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## MEMORANDUM

### **FDA Releases Draft Guidance for Substantiation of Dietary Supplement Claims as Part of Agency's New Dietary Supplement Initiatives**

On November 4, 2004, the U.S. Food and Drug Administration ("FDA") announced the availability of a new Draft Guidance for Industry entitled, "Substantiation for Dietary Supplement Claims Made Under Section 403(r)(6) of the Federal Food, Drug, and Cosmetic Act" ("Draft Substantiation Guidance"), as part of the agency's recently announced set of regulatory initiatives aimed at addressing dietary supplement safety<sup>1</sup> and labeling issues under the Dietary Supplement Health and Education Act of 1994 ("DSHEA") amendments to the Federal Food, Drug, and Cosmetic Act ("FDCA"). FDA has characterized the new regulatory initiatives as constituting a series of integrated steps that are intended to advance the policy objectives FDA has articulated previously in its "Dietary Supplement Strategy: Ten Year Plan" announced in 2000, its "Dietary Supplement Enforcement Report" announced in December 2002, and its "CFSAN's 2004 Program Priorities."

The new FDA regulatory initiatives are designed to strengthen the agency's capabilities in monitoring and evaluating dietary supplement product safety and labeling, to emphasize risk-based management practices in the agency's compliance and enforcement activities, and to empower consumers to achieve better health by promoting the use of accurate, substantiated health information in dietary supplement product labeling.

#### I. Scope and Purpose of the Draft Substantiation Guidance

Section 403(r)(6)(A) of the FDCA, as amended by DSHEA, requires that a manufacturer making nutritional deficiency, structure/function, or general well-being claims in dietary supplement labeling have substantiation that the claim is truthful and not misleading. Because DSHEA establishes no particular or distinctive substantiation standard, the FDA Draft Substantiation Guidance relies on general antideception law standards established under the

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<sup>1</sup> See also Covington & Burling memorandum on FDA's Dietary Ingredient Safety Initiative (November 30, 2004).

misbranding provisions of the FDCA<sup>2</sup> and related consumer protection laws<sup>3</sup> in characterizing the nature, quality, and amount of scientific evidence that typically is necessary to substantiate health benefit claims for dietary supplement products. While FDA makes clear that the guidance applies specifically to dietary supplement claims made under FDCA section 403(r)(6), the guidance merits consideration by manufacturers developing claims of this type for food products generally (e.g., “structure/function” claims).

Under the governing statutory schemes, FDA has exclusive jurisdiction over the safety, and primary jurisdiction over the labeling, of dietary supplements under the FDCA, while the Federal Trade Commission (“FTC”) has primary jurisdiction over advertising and other promotional activities for dietary supplements under the FTC Act. Consequently, FDA notes that both agencies share an interest in providing guidance to the public concerning substantiation principles. FDA indicates that, in developing the Draft Substantiation Guidance, the agency drew significantly upon FTC substantiation principles derived from consumer protection cases litigated under the FTC Act. Specifically, FDA explains that FTC’s guidance entitled, “Dietary Supplements: An Advertising Guide for Industry,” issued in April 2001,<sup>4</sup> served as a model for the new FDA Guidance.

While the new FDA Draft Substantiation Guidance generally harmonizes with current FTC policy, there are some obvious distinctions. In contrast to FTC policy, the FDA policy fails to account for cost and feasibility in requiring companies to develop certain kinds of evidence to substantiate claims characterizing product benefits. Based on FTC studies and policy analyses concerning the public health implications of various nutrition and health benefit claim policies, it appears that such cost and feasibility considerations may be important for substantiation policies to avoid the adverse public health consequences resulting when valuable claims are chilled by unduly rigid standards for claims.<sup>5</sup>

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<sup>2</sup> See, e.g., 21 U.S.C. §§ 321(n) and 343(a).

<sup>3</sup> See, e.g., Federal Trade Commission Act, 15 U.S.C. §§ 45, 54-56.

<sup>4</sup> Available at <http://www.ftc.gov/bcp/online/pubs/buspubs/dietsupp.pdf>.

<sup>5</sup> See, e.g., In the Matter of Request for Comment on First Amendment Issues, FDA Docket No. 02N-0209 (Sept. 13, 2002) (detailing FTC’s law enforcement approach to prevent deceptive marketing of food, dietary supplements and other health-related products; presenting FTC policy as a model fully compatible with the First Amendment commercial speech doctrine; and discussing empirical evidence on the benefits to consumers from the free flow of true and nonmisleading commercial information concerning diet and health); Pauline M. Ippolito and Alan D. Mathios, Information and Advertising Policy, A Study of Fat and Cholesterol Consumption in the United States, 1977-1990, Bureau of Economics Staff Report, Federal Trade Commission, September 1996 (finding that consumption of unhealthy lipids fell faster during the (continued...))

