

G R A D I E N T  
**TRENDS**

R i s k S c i e n c e & A p p l i c a t i o n

Winter 2006

Letter to our Readers

January 2006

Dear Colleague,

Dietary supplements and nutraceuticals are taking over the shelves of our supermarkets and the cupboards of our kitchens as the American population searches for good health through better eating habits. But do these products help us as they claim? And what if they contain contaminants? This issue of *Trends* explores this burgeoning industry and what we can expect to learn from the labels we find on these products.

Contributors to this issue include Ms. Ari Lewis and Ms. Leslie Beyer, both Gradient toxicologists, and Dr. A. Dallas Wait, Gradient Principal and an expert in analytical chemistry. Joining them as our guest author is Charles F. Gfeller, Esq., an attorney at Edwards Angell Palmer & Dodge, LLP, who has a litigation practice focused on the food and drug industry. Mr. Gfeller shares his perspective on liabilities associated with the labeling of supplements.

We hope you find this issue of *Trends* enlightening, and perhaps you will want to carry it with you on your next trip to the grocery store.

Yours truly,



Neil Shifrin, Ph.D.  
 President and Founder

# Overview of Dietary Supplements

By Ari S. Lewis, M.S.

*The dietary supplement industry is facing increased regulatory pressure from the FDA.*

With the passage of the Dietary Supplement Health and Education Act (DSHEA) of 1994, which decisively segregated the regulation of dietary supplements from food additives, the dietary supplement industry has expanded rapidly. Prior to 1994, approximately 4,000 dietary supplements were available to the U.S. public. Today, an estimated 29,000 products, representing over \$18 billion in sales, line the shelves of health food stores, pharmacies, and supermarkets. In the wake of this great market expansion, however, consumers are asking questions: Does this product really work? What exactly is in this supplement? Is this product safe? Responding to such concerns, the Food and Drug Administration (FDA) has recently taken actions to help answer these questions.

The DSHEA defines a dietary supplement as “a product (other than tobacco) that is intended to supplement the diet that contains one or more of the following dietary 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 daily intake, or a concentrate, metabolite, constituent, extract, or combinations of these ingredients.” A dietary supplement must be labeled as such and must not be represented as food. Under the DSHEA, unlike food additives, dietary supplements do not require formal pre-market approval; it is the responsibility of the FDA to demonstrate that a dietary supplement presents “a significant or unreasonable risk of

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# Overview of Dietary Supplements

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illness or injury.”

Under the DSHEA, dietary supplement manufacturers and suppliers should fulfill certain requirements. First, any health or structure-function claim must be substantiated (similar substantiation requirements also exist for food). While the FDA requires manufacturers to substantiate all claims, the FDA will only perform a pre-market data review for health claims (see related article). The dietary supplement manufacturer or supplier must also notify the FDA of intent to market a new dietary ingredient (NDI) and provide evidence demonstrating that the product is “reasonably expected to be safe.” As a matter of law, all dietary supplements that were available in the U.S. pre-DSHEA, are “grandfathered” and, thus, considered to be “safe.” Finally, the manufacturers must specify the “level of the new dietary ingredient in the product.” This can be especially challenging given the analytical uncertainties involved in testing (see related article).

As a practical matter, it is unclear how the dietary supplement industry will meet these requirements. Responsible companies try in earnest to comply, while others simply ignore the regulations because guidance is ambiguous and enforcement is weak. For example, the FDA has not specified the type and amount of evidence required to establish the safety of an NDI. The regulation ambiguously states that “a history of use or other evidence” can be used to demonstrate safety. Because the criteria to meet the safety standard are largely unspecified, many NDI applications are denied. Since 1994, 61% of all NDI applications have been rejected. Failure to establish a product as “reasonably expected to be safe” accounts for about 67% of the reasons an NDI application is rejected (see figure).

