Supplement Claims Made Under Section 403(r)(6) of the Federal Food, Drug, and Cosmetic Act." This draft guidance describes the amount, type, and quality of evidence that FDA recommends a manufacturer have to substantiate a claim under section 403(r)(6) of the Federal Food, Drug, and Cosmetic Act (act). FDA is also announcing its decision not to publish additional guidance on applying the structure/function rule at this time.

DATES: Submit written or electronic comments on the draft guidance and the collection of information provisions by January 10, 2005, to ensure adequate consideration in preparation of any final guidance document. General comments on agency guidance documents are welcome at any time.

ADDRESSES: Submit written comments on the draft guidance document and the collection of information provisions to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments on the draft guidance and the collection of information to <http://www.fda.gov/dockets/ecomments>. See the

SUPPLEMENTARY INFORMATION section for electronic access to the draft guidance document.

FOR FURTHER INFORMATION CONTACT: Vickie Lutwak, Center for Food Safety and Applied Nutrition, Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, 301-436-2375, fax: 301-436-2636, e-mail: Vickey.Lutwak@cfsan.fda.gov

SUPPLEMENTARY INFORMATION:

I. Background—Substantiation Draft Guidance

Section 403(r)(6) of the act (21 U.S.C. 343(r)(6)) 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.¹

This draft guidance document is intended to describe the amount, type, and quality of evidence FDA recommends a manufacturer have to substantiate a claim under section 403(r)(6) of the act. This draft guidance document is limited to issues pertaining to substantiation under section 403(r)(6) of the act; it does not extend to substantiation issues that may exist in other sections of the act.

FDA intends to apply a standard for substantiating claims for dietary supplements that is consistent with the Federal Trade Commission's (FTC's) standard for dietary supplements and other health related products of "competent and reliable scientific evidence." FDA seeks comments on this draft guidance only as they relate to FDA's use and application of the standard and approach that are described in the guidance. We (FDA) are not seeking comment on FTC's application, use, or interpretation of their standard.

The agency has adopted good guidance practices (GGPs) that set forth the agency's policies and procedures for the development, issuance, and use of guidance documents (21 CFR 10.115). The draft guidance document is being issued as a Level 1 guidance consistent with FDA's GGPs. The draft guidance document represents the agency's current thinking on the amount, type, and quality of evidence FDA recommends a manufacturer have to substantiate a claim under section 403(r)(6) of the act. It does not create or

¹ Under section 403(r)(6)(A) of the act (21 U.S.C. 343(r)(6)(A)), such a statement is one that "claims a benefit related to a classical nutrient deficiency disease and discloses the prevalence of such disease in the United States, describes the role of a nutrient or dietary ingredient intended to affect the structure or function in humans, characterizes the documented mechanism by which a nutrient or dietary ingredient acts to maintain such structure or function, or describes general well-being from consumption for a nutrient or dietary ingredient."

confer any rights for or on any person and does not operate to bind FDA or the public. An alternative method may be used as long as it satisfies the requirements of the applicable statutes and regulations.

II. Paperwork Reduction Act of 1995—Substantiation Draft Guidance

This draft guidance document contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501-3520). Under the PRA, Federal agencies must obtain approval from the OMB for each collection of information they conduct or sponsor. "Collection of information" is defined in 44 U.S.C. 3502(3) and 5 CFR 1320.3 and includes agency requests or requirements that members of the public submit reports, keep records, or provide information to a third party. Section 3506(c)(2)(A) of the PRA (44 U.S.C. 3506(c)(2)(A)) requires Federal agencies to provide a 60-day notice in the **Federal Register** concerning each proposed collection of information before submitting the collection to OMB for approval. To comply with this requirement, FDA is hereby publishing notice of the proposed collection of information set forth in this document.

FDA invites comments on: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Draft Guidance for Industry: Substantiation for Dietary Supplement Claims Made Under Section 403(r)(6) of the Federal Food, Drug, and Cosmetic Act; Availability

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 statement is truthful and not misleading. This draft guidance document is intended to describe the amount, type, and quality of evidence FDA recommends a dietary supplement manufacturer have to

substantiate a claim under section 403(r)(6) of the act. This guidance does not discuss the types of claims that can be made concerning the effect of a

dietary supplement on the structure or function of the body, nor does it discuss criteria to determine when a statement

about a dietary supplement is a disease claim.

FDA estimates the burden for this information collection as follows:

TABLE 1.—ESTIMATED REPORTING BURDEN¹

Claim type	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
Widely known, established	667	1	667	1	667
Pre-existing, not widely established	667	1	667	120	80,040
Novel	667	1	667	120	80,040
Annual one time burden hours					160,747

¹ There are no capital costs or operating and maintenance costs associated with this information collection.

Dietary supplement manufacturers will only need to collect information to substantiate their product's nutritional deficiency, structure/function, or general well-being claim if they chose to place a claim on their product's label. Gathering evidence on their product's claim is a one time burden; they collect the necessary substantiating information for their product as required by section 403(r)(6) of the act.

