



Woodrow Wilson
International
Center
for Scholars
*Project on Emerging
Nanotechnologies*



A HARD PILL TO SWALLOW:

Woodrow Wilson International
Center for Scholars

One Woodrow Wilson Plaza
1300 Pennsylvania Ave., N.W.
Washington, DC 20004-3027

T 202.691.4000

F 202.691.4001

www.wilsoncenter.org/nano

www.nanotechproject.org



FSC Logo??



This publication has been
printed on 100% recycled
paper with soy-based inks.

Barriers to Effective FDA Regulation of Nanotechnology-Based Dietary Supplements

*William B. Schultz
Lisa Barclay*

*Project on Emerging Nanotechnologies is supported
by THE PEW CHARITABLE TRUSTS*



PEN 17
JANUARY 2009

WOODROW WILSON INTERNATIONAL CENTER FOR SCHOLARS

Lee H. Hamilton, President and Director

BOARD OF TRUSTEES

Joseph B. Gildenhorn, Chair

David A. Metzner, Vice Chair

PUBLIC MEMBERS

James H. Billington, Librarian of Congress; G. Wayne Clough, Secretary, Smithsonian Institution; Bruce Cole, Chair, National Endowment for the Humanities; Mark R. Dybul, designated appointee within the federal government; Michael O. Leavitt, Secretary, U.S. Department of Health and Human Services; Condoleezza Rice, Secretary, U.S. Department of State; Margaret Spellings, Secretary, U.S. Department of Education; Allen Weinstein, Archivist of the United States

PRIVATE CITIZEN MEMBERS

Robin B. Cook, Donald E. Garcia, Bruce S. Gelb, Sander Gerber,

Charles L. Glazer, Susan Hutchison, Ignacio E. Sanchez

The **PROJECT ON EMERGING NANOTECHNOLOGIES** was launched in 2005 by the Wilson Center and The Pew Charitable Trusts. It is dedicated to helping business, governments, and the public anticipate and manage the possible human and environmental implications of nanotechnology.

THE PEW CHARITABLE TRUSTS serves the public interest by providing information, advancing policy solutions and supporting civic life. Based in Philadelphia, with an office in Washington, D.C., the Trusts will invest \$248 million in fiscal year 2007 to provide organizations and citizens with fact-based research and practical solutions for challenging issues.

The **WOODROW WILSON INTERNATIONAL CENTER FOR SCHOLARS** is the living, national memorial to President Wilson established by Congress in 1968 and headquartered in Washington, D.C. The Center establishes and maintains a neutral forum for free, open and informed dialogue. It is a nonpartisan institution, supported by public and private funds and engaged in the study of national and international affairs.

A HARD PILL TO SWALLOW:

Barriers to Effective FDA Regulation of Nanotechnology-Based Dietary Supplements

*William B. Schultz
Lisa Barclay*

PEN 17 JANUARY 2009

The opinions expressed in this report are those of the author and do not necessarily reflect views of the Woodrow Wilson International Center for Scholars or The Pew Charitable Trusts.



CONTENTS

4	FOREWORD
5	EXECUTIVE SUMMARY
7	ABOUT THE AUTHORS
8	I. OVERVIEW OF THE PROBLEM
11	II. THE FORMATIVE YEARS: REGULATION OF DIETARY SUPPLEMENTS PRIOR TO 1994
16	III. THE WATERSHED: THE DIETARY SUPPLEMENT HEALTH AND EDUCATION ACT OF 1994
20	IV. RESOURCE CONSTRAINTS HAMPER FDA'S CAPABILITY TO REGULATE DIETARY SUPPLEMENTS
23	V. LIMITATIONS ON FDA'S AUTHORITY TO REGULATE DIETARY SUPPLEMENTS MADE FROM NANOTECHNOLOGY
24	VI. RECOMMENDATIONS
25	VII. CONCLUSIONS
26	APPENDIX: NANOTECHNOLOGY-BASED DIETARY SUPPLEMENTS (AS OF MARCH 2008)

FOREWORD

When our Project took its first look at the capacity of the U.S. Food and Drug Administration (FDA) to address nanotechnology, there were 11 dietary supplements on the market that claimed to use nanoscale ingredients, such as calcium, magnesium and silver. Now, less than two years later, our research has found indications that the number of manufacturer-identified dietary supplement products claiming to use nanoscale ingredients has more than tripled to over 40 products. Because of this significant increase in products and early concerns about the weakness of FDA's oversight of supplements, we decided to take a deeper look at the issue of nanotechnology and dietary supplements.

This report provides a comprehensive history of FDA's evolving role with dietary supplements, highlighting key changes in laws, legislation and resources that have significantly affected the agency's ability to provide oversight of the burgeoning supplements market. The increased use of nanomaterials in dietary supplements comes at a time when our understanding of the biological impact of these materials is limited. According to an inventory of federal environmental, health and safety research on nanotechnology maintained by the Project on Emerging Nanotechnologies, the U.S. government is spending less than \$1 million annually to study the direct impact of nanoscale materials on the gastrointestinal tract.¹ It is not clear that the supplement industry is conducting the rigorous testing needed either to understand the effects of nanoscale ingredients in its products or to back up product claims. This means that consumers are potentially exposed to unknown risks that must be balanced with the possible benefits of taking these supplements.

Improving FDA's capacity to provide oversight of new dietary supplements based on new science will require increased regulatory authority, better information and more resources to support scientific analysis. Fortunately, there are efforts in Congress to increase FDA's funding and improve oversight. We hope that this new capacity will extend to the area of dietary supplements containing engineered nanoparticles.

David Rejeski
Director,
Project on Emerging Nanotechnologies

1. This database includes only federally-funded studies directly looking at the environmental, health and safety risks of nanotechnology. It is possible that other studies (*e.g.*, medical trials) are being conducted that look at the effect of nanomaterials on the gastrointestinal tract that are not included in the database.

EXECUTIVE SUMMARY

Historically, the regulation of dietary supplements has been a significant challenge for the Food and Drug Administration (FDA), and the fact that some of those products are now being manufactured using nanotechnology creates an additional layer of complexity. This paper addresses the issue of whether FDA is equipped to meet the emerging regulatory challenge of dietary supplements that use engineered nanomaterials. The short answer is no.

The FDA's ability to regulate the safety of dietary supplements using nanomaterials is severely limited by lack of information, lack of resources and the agency's lack of statutory authority in certain critical areas. Three main problems need to be addressed:

1. FDA does not have the capacity to identify nano-based dietary supplements that are being developed and marketed, unless manufacturers submit to the pre-market notification process for new dietary ingredients.
2. To the extent that FDA is aware of nano-based dietary supplements, it has little regulatory authority over them.
3. Even if it were granted increased regulatory authority, FDA lacks the scientific expertise and resources to effectively regulate nanomaterials in supplements.

We recommend that the following steps be taken:

Increased Regulatory Authority. Congress should require that dietary supplements containing engineered nanoparticles be safe, and it should provide FDA with regulatory authority in the following areas:

1. Product Registration
2. Establishment of Safety Standards
3. Market Review
4. Pre-Market Testing
5. Improved Adverse Event Reporting

Increased Information. FDA should be provided with more information on currently marketed dietary supplement products that contain engineered nanoparticles. The agency should then determine whether safety testing should be performed on those products and, if so, what types of testing.