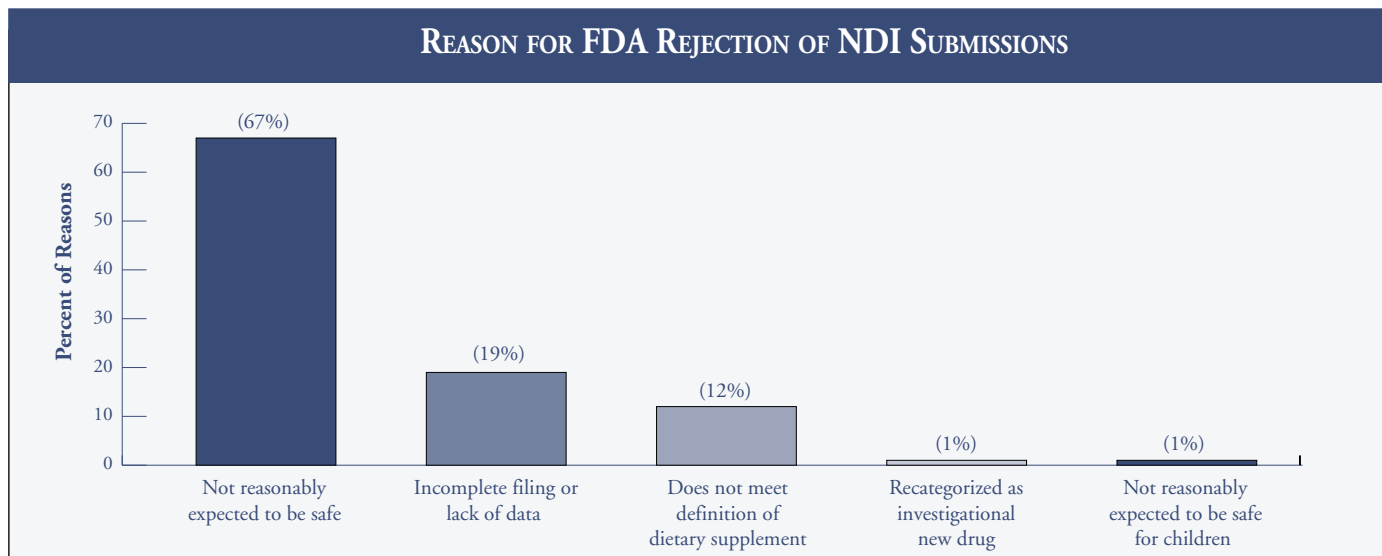
Recent actions taken by the FDA indicate that standardizing the industry and increasing compliance are becoming agency priorities. In 2004, the FDA published a proposed rule clarifying how the industry should evaluate the “identity, purity, quality, strength, and composition” of dietary supplements. Additionally, the FDA has released recent guidance on the nature and extent of evidence needed to substantiate claims. The agency also has immediate plans to release guidance on the “type, quantity, and quality of evidence” manufacturers should provide to the FDA for NDI notification. Interestingly, the National Research Council with the Institute of Medicine has just published a framework for evaluating the safety of supplements currently on the market (NRC, 2005). Although their framework does not directly affect dietary supplement manufacturing procedures, more formal and methodical scientific inquiries into supplement safety by regulatory agencies will push the industry to improve analytical and safety documentation.

Given the planned release of guidance that will affect all aspects of the industry, the intent of the FDA to “raise the bar” for data requirements cannot be ignored. As the FDA works to standardize the dietary supplement industry with a scientifically sound foundation, companies that have invested in the science to support safety and substantiation claims, and have met analytical challenges, will likely limit adverse regulatory and legal consequences, giving them a competitive edge within the industry.

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## Reference:

Institute of Medicine (IOM) and National Research Council (NRC). 2005. *Dietary Supplements: A Framework for Evaluating Safety*. The National Academies Press, Washington, D.C., 526p.



Source: NDI submissions from October 1994 to October 2004. Tabulated by W. Patrick Noonan and presented in “FDA Regulatory Requirements for the Use of Novel Ingredients in New Food, Dietary Supplement, and Cosmetic Products,” WorldNutra 2005 Conference, Anaheim, CA, October 18, 2005.

# Documenting Benefits of Use

By Leslie A. Beyer, M.S., DABT

*Specific types of experimental data can be used to substantiate claims of dietary supplement efficacy.*

Under the Dietary Supplement Health and Education

**All the information amassed must be critically evaluated in its totality to determine whether there is adequate evidence to substantiate a claim.**

Act (DSHEA) of 1994, all health/efficacy claims made by dietary supplements must be substantiated – not unlike the requirements when such claims are made for foods. There are

two distinct categories of claims: health claims and structure/function claims (safety claims are not included). Health claims are claims regarding diagnosis, mitigation, treatment, cure, or prevention of a specific disease or class of diseases. The manufacturer has to submit the proposed label wording and supporting documentation to the Food and Drug Administration (FDA), which then makes a ruling on the exact wording that can be used. For example, the FDA recently ruled that companies can now say that eating tomatoes and tomato sauce is linked with a reduced risk of gastric, ovarian, pancreatic, and prostate cancers (Henderson, 2005; FDA, 2005).

