

APPENDIX A



Council for Responsible Nutrition

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Mr. Michael Landa
Acting Director
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Food and Drug Administration
5100 Paint Branch Pkwy
College Park, MD 20740

Re: Docket No. FDA-2009-P-0298 -- Defining a “Dietary Ingredient”

The Council for Responsible Nutrition (CRN) is the leading trade association for the dietary supplement industry, representing manufacturers of dietary ingredients and of national brand name and private label dietary supplements.

CRN submits these comments to express its concern about FDA’s erroneous and unduly narrow interpretation of the definition of a “dietary ingredient.” In responses to manufacturers seeking to market new products, including in its response to the petition filed under the docket number referenced above, FDA has stated that synthetic ingredients cannot be dietary ingredients if they have not already been marketed as dietary substances prior to 1994, even if they are chemically identical to substances present in the food supply or in botanicals. CRN believes that this restriction of the dietary ingredient definition is not supported either by law or sound policy and in fact contradicts longstanding FDA regulations. The agency’s continued application of this approach would have a significant adverse impact on product innovation, thereby denying consumers access to safe, healthful products without scientific justification. CRN asks the agency to reconsider its approach in future responses to new dietary ingredient notifications and related documents.

I. Key Language and Purpose of DSHEA

Congress created the framework under which dietary supplements are currently regulated and marketed when it enacted the Dietary Supplement Health and Education Act (DSHEA) in 1994 as an amendment to the Federal Food, Drug, and Cosmetic Act (FDCA). The primary purpose of DSHEA was to ensure a suitable balance between securing consumer access to a wide variety of dietary supplements and providing FDA with appropriate regulatory oversight over the safety of dietary supplements and dietary ingredients. To help ensure broad access to products, dietary ingredients were excluded from the definition of “food additives” and, therefore, from the cumbersome premarket approval process imposed upon food additives. Dietary ingredients already on the market were excluded from the definition of a new dietary ingredient (NDI). To ensure FDA oversight over the safety of dietary ingredients, DSHEA required premarket

notification to the agency for NDIs, except for those that are a constituent of a food and have not been chemically altered.

A. Congress provided for a broad range of dietary ingredients.

Congress expressly intended to allow a broad range of dietary ingredients to be available in dietary supplements, limited only by the requirements that such ingredients not be previously-authorized drugs, antibiotics, or biologics, or ingredients previously authorized for investigation as a new drug, antibiotic, or biologic for which substantial clinical investigations have been instituted and made public.¹ To facilitate this broad goal, Congress drafted a “catch-all” provision in the dietary supplement definition in section 201(ff)(1)(E) of the FDCA, effectively sweeping into this category a limitless variety of dietary ingredients, provided that they are intended to supplement the diet and meet other provisions of the statute.

In drafting subparagraph (E), Congress provided that this subsection would not be limited to substances commonly used for human food or drink. The Senate Report, for example, identified Coenzyme Q 10 (commonly synthesized), glucosamine, and primrose oil as examples of substances expected to be included in the provision.² Notably, the language in this provision had shifted from “nutritional substance” in earlier draft bills to “dietary substance” in the enacted DSHEA so that a wider range of products would be covered.

FDA itself acknowledged the breadth of subparagraph (E) in the preamble to its regulation on requirements for nutrient content claims, health claims, and statements of nutritional support for dietary supplements.³ In explaining why it had authority to extend its rules governing nutrient content claims under the Nutrition Labeling and Education Act of 1990 (NLEA) to a broad range of dietary ingredients in dietary supplements, the agency stated:

. . . the legislative history of “other nutritional substances” reveals that its coverage is broad and could, in appropriate circumstances, include dietary ingredients without RDI’s or DRV’s (136 Congressional Record S 16609 (October 24, 1990)). In a discussion between Senators Metzenbaum and Symms before the passage of the 1990 amendments, Senator Symms stated: * * *
‘What follows is a list of a few of the items and foods that I believe would fall under the “other similar nutritional substances” category established by this bill: Primrose oil, black currant seed oil, coldpressed flax seed oil, “Barleygreen” and similar nutritional powdered drink mixes, Coenzyme Q 10, enzymes such as bromelain and quercetin, amino acids, pollens, propolis, royal jelly, garlic, orotates, calcium-EAP (colamine phosphate), glandulars,

¹ FDCA § 201(ff).

² S. REP. NO. 103-410 (1994), at 8-9.

³ 62 Fed. Reg. 49859 (Sept. 23, 1997).

hydrogen peroxide (H₂O₂), nutritional antioxidants such as superoxide dismutase (SOD), and herbal tinctures.’ Based on this colloquy, the agency interprets the list of dietary ingredients that fall under the definition of “dietary supplement” in section 201(ff) of the act as an explication of “other similar nutritional substances.”⁴

Included in this list are dietary ingredients that are generally marketed in synthetic form, such as Coenzyme Q10, and dietary ingredients that had not historically been used to supplement the diet, such as hydrogen peroxide. FDA’s acceptance of this broad range of dietary ingredients is consistent with the fact that neither the language of DSHEA nor the legislative history reveals any Congressional intent to exclude from the definition of “dietary ingredient” synthetic versions of food or botanical components if those synthetic ingredients had not previously been used to supplement the diet.