Increased Resources. Congress should provide FDA with resources sufficient to regulate dietary supplements that contain nanoparticles under the new regulatory authority described above.

While it is not possible to precisely determine the prevalence of dietary supplements using engineered nanoparticles, it is likely that the public's exposure to these products will grow significantly in the next several years. Congress should adopt legislation granting FDA the authority to collect additional information about those products and to ensure that they are tested for their effects on human health. Such legislation should prohibit the sale of new dietary supplements made with nanotechnology until they have been demonstrated to be safe, and it should provide FDA with sufficient resources to regulate these products. Until Congress acts, consumers who take dietary supplements containing engineered nanoparticles will be at additional, unknowable and potentially serious risk.

ABOUT THE AUTHORS

WILLIAM B. SCHULTZ

A partner at Zuckerman Spaeder LLP, William Schultz focuses on food and drug law, civil litigation, administrative law and public interest law. Drawing on his experience in these areas, he represents individuals (including those who have been injured by foods, drugs and other products), generic drug companies, state and local governments, associations and advocacy organizations before the courts, federal government agencies and Congress.

Before joining Zuckerman Spaeder, Mr. Schultz held the position of Deputy Assistant Attorney General in the U.S. Department of Justice (DOJ). During his tenure, he supervised all appellate litigation conducted by DOJ's Civil Division and the department's lawsuit against the tobacco industry, one of the largest lawsuits ever initiated by the U.S. government. He also served as the Deputy Commissioner for Policy at the Food and Drug Administration (FDA), overseeing the development of all FDA policies, regulations and legislation, and was counsel to Representative Henry A. Waxman (D-CA), the Chairman of the House Subcommittee on Health and the Environment, assisting in the development of food and drug and other health care legislation. At Public Citizen Litigation Group, where he began his legal career, Mr. Schultz tried and argued cases in federal and state trial and appellate courts, including several cases before the U.S. Supreme Court for the District of Columbia. Before entering law practice, he clerked for the Honorable William B. Bryant, U.S. District Court, Washington, D.C.

Between 1983 and 1996, Mr. Schultz taught civil litigation and food and drug law at Georgetown University Law Center. He is a graduate of Yale University and the University of Virginia Law School.

LISA BARCLAY

An associate at Zuckerman Spaeder LLP, Lisa Barclay practices in the areas of complex civil litigation, food and drug law and professional ethics. During her time at Zuckerman Spaeder, Ms. Barclay has represented a variety of clients, including non-profit groups, generic pharmaceutical companies and individual attorneys and law firms. She frequently works with clients on matters involving professional ethics, counseling lawyers and law firms on ethics requirements and compliance.

Prior to joining Zuckerman Spaeder, Ms. Barclay clerked for the Honorable Judge William B. Bryant, U.S. District Court for the District of Columbia, and practiced civil litigation in the Washington, D.C., office of Weil, Gotshal & Manges LLP. Between 1995 and 2001, she worked in the Office of the Commissioner at the Food and Drug Administration. Ms. Barclay is a graduate of The George Washington University and Georgetown University Law Center.

I. OVERVIEW OF THE PROBLEM

For more than a century, the Food and Drug Administration (FDA) has been entrusted with ensuring the safety of foods and drugs. Over the years, Congress has given FDA additional authority over these products and expanded the agency's jurisdiction to cover additional product categories. Today, FDA has a nuanced arsenal of regulatory tools for protecting consumers that vary depending on the category of product. For prescription drugs, biologics (products made from a living organism or its components), food additives and certain medical devices, FDA's pre-market approval authority places the burden on the industry to prove the safety of the product. For other products, such as cosmetics and food, FDA has the burden to show that any given product is unsafe before it may take regulatory action.

The regulatory authorities applicable to dietary supplements are more analogous to that of foods than drugs. Historically, the regulation of dietary supplements has been a significant challenge for the agency, and the fact that some of those products are now being manufactured using nanotechnology creates an additional layer of complexity. This report addresses the issue of whether FDA is equipped to meet the emerging regulatory challenge of dietary supplements that are made from nanotechnology. The short answer is no.

Nanotechnology is the art and science of manipulating matter at the nanoscale to create new and unique materials and products. A nanometer, one billionth of a meter, is roughly 1/100,000th the width of a strand of human hair. Nanotechnology was used in the manu-

facture of \$147 billion in manufactured goods in 2007, and by 2015, the market is expected to grow to \$3.1 trillion.¹ The United States invests both publicly and privately approximately \$4 billion annually in nanotechnology research and development, which accounts for approximately one-third of the total public and private sector investments worldwide.²

The National Nanotechnology Initiative (NNI), a federal research and development program that coordinates the activities of FDA and 24 other government agencies regarding nanoscale research and technology, defines *nanotechnology* as an activity possessing the following elements: (1) research and technology development at the atomic, molecular or macromolecular level, in the length scale of 1–100 nanometers; (2) creating and using structures, devices and systems that have novel properties and functions because of their small or intermediate size; and (3) ability to control or manipulate on the atomic scale.³ All of the research and development in this area is designed to answer a central question: How do substances change when created or altered at the nanoscale?

The food industry is one field where advances in nanotechnology are rapidly emerging. Today, nanotechnology is being used in the development of advancement both in food packaging and in food itself.⁴ Potential applications of this technology include the creation of nanomaterials whose small size provides the ability to deliver nutrients to human cells that previously could not be reached or to block certain substances in food, such as cholesterol or food allergens,

Examples of Claims Made on Currently Marketed Nano Dietary Supplements

"Nutri-Nano™ is a patent-protected nanotechnology that transforms fat-soluble nutrients into water-soluble ones—significantly increasing absorption."

"Internal cleansing and detoxing with Artichoke NanoClusters promotes proper liver function and radiant skin."

"Lifepak® nano... protects DNA and cells, nourishes and protects the brain, bolsters the immune system."

from reaching certain parts of the body.⁵ Recently, a non-governmental organization, Friends of the Earth, issued a report calling for a moratorium on the use of nanotechnology in both food and food packaging, claiming that not enough is known about its potential risks to humans.⁶

Extremely little is known about the use of engineered nanoparticles in the dietary supplement market. Current law requires supplement manufacturers to disclose relatively little information about their products. Federal regulators have limited information about the size of this market or the manner in which engineered nanoparticles are being used to manufacture dietary supplements. Some limited information is available because dietary supplement manufacturers have been touting the use of nanotechnology when marketing their products. On the basis of manufacturers' claims, it appears that the number of these products entering the market is increasing. Informal monitoring by the Project on Emerging Nanotechnologies (PEN) has indicated that, during the past two years, the number of manufacturer-identified nanotechnology-based dietary supplement products has quadrupled—increasing from 11 to 44.⁷

While the claims made about these nano dietary supplements vary, most focus on how the body metabolizes these products. For example, some manufacturers claim that their products can be absorbed by the body more rapidly or are more bioavailable because they contain ingredients that were engineered at the nanoscale. Examples of product claims that tout special properties due to the use of nanotechnology include: increased effectiveness in a calcium/magnesium product; more rapid, uniform and complete absorption of nutrients in a spray form; increased absorption of a B₁₂ vitamin spray; supplements that pass through membranes directly into human cells; and increased absorption of gel supplements by transforming fat-soluble nutrients into water-soluble ones. FDA generally does not have the capacity to evaluate the claims made by these products. This means that consumers are being exposed to—and could be relying on—product claims that may not be accurate.