By contrast, structure/function claims are much more general (e.g., “supports the body’s natural defenses” on packages of zinc lozenges). The FDA does not review these types of claims, and consequently such dietary supplements must be labeled with the following disclaimer: “These statements have not been evaluated by the Food and Drug Administration. This

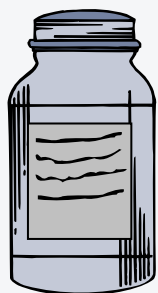
product is not intended to diagnose, treat, cure, or prevent any disease.” Nonetheless, even these types of claims must be substantiated.

Because the DSHEA and the accompanying legislative history do not define “substantiation,” the FDA drafted a guidance document addressing claims made under Section 403(r)(6) (structure/function claims) of the Federal Food, Drug, and Cosmetic Act. There are four aspects to evaluating substantiation: 1) the meaning of the claim being made, 2) the relationship of the evidence to the claim, 3) the quality of the evidence, and 4) the totality of the evidence. This guidance defines reliable scientific evidence as “tests, analyses, research, studies, or other evidence...conducted and evaluated in an objective manner by persons qualified to do so...to yield accurate and reliable results” (FDA, 2004).

The FDA’s guidance describes the types of studies, *etc.* needed to make various claims. Intervention studies with humans are the “gold standard” of substantiation, especially if they are randomized, double blind, parallel group, placebo-controlled trials (FDA, 2004). In addition, the study population and conditions should be as similar as possible to the anticipated usage. For example, if the product’s claims involve conditions seen primarily in the elderly, the trial should be conducted in the elderly. The trial should use the same route of administration as the supplement (e.g., topical supplements should not use ingestion studies for substantiation). Further, the endpoint evaluated has to be specific to the claim being made. For example, if a dietary supplement is labeled as “promotes weight

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## CLAIMS MADE FOR SOME DIETARY SUPPLEMENTS AND FOOD



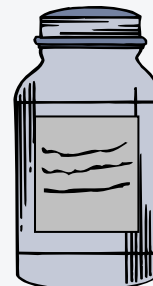
### Glucosamine/Chondroitin Sulfate Complex

*Structure/Function:* “Helps renew cartilage and lubricate joints for joint comfort.”



### Tomatoes/Tomato Sauce

*Health Claim:* “Very limited and preliminary scientific research suggests that eating one-half to one cup of tomatoes and/or tomato sauce a week may reduce the risk of prostate cancer.”



### Vitamins

*Structure/Function:* “This multivitamin multimineral formula contains every vitamin considered to be essential for the body, plus 13 key minerals.”

# Limitations of Test Methods

By A. Dallas Wait, Ph.D.

*Analytical challenges in the nutraceutical industry are as basic as knowing what active ingredient to analyze.*

Manufacturers of dietary supplements are confronted with numerous testing challenges to properly ensure that their products are safe to consume. The scope of testing may run the gamut from determining a supplement's constituent properties to studying its pharmacological and toxic effects. Reliable constituent testing, which can be difficult, targets both intended

*The lack of standardized test methods can stymie a manufacturer's ability to produce reliable ingredient data, frustrate regulatory oversight, and hamper a manufacturer's ability to ensure that its competitors are playing by the same rules.*

components (such as active ingredients) and contaminants.

The presence of contaminants in supplements may result from processing, such as solvent residuals or cross contamination, or may be environmentally derived from raw materials, such as heavy metals and pesticides. Analytical

methods for many contaminants are available. An effective Good Manufacturing Practices (GMPs) program should evaluate potential contamination by routine monitoring of raw materials for environmental contaminants and final product analysis for process contaminants. The importance of product testing for contamination was highlighted in a 2004 survey of Ayurvedic herbal medicine products (Saper *et al.*, 2004). Seventy products imported from South Asian markets and sold in Boston area stores as dietary supplements were tested, and twenty percent of the products were found to contain lead, mercury, and/or arsenic at levels that when the product is used at manufacturer's dosage recommendations, are above the U.S. Pharmacopeia and the U.S. EPA regulatory standards. In a few instances, lead and arsenic concentrations were 1,000 to 10,000 times higher than regulatory limits.

