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Between a Rock and a Hard Place: FDA's Regulation of Dietary Ingredients in Dietary Supplements

by

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BETWEEN A ROCK AND A HARD PLACE: FDA'S REGULATION OF DIETARY INGREDIENTS IN DIETARY SUPPLEMENTS

*Cassandra A. Soltis**

I. INTRODUCTION

The Dietary Supplement Health and Education Act of 1994 (DSHEA)[1] was passed by Congress, in part, to encourage the use of dietary ingredients in dietary supplements and increase the availability of such products in the marketplace.[2] To facilitate the route-to-market process, DSHEA exempted dietary ingredients in dietary supplements from the definition of "food additive" so that the dietary ingredients need not be either Food and Drug Administration (FDA)-approved food additives or generally recognized as safe substances, both of which are costly and time-consuming processes.[3] FDA has therefore had the difficult duty of balancing its mandate to protect the public's health, which often requires more restricted access to products, with the spirit of DSHEA, which promotes increased consumer access to dietary supplements. FDA's efforts in this regard have been criticized by industry due to the agency's narrow interpretation of key provisions of DSHEA. Although FDA's actions and policy are undoubtedly intended to ensure that only safe dietary ingredients are

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1. Pub. L. No. 103-417, 108 Stat. 4325 (codified as amended in scattered sections of 21 U.S.C.).

2. *See* Pharmanex v. Shalala, 221 F.3d 1151 (10th Cir. 2000) (referring to DSHEA's general purpose "to assuage the regulatory burdens on the dietary supplement industry").

3. *See* 21 U.S.C. § 321(s)(6) (2000) (excluding dietary supplements from the definition of food additives).

available to consumers, the dietary supplement industry is frustrated and senses a shift in the regulatory climate towards that of the pre-DSHEA era.

In order to fully understand the issues concerning FDA's regulation of dietary ingredients in dietary supplements under DSHEA, one must first understand the events leading up to the law's passage. This paper will begin by examining the impetus for the legislation, followed by a discussion of requirements for dietary ingredients in dietary supplements and how FDA currently regulates these substances in practice. This paper will also examine some unanswered questions concerning the interpretation of the new dietary ingredient provisions of DSHEA.

II. THE FEDERAL FOOD, DRUG, AND COSMETIC ACT PRIOR TO DSHEA

Since 1938, when the Federal Food, Drug, and Cosmetic Act (FDCA) was passed by Congress, "food" has been defined as "(1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article."[4] In 1958, the Food Additives Amendment amended FDCA to define the term "food additive."[5] The purpose of the Food Additives Amendment was "(1) [t]o protect the health of consumers by requiring manufacturers of food additives and food processors to pretest any potentially unsafe substances which are to be added to food; and (2) to advance food technology by permitting the use of food additives at safe levels."[6]

The 1958 Food Additives Amendment defined a "food additive," in pertinent part, as

> any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food . . . if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use.[7]

Essentially, this "food additive" definition, which remains in FDCA today, requires any food or food ingredient meeting the definition to be approved by FDA prior to marketing *unless* the substance falls within one of the statutory exemptions from the definition. Among the substances exempt

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4. FDCA § 201(f), Ch. 675, 52 Stat. 1040 (1938) (codified at 21 U.S.C. § 321(f)).

5. Food Additives Amendment of 1958, Sec. 2, § 201(s), 72 Stat. 1784 (1958) (codified as amended at 21 U.S.C. § 321(s)).

6. H.R. REP. NO. 85-2284, at 1 (1958).

7. 21 U.S.C. § 321(s) (2000). The law exempts additional articles from the "food additive" definition, including pesticides. *Id.* § 321(s)(1)-(2).

from regulation as food additives by the 1958 Food Additives Amendment are food ingredients found by qualified experts to be "generally recognized as safe" (GRAS)[8] for their intended use based on scientific procedures or common use in food prior to 1958.[9] Thus, under the regulatory framework of pre-1958 FDCA, a food such as a peach logically was not a "food additive"; the peach itself was a food and need not be FDA-approved or found to be GRAS for its intended use. However, the 1958 Food Additives Amendment defined "food additive" so broadly that if a peach was added to sugar and flour to make a cobbler, it could be viewed as a "food additive" unless, of course, it qualified for one of the exemptions from the food additive definition, such as GRAS.[10]

A. Requirements for Food Additives and GRAS Substances

It is illegal to use a food additive unless FDA has first approved its use by issuing a food additive regulation.[11] A company may ask FDA to issue a food additive regulation by filing a food additive petition.[12] Obtaining the issuance of a food additive regulation can be a difficult, drawn out process.[13] A food additive petition must contain extensive information about the identity of the substance, its intended use, and, perhaps most importantly, its safety.[14] The food additive safety standard requires "a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use."[15] Determining that a food additive is safe requires only technical evidence of safety.[16] Although FDCA requires FDA to issue an order ruling on food additive petitions within ninety days after the date of a petition's filing, FDA may take five or more years to promulgate an approving food additive regulation.[17]

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8. A discussion of the term "generally recognized as safe" is provided *infra* Section II.A.

9. 21 U.S.C. § 321(s). FDA published a non-comprehensive compilation of common food ingredients that the agency listed or affirmed as GRAS. 21 C.F.R. pts. 182, 184 & 186 (2005).

10. *See* 21 U.S.C. § 321(s).

11. *Id.* §§ 321(s), 342(a)(2)(C), 348(a) (2000).

12. *Id*. § 348(b)-(c).

13. *See* Stephen H. McNamara & A. Wes Siegner, Jr., *FDA Has Substantial and Sufficient Authority to Regulate Dietary Supplements*, 57 FOOD & DRUG L.J. 15, 16 (2002) (referring to a Senate Committee discussion regarding the "prohibitive costs and delays" to obtain food additive approval).

14. 21 U.S.C. § 348(b)(2); 21 C.F.R. § 171.1(c) (2005).

15. 21 C.F.R. § 170.3(i) (2005).

16. Substances Generally Recognized as Safe, 62 Fed. Reg. 18,937, 18,940 (Apr. 17, 1997).

17. McNamara & Siegner, *supra* note 13, at 16 (quoting a Senate Committee finding that FDA approval of a food additive petition generally takes 2 to 6 years).

Although GRAS substances do not need FDA approval, establishing GRAS status that withstands FDA challenge can be a difficult task. In order for a substance to be GRAS, there must be "common knowledge about the substance throughout the scientific community knowledgeable about the safety of substances directly or indirectly added to food."[18] A substance may be generally recognized as safe by qualified experts based on scientific procedures or on common use in foods prior to January 1, 1958.[19] GRAS status based on scientific procedures requires the "same quantity and quality of scientific evidence as is required to obtain approval of a food additive regulation," but it must "ordinarily be based upon published studies which may be corroborated by unpublished studies and other data and information."[20] GRAS status based on common use in foods must "ordinarily be based upon generally available data and information."[21] "[A] determination that a particular use of a substance is GRAS requires both technical evidence of safety and a basis to conclude that this technical evidence of safety is generally known and accepted."[22] The data and information relied upon must be generally available *and* there must be evidence of a consensus among qualified experts about the safety of the substance for its intended use.[23]

Although an FDA regulation provides that companies may petition FDA to affirm a substance as GRAS, in practice, FDA no longer accepts such petitions.[24] Instead, FDA accepts voluntary GRAS "notifications" pursuant to a 1997 proposed rule.[25] Nevertheless, there is no requirement of law that a substance that is in fact GRAS for its intended use be so recognized by FDA in a regulation or otherwise before it may be used in

18. 21 C.F.R. § 170.30(a) (2005).

19. *See* 21 U.S.C. § 321(s); 21 C.F.R. § 170.30(a).

20. 21 C.F.R. § 170.30(b). This contrasts with food additives, where the data supporting the finding of safety are not required to be peer-reviewed and published in a scientific journal. 62 Fed. Reg. at 18,941.