At the same time, the potential changes to a product containing engineered nanoparticles—how it is absorbed, how it is metabolized, whether it crosses various natural barriers in the human body—raise significant

The Dietary Supplement Industry Today

Nearly 150 million Americans use dietary supplements annually. The size of the market has increased dramatically since the passage of the Dietary Supplement Health and Education Act (DSHEA) and is continuing to grow, presumably in part because of the lack of pre-marketing regulatory hurdles and exploding customer demand. As of 2005, the dietary supplement industry in the United States was a \$21.4 billion business.¹ There are more than 29,000 dietary supplement products on the market.²

1. "Fact Sheet—Dietary Supplements: Safe, Beneficial, and Regulated," Council for Responsible Nutrition. Available at http://www.crnusa.org/pdfs/CRN_FACT_DSsafeRegulatedBeneficial_07.pdf.

2. *Id.*

concerns with respect to products such as drugs and medical devices, where FDA has broad authority to review pre-market safety data and post-market adverse event data. They raise even more serious concerns with respect to dietary supplements, where there is only limited FDA authority to regulate safety and no pre-market approval authority.

The following analysis traces the evolution of the regulatory system governing dietary supplements and explores whether this system is designed to monitor and regulate products containing engineered nanoparticles.

As is explained below, using an emerging technology that could dramatically alter how the body absorbs and metabolizes a product that is largely unregulated creates the potential for serious risks to consumers in the coming years.

Notes

1. "Nanomaterials State of the Market Q3 2008: Stealth Success, Broad Impact," Lux Research.

2. The Nanotech Report: Investment Overview and Market Research for Nanotechnology 5th Edition. Lux Research, 2007.

3. "FDA and Nanotechnology Products: Frequently Asked Questions," U.S. Food and Drug Administration. Available at <http://www.fda.gov/nanotechnology/faqs.html>. While FDA has not adopted its own definition of nanotechnology, it participated in the development of NNI's definition.

4. Jennifer Kuzma and Peter VerHage, *Nanotechnology in Agriculture and Food Production: Anticipated Applications*. Washington, DC: Woodrow Wilson International Center for Scholars, Project on Emerging Nanotechnologies, September 2006, pp. 9-10.

5. *Id.*

6. "Out of the Laboratory and On to Our Plates: Nanotechnology in Food and Agriculture," Friends of the Earth, 2d ed., April 2008. Available at http://www.foe.org/pdf/nano_food.pdf.

7. See the appendix for a list of currently available nanotechnology-based dietary supplements. Available at <http://www.nanotechproject.org/inventories/consumer/>.

II. THE FORMATIVE YEARS: REGULATION OF DIETARY SUPPLEMENTS PRIOR TO 1994

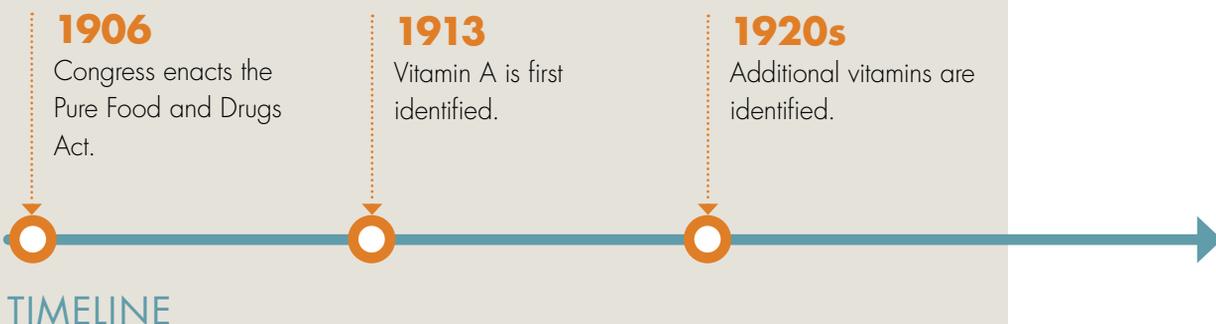
FDA's regulatory authority over all products within its jurisdiction has evolved over the past century.¹ Typically, FDA has been given greater regulatory authority over a certain type of product in response to a public health crisis. For example, FDA's governing statute, the Federal Food, Drug and Cosmetic Act (FFDCA), was passed in the wake of a public health disaster involving elixir sulfanilamide, an untested sulfa drug that caused the deaths of nearly 100 people.² In enacting that statute, Congress for the first time required pre-marketing approval for drugs, mandating that drug manufacturers demonstrate safety before a new drug could be marketed.³ Similarly, in 1962, following the thalidomide tragedy, where a sedative caused deformities in children born to women who took the drug during their pregnancies, Congress enacted the Kefauver-Harris Amendments, which require that drugs be proven effective prior to being marketed.⁴

Establishing meaningful FDA oversight of dietary supplements, however, has proven to be difficult, given the popularity of

and grassroots support for these products. Indeed, over the past 40 years, virtually every time that FDA has attempted to increase its regulation of dietary supplements, the public outcry has been strong and often Congress then has enacted legislation specifically to limit FDA's authority.

Congress enacted the Pure Food and Drugs Act of 1906,⁵ the first comprehensive regulatory statute applicable to foods and drugs, before vitamins had even been identified. In 1913, researchers at the Wisconsin College of Agriculture published a paper that first identified vitamin A.⁶ Additional vitamins were identified in the 1920's. In the 1930's, FDA's Division of Vitamins began conducting assays of products that were being promoted with general or specific claims of vitamin efficacy, finding that manufacturers' therapeutic claims were exaggerated and that the products' vitamin content was low or missing.⁷

In 1938, Congress enacted the FFDCA and included a reference to the "the vitamin, mineral, and dietary properties" of foods "for special dietary use."⁸ In 1941,



the National Research Council published the first recommended daily allowances (RDAs) and FDA established regulations governing the labeling of vitamin and mineral supplements and foods for special dietary use, establishing minimum daily requirements (MDRs).⁹ In 1962, FDA published a notice proposing that only those nutrients recognized by “competent authorities” as essential for human nutrition could be offered for sale and establishing RDAs for minimum and maximum amounts of recognized nutrients for adults and children.¹⁰ Following an outcry from the dietary supplement industry in response to this regulatory effort, the proposals ultimately were withdrawn.

In 1966, FDA issued regulations pertaining to the labeling and content of “food for special dietary use” and setting a standard of identity for dietary supplements.¹¹ The regulations included a chart of RDAs for various vitamins and minerals as well as a requirement that supplement labels contain a statement regarding the limited scientific basis for recommending routine use of such

products.¹² Again, there was strong public opposition to the proposal. As a result, the regulation was stayed the day before it was scheduled to become effective to allow for additional hearings on the objections that had been raised.¹³ Ultimately, FDA did away with the proposed disclaimer language.¹⁴

In 1973, FDA published final regulations requiring that most vitamins and minerals with a potency greater than 150% of their RDA be classified as drugs and setting individual limits for certain vitamins.¹⁵ In response to this regulation, on April 22, 1976 Congress enacted the Proxmire Amendment, which limited FDA’s authority to regulate high-potency dietary supplements. The legislation precluded FDA from declaring a vitamin or mineral to be a drug solely because it exceeded the level of potency the agency had determined to be nutritionally rational or useful, focusing instead on considerations of human toxicity.¹⁶

In 1979, FDA again tried to regulate vitamins and minerals by publishing a proposed regulation, the Over-the-Counter Vitamin and Mineral Drug Products

1930s

FDA creates a Division of Vitamins.