B. The language of DSHEA anticipates nature-identical synthetic dietary ingredients and those not previously intended to supplement the diet.

The statutory provisions relating to new dietary ingredients make clear that both nature-identical synthetic ingredients and those not previously used to supplement the diet may be dietary ingredients within the meaning of section 201(ff)(1)(E). Section 413 defines “new dietary ingredient” as a dietary ingredient not marketed in the United States before October 15, 1994, and which does not include any dietary ingredient marketed in the United States before that date.⁵ That section also requires that an NDI be the subject of a notification to FDA unless the dietary ingredients “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.”⁶ It is readily apparent from these provisions that when Congress treated chemically altered or synthesized materials differently from substances found in nature or wanted to impose a historical use requirement on dietary ingredients, it did so plainly. These provisions stand in marked contrast to section 201(ff)(1)(E), which includes no such limitations on chemically altered or synthesized ingredients nor any requirement for historical use of a substance to supplement the diet. FDA’s attempt to impose such requirements in the cases of synthetic conjugated linoleic acid (CLA) and homotaurine, discussed below, run afoul of the fundamental canon of statutory interpretation, “*expressio unius est exclusio alterius*” (the inclusion of one is the exclusion of others). That is, in light of the special and specific provisions for non-natural dietary ingredients and for historical uses in section 413 of the FDCA, the absence of such provisions in section 201(ff)(1)(E) makes clear that Congress intended to apply no such limitations on the dietary ingredients encompassed by subparagraph (E).

⁴ *Id.* at 49859-60.

⁵ FDCA § 413(c).

⁶ FDCA § 413(a)(1).

II. FDA’s Erroneous Approaches Toward Synthetic CLA and Homotaurine

CRN is highly concerned that in cases detailed further below, FDA appears to have interpreted DSHEA to exclude – on principle – synthetically derived dietary ingredients not previously used to supplement the diet. In the cases discussed below, the agency took the position that unless a synthetic ingredient has *historically* been used as a dietary substance, it can never be legally marketed as a dietary supplement under subparagraph (E). Citing an alleged lack of evidence that humans have used synthetic CLA or homotaurine for dietary purposes, the agency used this argument to block these products from the market.

A. FDA erroneously required evidence that humans commonly consumed synthetic CLA.

In August 2002, FDA responded negatively to an NDI notification for synthetic CLA, arguing that the substance did not fit the definition of a dietary supplement under the FDCA.⁷ CLAs are a group of polyunsaturated fatty acids commonly found in food. In the case of *synthetic* CLA, however, FDA focused on the fact that the ingredient did not come from a natural source, stating that “[h]umans do not commonly use *chemically manufactured or synthetic* CLA in food or drink.”⁸

As it would later do again in the homotaurine case discussed below, FDA erroneously imposed a historical use limitation on the dietary supplement definition to initially bar synthetic CLA from the market. In its response, the agency argued that the statutory language in section 201(ff)(1)(E) – “for use by man to supplement the diet by increasing the total dietary intake” – supported its interpretation of DSHEA.⁹ FDA reasoned that “one cannot increase the total dietary intake of something that is not customarily part of the diet in the first place.”¹⁰ Furthermore, the agency argued that the fact that synthetic CLA compounds may be “chemically indistinguishable from naturally occurring CLA compounds” was irrelevant to the analysis.¹¹ FDA took the position that, without evidence that *synthetic* CLA was historically a part of the diet, the substance could not be a dietary supplement. For the reasons set forth above, this argument finds no support either in the statutory text or in light of Congress’s intent in DSHEA.

⁷ Letter from Felicia B. Satchell, Director, Division of Standards and Labeling Regulations, Office of Nutritional Products, Labeling and Dietary Supplements, Center for Food Safety and Applied Nutrition, Food and Drug Administration to Jason Crush (Aug. 29, 2002).

⁸ *Id.* at 2 (emphasis added).

⁹ *Id.*

¹⁰ *Id.*

¹¹ *Id.* at 3.

The manufacturer responded to FDA’s denial with a detailed explanation of the language and Congressional intent behind the applicable provision – section 201(ff)(1)(E).¹² In a subsequent reevaluation of the ingredient, FDA avoided confronting these issues and instead relied on apparently later-discovered evidence that even *synthetic* CLAs are constituents of products already in the food supply.¹³ The agency thus ultimately accepted the NDI notification.

Although this development was fortunate for this particular manufacturer, the fact remains that FDA did not retract its historical use analysis for synthetic ingredients. Because the agency subsequently went on to apply its erroneous statutory interpretation to homotaurine, manufacturers of synthetic dietary ingredients still have ample reason to question whether FDA will attempt unjustly to bar from marketing such ingredients that have not historically been part of the human diet.