21. 21 C.F.R. § 170.30(c)(1).

22. 62 Fed. Reg. at 18,940.

23. *See id.* For food additives, it is irrelevant whether the safety data are available to the scientific community for peer review. *Id*. at 18,941.

24. 21 C.F.R. § 170.35(c)(1) (2005).

25. 62 Fed. Reg. at 18,938. FDA's proposal would replace the GRAS affirmation petition process with a notification procedure, whereby companies would "provide specific information about a GRAS determination." *Id*. at 18,941. However, FDA stated that "[b]etween the time of publication of this proposal and any final rule based on this proposal, FDA invites interested persons who determine that a use of a substance is GRAS to notify FDA of such GRAS determinations." *Id*. at 18,954.

food.[26] In other words, companies have the right to make their own GRAS determinations without even notifying FDA.[27]

B. FDA's Application of the Food Additive Definition to Dietary Supplements

Prior to DSHEA, in the absence of a food additive regulation authorizing use of a substance, FDA commonly challenged a dietary supplement ingredient as not GRAS and, therefore, an unapproved food additive that rendered the product adulterated.[28] For example, FDA viewed the non-traditional dietary supplement ingredients as peaches that were part of peach cobbler (i.e., food additives) rather than as peaches (i.e., whole foods) themselves. Many of these non-traditional products were not marketed in the United States because FDA either refused to respond to GRAS affirmation petitions pertaining to the products or seized the products upon import into the United States, alleging that the products contained non-GRAS substances that were unapproved food additives. FDA successfully litigated a number of product seizure actions and built a body of case law favorable to the agency's position. FDA argued that the addition of *any* food ingredient to another ingredient in a dietary supplement product subjected the product to the "food additive" pre-market approval requirements unless the manufacturer could prove in court that all of the ingredients in question were either approved food additives or GRAS.[29]

Companies marketing these non-traditional dietary supplement products were usually unable to convince the courts that their products' ingredients were GRAS, even when the ingredients at issue were essentially the same as staple foods. This controversy ultimately came to a head with protracted litigation over non-traditional dietary supplement products consisting of evening primrose oil (EPO)[30] and black currant oil (BCO),[31]

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26. *See* 21 C.F.R. § 182.1(a) (stating that it would be "impracticable" for FDA's regulations to identify all GRAS substances).

27. FDA has historically been doubtful with respect to GRAS determinations that are not FDA-affirmed or notified. Thus, it is prudent that companies making their own GRAS determinations have the requisite data, tests, and expert statements supporting the GRAS determination. *See generally* 21 C.F.R. § 170.30.

28. *See* Ali Sachani, Comment, *Warning: Over-Consumption of This Product May Be Harmful to Your Health! Applying the Proposed Canadian Natural Health Product Regulatory Framework to Clarify the Level of Substantiation Required for Dietary Supplement Claims in the United States*, 9 SW. J. L. & TRADE AM. 391, 396 (2002-2003).

29. *See, e.g.*, Nutrilab, Inc. v. Schweiker, 713 F.2d 335, 337 (7th Cir. 1983).

30. EPO is an oil derived from the seeds of the evening primrose plant. *See* University of California-Berkeley, *Wellness Letter*, Nov. 2003, *at* http://www.berkeleywellness.com/html/ds/dsEveningPrimrose.php (lasted visited Feb. 15, 2007).

31. BCO is a plant seed oil. *See* PDR Health, *Black Currant Oil*, *at* http://pdrhealth.com/drug_info/nmdrugprofiles/nutsupdrugs/bla_0036.shtml (last visited Feb. 15, 2007).

which FDA challenged as unapproved food additives. In these and other cases, FDA's use of the food additive requirements to try to prevent unconventional dietary supplements from coming to the market helped lead to the passage of DSHEA.

1. The EPO Litigation

In 1985, FDA issued an Import Alert for EPO.[32] The alert required that all imports of EPO be detained, and if the product was intended for food use, the "charge" for the detention must be that the product contains EPO, "an unsafe food additive within the meaning of section 409" of FDCA.[33] A few years later, FDA initiated two seizure actions of EPO products alleging, among other things, that EPO was not GRAS and was, therefore, an unapproved food additive.[34] The products contained EPO and other ingredients, such as Vitamin E and fish oil.[35]

One of the cases was appealed to the Ninth Circuit, where the manufacturer argued that EPO was GRAS and, therefore, was not an unapproved food additive.[36] However, the court noted that

> Some of the data considered by [the manufacturer's] experts concerns EPO's use as a drug and not as a dietary supplement. Other data was based on unpublished materials, which were not subjected to peer evaluation. Thus, the opinions of [the manufacturer's] experts were contaminated by their consideration of unsuitable evidence.[37]

Affirming the district court's summary judgment finding, the court concluded that EPO was a food additive and that the manufacturer "failed to show that EPO is" GRAS.[38]

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32. FDA, IMPORT ALERT NO. 66-04: OIL OF EVENING PRIMROSE (Feb. 12, 1985).

33. *Id*. at 1. If the product was intended for drug use and contained labeling, the charge would instead be that the product is a new drug without an approved new drug application. *Id.* As noted in Section II, a substance is a "food additive" if (1) the intended use of the substance results or may reasonably be expected to result in its becoming a component or otherwise affecting the characteristics of any food and (2) the substance is not eligible for one of the exemptions from the food additive definition. A "food additive" is deemed unsafe and, therefore, adulterated unless FDA has promulgated a regulation allowing its use. 21 U.S.C. §§ 342(a)(2)(C)(i), 348(a).

34. United States v. 45/194 Kg. Drums of Pure Vegetable Oil, No. CV 89-73 MRP, 1989 WL 248572 (C.D. Cal. Nov. 30, 1989), *aff'd*, 961 F.2d 808 (9th Cir. 1992); United States v. 21 Approximately 180 Kg. Bulk Metal Drums, 761 F. Supp. 180 (D. Me. 1991).

35. *45/194 Kg. Drums of Pure Vegetable Oil*, 961 F.2d at 810; *21 Approximately 180 Kg. Bulk Metal Drums*, 761 F. Supp. at 182.

36. *45/194 Kg. Drums of Pure Vegetable Oil*, 961 F.2d at 812.

37. *Id*. at 813.

38. *Id*.

2. The BCO Litigation

In 1992 and 1993, FDA challenged the marketing of BCO dietary supplement products in which BCO was encased in capsules that consisted of gelatin and glycerin.[39] Although BCO was a pure food, like peaches, FDA argued in court that BCO was a "food additive" because the product consisted of three components–BCO, gelatin, and glycerin–and, therefore, each component, including BCO, must be either an FDA-approved food additive or a GRAS substance.[40] In one of the cases, however, FDA acknowledged "that if the BCO alone was marketed in bottles for teaspoon consumption, it would not be a food additive."[41]

The courts thus had to decide whether pure BCO encased in capsules of gelatin and glycerin is deemed to be a pure food, like peaches, or a food additive. If BCO was found to be a pure food, it would not need to be FDA-approved or qualify for the GRAS exemption from the food additive definition.[42]

Both the United States Court of Appeals for the Seventh Circuit and the First Circuit held in favor of the BCO manufacturers, finding that FDA erred in applying the food additive provisions (and, therefore, the GRAS exemption) to BCO. The Seventh Circuit stated that "simply becoming a 'component' of food does not, in and of itself, satisfy the definition of a food additive. To be a food additive, a substance must not only be added to food, but it must also have the purpose or effect of altering a food's characteristics."[43] The court continued, stating:

> [I]t would seem, [in FDA's view, that] even the addition of water to food would make the food a food additive. The only justification for this Alice-in-Wonderland approach [i.e., FDA's "food additive" allegation] is to allow the FDA to make an end-run around the statutory scheme and shift to the processors the burden of proving the safety of a substance in all circumstances.[44]

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39. United States v. 29 Cartons of . . . an Article of Food, 987 F.2d 33, 35 (1st Cir. 1993); United States v. Two Plastic Drums of An Article of Food, 984 F.2d 814, 816 (7th Cir. 1993).