The standard discussed in the guidance for substantiation of a claim on the labeling of a dietary supplement is consistent with standards set by the FTC for dietary supplements and other health related products that the claim be based on competent and reliable scientific evidence. This evidence standard is broad enough that some dietary supplement manufacturers may only need to collect peer-reviewed scientific journal articles to substantiate their claims; other dietary supplement manufacturers whose products have properties that are less well documented may have to conduct studies to build a body of evidence to support their claims. It is unlikely that a dietary supplement manufacturer will attempt to make a claim when the cost of obtaining the evidence to support the claim outweighs the benefits of having the claim on the product's label. It is likely that manufacturers will seek substantiation for their claims in the scientific literature.

The time it takes to assemble the necessary scientific information to support their claims depends on the product and the claimed benefits. If the product is one of several on the market making a particular claim for which there is adequate publicly available and widely established evidence supporting the claim, then the time to gather supporting data will be minimal; if the product is the first of its kind to make

a particular claim or the evidence supporting the claim is less publicly available or not widely established, then gathering the appropriate scientific evidence to substantiate the claim will be more time consuming.

FDA assumes that it will take only about an hour to assemble information needed to substantiate a claim on a particular dietary supplement when the claim is widely known and established. These are likely products whose claimed effects have been long studied and the results of the studies are widely available in credible textbook and reference books, therefore making the substantiation burden minimal. FDA believes it will take closer to 120 hours to assemble supporting scientific information when the claim is novel or when the claim is pre-existing but the scientific underpinnings of the claim are not widely established. These are claims that may be based on emerging science, where conducting literature searches and understanding the literature takes time. It is also possible that references for claims made for some dietary ingredients or dietary supplements may primarily be found in foreign journals and in foreign languages or in the older, classical literature where it is not available on computerized literature databases or in the major scientific reference databases, such as the National Library of Medicine's literature database, all of which increases the time of obtaining substantiation.

In the final rule on statements made for dietary supplements concerning the effect of the product on the structure or function of the body (structure/function final rule (65 FR 1000, January 6, 2000)), FDA estimated that there were 29,000 dietary supplement products marketed in the United States (65 FR 1000 at 1045). Assuming that the flow of new products is 10 percent per year, then

2,900 new dietary supplement products will come on the market each year. The structure/function final rule estimated that about 69 percent of dietary supplements have a claim on their labels, most probably a structure/function claim (65 FR 1000 at 1046). Therefore, we assume that supplement manufacturers will need time to assemble the evidence to substantiate each of the 2,001 claims (2,900 x 69%) made each year. If we assume that the 2,001 claims are equally likely to be pre-existing widely established claims, novel claims, or pre-existing claims that are not widely established, then we can expect 667 of each of these types of claims to be substantiated per year. Row 1 of Table 1 of this document shows that the annual burden hours associated with assembling evidence for claims is 160,747 (667 x 1hr, 667 x 120 hrs, and 667 x 120 hrs).

There are no capital costs or operating and maintenance costs associated with this information collection.

III. Guidance on Applying the Structure/Function Rule

On January 6, 2000, FDA published a final rule, often referred to as the "structure/function rule," implementing section 403(r)(6) of the act concerning the types of statements that can be made regarding the effect of a dietary supplement on the structure or function of the body (65 FR 1000). This rule, codified in § 101.93(f) (21 CFR 101.93(f) and (g)), distinguishes between disease claims and structure/function claims. As discussed in § 101.93, if the label or labeling of a product marketed as a dietary supplement bears a disease claim as defined in that rule, the product will be subject to regulation as a drug unless the claim is an authorized health claim for which the product qualifies.

In the preamble to the final rule, FDA stated that it intended to publish a guidance on applying this rule. In a notice published in the **Federal Register** on February 22, 2001 (66 FR 11172), FDA invited public comments on the topics that should be included in such a guidance. FDA agrees with the comments that were submitted stating that the preamble to the structure/function rule and the numerous courtesy letters that the agency has issued since the enactment of section 403(r)(6) provide considerable guidance to dietary supplement manufacturers about the types of claims that the agency considers to be disease claims. Therefore, FDA has decided not to issue such a guidance at this time. FDA will continue to monitor dietary supplement manufacturers' compliance with section 403(r)(6) of the act and § 101.93, take enforcement action where appropriate, and reconsider the possibility of issuing guidance if future developments warrant.

IV. Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding the substantiation draft guidance document. (FDA is not specifically seeking comment on its decision not to publish additional guidance on the structure/function rule.) Two copies of mailed comments are to be submitted, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The draft guidance and received comments are available for public examination in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

V. Electronic Access

Persons with access to the Internet may obtain the document at <http://www.cfsan.fda.gov> or <http://www.fda.gov/dockets/ecomments>. Once on this site, select 2004D-0466 "Guidance for Industry: Substantiation for Dietary Supplement Claims Made Under Section 403(r)(6) of the Federal Food, Drug, and Cosmetic Act" and follow the directions. Copies of this draft guidance may be obtained on the Internet from the CFSAN homepage at <http://www.cfsan.fda.gov>.