## II. FDA's Draft Substantiation Standard

The Draft Substantiation Guidance states that FDA intends to apply a standard for the substantiation of dietary supplement claims that is consistent with the FTC standard of "competent and reliable scientific evidence." FDA observes that this standard has been defined in FTC case law as encompassing "tests, analyses, research, studies, or other evidence based on the expertise of professionals in the relevant area, that has been conducted and evaluated in an objective manner by persons qualified to do so, using procedures generally accepted in the profession to yield accurate and reliable results." The agency notes that there is no pre-established formula defining the amount or type of studies that are needed to substantiate a claim, but states that, like the FTC, FDA will consider the norms accepted in the relevant research fields in consultation with experts from the appropriate disciplines. FDA states that it may accord some deference to any existing standard for substantiation developed by a government agency or other authoritative body.

The Draft Substantiation Guidance recommends that, in determining whether the substantiation standard has been met with competent and reliable scientific evidence, firms should consider the following issues: the meaning of the claim(s) being made; the relationship of the evidence to the claim; the quality of the evidence; and the totality of the evidence.

### A. The Meaning of the Claim(s) Being Made

FDA states that, in order to determine what information is needed to substantiate a claim for a dietary supplement, a firm must first understand the meaning of the claim and clearly identify each express and implied claim. FDA asserts that it is important that the overall "message," as well as individual statements, be substantiated. The agency notes that consumer testing may be useful to determine consumer understanding of each claim in the context of actual labeling. When a claim may have more than one reasonable interpretation, FDA recommends that a firm have substantiation for each interpretation. FDA explains that a firm should have a clear understanding of the meaning of the claim in order to help identify appropriate study hypotheses and develop endpoints that could be measured and replicated in studies used as a basis for substantiation. Notably, if FDA were to bring an enforcement action against a manufacturer asserting that its product labeling conveyed an unsubstantiated implied claim that was not intended by the company, then under established First Amendment jurisprudence the agency would bear the burden of proof to establish that the implied claim is misleading.

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period when the policy towards health claims was relaxed (between 1985 and 1990) than during prior years (between 1977 and 1984)).

B. The Relationship of the Evidence to the Claim

The Draft Substantiation Guidance emphasizes that scientific evidence must substantiate the claim made in labeling in the actual context of the specific dietary supplement product that the firm is marketing. The FDA guidance recommends that companies consider the following threshold questions in evaluating whether the scientific evidence is sufficiently related and relevant to the specific dietary supplement product to support claims in product labeling.

1. Have the studies specified and measured the dietary supplement that is the subject of the claim?

The Draft Substantiation Guidance advises companies to consider whether the scientific evidence can be generalized to the dietary supplement formulation under the actual conditions of use. FDA notes, for example, that a study demonstrating that an ingredient is effective when used topically would generally not be useful to substantiate a claim for a dietary supplement, which is, by definition under section 201(ff)(2)(A) of the FDCA, a product that is intended for ingestion. The agency also observes that studies involving the impact of a specific ingredient in foods on the human body might not be applicable to a dietary supplement that is or contains that ingredient. FDA recommends that studies designed to provide support for dietary supplement product claims employ study conditions of use that would be similar to those recommended in labeling for the product for which claims would be made. The FDA Guidance identifies several factors that determine the extent to which research concerning the benefits of a substance under research conditions can be generalized to support claims promoting consumption of a particular dietary supplement product formulated with the substance, including formulation, serving size, route of administration, total length of exposure, and frequency of exposure.

2. Have the studies appropriately specified and measured the nutritional deficiency, structure/function, or general well-being that is the subject of the claim?

The Draft Substantiation Guidance recognizes that certain biomarkers may serve as surrogate clinical endpoints for purposes of determining health benefits attributable to dietary supplement consumption. The Guidance acknowledges that scientific evidence showing beneficial effects on a specific biomarker can provide support for dietary supplement claims where the validity of the specific biomarker has been established for the health benefit claimed. The FDA Guidance advises companies to consider whether the scientific evidence relating to biomarkers can be generalized to support the specific benefits for the dietary supplement product that would be claimed. For example, the agency observes that studies showing that an amino acid improves blood flow generally would not be adequate to support claims that an amino acid product “improves blood circulation” and “improves sexual performance.”

3. Were the studies based on a population that is similar to that which will be consuming the dietary supplement product?

The Draft Substantiation Guidance advises companies to consider whether the scientific evidence of benefits observed in study populations can be generalized to promote benefits for the population to which the dietary supplement product would be marketed. The FDA guidance stresses the need for the study population to resemble the population to which the dietary supplement is marketed in material respects. For example, the agency cautions that a study involving young adults may not support claims for a product marketed for conditions manifested only in the elderly. Similarly, a study showing benefits from a supplemental mineral product in foreign subjects consuming diets deficient in that mineral could not be extrapolated to substantiate claims promoting the same benefit for the general U.S. population. The FDA Guidance indicates that appropriately designed foreign research may be sufficient to substantiate claims, but warns that population differences with respect to dietary intake patterns and other factors affecting general health can confound results and limit the value of evidence for claim substantiation purposes.