40. *29 Cartons of . . . an Article of Food*, 987 F.2d at 36; *Two Plastic Drums of An Article of Food*, 984 F.2d at 816.

41. *Two Plastic Drums of an Article of Food*, 984 F.2d at 816.

42. Pure foods, like peaches, are subject to the adulteration provision of FDCA, which provides, in pertinent part, that a "food shall be deemed to be adulterated . . . [i]f it bears or contains any poisonous or deleterious substance which may render it injurious to health." 21 U.S.C. § 342 (2000).

43. *Two Plastic Drums of An Article of Food*, 984 F.2d at 818.

44. *Id*. at 819.

The First Circuit, agreeing with the Seventh Circuit's opinion,[45] noted that "[t]he proposition that placing a single-ingredient food product into an inert capsule as a convenient method of ingestion converts that food into a food additive perverts the statutory text, undermines legislative intent, and defenestrates common sense. We cannot accept such anfractuous reasoning."[46]

The end result of this litigation was that the BCO dietary supplements remained legally on the market. The EPO dietary supplements were reintroduced to the market based on the BCO precedents, which found that FDA could not regulate a single ingredient in a capsule as a "food additive."[47] However, FDA's erroneous application of the food additive provisions to dietary supplements resulted in much wider repercussions. Industry and consumers complained to Congress about FDA's stance on dietary supplements.[48] Congress determined that it needed to pass DSHEA so as to prevent FDA from applying the food additive definition to dietary supplements:

> Although a fair reading of the current statute [i.e., the "food additive" provisions of FDCA], as most recently interpreted by two United States courts of appeal, should make . . . amendment [of FDCA by DSHEA] unnecessary, the committee has heard testimony that the FDA has rejected these [judicial] holdings. The committee is therefore concerned that the FDA will persist in such litigation, and thereby continue to subject small manufacturers to the choice of abandoning production and sale of lawful products, or accepting the significant financial burden of defending themselves against baseless lawsuits [brought by FDA].[49]

Industry and consumer frustration, as well as the views set forth in the Senate report, prompted Congress to amend FDCA in order to change the regulatory scheme for dietary supplement products and their ingredients.

C. The Dietary Supplement Health and Education Act of 1994

Congress passed DSHEA with the intent to facilitate the process by which companies may market dietary supplements and at the same time

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45. *29 Cartons of . . . an Article of Food*, 987 F.2d at 37 ("Given the existence of a cogent, well-reasoned, eminently correct opinion closely on point, we embrace [the Seventh Circuit's opinion].").

46. *Id*. at 39.

47. To prevent FDA from asserting that EPO was a food additive, the EPO products were reformulated so that they did not include vitamin E or any other dietary ingredients.

48. In testimony on DSHEA, Representative Richardson noted that the popularity of vitamins and other dietary supplements with consumers "led to an unprecedented outpouring of support for their continued availability in the marketplace." 103 CONG. REC. E919 (daily ed. Apr. 7, 1993) (statement of Rep. Richardson).

49. S. REP. NO. 103-410, at 21 (1994).

provide mechanisms for ensuring that such products will be safe.[50] Significantly, in DSHEA Congress expressly excluded "ingredient[s] . . . intended for use in, a dietary supplement" from regulation as food additives.[51] As a result, FDA could no longer demand that dietary ingredients in dietary supplements be FDA-approved food additives or GRAS substances.

DSHEA defined the term "dietary supplement" very broadly so as to include, in addition to vitamins and minerals, non-traditional dietary ingredients such as herbs and botanicals that in the past were frequently challenged by FDA as unapproved food additives or non-GRAS substances.[52] To address the safety of dietary ingredients and supplements, DSHEA added a new standard to the adulteration provisions of FDCA.[53] The new standard provides that a dietary supplement will be adulterated if it "presents a significant or unreasonable risk of illness or injury under . . . conditions of use recommended or suggested in labeling . . . or under ordinary conditions of use," if no conditions of use are recommended.[54] Through DSHEA, Congress also provided a means to keep dangerous products off the market by allowing the Secretary of Health and Human Services to declare that a dietary supplement "pose[s] an imminent hazard to public health or safety."[55] However, in implementing DSHEA, Congress made sure that FDA, not industry, had the burden of proof in any proceeding arising from the new dietary supplement adulteration provisions.[56]

DSHEA has definitely impacted the dietary supplement industry: there are more dietary supplements on the market now than ever before,[57] companies are studying the effects of various non-traditional dietary ingre-

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50. Representative Richardson, in testimony on DSHEA, stated that the legislation "will create an appropriate regulatory framework for dietary supplements" so that they "will no longer be arbitrarily classified as food additives," and it will ensure that dietary supplements are "safe [and] of high quality." 103 CONG. REC. E919, *supra* note 48.

51. 21 U.S.C. § 321(s)(6).

52. *Id.* § 321(ff) (2000). DSHEA defines a dietary supplement, in pertinent part, as

> a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: (A) a vitamin; (B) a mineral; (C) an herb or other botanical; (D) an amino acid; (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E).

Id. § 321(ff)(1).

53. *Id.* § 342(f)(1).

54. *Id.* § 342(f)(1)(A).

55. *Id.* § 342(f)(1)(C).

56. *Id.* § 342(f)(1).

57. INSTITUTE OF MEDICINE, DIETARY SUPPLEMENTS: A FRAMEWORK FOR EVALUATING SAFETY 19 (2005).

dients on human health, and more consumers are taking supplements[58]—and not just traditional vitamins and minerals.

Unfortunately, "bad players" in the marketplace also increased with the passage of DSHEA. For example, it is not difficult to find products that make far-fetched claims with little or no science to back them up, especially on the Internet.[59] In addition, there are some products that contain ingredients that might not be safe.[60] These more extreme cases have led to some criticism of DSHEA. For example, in the United States Government Accountability Office's (GAO's) July 2000 report titled *Food Safety – Improvements Needed in Overseeing the Safety of Dietary Supplements and "Functional Foods,"* GAO noted that "potentially unsafe products may reach consumers for a variety of reasons, including the lack of a clearly defined safety standard for new dietary ingredients in dietary supplements."[61] It is in this vein that FDA has tried to narrowly interpret certain provisions of DSHEA.

III. CURRENT FDA REGULATION OF DIETARY INGREDIENTS IN DIETARY SUPPLEMENTS

As noted in Section II, pre-DSHEA, FDA attempted to regulate non-traditional dietary ingredients in dietary supplements by requiring that such ingredients be either FDA-approved food additives or GRAS substances. Because DSHEA exempts dietary ingredients in dietary supplements from the food additive definition, these substances need not be FDA-approved food additives or GRAS substances. As explained below, DSHEA replaced that approach with one that relies in part on the history of use and experience with the ingredient in the food supply, coupled with assurance that the ingredient is not unreasonably risky for food use, with pre-market

58. *Id.*

59. *See, e.g.*, Warning Letter from Joseph R. Baca, Director, Office of Compliance, Center for Food Safety and Applied Nutrition, FDA, to Shirley Baisden, Beyond Muscle.com (Feb. 28, 2003) (noting that the claim "increase lean muscle mass" did not appear to be substantiated by scientific data), *available at* http://www.casewatch.org/fdawarning/prod/2003/beyondmuscle.shtml.

60. *See, e.g.*, Letter from Christine J. Lewis, Director, Office of Nutritional Products, Labeling, and Dietary Supplements, FDA, to American Botanical Council et al. (July 6, 2001) (advising dietary supplement manufacturers to remove comfrey products from the market), *available at* http://www.cfsan.fda.gov/~dms/dspltr06.html.