Constituent analysis is a particularly daunting endeavor for botanicals. Knowledge about the chemistry of constituents in natural products is vital to understanding their biological activity. Methodologies to characterize supplement constituents are sporadically documented in the literature and proprietary methods may exist in the laboratories of supplement manufacturers (Jaksch *et al.*, 2005). Moreover, standardized constituent test methods endorsed by the Food and Drug Administration (FDA) are nearly nonexistent. Disagreements

between raw material suppliers and manufacturers over potency, challenges to label claims by a reference laboratory or government agency, and concerns reflected in news reports over supplement potencies are often rooted in test method issues. The lack of guidance for obtaining representative samples to test creates further concerns about the reliability of botanical data. Confounding factors include sample heterogeneity (different plant parts), seasonal and geographical variations, and plant species differences (WHO, 1998).

The lack of standardized test methods can stymie a manufacturer's ability to produce reliable ingredient data, frustrate regulatory oversight, and hamper a manufacturer's ability to ensure that its competitors are playing by the same rules. In response, the National Institutes of Health's (NIH) Office of Dietary Supplements retained the Association of Official Analytical Chemists (AOAC) to develop 20 standardized analytical methods for measuring constituents in dietary supplements and foods. The result of this initiative was the formation of the AOAC Presidential Task Force for Dietary Supplements. Several methods have been developed under a five-year contract that expires in 2007. Five methods are currently in the approval process, and another 22 methods are in some phase of evaluation. Examples of test method target analytes include aristocholic acid, chondroitin sulfate, six alkaloids contained in ephedra, and phytosterols contained in saw palmetto.

To date, the NIH, the AOAC, and the industry all believe that the method development and approval process is not proceeding fast enough. Hundreds of standardized test methods are likely needed to provide the level of data quality that a reputable supplement industry requires. As such, it behooves supplement manufacturers to provide even greater and more rigorous support for the development of standardized methods to ensure the "health" of the industry.

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## References:

- Jaksch, F., M. Wang, and M. Roman. 2005. Handbook of Analytical Methods for Dietary Supplements. American Pharmacists Association.
- Saper, R.B., S.N. Kales, J. Paquin, M.J. Burns, D.M. Eisenberg, R.B. Davis, and R.S. Phillips. 2004. Heavy Metal Content of Ayurvedic Herbal Medicine Products. *J. American Medical Assoc.* 292(23):2868-2873.
- World Health Organization (WHO). 1998. Quality Control Methods for Medicinal Plant Materials.

## What's New at Gradient

### Appointments

**Dr. Barbara Beck** was elected to the Board of the Academy of Toxicological Sciences.

**Dr. Tom Lewandowski** was re-appointed to the position of Affiliate Assistant Professor at the University of Washington, Department of Environmental and Occupational Health Sciences.

**Dr. Julie Goodman** has become a Diplomate of the American Board of Toxicology.

### Upcoming Presentations

**Miami, FL. January 29-February 1, 2006. Barbara D. Beck and Noelle M. Cocoros.** "A Qualitative Risk Assessment to Evaluate the Remediation of Trichloroethylene by Nanoscale Zero-Valent Iron Particles," presentation at the 1st International Conference on Nanotoxicology: Biomedical Aspects.

**San Diego, CA. March 5-9, 2006.** 45th Annual Meeting of The Society of Toxicology.

- **Thomas A. Lewandowski and Barbara D. Beck,** "Evaluation of Potential Lithium Toxicity Associated with a Monitoring Device Used in Elephants."

- **Barbara D. Beck, Thomas A. Lewandowski,** and J.W. Yager, "Evaluation of the Possible Toxicological Interaction of Lead and Mercury for Use in Risk Assessment."
- **Ari S. Lewis, Barbara D. Beck, Julie E. Goodman,** and M. Eldan, "DMAV-Induced Bladder Tumors: Unique Rat Susceptibility."
- **Teresa S. Bowers and Barbara D. Beck,** "Distributional Controls on Non-Linear Dose-Response Relationships."
- **Mara Seeley and Teresa S. Bowers,** "Developing Recommended Exposure Levels for Airborne Arsenic."
- **Leslie A. Beyer, Christopher M. Long, Barbara D. Beck,** and **Tracey M. Slayton,** "Ambient Concentrations of Benzene are Below Those Associated with Significant Cancer Risk."

**San Diego, CA. March 5-9, 2006. Barbara D. Beck** will chair the symposium entitled "Does the Methylation of Inorganic Arsenic Affect its Toxicity and Mode(s) of Action: A Critical Discussion" at the 45th Annual Meeting of the Society of Toxicology.

**San Francisco, CA. May 3, 2006. Lorenz R. Rhomberg.** Lecture in American Chemical Society continuing education course "Principles of Toxicology."