4. Does the claim accurately convey to consumers the extent, nature, or permanence of the effect achieved in the relevant studies and the level of scientific certainty for that effect?

The Draft Substantiation Guidance advises companies to consider whether the scientific evidence concerning the extent, nature, and permanence of the benefits observed in study populations can be generalized to support particular benefits from consuming the dietary supplement product. FDA observes, for example, that a claim such as “Recommended by Scientists” in connection with the product’s claim would give consumers the impression that there is a body of qualified experts who believe that the claim is supported by evidence, and that consumers might also reasonably interpret the statement as meaning there is general scientific consensus regarding the claim.

### C. The Quality of the Evidence

The Draft Substantiation Guidance advises companies to consider the scientific quality of studies in determining whether the findings have weight for claim substantiation purposes. The Guidance explains that, ultimately, scientific quality is based on several criteria concerning study design and research methods with respect to study populations (*e.g.*, presence of a placebo control), data collection (*e.g.*, dietary assessment method), statistical analyses, and outcome measures. FDA states that the “gold” standard is the randomized, double blind, parallel group, placebo-controlled clinical trial design, although the agency notes that clinical trials of this type may not always be possible, practical or ethical to undertake.

FDA asserts that competent and reliable scientific evidence adequate to substantiate a claim would generally consist of information derived primarily from human

studies. The agency maintains that clinical intervention studies provide the most persuasive form of evidence to substantiate the effect of a dietary supplement in humans because they can evaluate the direct effect of a product in the human body. In contrast, observational studies have a more limited capacity for distinguishing relationships attributable to a dietary supplement substance and the health outcomes being evaluated. FDA reiterates the importance of determining the hypothesis that should be supported or tested prior to identifying supportive documentation or developing a study protocol. The agency observes that the following types of information generally would be considered background information and may not be adequate to substantiate a claim independently: animal studies, in vitro studies, testimonials and other anecdotal evidence, meta-analyses, review articles, comments and letters to the editor, and product monographs.

The FDA Guidance highlights factors that contribute to the quality of studies, including: adequate and well-defined study design; appropriate, representative population in large enough sample size to detect a significant effect; adequate and appropriate assessment of intervention or exposure and outcomes; appropriate statistical analyses and data assessment; and peer review. The agency notes that publication in a peer-reviewed journal is not required for studies to substantiate a claim. FDA observes that there are several systems available to rate the quality of scientific evidence, and cites in particular the Agency for Healthcare Research and Quality (“AHRQ”) Evidence Report/Technology Assessment Number 47 entitled “Systems to Rate the Strength of Scientific Evidence,” which identified 19 study-quality and 7 strength-of-evidence grading systems. AHRQ Publication No. 02-E016, April 2002.<sup>6</sup>

#### D. The Totality of the Evidence

The Draft Substantiation Guidance emphasizes that the strength of the total body of scientific evidence is the critical factor in assessing whether a claim is substantiated. To determine how well the total body of evidence supports the claim, FDA advises firms to consider criteria such as quality, quantity (number of various types of studies and sample sizes), consistency, relevance of exposure, and persuasiveness. The agency notes, however, that there is no general rule for how many studies, or what combination of types of evidence, is sufficient to support a claim.

The agency stresses the need to consider all relevant research, both favorable and unfavorable. While ideally the substantiating evidence should agree with the surrounding body of evidence, where there are conflicts or inconsistencies a firm should determine whether there are plausible explanations for these discrepancies. Where multiple studies exist, FDA will

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<sup>6</sup> FDA also relied upon this AHRQ publication in its Guidance: Interim Evidence-Based Ranking System for Scientific Data for qualified health claims (July 10, 2003), available at <http://www.cfsan.fda.gov/~dms/nuttf-b.html>.

consider whether the studies that have the most reliable methodologies suggest a particular outcome.

### III. Conclusion

The new FDA Draft Substantiation Guidance articulates principles for substantiating claims made in dietary supplement product labeling under section 403(r)(6) that are generally consistent with FTC dietary supplement advertising policy. The FDA Guidance establishes that claims must be supported by “competent and reliable scientific evidence,” and sets forth the criteria by which the agency will evaluate such claims for enforcement purposes. FDA emphasizes that firms must understand the meaning of the claim being made, and must consider the quality and totality of the evidence in support of the claim as phrased and qualified.

Interested parties may submit written or electronic comments on the Draft Substantiation Guidance, bearing the Docket No. 2004D-0466, by January 10, 2005. The Guidance is available through FDA’s website and may be accessed by clicking [here](#).

<b>For more information, contact:</b>			
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