1938

Congress includes reference to the “vitamin, mineral, and dietary properties” of foods “for special dietary use” in FFDCA.

1941

The National Research Council publishes first RDAs.

Monograph, which established certain conditions under which over-the-counter vitamin and mineral products are generally recognized as safe and which contained potency limitations for certain dietary supplements.¹⁷ And again, criticism of this action as being beyond FDA's authority led to FDA's withdrawal of the proposal.¹⁸ In the late 1970s, FDA began regulating dietary supplements as food additives that required pre-market approval prior to being sold, having adopted a legal theory that the dietary ingredient was "added" to a capsule or tablet prior to being consumed.¹⁹ The industry responded to FDA lawsuits asserting this theory by arguing that the products were generally recognized as safe and thus eligible for an exception to the FDCA definition of food additive.²⁰

Ultimately, FDA's interpretation that single-ingredient dietary supplements should be treated as food additives (if the dietary ingredient was added to a capsule) was rejected by the courts, which found that single-ingredient dietary supplements were instead foods under the FDCA.²¹

In the late 1980s and early 1990s, FDA began to focus on the types of claims made on dietary supplement products. In doing so, it evaluated the statements made by manufacturers about certain dietary supplements to determine whether they were claims for the prevention of a disease or condition that would warrant treating the products as unapproved drugs. In 1990, Congress passed the landmark Nutrition Labeling and Education Act (NLEA), which required certain ingredient and nutrition information on all food labeling and created a regulatory framework for allowing manufacturers to receive FDA approval to make certain health claims on foods.²² During the congressional debates on the NLEA, the dietary supplement industry sought an exemption from the new health claims process established by the statute. When Congress was unable to reach an agreement, it included a specific provision that directed FDA to adopt a standard and procedure for evaluating and approving claims on dietary supplements.

After evaluating the issue, FDA adopted the same standard and procedure for dietary

1962

FDA publishes a notice proposing that only nutrients recognized as essential by "competent authorities" be offered for sale. The notice also sets RDA minimum and maximum amounts. FDA withdraws the notice after outcry from the dietary supplement industry.

1966

The FDA proposes regulations pertaining to the labeling and content of "special dietary food products." Strong public opposition causes the regulation to become stayed.

supplements as Congress had adopted in the NLEA for foods.²³ The supplement industry vehemently denounced FDA's regulations as being issued in direct contravention of the intent of Congress, which, it claimed, was to create a more permissive mechanism for the approval of such claims for dietary supplements than for foods.

Subsequently, Senator Orrin Hatch (R-UT) introduced the Health Freedom Act of 1992 (HFA). The HFA outlined many of the same principles as the Dietary Supplement Health and Education Act (DSHEA), which Senator Hatch would introduce a year later. These principles included broadening the definition of dietary supplements, precluding FDA regulation of dietary supplements as drugs, exempting dietary supplements from pre-market approval, and establishing a separate standard for the approval of health claims for dietary supplements.

In 1992, negotiations to compromise on the HFA were unsuccessful, and the date on

which the NLEA dietary supplement health claims regulations were scheduled to become effective was approaching. Senator Hatch proposed a moratorium on the implementation of these regulations. After negotiations, legislation containing a one-year moratorium on health claims, labeling, nutrient content claims and Reference Daily Intake (RDI) regulations for dietary supplements was passed. The stage was set for additional negotiations in the next Congress.²⁴

Notes

1. See I. Scott Bass and Anthony L. Young, "Dietary Supplement Health and Education Act: A Legislative History and Analysis" (Food and Drug Law Institute, 1996) for a discussion of FDA's history of dietary supplement regulation prior to enactment of the Dietary Supplement Health and Education Act in 1994.

2. For more information on elixir sulfanilamide, see <http://www.fda.gov/oc/history/elixir.html>.

3. FFDCA, Pub. L. No. 75-77, 52 Stat. 1040 (1938)

1973

Congress enacts the Proxmire Amendment in response to FDA's published final regulations requiring that most vitamins and minerals with a potency greater than 150% of the RDA be classified as drugs.

Late 1970s

FDA begins regulating supplements as food additives, but courts ultimately reject this approach.

1979

FDA begins regulating supplements as food additives. Industry responds with legal action.

4. FFDCFA, Pub. L. No. 87–261. 76 Stat. 780 (1962).
5. Pub. L. 59–384. 34 Stat. 768 (1906).
6. George Wolf, “A History of Vitamin A and Retinoids,” *Journal of the Federation of American Societies for Experimental Biology*, vol. 10, July 1996, p. 1104.
7. *See, e.g., United States v. Lee*, 107 F.2d 522 (7th Cir. 1939) (affirming conviction of head of vitamin company whose products made false and fraudulent claims, including false claims that the products contained certain vitamins).
8. Pub. L. No. 75–717, 52 Stat. 1040 (1938), as amended 21 U.S.C. § 301, *et seq.*
9. Regulations for the Enforcement of the Federal Food, Drug and Cosmetic Act, 6 Fed. Reg. 5921 (Nov. 22, 1941).
10. Notice of Proposal to Revise Regulations, 27 Fed. Reg. 5815, 5817 (June 20, 1962).
11. Regulations for Enforcement of Federal Food Drug, and Cosmetic Act, Food for Special Dietary Uses, 31 Fed. Reg. 8521 (June 18, 1966).
12. *Id.* at 8525.
13. Order Staying Effective Date of Regulations; Amending Regulations; and Allowing Additional Time for Filing Objections, 31 Fed. Reg. 15730 (Dec. 14, 1966).
14. *See Vitamin and Mineral Products for Over-the-Counter Human Use; Withdrawal of the Proposed Monograph* (“Vitamin Monograph Withdrawal”) 46 Fed. Reg. 57914, 57915 (Nov. 27, 1981).
15. Dietary Supplements of Vitamins and Minerals, 38 Fed. Reg. 20,730, 20,732 (Aug. 2, 1973).
16. *Report of the Commission on Dietary Supplement Labels*, Commission on Dietary Supplement Labels, November 1997, p. 11.
17. Vitamin and Mineral Drug Products for Over-the-Counter Human Use, Establishment of a Monograph; Notice of Proposed Rulemaking, 44 Fed. Reg. 16,126 (Mar. 16, 1979).
18. Vitamin Monograph Withdrawal, 46 Fed. Reg. 57914.
19. *See, e.g., United States v. Article of Food Consisting of 10 Drums, More or Less, of Orotic Acid*, 414 F. Supp. 793 (E.D. Mo. 1976).
20. *See* 21 U.S.C. § 321(s) (definition of food additive); *United States v. 45/194 Kg Drums of Pure Vegetable Oil*, 961 F.2d 808 (9th Cir. 1992).
21. *See United States v. Two Plastic Drums ... Black Currant Oil Batch No. B00SF039, etc.*, 984 F.2d 814 (7th Cir. 1993); and *United States v. 29 Cartons of ... An Article of Food*, 987 F.2d 33 (1st Cir. 1993).
22. Nutrition Labeling and Education Act, Pub. L. No. 101-535, 104 Stat. 2353 (1990).
23. Labeling; Gen. Requirements for Health Claims for Food, 56 Fed. Reg. 60, 537; 60, 539 (Nov. 27, 1991).
24. This moratorium was included in the Prescription Drug User Fee Act of 1992, Pub. L. No. 102-571, 106 Stat. 4500 (1992).