61. GENERAL ACCOUNTING OFFICE, FOOD SAFETY, IMPROVEMENTS NEEDED IN OVERSEEING THE SAFETY OF DIETARY SUPPLEMENTS AND "FUNCTIONAL FOODS" 12 (July 2000). (The GAO's legal name became the Government Accountability Office on July 7, 2004.)

interferences by FDA limited to notification of the marketing of certain "new" dietary ingredients.[62]

Before deciding whether a dietary ingredient is "old" or "new," however, one must confirm that the substance meets the definition of a dietary supplement.[63] FDCA, as amended by DSHEA, defines "dietary supplement," in pertinent part, as:

> (1) . . . a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:
>
> (A) a vitamin;
> (B) a mineral;
> (C) an herb or other botanical;
> (D) an amino acid;
> (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or
> (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E);
>
> (2) means a product that –
>
> (A) (i) is intended for ingestion . . .
> (B) is not represented for use as a conventional food or as a sole item of a meal or the diet; and
> (C) is labeled as a dietary supplement; and
>
> (3) does –
>
> (A) include an article that is approved as a new drug . . . or licensed as a biologic . . . and was, prior to such approval, certification, or license, marketed as a dietary supplement or as a food unless the Secretary has issued a regulation, after notice and comment, finding that the article, when used as or in a dietary supplement under the conditions of use and dosages set forth in the labeling for such dietary supplement, is unlawful . . . ; and
>
> (B) not include –
>
> (i) an article that is approved as a new drug . . . , certified as an antibiotic . . . , or licensed as a biologic . . . , or
>
> (ii) an article authorized for investigation as a new drug, antibiotic, or biological for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, which was not before such approval, certification, licensing, or authorization marketed as a dietary supplement or as a food unless the

62. 21 U.S.C. § 350b. Of course, whether old or new, a dietary ingredient must still be safe. *See id.* § 342(f)(1)(A) (providing that a dietary supplement will be adulterated if it contains an ingredient that "presents a significant or unreasonable risk of illness or injury" under its recommended conditions of use).

63. *But cf.* Scott Bass & Emily Marden, *The New Dietary Ingredient Safety Provision of DSHEA: A Return to Congressional Intent*, 31 AM. J.L. & MED. 285 (2005) (arguing that 21 U.S.C. § 350b does not require that FDA-notified new dietary ingredients meet the definition of a dietary supplement).

> Secretary, in the Secretary's discretion, has issued a regulation, after notice and comment, finding that the article would be lawful.[64]

Although an examination of what meets the definition of a "dietary supplement" is outside the scope of this paper, it is worth noting that such a determination is not always clear.[65] In addition, it is important to confirm that a dietary ingredient not previously marketed as a dietary supplement or as a food is not an approved new drug or an article that has been investigated for drug use and for which substantial investigations have been made public; otherwise, the dietary ingredient will not qualify as a "dietary supplement" unless FDA promulgates a regulation permitting its use as a dietary supplement.[66]

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64. FDCA § 201(ff) (codified at 21 U.S.C. § 321(ff)).

65. *See, e.g.*, Warning Letter from Edward W. Thomas, Acting District Director, New York District Office, FDA, to Chao Zhang, President, Blue Light Inc. 3 (Dec. 18, 2000), *available at* http://www.fda.gov/foi/warning_letters/m4975n.pdf. The letter noted that:

> [t]he products Sheng Bai Wan and ChemoAid are adulterated because they contain human placenta. Human placenta is not a dietary ingredient under section 201(ff)(1) of the Act [i.e., 21 U.S.C. § 321(ff)]. . . . It is not a 'dietary substance for use by man to supplement the diet by increasing the total dietary intake.' . . . While the term 'dietary substance' is not defined in either the Act itself or the statute's legislative history, the term must be interpreted in accordance with its common, usual meaning . . . . 'Dietary substance,' therefore, under a commonsense understanding of the term, means simply substances customarily used as human food or drink.

See also Letter from Susan J. Walker, Director, Division of Dietary Supplement Programs (DDSP), FDA, to James Komorowski, Vice President, Technical Services and Scientific Affairs, Nutrition 21 at 2 (Jan. 28, 2005) ("[I]t is not readily apparent whether the 'ASI Complex' that is the subject of your notification is a 'dietary ingredient' within the meaning of 21 U.S.C. 321(ff)(1)."), *available at* http://origin.www.fda.gov/ohrms/dockets/dockets/95s0316/95s-0316-rpt0263-02-vol192.pdf.

66. 21 U.S.C. § 321(ff)(3)(B). On July 29, 2005, a citizen petition was filed with FDA requesting that FDA "remove dietary supplements that contain the drug pyridoxamine from United States interstate commerce" because a company had submitted an investigational new drug application (IND) for the ingredient. Citizen Petition from Mark Mansour et al., Morgan, Lewis & Bockius LLP, to FDA 1 (July 29, 2005), *available at* http://www.fda.gov/ohrms/dockets/dockets/05p0305/05p-0305-cp00001-vol1.pdf. The company that filed the IND for Pyridorin (pyridoxamine dihydrochloride) "was not aware of any of these [pyridoxamine–containing dietary supplements] being marketed prior to the date on which it filed the Pyridorin IND, and no subsequent evidence has been uncovered to suggest that pyridoxamine was marketed as a dietary supplement prior to the Pyridorin IND filing." *Id*. at 2. In response to the citizen petition, FDA issued a request for comments on the substance's status but tentatively concluded that pyridoxamine "is excluded from the dietary supplement definition under the exclusion clause in 21 U.S.C. 321 (ff)(3)(B)(ii) and therefore may not be marketed as or in a dietary supplement." Request for Comment on the Status of Pyridoxamine, 70 Fed. Reg. 69,976 (Nov. 18, 2005). *See also* United States v. Syntrax Innovations, Inc., 149 F. Supp. 2d 880, 882 (E.D. Mo. 2001) (noting that tiratricol could not be a "dietary supplement as a matter of law" because it "was not marketed as a dietary supplement or as a food prior to the authorization of" an investigational new drug application for the substance, for which there were substantial public clinical investigations).

A. "New Dietary Ingredient" Versus "Old Dietary Ingredient"

FDCA, as amended by DSHEA, defines a "new dietary ingredient" as "a dietary ingredient that was not marketed in the United States before October 15, 1994 and does not include any dietary ingredient which was marketed in the United States before October 15, 1994."[67] In other words, dietary ingredients that are first marketed in the United States *on* or *after* October 15, 1994, the date DSHEA was passed by Congress, are by definition new dietary ingredients. Dietary ingredients marketed in the United States *before* October 15, 1994 are referred to in industry as "old dietary ingredients."[68] Old dietary ingredients may be immediately marketed in dietary supplements; there is no FDA approval or notification required.[69]

> FDCA provides that:
>
> A dietary supplement which contains a new dietary ingredient shall be deemed adulterated under section 402(f) unless it meets *one* of the following requirements:
>
> (1) The dietary supplement contains only dietary ingredients which have been present in the food supply as an article used for food in a form in which the food has not been chemically altered.
>
> (2) There is a history of use or other evidence of safety establishing that the dietary ingredient when used under the conditions recommended or suggested in the labeling of the dietary supplement will reasonably be expected to be safe and, at least [seventy-five] days before being introduced or delivered for introduction into interstate commerce, the manufacturer or distributor of the dietary ingredient or dietary supplement provides the Secretary with information, including any citation to published articles, which is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such dietary ingredient will reasonably be expected to be safe.[70]

Thus, a new dietary ingredient may be marketed immediately—that is, without FDA approval or notification—*if* it is "present in the food supply as an article used for food in a form in which the food has not been chemically altered."[71] If there is no such evidence, however, the new dietary ingredient may *still* be marketed provided that a seventy-five day premarket notification is submitted to FDA, and the notification contains, among other things, evidence that the dietary supplement containing the new dietary ingredient will "reasonably be expected to be safe."[72]

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67. 21 U.S.C. § 350b(c).
68. Some in industry refer to "old dietary ingredients" as "grandfathered" dietary ingredients. *See, e.g.*, American Botanical Council, *ABC's Comments to FDA Regarding Pre-Market Notification for New Dietary Ingredients*, *available at* http://www.herbalgram.org/default.asp?c=ndicomments.
69. 21 U.S.C. § 350b(a), (c).
70. FDCA § 413(a) (emphasis added) (codified at 21 U.S.C. § 350b(a)).
71. 21 U.S.C. § 350b(a)(1).
72. *Id.* § 350b(a)(2).