Dated: October 25, 2004.

Jeffrey Shuren,

Assistant Commissioner for Policy.

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DEPARTMENT OF HOMELAND SECURITY

Border and Transportation Security; Notice to Aliens Included in the United States Visitor and Immigrant Status Indicator Technology System (US-VISIT)

AGENCY: Border and Transportation Security Directorate, DHS.

ACTION: Notice.

SUMMARY: The Department of Homeland Security (Department or DHS) has established the United States Visitor and Immigrant Status Indicator Technology Program (US-VISIT), an integrated, automated entry-exit system that records the arrival and departure of aliens; verifies aliens' identities; and authenticates aliens' travel documents through comparison of biometric identifiers. On August 31, 2004, DHS implemented the second phase of US-VISIT by publishing an interim final rule in the **Federal Register** at 69 FR 53318 authorizing DHS to require certain aliens to provide fingerprints, photographs or other biometric identifiers upon arrival in the United States at the 50 most trafficked land ports of entry. The interim rule also authorized DHS to identify the specific land border ports in a separate notice published in the **Federal Register**.

This notice identifies the 50 most trafficked land ports of entry where US-VISIT will be implemented. The notice further provides an estimated date when each port will begin enrolling aliens in US-VISIT at the secondary inspection area. Pursuant to the August 31, 2004 interim rule, all 50 ports of entry will begin enrolling aliens in US-VISIT no later than December 31, 2004.

In addition, as stated in the August 31, 2004 interim rule, this notice identifies only land ports of entry in which aliens will be enrolled in US-VISIT upon entry into the United States. DHS will announce, through a future notice in the **Federal Register**, the piloting of a biometric data collection program at a limited number of sites as part of US-VISIT processing upon departure from the United States.

FOR FURTHER INFORMATION, CONTACT: Michael Hardin, Senior Policy Advisor, US-VISIT, Border and Transportation Security, Department of Homeland Security, 1616 N. Fort Myer Drive, 18th Floor, Arlington, Virginia 22209, (202) 298-5200.

The 50 Land Border Ports of Entry (POEs) that will begin biometric data collection as part of US-VISIT processing no later than December 31, 2004 are as follows:

Estimated start date of November 15, 2004 (6):

Port Huron POE, Blue Water Bridge, Highway 69 and International Border, Port Huron, Michigan
Douglas POE, Rte 191 and International Border, Douglas, AZ
Lincoln-Juarez Bridge POE, Laredo, TX
Gateway to the Americas International Bridge POE, Laredo, TX
Columbia Solidarity Bridge POE, Laredo, TX

World Trade Bridge POE, Laredo, TX
Estimated start date of December 6, 2004 (11):

Niagara Falls POE (to include Lewiston-Queenstown, Whirlpool, and Rainbow Bridges), Niagara Falls, NY
Peace Bridge POE, Moore Drive and International Border, Buffalo, NY
Detroit Ambassador Bridge POE, Detroit, MI
Detroit-Windsor Tunnel POE, Detroit, MI
Lukeville POE, Highway 85 & International Border, Lukeville, AZ
Nogales East (Deconcini POE), Nogales, AZ
Nogales West (Mariposa POE), Nogales, AZ

San Luis POE, Highway 95 & International Border, San Luis, AZ
Andrade POE, Andrade, CA
Calexico East-Imperial Valley POE, Rte 111 and International Border, Calexico, CA

Calexico West POE, Rte 111 and International Border, Calexico, CA
Estimated start date of December 13, 2004 (11):

Fabens POE 18051, Island Guadalupe, Fabens, TX
Presidio POE, Border Station Highway 67, Presidio, TX 79845
Santa Teresa POE, Santa Teresa, NM
Otay Mesa POE, 9777 Via De La Amistad, San Diego, CA
San Ysidro POE, Highway 5 and International Border, San Diego, CA
Tecate POE, Hwy 188 and International Border, Tecate, CA

Blaine-Pacific Highway POE, Rte. 543 and International Border, Blaine, WA
Blaine-Peace Arch POE, Interstate 5 and International Border, Blaine, WA
Lynden POE, Rte. 539 and International Border, Lynden, WA
Point Roberts POE, Tyee Drive and Roosevelt Way, Point Roberts, WA
Sumas POE, Cherry Street and International Avenue, Sumas, WA
Estimated start date of December 20, 2004 (10):

Champlain POE, Highway 87 and International Border, Champlain, NY
Massena POE, Rte. 45 and International Border, Rooseveltown, NY
Thousand Islands POE, Highway 81 and International Border, Alexandria Bay, NY