Late 1980s, early 1990s

FDA begins focusing on types of claims being made by dietary supplement products.

1992

Senator Hatch introduces DSHEA.

III. THE WATERSHED: THE DIETARY SUPPLEMENT HEALTH AND EDUCATION ACT OF 1994

At the time of the negotiation and enactment of DSHEA in 1994, the dietary supplement industry was growing and had a loyal grassroots following, but a fraction of the size of the present day market. In 1994, there were roughly 600 manufacturers of dietary supplements in the United States who were making approximately 4,000 different products.¹ Annual sales for these products totaled \$4 billion.² The industry galvanized its customers and organized an energetic and highly-focused effort to have legislation enacted. Customers and lobbyists inundated Congressional offices with letters and phone calls registering opposition to FDA regulation of dietary supplement products. This mobilization of public support eventually led to the enactment of DSHEA, which erects significant hurdles that FDA must overcome prior to taking any regulatory action against a potentially unsafe dietary supplement.

DSHEA sets forth a broad definition of the term *dietary supplement* that includes products, other than tobacco, intended to supplement the diet and that contain a wide range of dietary ingredients, including vitamins, minerals, herbs or other botanicals and amino acids.³ This definition could include almost any product that is ingested that is not “represented for use as a conventional food or as a sole item of a meal or the diet” and is labeled as a dietary supplement, except products making certain claims of effectiveness against diseases and which, as will be discussed, are regulated as drugs.⁴

Significantly, DSHEA explicitly states that dietary supplements are not food additives.

In contrast to the broad authority that the FFDCAs grants FDA over food additives and drugs, DSHEA gives the agency only limited authority to regulate dietary supplements. One fundamental reason for this approach was the general assumption that most dietary supplements were not actually “new” products, but, like many food products, had been used by consumers for a sufficient number of years to provide a level of confidence as to their safety. In essence, Congress determined that these products were essentially foods, and that foods were, *per se*, safe. However, that is not always the case: some dietary supplement products have properties—and risks—associated with their use that go beyond those of traditional foods.

Given this backdrop, and in light of the limited regulatory authority that Congress has granted it over these products in the DSHEA, FDA faces three significant challenges:

1. Dietary supplements may be marketed to the public even though FDA has not reviewed studies and other information and before the agency has determined whether these products have met the statutory safety standard.
2. In order to remove a dietary supplement (other than a new dietary ingredient) from the market, FDA must demonstrate

that the product presents “a significant or unreasonable risk of illness or injury.”⁵

3. When FDA compiles an administrative record to support a regulatory action, the courts ordinarily will give deference to the agency’s decision and will not overturn that decision unless it is arbitrary and capricious. However, in the case of dietary supplements, the court must review the scientific determination *de novo*, giving no deference to FDA’s decision.

In the high-profile case of ephedrine alkaloids, FDA took nearly seven years to remove dietary supplements containing ephedra from the market. By this time, hundreds of reports of serious illness from the use of ephedra-containing products had raised safety concerns (see story in box). Under DSHEA, dietary supplements may be marketed to millions of consumers even after safety concerns have been raised, unless FDA can demonstrate that they are associated with a significant or unreasonable risk of illness or injury.

DSHEA also provided FDA with limited pre-market review authority for “a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury.”⁶ Dietary ingredients are considered to be “new” if they were not marketed in the United States prior to October 15, 1994, the date DSHEA was enacted.⁷ Under the statute, new dietary ingredients are deemed adulterated unless the supplement contains ingredients previously found in food or there is a history of use or “other evidence of safety,” the manufacturer has given FDA 75 days’ notice prior to marketing and has

submitted information that is the basis for the conclusion that the dietary supplement is reasonably expected to be safe.⁸ Ninety days after this information is submitted, FDA must place it on public display, unless it is confidential or considered a trade secret.⁹ As an alternative, a manufacturer may file a petition seeking an order from FDA setting forth the conditions under which a new dietary ingredient will reasonably be expected to be safe.¹⁰

Thus, if FDA deemed all dietary supplements containing engineered nanoparticles to be “new dietary ingredients,” the agency would receive a 75-day notice that the manufacturer intended to market the product and information upon which the manufacturer based its determination that the product is reasonably expected to be safe.¹¹ The manufacturer still has the right, however, to market the product after 75 days unless the FDA demonstrates that “there is inadequate information to provide a reasonable assurance that such ingredient does not provide a significant or unreasonable risk of illness or injury.”¹² However, so little information is available about these products that it is not possible to state with certainty that FDA has the legal authority to deem all dietary supplements made with nanotechnology to be new dietary ingredients. Such an approach would almost certainly be subject to legal challenge in court.

DSHEA also provided FDA with the authority to issue regulations on Good Manufacturing Practices (GMPs).¹³ Issued in 2007, the GMP regulations for dietary supplements are intended to establish process controls that can minimize the likelihood of problems and variances in manufacturing as they occur in order to ensure that dietary supplements are manufactured, packaged,

EPHEDRA: A Decade-Long Saga

As early as 1994, FDA began receiving reports of adverse events associated with the use of ephedra.

FDA first proposed regulating ephedra in 1997, but many of those who commented on that proposal, including the U.S. General Accounting Office, believed that FDA had not developed sufficient evidence to support its proposed actions.

In 2003, after reviewing peer-reviewed scientific literature, thousands of adverse event reports and the conclusion of a study by the RAND corporation reporting “more than 16,000 adverse events associated with the use of ephedra-containing dietary supplements, including heart palpitations, tremors and insomnia,” FDA reopened the comment period on its 1997 proposed rulemaking on ephedra products.

In December 2003, FDA issued a press release recommending that consumers stop buying and using ephedra. FDA banned the sale of dietary supplements containing ephedra in April 2004, when it issued a final rule concluding that such products presented an unreasonable risk of illness or injury.

Dietary supplement manufacturers challenged the ban, but it was upheld by a Tenth Circuit Court of Appeals in 2006. In 2007, the Supreme Court declined to review the ruling.

Sources: <http://www.npr.org/templates/story/story.php?storyId=850679>, <http://www.cfsan.fda.gov/~dms/ds-ephed2.html>, <http://www.fda.gov/oc/initiatives/ephedra/february2004/>

held and labeled in a consistent and reasonable manner. FDA has the authority to find a dietary supplement product adulterated if the manufacturer does not comply with GMP regulations.