The language defining the term "new dietary ingredient" and the language explaining the two routes to market for new dietary ingredients is, in some respects, ambiguous and contains terms not defined elsewhere in FDCA or FDA's implementing regulations. This uncertainty has caused some confusion among those companies wishing to market new dietary ingredients in dietary supplements. In addition, it provides FDA an opportunity to interpret the law as the agency sees fit. However, some of FDA's interpretations seem to be in error or, at a minimum, contrary to the spirit of DSHEA, as explained below.

B. Old Dietary Ingredients

As noted in Section II.A, although not expressly defined in FDCA, old dietary ingredients are those that were marketed in the United States before October 15, 1994.[73] Old dietary ingredients may be immediately marketed in a dietary supplement provided that the dietary supplement, as formulated, does not present "a significant or unreasonable risk of illness or injury under" its recommended conditions of use or ordinary conditions of use, if no conditions of use are recommended.[74] Establishing a dietary ingredient as old, however, can be a challenge. Without formal FDA guidance on this issue, companies have used different methods to evidence pre-DSHEA marketing of a dietary ingredient, and the agency does not agree with all of the methods used by industry.

For example, to confirm that a dietary ingredient is old, some companies have relied on industry publications that list those dietary ingredients that are believed to be old.[75] However, FDA stated that it was "unable to determine what criteria were used by these trade associations to identify ingredients marketed prior to October 15, 1994," and "inclusion of . . . a substance in one . . . of these published lists does not, by itself, suffice to show that the substance" is an old dietary ingredient.[76] Another source relied upon by some companies to establish old dietary ingredient status is the American Herbal Products Association's (AHPA's) *Herbs of Commerce*,[77] which is cited in an FDA regulation governing ingredient declarations as the source to consult for the common or usual name of dietary ingredients that are botanicals.[78] FDA does not acknowledge this source as

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73. *Id*. § 350b(c).

74. *Id*. § 342(f)(1)(A).

75. *See, e.g.*, UTAH NATURAL PRODUCTS ALLIANCE, OLD DIETARY INGREDIENT LIST (Sept. 17, 1999).

76. Letter from Felicia B. Satchell, Director, Division of Standards and Labeling Regulations (DSLR), FDA, to Holly M. Bayne, Hyman, Phelps & McNamara, P.C. 2 (July 15, 2001) (hereinafter Bayne Letter) (on file with author).

77. AMERICAN HERBAL PRODUCTS ASSOCIATION, HERBS OF COMMERCE (2d ed. 2000).

78. 21 C.F.R. § 101.4(h) (2005).

an authority for old dietary ingredients, stating that an ingredient's "listing in [*Herbs of Commerce*] prior to October 15, 1994, does not establish that [the dietary ingredient] was marketed as a dietary ingredient before that date"; rather, it shows "only that [the dietary ingredient] was known to serve some commercial purpose at the time of publication."[79] FDA further noted that "[b]y its own terms, *Herbs of Commerce* sets forth only nomenclature for various commercial substances . . . [it] does not purport to list substances used as dietary ingredients."[80]

FDA provided some informal guidance on how to establish pre-October 15, 1994 marketing by noting that "an invoice, a bill of lading, or a product label" that establishes that a substance was marketed prior to October 15, 1994 can evidence an ingredient's old dietary ingredient status.[81] However, such records are unlikely to be readily found, and those companies new to the dietary supplement market would not have any such records.

FDA did indicate that if a dietary ingredient is old, those substances chemically identical to the old dietary ingredient are also deemed to be old.[82] Thus, it would appear that any synthetic substance that is "nature identical" to an old dietary ingredient is old and, therefore, can be immediately marketed in dietary supplements. The same would appear to hold true for any genetically-modified substance that is chemically identical to an old dietary ingredient.[83] However, FDA has also indicated in at least one significant instance involving ephedra and synthetic ephedrine salts that synthetic dietary ingredients that are copies of herbal extracts do not meet the definition of "dietary supplement" and, consequently, are not appropriate dietary ingredients.[84] This view seems to contradict FDCA and FDA regulations.

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79. Bayne Letter, *supra* note 76, at 2.

80. *Id*.

81. *Id*. at 2-3.

82. *Id*. at 2 ("To establish that glucose metabolism modulator [GMM] is not a new dietary ingredient, you must present evidence showing that GMM, *or a substance chemically identical to GMM*, was actually marketed as a dietary ingredient in the United States before October 15, 1994.") (emphasis added).

83. Of course, companies manufacturing a dietary ingredient by use of a genetically-modified organism (GMO) must be sure that use of the GMO does not raise any safety issues.

84. Final Rule Declaring Dietary Supplements Containing Ephedrine Alkaloids Adulterated Because They Present an Unreasonable Risk, 69 Fed. Reg. 6788, 6793 (Feb. 11, 2004) (codified at 21 C.F.R. § 119.1). In the preamble to the final rule, FDA stated that "ephedrine hydrochloride and other synthetic sources of ephedrine cannot be dietary ingredients because they are not constituents or extracts of a botanical, nor do they qualify as any other type of dietary ingredient. For these reasons, products containing synthetic ephedrine cannot be legally marketed as dietary supplements." *Id*. (citing 21 U.S.C. § 321(ff)(1), (3)(B)). *But cf*. Letter from Susan Walker, Acting Director, DDSP, FDA, to I. Scott Bass & Diane C. McEnroe, Sidley Austin Brown & Wood LLP 1 (Mar. 12, 2003) (on file with author)

FDCA recognizes the equivalence of marketed natural and synthetic vitamins and minerals by providing that "the Secretary may not establish . . . maximum limits on the potency of any *synthetic* or natural vitamin or mineral."[85] In addition, an FDA regulation provides that a food will be misbranded if its labeling implies "[t]hat a natural vitamin in a food is superior to an added or *synthetic* vitamin."[86] Thus, FDA's pronouncement that synthetic substances do not meet the definition of "dietary supplement" does not appear to be well-founded.

FDA has acknowledged certain problems with DSHEA's new dietary ingredient provisions, including the uncertainty of whether an ingredient is "old" or "new." In October 2004, FDA published a request for comments on many aspects of the new dietary ingredient notification requirements, listing, among others, questions as to whether the agency should recognize "an authoritative list" of old dietary ingredients and what criteria should be considered for an ingredient's placement on the list.[87] FDA held a public meeting in November 2004 to provide a forum for new dietary ingredient issues to be discussed.[88] FDA reportedly expects to issue guidance on the new dietary ingredient provisions in the future,[89] but whether FDA will acknowledge any particular old dietary ingredient list at that time is uncertain.

C. New Dietary Ingredients Exempt from FDA Notification

If a dietary ingredient does not qualify as an old dietary ingredient, then the dietary ingredient is deemed to be a new dietary ingredient. A new dietary ingredient may be immediately marketed in a dietary supple-

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(stating that synthetic dietary ingredients that are constituents of foods do meet the definition of "dietary supplement" in 21 U.S.C. § 321(ff)). A citizen petition has been filed with FDA concerning the agency's position on synthetic dietary ingredients. Citizen Petition, Coalition to Preserve DSHEA, FDA Dkt. No. 2004-0169 (Apr. 8, 2004), *available at* http://www.fda.gov/ohrms/dockets/dailys/04/apr04/040804/04p-0169-cp00001-vol1.pdf.