## Documenting Benefits of Use

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loss," and the clinical study documents a significant increase in metabolism, the claim is not substantiated because the effect of the supplement on weight loss has not been evaluated (FDA, 2004). However, there are circumstances where a chain of information can create adequate substantiation. The guidelines recommend that an industry not use the results of studies done by others without reviewing the underlying studies themselves.

The guidelines do not recommend what they refer to as observational studies, meaning case reports, case-series studies, and epidemiology studies such as case-control studies, cross-sectional studies, and cohort studies. Information that does not constitute substantiation, although it may provide background to support a claim, includes anecdotal evidence, animal studies, *in vitro* studies, meta-analysis, review articles, comments and letters to the editor, and product monographs.

All the information amassed must be critically evaluated in

its totality to determine whether there is adequate evidence to substantiate a claim. Criteria to use in this evaluation include the quality and quantity of studies, consistency in results, relevance of the exposure (route, dose, age of subject), and overall persuasiveness. Completing the analysis, and thoroughly and completely documenting it, are key steps to avoiding problems with the FDA regarding structure/function claims, and in expediting the FDA review of health claims.

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### References:

- FDA. 2004. Guidance for Industry: Substantiation for Dietary Supplement Claims Made Under Section 403 (r)(6) of the Federal Food, Drug, and Cosmetic Act. November.
- FDA. 2005. Qualified Health Claims: Letter of Partial Denial – "Tomatoes and Prostate, Ovarian, Gastric and Pancreatic Cancers (American Longevity Petition)" (Docket No. 2004Q-0201). November 8.
- Henderson, D. 2005. "FDA limits tomato cancer claims." *Boston Globe*. November 10. Pages E1 and E4.

# Guest Editorial: Supplement Labeling Liability

By Charles F. Gfeller, Esq.

*The nexus between substantiation claims and notification requirements places some unique burdens on dietary supplement manufacturers.*

*The FDA assumes that these notifications have been made in good faith, and the submitters were confident that they were in possession of adequate substantiation.*

The Food and Drug Administration (FDA), which has primary responsibility for labeling of dietary supplements, has not issued a specific set of procedures, guidelines, or standards for identifying the type and amount of evidence needed to support a claim made in relation to a dietary supplement. The FDA's standard Warning Letter simply states, "[b]ased on the scientific data available to us, we do not believe that these claims are substantiated" (FDA, 2003). However, the notification requirements imposed by the Dietary Supplement Health and Education Act (DSHEA) are connected to the substantiation requirement. The FDA has taken the position that because DSHEA, on its face, connects the notification and substantiation requirements, "a manufacturer who submits a notification under § 403(r)(6) of [DSHEA] without being in possession of substantiation that the claim that it intends to make, or is making, is truthful and not misleading is making a false statement to the Government."

The FDA has also stated that DSHEA is "clear on its face: [t]he manufacturer must have substantiation that the statement is truthful and not misleading" (FDA, 1997). According to the FDA, "[i]f the manufacturer has any doubts as to whether it has substantiation to meet this standard, it should not make the statement in question on its label or in its labeling" (FDA,

1997). Though the FDA has received many complaints from manufacturers who feel that the substantiation standard is too vague, the FDA's position is that these complaints are contradicted by the hundreds of notices that it has received under DSHEA. The FDA "assumes that these notifications have been made in good faith, and the submitters were confident that they were in possession of adequate substantiation" (FDA, 1997). Accordingly, the FDA has stated that it "finds no need for it to elaborate on the substantiation standard that appears in [DSHEA]" (FDA, 1997).

Although DSHEA does not directly apply to claims made in the advertising context, the requirement that claims be truthful and not misleading is common to both labeling and advertising. The Federal Trade Commission (FTC), which scrutinizes advertising, requires claims about the efficacy of nutritional supplements to be supported with "competent and reliable scientific evidence" (FTC, 2001).

In short, manufacturers of nutritional supplements should do their homework, and properly document their product development, before putting a product on the market. Failure to do so could lead to trouble with both the FDA and the FTC.

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## References:

- FTC. 2001. Dietary Supplements: An Advertising Guide for Industry.
- FDA. 1997. Food Labeling, Final Rule. Fed. Reg. 62(184): 49826-48892.
- FDA. 2003. Warning Letter, February 23, 2003, directed at Advanced Sports Nutrition.

## In the next issue:

*Environmental Liability Management*

*M&A: Emerging Issues and Requirements*

*Liability Estimation Frameworks*

*Guest Editorial: Asset Retirement Obligations*

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