Thus, while DSHEA established a regulatory framework for FDA regulation of dietary supplements, FDA has limited pre-market authority over these products, namely pre-market notification for new dietary ingredients and authority to issue GMP regulations. FDA also has no authority to require post-market monitoring or testing and no authority to require a recall of unsafe products. DSHEA did not require the reporting of adverse events, but Congress gave

FDA the authority to require such information in December 2006.¹⁴

DSHEA also created a safe harbor for manufacturers to make certain statements on dietary supplement labels and labeling.¹⁵ While DSHEA did not permit traditional disease-related claims, it does allow “statements of nutritional support” for dietary supplements, which are often referred to as “structure/function claims.” Thus, certain claims about the effect of a dietary supplement on the structure or function of the human body as a result of its use (for example, “Calcium builds strong bones and teeth”) are permissible and will not render the product a drug. For claims that involve

a new statement describing the nutritional function of a nutrient (e.g., “Niacin lowers cholesterol”), the manufacturer must (1) have substantiation that such statement is truthful and not misleading, (2) prominently display a disclaimer that FDA has not evaluated the statement and (3) notify FDA within 30 days of marketing a dietary supplement making such a statement.¹⁶ To the extent that a dietary supplement product containing engineered nanoparticles makes a disease claim, that product will be regulated as a drug and will need to meet FDA standards for safety and efficacy prior to being marketed.

Finally, DSHEA required that dietary supplements list dietary ingredients present in a significant amount and for which a recommendation for daily consumption has been established on the product’s label in a manner similar to that required for foods.¹⁷

Notes

1. Dietary Supplement Health and Education Act, Pub. Law No. 103-417, 108 Stat. 4325, 4326 (1994) (Congressional Findings).

2. *Id.*

3. 21 U.S.C. § 321(ff).

4. 21 U.S.C. § 321(ff)(2)(B).

5. 21 U.S.C. § 342(f)(1)(A).

6. 21 U.S.C. § 342(f)(1)(B).

7. 21 U.S.C. § 350b(c).

8. 21 U.S.C. § 350b.

9. 21 U.S.C. § 350b(a).

10. 21 U.S.C. § 350b(b).

11. To date, FDA only has received one new dietary ingredient notification for a product that may contain engineered nanoparticles. That submission was for an ingredient called “Nano Red Elemental Selenium.” FDA determined that the manufacturer had provided inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury. Neither the submission nor FDA’s response addressed the issue of whether the product actually contained engineered nanoparticles. Letter from Susan J. Walker, M.D., Acting Division Director, Division of Dietary Supplement Programs, to Har Fei, President, Nano Port (USA), August 19, 2003. Available at <http://www.fda.gov/ohrms/dockets/dockets/95s0316/95s-0136-rpt0196-01-vol.144.pdf>.

12. 21 U.S.C. § 342(f)(1)(B).

13. 21 U.S.C. § 342(g)(2). While DSHEA gave FDA the authority to issue GMP regulations for dietary supplements when it was passed in 1994, FDA did not issue final regulations on GMPs until 2007.

14. The Dietary Supplement and Nonprescription Drug Consumer Protection Act became effective in December 2007. Pub. Law No. 109-462, 120 Stat. 3469 (Dec. 22, 2006), codified at 21 U.S.C. § 379aa-1, *et seq.* Under that statute, manufacturers, packers and distributors of dietary supplements whose names appear on the label must report any serious adverse event within 15 days of receipt of a report. A *serious adverse event* is defined as one that results in death, a life-threatening experience, inpatient hospitalization, a persistent or significant disability or incapacity or a congenital anomaly or birth defect, or that requires medical or surgical intervention to prevent such an outcome. 21 U.S.C. § 379aa-1(a)(2). Records of these adverse event reports must be kept for six years. 21 U.S.C. § 379aa-1(e).

15. 21 U.S.C. § 343(r).

16. 21 U.S.C. § 343(r)(6).

17. 21 U.S.C. § 343(s).

IV. RESOURCE CONSTRAINTS HAMPER FDA'S CAPABILITY TO REGULATE DIETARY SUPPLEMENTS

In recent years, criticism has mounted regarding FDA's inability to keep pace with emerging science and technology, ranging from genomics to nanotechnology. In December 2006, FDA Commissioner Dr. Andrew von Eschenbach requested that FDA's Science Board establish a Subcommittee on Science and Technology to assess whether FDA's scientific and technological infrastructure could support current and future regulatory needs.

The 33-member subcommittee issued its report, "FDA Science and Mission at Risk: Report of the Subcommittee on Science and Technology" (Science Board Subcommittee Report), in November 2007.¹ The Science Board Subcommittee Report noted that aspects of recent advances in nanotechnology are revolutionizing both science and biology and are a part of the changing nature of science. The report, which had panel members' unanimous approval, identified serious deficiencies in the present system, including too few scientists who understand emerging science and technology, a flawed system for regulating imports into the United States and an information infrastructure that was deeply flawed and unable to support various parts of the agency.²

While the subcommittee's original mandate had been to evaluate the scientific infrastructure without regard to resource concerns, the panel ultimately found that the lack of scientific expertise and other technological shortcomings were intertwined with FDA's ongoing lack of resources.

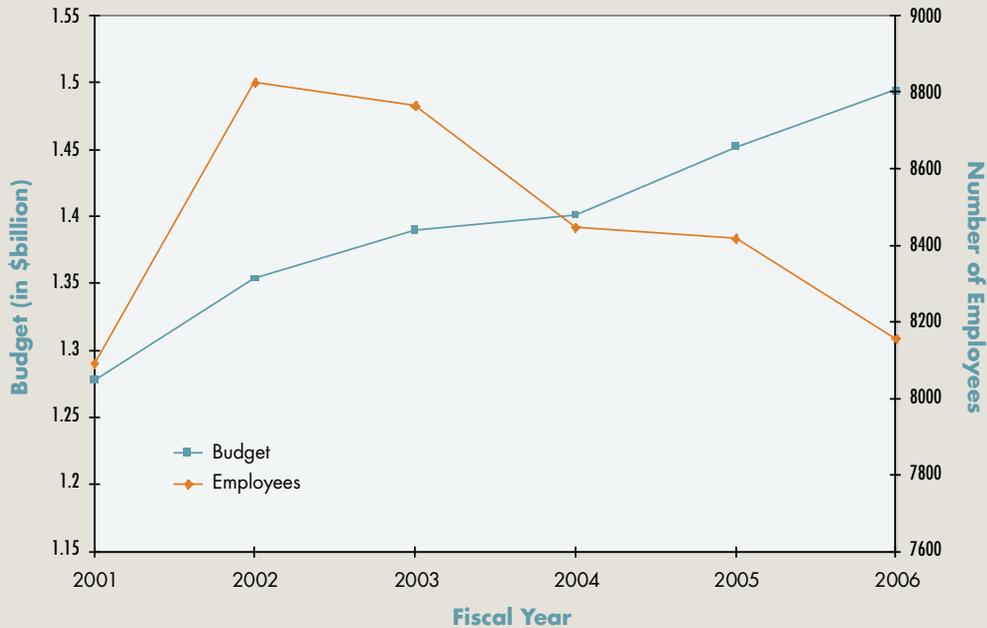
The subcommittee further noted that "the capacity for science to support the FDA mission is dangerously constrained from the effects of a long period of expanding agency mandates and responsibilities, chronic underfunding, the extraordinary advance of scientific discoveries, the complexity of new products and claims submitted to FDA for pre-market approval, the emergence of challenging safety problems, and the globalization of the industries that FDA regulates."³ It concluded that FDA cannot fulfill its mission because its scientific base has eroded, its scientific workforce does not have sufficient capacity and capability and its information technology infrastructure is inadequate.⁴

Several of the limitations identified by the subcommittee are directly relevant to the use of engineered nanoparticles in dietary supplements:

- The development of medical products based on "new science" cannot be adequately regulated by FDA.
- There is insufficient capacity in modeling, risk assessment and analysis.
- The FDA science agenda lacks a coherent structure and vision, as well as effective coordination and prioritization.