85. 21 U.S.C. § 350(a)(1)(A) (emphasis added). This provision resulted from the "Proxmire Amendments" to FDCA in 1976. Health Research and Health Services Amendments of 1976, Pub. L. No. 94-278, 90 Stat. 401, 410. Congress enacted the amendments so that FDA could no longer limit the maximum potency of vitamins and minerals in dietary supplements or classify any vitamin or mineral as a drug "solely because it exceeds the level of potency" that FDA finds is "nutritionally rational or useful" unless the vitamin or mineral is represented for pregnant or lactating women, children, or persons suffering from certain diseases or disorders. 21 U.S.C. § 350(a)(1)(A)-(B), (2) (2000).

86. 21 C.F.R. § 101.9(k)(4) (2005) (emphasis added).

87. Dietary Supplements; Premarket Notification for New Dietary Ingredient Notifications; Public Meeting, 69 Fed. Reg. 61,680, 61,681-82 (Oct. 20, 2004).

88. *Id*. at 61,680-81.

89. *FDA Accomplishes A-List Goals, Will Publish NDI Guidance – CFSAN*, THE TAN SHEET, Aug. 22, 2005, at 8.

ment if the ingredient is "present in the food supply as an article used for food in a form in which the food has not been chemically altered."[90] New dietary ingredients meeting this requirement need not be FDA-notified, unlike all other new dietary ingredients.[91] Given the unclear language of this first requirement, it is difficult for companies to know whether a new dietary ingredient qualifies for exemption from FDA notification.

1. "Present in the food supply"

The requirement that the new dietary ingredient be "present in the food supply" is unclear. The text "present in the food supply" is not qualified and, therefore, arguably means present in any country's food supply. Unlike 21 U.S.C. § 350b(c), which specifies that to be an old dietary ingredient, an ingredient must have been marketed *in the United States* prior to October 15, 1994, § 350b(a)(1) makes no such specification. Thus, for example, if oat extract is eaten in Scotland (and assuming oat extract is *not* an old dietary ingredient),[92] then one could argue that oat extract is "present in the food supply"–the Scottish food supply–and that it is an "article used for food in a form in which the food has not been chemically altered."

FDA might disagree with this interpretation, but case law supports the notion that Congress did not intend the phrase "in the United States," which is found in 21 U.S.C. § 350b(c), to modify the text "present in the food supply" in § 350b(a)(1). "Where Congress includes particular language in one section of a statute but omits it in another section of the same Act, it is generally presumed that Congress acts intentionally and purposely in the disparate inclusion or exclusion."[93]

Furthermore, in the 1980s, the Court of Appeals for the Ninth Circuit struck down FDA's regulation defining "common use in food" for purposes of determining an ingredient's eligibility for classification as GRAS "based on its common use in food" prior to January 1, 1958 because the definition limited the evidence of use to "consumers *in the United States.*"[94] The regulation was challenged by an importer of Chinese food

90. 21 U.S.C. § 350b(a)(1).

91. *Id.* § 350b(a).

92. Oat extract may well be an "old" dietary ingredient. For the purpose of this paper, it is assumed to be a new dietary ingredient.

93. Russello v. United States, 464 U.S. 16, 23 (1983) (notation of alteration omitted); *accord* Keene Corp. v. United States, 508 U.S. 200, 208 (1993); Gozlon-Peretz v. United States, 498 U.S. 395, 405 (1991); *cf.* Field v. Mans, 516 U.S. 59, 75-76 (1995).

94. Fmali Herb, Inc. v. Heckler, 715 F.2d 1385, 1386 (9th Cir. 1983) (Pregerson, H., dissenting) (emphasis added by court) (quoting 21 C.F.R. § 170.3(f) (1982)). The food additive definition provides that a substance may be exempt from the definition if it is GRAS based on common use in food. 21 U.S.C. § 321(s). The definition does not specify a geographic location.

products, who argued that certain ingredients in his products were GRAS "based on common use in food prior to 1958" in China.[95] After considering the language in 21 U.S.C. § 321(s) and its legislative history, the court ruled in favor of the importer, stating that:

> 21 C.F.R. § 170.3(f) does not establish an evidentiary standard. Rather, it operates as a blanket exclusion of evidence of safety based on use of food outside the United States. As such, it fails to comport either with the express terms of the statute that contain no such restriction, or with the purpose of the "common use" exception as articulated by legislators, that was to allow use of "any substances which over the years have been clearly demonstrated by long use to be completely safe."[96]

Because this case declared the definition of "common use in food" to be invalid, FDA was forced to revise the regulation to remove the phrase "in the United States" from the definition.[97] FDA added a new paragraph to its regulations governing the eligibility of a substance for classification as GRAS to make it clear that common use of a food outside of the United States may be considered. This paragraph provides that a substance may be GRAS "through experience based on its common use in food when that use occurred *exclusively or primarily outside of the United States* if the information about the experience establishes that the use of the substance is safe."[98]

2. "As an article used for food"

The text "as an article used for food" is also unclear. However, FDA has stated the following with respect to this part of 21 U.S.C. § 350b(a)(1)'s requirement:

> In order to establish that [a dietary ingredient] qualifies as an "article used for food in a form in which the food has not been chemically altered" within the meaning of 21 U.S.C. 350b(a)(1), [one] would have to show that the dietary ingredient itself has been used as a food or as an ingredient in a food, without chemical alteration. The mere incidental presence of components of [the dieta-

95. *Fmali Herb*, 715 F.2d at 1386.

96. *Id*. at 1391 (quoting 104 CONG. REC. 17,424 (statement of Rep. Sullivan)).

97. Eligibility for Classification of Food Substances as Generally Recognized as Safe, 53 Fed. Reg. 16,544 (May 10, 1988) (revising 21 C.F.R. § 170.3(f)).

98. 21 C.F.R. § 170.30(c)(2) (emphasis added). The regulation further requires that "[t]he information used to document and to corroborate the history and circumstances of use of the substance must be generally available; that is, it must be widely available in the country in which the history of use has occurred and readily available to interested qualified experts in this country." *Id.*

> ry ingredient] or [the dietary ingredient] itself as inherent components of articles used for food does not establish that section 350b(a)(1) applies.[99]

Applying this interpretation to the new dietary ingredient oat extract example, FDA would require that the oat extract itself was used as a food or an ingredient in a food. However, this position is contrary to the plain language of the statute and is incorrect as a matter of law.

There is no exception for "mere incidental presence" of food components in § 350b(a)(1) or anywhere else in FDCA. The plain language of § 350b(a)(1) states that the dietary ingredient must "have been present in the food supply as an article used for food." There is no quantitative or de minimus exception from the "presence" requirement in the statute.

Moreover, it is factually inaccurate to regard a component of a food that is inherent in, or integral to, the food as "mere incidental presence." For example, oat extract is not an incidental component or additive. It is an inherent component of oats, and it would require deliberate, additional processing to *remove* its "presence" from oats.

In addition, the assertion that under § 350b(a)(1), the dietary ingredient itself had to have been "used" as a food or food ingredient would, in effect, simply repeat the requirement of § 350b(c) and would render the former provision meaningless. Section 350b(c) defines "new dietary ingredient" as "a dietary ingredient that was *not marketed* in the United States before October 15, 1994 and does not include any dietary ingredient which was marketed in the United States before October 15, 1994."[100] If a dietary ingredient was not "marketed" in the United States before October 15, 1994, then it is a new dietary ingredient and will be subject to § 350b(a)(2)'s notification procedure unless it can be shown that the dietary ingredient has "been *present in the food supply* as an *article used for food* in a form in which the food has not been chemically altered."[101] Applying § 350b(a)(1) only to dietary ingredients that have been "used as a food or as an ingredient in a food" is tantamount to requiring that the food have been "marketed" as a food or food ingredient and essentially reads § 350b(a)(1) out of FDCA. This cannot be what Congress intended.