The report also addressed resources available for the regulation of dietary supplements, which are the responsibility of the Office of Nutritional Products, Labeling, and Dietary Supplements in the Center

Figure 1. FDA budget and staff, FY2001–FY2006.



Sources: www.fda.gov, http://www.bestplacetowork.org/BPTW/rankings/agency.php?code=HE36&q=scores_subcomponent, <http://69.20.19.211/oc/oms/ofm/accounting/cfo/2002/FinPerf.htm>

for Food Safety and Applied Nutrition (CFSAN). It stated that:

Efforts to strengthen the food safety mission of FDA must not adversely impact CFSAN's legislatively mandated mission to address the science behind nutrition, and the safety of dietary supplements and cosmetic safety. In fact, these areas must be revitalized and prioritized independently of both food and drug issues to redress decades of neglect before a serious crisis emerges. The dietary supplement industry has grown to more than \$20 billion in annual sales, and millions of Americans use those products every day. But the legislation authorizing FDA regulation of these products has never been funded, the practical effect being

that the products and their health claims go essentially unregulated. The same can be said of the cosmetics industry, which has more than \$60 billion in annual sales, but is overseen by a staff of 14 supported by a \$3.5 million budget. This industry is rapidly integrating nanotechnology for product delivery and yet, very limited expertise in this newly emerging area of science exists in the entire FDA.⁵

The CFSAN office regulating dietary supplements has seen a dramatic reduction in resources in recent years. While the number of full time equivalent employees currently dedicated to oversight of dietary supplement products is difficult to detect (particularly since portions of these efforts

are spread throughout the Agency, including inspectors and scientists), current and former CFSAN staff uniformly confirm that the resources and staffing for this important area have always been woefully inadequate and have decreased dramatically in recent years. For example, according to one former CFSAN official, in 2003, there were only three-and-a-half full time staff equivalents reviewing drug and structure/function claims, now there are only two. Moreover, the dietary supplement program only has four employees dedicated to the review of adverse reaction data from dietary supplement use.

As noted earlier, the dietary supplement industry is a roughly \$21 billion industry. Nonetheless, a small staff of CFSAN employees must:

- review pre-market notifications and information submissions (91 new dietary ingredient notifications in FY 2007)⁶
- check health claims and promotional materials (more than 2500 structure/function claims notifications in FY 2007);⁷ and
- monitor adverse event reports

Even in the face of a public outcry for more resources for FDA's dietary supplement program and for FDA's scientific infrastructure to review nanotechnology, the resource deficiency is likely to persist.

President Bush's fiscal year 2009 budget for CFSAN provides inadequate resources across the board, with a specific shortfall in CFSAN programs that are unrelated to food safety, including those for dietary supplements. FDA's dietary supplement program is critically under-funded and unable to meet even current demands; there is no capacity to meet the demands associated with the ever-increasing number of products on the market being manufactured with emerging technologies, including nanotechnology.

Notes

1. "FDA Science and Mission at Risk: Report of the Subcommittee on Science and Technology," U.S. Food and Drug Administration. *available at* http://www.fda.gov/ohrms/dockets/AC/07/briefing/2007-4329b_02_01_FDA%20Report%20on%20Science%20and%20Technology.pdf.

2. *Id.* at 7.

3. FDA Science and Mission at Risk: Report of the FDA Science Board's Subcommittee on Science and Technology. Estimated Resources Required for Implementation, Gail Cassell, Ph.D., on behalf of the Subcommittee and its members. February 25, 2008. at p. 7. *available at*: http://energycommerce.house.gov/Press_110/022508.ScienceBoardReport.EstimatedResources.pdf.

4. *Id.*

5. *Id.* at 24.

6. See Narrative accompanying FDA Foods Program Resources Table for FY 2009 FDA Budget, *available at* <http://www.fda.gov/oc/oms/ofm/budget/2009/toc.htm>.

7. *Id.*

V. LIMITATIONS ON FDA'S AUTHORITY AND REASONS FOR REGULATING DIETARY SUPPLEMENTS CONTAINING ENGINEERED NANOPARTICLES

The FDA's ability to regulate the safety of dietary supplements containing engineered nanoparticles is severely limited by resources and by the agency's statutory authority. Three main problems need to be addressed:

1. FDA does not have the capacity to identify nano-based dietary supplements that are being developed and marketed, unless manufacturers submit to the pre-market notification process for new dietary ingredients.

This difficulty exists for two reasons: 1) the constantly emerging nature of nanotechnology; and 2) FDA's lack of authority to require and collect information about dietary supplement products. It is a particular challenge to evaluate the impact of FDA's lack of regulation in this area when the scope of products that fall into this category is unknown and constantly evolving.

2. To the extent that FDA is aware of nano-based dietary supplements, it has little regulatory authority over them.

FDA has limited authority to regulate dietary supplements: there is no pre-market review or approval; there is no mandatory pre- or post-market testing, and the agency carries the

burden of establishing that a dietary supplement product is unsafe. Only when a product contains a "new dietary ingredient" must the manufacturer notify the agency prior to marketing. While this gives FDA some ability to review information about the product before it is marketed, the agency still must demonstrate that the manufacturer has not provided adequate information to provide a reasonable assurance that the ingredient does not present a significant or unreasonable risk of illness or injury. Moreover, if history is any guide, attempts by FDA to take such action would be strongly contested by the industry and litigated in court.

3. Even if it were granted increased regulatory authority over these products, FDA lacks the scientific expertise and resources to deal with nanotechnology in supplements.

The absence of adequate resources is a separate and distinct barrier to the regulation of dietary supplements in general and to dietary supplements containing engineered nanoparticles in particular. Without scientists who understand the technology and the scientific hardware and software necessary to review the data submitted, the unpredictable nature of nanotechnology cannot be fully understood.

VI. RECOMMENDATIONS

Based on the foregoing, in order to prevent a potential harm to public health stemming from the use of engineered nanoparticles in dietary supplement products, we make the following recommendations.

1. Product Registration. Congress should give FDA the authority to require the registration of all dietary supplement products containing engineered nanoparticles that are being marketed and sold in the United States.

2. Safety Standards. Congress should give FDA the authority to establish safety standards for dietary supplements containing engineered nanoparticles. (Standard development may be informed by studies done for FDA by external advisory bodies.)

3. Market Review. Congress should give FDA the authority to undertake a systematic review of all dietary supplements containing engineered nanoparticles that are on the market at the time of the enactment of new legislation and to require, within a specified period, that the manufacturers of these products demonstrate that they are safe or remove them from the market.

4. Pre-Market Testing. Congress should give FDA the authority to require that manufacturers of dietary supplements containing engineered nanoparticles that are not on the market at the time of the enactment of new legislation perform studies to establish

that their products meet FDA safety standards prior to being approved for sale in the United States. FDA should have the authority to waive pre-market review of safety data for specific classes of dietary supplements containing engineered nanoparticles where it finds that such a waiver is consistent with the protection of the public health.

5. Adverse Event Reporting. Congress should give FDA the authority to require that manufacturers report to FDA all adverse events including those that do not qualify as serious events, that are associated with dietary supplements containing engineered nanoparticles. FDA should also have the authority to require that manufacturers keep records of all adverse events, serious and non-serious, for six years. FDA should make this information available to the public (after deletion of personal, identifying information).

6. Increased Information. The Institute of Medicine (or another appropriate body) should commission a survey of currently marketed dietary supplement products that contain engineered nanoparticles and provide guidance as to whether and what safety testing should be performed on those products. The same results should be provided to FDA.

7. Increased Resources. Congress should provide FDA with the resources necessary to regulate dietary supplements containing engineered nanoparticles under the new regulatory authority proposed above.

VII. CONCLUSION

The use of engineered nanoparticles in dietary supplements raises serious questions about whether such products are safe. Congress has generally allowed dietary supplements to be marketed without any pre-market demonstration of safety, based largely on the assumption that these products have been used for many years. There is, however, no basis for concluding that dietary supplements containing engineered nanoparticles are safe. While it is not possible to determine the prevalence of dietary supplements containing engineered nanoparticles, it is likely that the public's exposure to these products will grow sig-

nificantly in the next several years.

Congress should adopt legislation granting FDA the authority to collect additional information about these products and to ensure that they are tested for their effects on human health. Such legislation should prohibit the sale of new dietary supplements containing engineered nanoparticles until they have been demonstrated to be safe, and it should provide FDA with sufficient resources to regulate these products. Until Congress acts, consumers who take dietary supplements containing engineered nanoparticles will be at additional, unknowable, and potentially serious risk.

APPENDIX: NANOTECHNOLOGY-BASED DIETARY SUPPLEMENTS (AS OF MARCH 2008)

Name of Supplement	Manufacturer	Web Site
Aquanova® Novasol®	Aquanova® GmbH	www.aquanova.de/index.php?site=index.html&dir=&nav=50
ASAP Health Max 30	American Biotech Labs	www.amsilver.com/ASAPHealthMax30.html
Bio-Sim	Nano Health Solutions	www.fulvic.org/html/nano_bio-sim.html
C.I.E.A.N. Products	SportMedix, Inc.	www.sportmedix.com/index.php?th=cat&cat_id=51
Colloidal Silver Cream	Skybright Natural Health	www.skybright.co.nz/product_info.php?cPath=24&products_id=102
Colloidal Silver Liquid	Skybright Natural Health	www.skybright.co.nz/product_info.php?cPath=32&products_id=139
Galaxia Nano Technology Limited™ Nano Oxygen Supply Living East Cup	Galaxia Nano Technology Limited™	http://64.233.179.104/translate_c?hl=en&langpair=zh%7Cen&u=dongfangxinghe.cn.alibaba.com/athena/offerdetail/sale/dongfangxinghe-0-16598349.html
Galaxia Nano Technology Limited™ Nano Oxygen Supply Wateractivater	Galaxia Nano Technology Limited™	http://64.233.179.104/translate_c?hl=en&langpair=zh%7Cen&u=dongfangxinghe.cn.alibaba.com/athena/offerdetail/sale/dongfangxinghe-0-16492181.html
Humic and Fulvic Acids	Nano Health Solutions	www.fulvic.org/html/nano_humic__fulvic_acid.html
LifePak® Nano	Pharmanex®	www.pharmanex.com/corp/product/lifepak/lifepaknano.shtml
Lypo-Spheric™ Vitamin C	LivOn Labs	www.livonlabs.com/
MaatShop™ Bio-Sim	MaatShop™	http://spiritofmaat.com/maatshop/n2_biosim.htm
MaatShop™ Crystal Clear Nano Silver	MaatShop™	http://spiritofmaat.com/maatshop/n2_silver.htm
MaatShop™ Nano Skin Rejuvenator	MaatShop™	http://spiritofmaat.com/maatshop/n2_skin.htm

Name of Supplement	Manufacturer	Web Site
MaatShop™ Nano-2+	MaatShop™	http://spiritofmaat.com/maatshop/n2_nano2.htm
MesoCopper®	Purest Colloids, Inc.	www.purestcolloids.com/mesocopper.htm
Mesogold®	Colloids for Life LLC	www.colloidsforlife.com/Mesogold_colloidal_gold.html
MesoGold®	Purest Colloids, Inc.	www.purestcolloids.com/mesogold.htm
Meso-Iridium™	Purest Colloids, Inc.	www.purestcolloids.com/mesoiridium.htm
MesoPalladium™	Purest Colloids, Inc.	www.purestcolloids.com/mesopalladium.htm
MesoPlatinum®	Purest Colloids, Inc.	www.purestcolloids.com/mesoplatinum.htm
MesoSilver®	Purest Colloids, Inc.	www.purestcolloids.com/mesosilver.htm
MesoTitanium™	Purest Colloids, Inc.	www.purestcolloids.com/mesotitanium.htm
MesoZinc™	Purest Colloids, Inc.	www.purestcolloids.com/mesozinc.htm
NANO B-12 Vitamin Spray	Nutrition By Nanotech, LLC	www.nutritionbynanotech.com/absorption.htm
Nano Calcium/Magnesium	Mag-I-Cal.com	www.mag-i-cal.com/calciummagnesium.htm
Nanoceuticals™ Artichoke Nanoclusters	RBC Life Sciences®, Inc.	http://813312.royalbodycare.com/Products.aspx?ItemID=118
Nanoceuticals™ Hydracel	RBC Life Sciences®, Inc.	http://813312.royalbodycare.com/Products.aspx?ItemID=142
Nanoceuticals™ Microbright Tooth Powder	RBC Life Sciences®, Inc.	http://813312.royalbodycare.com/Products.aspx?ItemID=152
Nanoceuticals™ Microhydrin® Products	RBC Life Sciences®, Inc.	http://813312.royalbodycare.com/Products.aspx?ItemID=161
Nanoceuticals™ Silver 22	RBC Life Sciences®, Inc.	http://813312.rbc Lifesciences.com/Products.aspx?ItemID=430

Name of Supplement	Manufacturer	Web Site
Nanoceuticals™ Spirulina Nanoclusters	RBC Life Sciences®, Inc.	http://813312.royalbodycare.com/Products.aspx?ItemID=183
Nanosiliceo Kapseln	Neosino	www.neosino.com/index.php?id=produkte
NanoSil™.10	Greenwood Consumer Products	www.nanosil10.com/products.html
Nano-Sized Self-assembled Liquid Structures (NSSL) Supplements	NutraLease Ltd.	www.nutralease.com/technology.asp
NanoSlim	NanoSlim	www.nanoslim.com/
Nanotrim™	NanoNutra™ Labs	www.nanonutra.com/nanotrim.html
Nutri-Nano™ CoQ-10 3.1x Softgels	Solgar	www.naturalgoodnessmarket.com/list2.cfm?cat=60
SilverBiotics	American Biotech Labs	www.silverbiotics.com/
Silvix3®	Natural Care® Products	www.enaturalcare.com/prod_silv.html
Sovereign Silver™	Natural-Immunogenics Corp.	www.natural-immunogenics.com/silver_why_sovereign.php
Spray for Life® Vitamin Supplements	Health Plus International®, Inc.	www.healthplusintl.com/products.html
Utopia Silver Supplements® Advanced Colloidal Silver	Utopia Silver Supplements®	www.utopiasilver.com/products/silver/