Proper statutory interpretation of the plain language of the provision requires that § 350b(a)(1) be interpreted to mean that new dietary ingredients (i.e., those not marketed in the United States before October 15, 1994) are exempt from the notification procedure in § 350b(a)(2) if the dietary ingredients have been "present in the food supply,"[102] without ref-

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99. Letter from Susan J. Walker, Acting Director, DDSP, FDA, to Beth Thompson, Global Regulatory Affairs Manager, Kemin Consumer Care, L.C. 2 (Apr. 2, 2003) (on file with author); *see also* Bayne Letter, *supra* note 76.

100. 21 U.S.C. § 350b(c) (emphasis added).

101. *Id.* § 350b(a)(1) (emphases added).

102. Note also that there is no time specified. It appears that this might apply to an ingredient first present in the food supply only this morning.

erence to their quantity or their identity as components, so long as they have "not been chemically altered." Using the oat extract example, because it is present in the food supply as a constituent of oats, the substance, although a new dietary ingredient, is exempt from the notification requirement set forth in 21 U.S.C. § 350b(a)(2) provided that it is not "chemically altered."

3. "In a form in which the food has not been chemically altered"

The text "in a form in which the food has not been chemically altered" is likewise subject to interpretation. The word "food" in this text could mean the food in which the dietary ingredient is present (e.g., oats) or it could mean that the dietary ingredient itself (e.g., oat extract) has not been chemically altered through the extraction process or other method to remove the dietary ingredient from the food. The most logical interpretation would appear to be that the "food" referred to is the dietary ingredient that will be marketed and not the food in which the dietary ingredient is present. FDA appears to apply this same interpretation.[103]

Regarding the text "chemically altered," a "Statement of Agreement" by the chief sponsors of DSHEA identifies several particular "physical modifications" that were not intended to be included within the term "chemically altered" as used in 21 U.S.C. § 350b(a)(1).[104] Specifically, the following physical modifications are deemed to *not* chemically alter a substance: "minor loss of volatile components, dehydration, lyophlization, milling, tincture or solution in water, slurry, powder, or solid in suspension."[105] Thus, for example, if oat extract is dehydrated, it will not be "chemically altered" for the purposes of 21 U.S.C. § 350b(a)(1). However, it is unclear what physical modifications other than those set forth in DSHEA's "Statement of Agreement" would not chemically alter the dietary ingredient.

One could argue, though, that if the dietary ingredient to be marketed is chemically identical to the dietary ingredient as it is present in its food source, then the dietary ingredient is not chemically altered. Using this approach, genetically-modified and synthetic substances that are chemically identical to dietary ingredients "present in the food supply as articles used for food" should qualify under 21 U.S.C. § 350b(a) as new dietary ingredients not subject to FDA notification.[106]

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103. *See* Bayne Letter, *supra* note 76, at 3 (noting that a new dietary ingredient need not be FDA-notified if it has been "present in the food supply as an article used for food in a form in which *the substance* has not been chemically altered") (emphasis added).

104. 140 CONG. REC. S14, 798-801 (daily ed. Oct. 7, 1994) (statement of Sen. Feingold).

105. *Id.*

106. Of course, FDA could disagree with this interpretation. *See* discussion *supra* Section III.B.

D. New Dietary Ingredients Required to Be FDA-Notified

If a new dietary ingredient is not "present in the food supply as an article used for food in a form in which the food has not been chemically altered," per 21 U.S.C. § 350b(a), then it may still be marketed as a dietary ingredient in a dietary supplement provided that FDA is notified seventy-five days prior to marketing the ingredient and information demonstrating that the dietary ingredient is "reasonably . . . expected to be safe" is included in the notification.[107]

1. Contents of a New Dietary Ingredient Notification

> A new dietary ingredient notification must contain the following information:
>
> (1) The name and complete address of the manufacturer or distributor of the dietary supplement that contains a new dietary ingredient, or of the new dietary ingredient;
>
> (2) The name of the new dietary ingredient that is the subject of the premarket notification, including the Latin binomial name (including the author) of any herb or other botanical;
>
> (3) A description of the dietary supplement or dietary supplements that contain the new dietary ingredient, including:
>
> > (i) The level of the new dietary ingredient in the dietary supplement; and
> >
> > (ii) The conditions of use recommended or suggested in the labeling of the dietary supplement, or if no conditions of use are recommended or suggested in the labeling of the dietary supplement, the ordinary conditions of use of the supplement;
>
> (4) The history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe, including any citation to published articles or other evidence that is the basis on which the distributor or manufacturer of the dietary supplement that contains the new dietary ingredient has concluded that the new dietary supplement will reasonably be expected to be safe . . .; and
>
> (5) The signature of the person designated by the manufacturer or distributor of the dietary supplement that contains a new dietary ingredient.[108]

If FDA has no questions regarding the safety information submitted (or regarding other aspects of the notification), FDA will "file" the notification

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107. 21 U.S.C. § 350b(a)(2); 21 C.F.R. § 190.6(a) (2005).

108. 21 C.F.R. § 190.6(b)(1)-(5). The regulation requires that "reference to published information offered in support of the notification . . . be accompanied by reprints or photostatic copies of such references" and that "[i]f any part of the material submitted is in a foreign language, it [must] be accompanied by an accurate and complete English translation." *Id.* § 190.6(b)(4). An original and two copies of the notification must be submitted to FDA. *Id.* § 190.6(a).

without comment. FDA's response informing the notifier of the filing advises that FDA's filing of the notification does "not constitute a finding by FDA that the new dietary ingredient . . . is safe or is not adulterated."[109] If FDA has concerns about the safety of the ingredient or of the adequacy of the notification, the agency will identify such concerns in its response to the notifier.

2. FDA Rejection of New Dietary Ingredient Notifications

In the last several years, FDA has rejected more new dietary ingredient notifications than it has filed with no comments.[110] Many notifications were "rejected"[111] because the notifier failed to provide sufficient evidence demonstrating that the dietary ingredient was reasonably expected to be safe.[112] Others were rejected because the agency could not determine whether or how the submitted safety evidence related to the dietary ingredient that was the subject of the notification.[113] Some rejected notifications included language that suggested that the dietary ingredient was intended to be used as a drug,[114] and others were rejected because the substance did not meet the definition of a "dietary ingredient."[115]

These numerous new dietary ingredient notification rejections caused FDA to recognize that there were problems with the notification procedure, in large part because of the unclear meaning of key terms in the new dietary ingredient notification requirements. Consequently, as noted in Section II.B above, FDA published a request for comments on the new dietary ingredient notification requirements and set forth questions for the public to consider, including the following: "[w]hat should FDA consider to determine whether a substance falls within a particular category of the statutory

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109. *See, e.g.*, Letter from FDA to Anita Lam, Assistant Marketing Manager, Care & Health Limited (Apr. 21, 2003) (on file with author).

110. Susan J. Walker, Director, DDSP, FDA, Remarks at the Food and Drug Law Institute Conference: Preparing for the Next Century of Food and Drug Regulation (Apr. 8, 2005); *see also* Michael McGuffin & Anthony L. Young, *Premarket Notifications of New Dietary Ingredients – A Ten-Year Review*, 59 FOOD & DRUG L.J. 229, 235 (2004).

111. The word "rejected" is used in this paper to describe those letters from FDA in which the agency raises issues concerning the notification. These letters are not formally termed "rejection" letters.

112. *See, e.g.*, Letter from Susan J. Walker, Acting Director, DDSP, FDA, to Holly Bayne, Counsel to PhytoMedica, LLC (Apr. 21, 2003) (on file with author).

113. *See, e.g.*, Letter from Susan J. Walker, Director, DDSP, FDA, to Robert DeWitty, Outsource Product Manufacture, LLC (Aug. 10, 2004) (on file with author).

114. *See, e.g.*, Letter from Felicia B. Satchell, Director, DSLR, FDA, to Fedra Sembiante, Power Africa, Inc. (Feb. 8, 2002) (on file with author).

115. *See, e.g.*, Letter from Felicia B. Satchell, Director, DSLR, FDA, to Sherman Ye, Yat Chau (USA) Inc. (Oct. 23, 2002) (on file with author).

definition of 'dietary ingredients' . . . ?";[116] "[w]hat changes in chemical composition to a dietary ingredient would cause it to become a substance that is not a dietary ingredient?";[117] and "[w]hat changes in chemical composition to [an old dietary ingredient] would lead to the dietary ingredient becoming [a new dietary ingredient] subject to the notification requirement . . . ?"[118]

In addition, FDA listed various possible requirements for new dietary ingredient notifications, including information on the empirical and structural formulas of a substance, its chemical characterization, and chemical specifications.[119] FDA also questioned whether certain types of studies, if any, should be included as part of the notification, including rat and human studies.[120]

This request for comments caused many in the dietary supplement industry to have flashbacks to the 1980s and 1990s, when FDA imposed the food additive/GRAS requirements on dietary ingredients in dietary supplements. The voluminous items detailed by FDA for consideration as part of a new dietary ingredient notification seemed more akin to a food additive petition and approval process than a notification process. FDA's request for comments also reinforced the fact that the new dietary ingredient provisions are ambiguous and could be interpreted either broadly or narrowly. Industry can only hope that FDA's upcoming guidance on this issue is fair and maintains the spirit of DSHEA.

3. Consequences of FDA's Rejection of a New Dietary Ingredient Notification

Marketing a new dietary ingredient despite FDA's rejection of the new dietary ingredient notification is not a violation of the FDCA. This is because DSHEA only requires that companies submit notifications to FDA.[121] DSHEA does not specify the consequences of rejection; rather, it places the burden on FDA to prove that a new dietary ingredient is adulterated.[122]

FDCA, as amended by DSHEA, provides, in pertinent part, that a food, which includes a dietary supplement,[123] will be adulterated (and, therefore, illegal) if "it is a dietary supplement or contains a dietary ingre-

116. Dietary Supplements; Premarket Notification for New Dietary Ingredient Notifications, 69 Fed. Reg. 61,680, 61,682 (Oct. 20, 2004).
117. *Id.*
118. *Id.*
119. *Id.*
120. *Id.*
121. 21 U.S.C. § 350b(a)(2).
122. *Id.* § 342(f)(1)(B), (D).
123. *Id.* § 321(ff) (defining dietary supplements as "foods").

dient that . . . is 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."[124] The law also provides that "[i]n any proceeding under this subparagraph, the United States shall bear the burden of proof on each element to show that a dietary supplement is adulterated."[125] Thus, unless and until FDA makes the determination that there is a lack of information to show that a new dietary ingredient "does not present a significant or unreasonable risk of illness or injury" *and* persuades a court to agree, a company may continue to market the new dietary ingredient and not be in violation of FDCA. With FDA's resources already strained, it seems unlikely that FDA will take action under 21 U.S.C. § 342(f)(1)(B) unless the dietary ingredient is thought to pose a significant risk to health.[126]

Nevertheless, if FDA lacks the time or resources to prove that a new dietary ingredient submission contains insufficient information to show that the dietary ingredient does not present a significant or unreasonable risk of illness or injury, FDA conceivably could instead initiate action against the product under 21 U.S.C. § 342(a), which provides that a food is adulterated if, for example, the food contains a "poisonous or deleterious substance which may render it injurious to health," "consists . . . of any filthy, putrid, or decomposed substance, or if it is otherwise unfit for food," or "has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth."[127] Although FDA would still have the burden to prove one of these violations of FDCA, it might be an easier burden for FDA to meet assuming, of course, that a violation occurred.

IV. UNANSWERED QUESTIONS CONCERNING FDA'S REGULATION OF DIETARY INGREDIENTS IN DIETARY SUPPLEMENTS

Given the vague terms used in the new dietary ingredient provisions of DSHEA and the drastically different possible interpretations of such

124. *Id.* § 342(f)(1).

125. *Id.*

126. In March 2004, FDA issued Warning Letters to several companies marketing dietary supplements containing androstenedione. *See, e.g.*, Warning Letter from Emma R. Singleton, Director, Florida District, FDA, to Lloyd Slabach, President and Owner, and Timothy Romero, Vice President and Owner, F.H.G. Corporation, Integrity Nutraceuticals Int'l (Sept. 29, 2004) [hereinafter F.H.G. Letter] (on file with author). FDA stated that "[a]ssuming that androstenedione is a 'dietary ingredient,' it would also be a 'new dietary ingredient' for which a notification is required under 21 U.S.C. § 350b(a)(2) and 21 C.F.R. § 190.6." *Id.* at 1. None of the companies had submitted a new dietary ingredient notification to FDA.

127. 21 U.S.C. § 342(a)(1), (3)-(4).

terms, it is not surprising that there are several unanswered questions concerning the regulatory status of many dietary ingredients. For example, once a company markets a new dietary ingredient that has been FDA-notified and filed, may other companies also market the new dietary ingredient on the basis of 21 U.S.C. § 350b(a)(1)? Does the FDA-notified and filed new dietary ingredient that is subsequently marketed meet the requirement of 21 U.S.C. § 350b(a)(1) in that it is present in the food supply as an article used for food in a form in which the food has not been chemically altered? Indeed, absent safety concerns, other companies could theoretically market the new dietary ingredient at a use level higher than the level provided for in the notification because once a new dietary ingredient meets the requirements of 21 U.S.C. § 350b(a)(1), the new dietary ingredient may be immediately marketed without regard to the level of use.

Of course, companies that might market a new dietary ingredient using this theory must still confirm that their dietary supplement or dietary ingredient does not present "a significant or unreasonable risk of illness or injury under . . . conditions of use recommended or suggested in labeling," or "under ordinary conditions of use," which is the safety standard for all dietary supplements and dietary ingredients, whether old or new, notified or not.[128]

In addition, it is uncertain whether dietary ingredients that were "unlawfully" marketed prior to October 15, 1994 qualify as old dietary ingredients. FDA appears to take the position that if a dietary ingredient was not an FDA-approved food additive or GRAS substance prior to the passage of DSHEA, the dietary ingredient is a new dietary ingredient and cannot benefit from its pre-DSHEA marketing.[129] However, the language of § 350b(c), which delineates "old" from "new" dietary ingredients, provides that old dietary ingredients are those "marketed in the United States before October 15, 1994," without reference to the lawfulness of the marketing. Thus, one could argue that FDA's interpretation is incorrect and goes against the intent of DSHEA, which was to facilitate the route to market for dietary ingredients. Indeed, an allegation that the ingredient was unlawfully marketed pre-1994 would essentially reopen the EPO and BCO cases—the very reason why this provision of DSHEA was enacted.[130]

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128. 21 U.S.C. § 342(f)(1).

129. *See* F.H.G. Letter, *supra* note 126, at 2. In its letter alleging that androstenedione was a new dietary ingredient, FDA stated that it "[was] not aware of any information demonstrating that androstenedione was *lawfully* marketed as a dietary ingredient in the United States before October 15, 1994." (emphasis added).

130. *See supra* Section I.

V. CONCLUSION

In its quest to ensure that only safe dietary supplements get to the market, FDA's regulation of these products appears to be reverting to the agency's pre-DSHEA policy. By applying a narrow interpretation of certain ambiguous provisions of the law, imposing more requirements, and increasing the regulatory hurdles for dietary supplement manufacturers, FDA defies the congressional intent behind DSHEA. The dietary supplement industry can only hope that FDA's forthcoming guidance on new dietary ingredient notifications will answer some of the outstanding questions presented by DSHEA and strike a fair balance between the agency's desire to assure the safety of dietary ingredients and the manufacturers' desire for a reasonable and timely regulatory path to market for dietary ingredients.