B. FDA wrongly concluded that synthetic homotaurine is not a dietary ingredient.

In February 2011, FDA denied a manufacturer’s petition that sought to have a synthetically manufactured seaweed extract called homotaurine classified as an NDI.¹⁴ The seaweed is a substance called dulse, which does have a history of human consumption. In its rationale for the denial, FDA alleged that homotaurine does not fit any of the dietary supplement categories defined in section 201(ff) of the FDCA. The agency first stated that it is not an “amino acid” within the meaning of section 201(ff)(1)(D) of the FDCA because FDA interprets that category to refer to a specific class of amino acids different from that of homotaurine. FDA next asserted that the ingredient is not a “botanical” under section 201(ff)(1)(C) because it was not extracted from dulse or any other botanical but rather was produced synthetically. Finally, the agency concluded that homotaurine could not fit under the catch-all provision in 201(ff)(1)(E), stating that “[h]omotaurine is not a vitamin, a mineral, an herb or other botanical, nor is there any *evidence that it has ever been a dietary substance for use by man to increase the total dietary intake.*”¹⁵

It is unclear from the language of FDA’s response whether the agency concluded that the manufacturer’s homotaurine could not fall within section 201(ff)(1)(E) because it is synthetic, or whether FDA also would have concluded that even homotaurine extracted from dulse could not come within that clause because homotaurine itself had not previously been a dietary substance

¹² Letter from L. Scott Bass and Diane C. McEnroe to Felicia B. Satchell, Director, Division of Standards and Labeling Regulations, Office of Nutritional Products, Labeling and Dietary Supplements, Center for Food Safety and Applied Nutrition, Food and Drug Administration (Sept. 13, 2002).

¹³ FDA found that synthetic CLAs are present in the food supply as components that form when vegetable oil undergoes processing. Letter from Susan J. Walker, Acting Director, Division of Dietary Supplement Programs, Office of Nutritional Products, Labeling and Dietary Supplements, Center for Food Safety and Applied Nutrition, Food and Drug Administration to L. Scott Bass and Diane C. McEnroe, at 2 (Mar. 12, 2003).

¹⁴ Letter from Michael M. Landa, Acting Director, Center for Food Safety and Applied Nutrition, Food and Drug Administration to Marc Ullman, Esq. (Feb. 23, 2011).

¹⁵ *Id.* at 6 (emphasis added).

intended to supplement the diet. In any event, both rationales stand at odds with the plain language of and Congressional intent behind DSHEA, for the reasons documented above.

III. FDA Should Refrain from Applying its Unfounded Narrow Definition of “Dietary Ingredient” in Future Evaluations of NDI Notifications

The cases above illustrate that FDA has taken an incorrect and unduly restrictive approach to determining what constitutes a dietary supplement. As discussed above, we believe the agency’s reading of DSHEA – particularly in light of Congress’s clear intent to expand access to dietary supplements – is erroneous and detrimental to the public. CRN has expressed its views on the intent and implementation of DSHEA in the past,¹⁶ and CRN urges FDA to consider the full impact that this particular misinterpretation of the statute will have.

A. FDA’s erroneous approach may have negative consequences for public health and the environment.

FDA’s misreading of the statute would have the unintended consequence of stifling scientific progress, perhaps even in ways that could prove detrimental to public health or have negative environmental consequences. Imagine that future research shows that a minor constituent of a particular fruit, *e.g.*, a banana, has demonstrable beneficial effects on the structure or function of the body, but it is impractical, infeasible, or worse – environmentally detrimental or unsustainable – to extract this component from its natural source on a commercial scale. Under the analysis FDA applied regarding synthetic CLA and homotaurine, the agency would not accept a nature-identical synthetic version of this newly-identified component as a dietary ingredient absent evidence that the *synthetic* version was a historical component in the human diet. The end result would be either denying consumers access to an ingredient shown to be beneficial to human health *or* forcing the production of such an ingredient in an environmentally irresponsible manner. Neither of these results makes for prudent policy, and neither is what Congress intended.

B. FDA’s erroneous approach disproportionately disfavors synthetically derived nature-identical ingredients and is inconsistent with the agency’s favorable treatment of synthetic products in the past.

While CRN is concerned that FDA could apply its erroneous historical use limitation to any dietary ingredient, the fact remains that synthetic versions of ingredients will be at a disproportionate disadvantage in the analysis. The simple fact is that it will be more difficult to establish the historical use of *synthetic* ingredients in the human diet, versus ingredients that come from natural sources.

Quite apart from the fact that DSHEA itself imposes no requirement that FDA consider the method by which a dietary ingredient is extracted, derived, or manufactured, FDA already

¹⁶ CRN Comments Re: Docket No. 2004N-0454, Premarket Notification for New Dietary Ingredients (Feb. 1, 2005); CRN Comments Re: Docket No. 2004N-0454, Premarket Notification for New Dietary Ingredients (Nov. 15, 2004).

has a history of recognizing the validity of synthetic ingredients. The agency has accepted synthetically derived nature-identical dietary ingredients as lawfully marketed dietary supplements in the past. Some examples are:

- melatonin (a substance found naturally in animal tissue, but produced synthetically);
- zeaxanthin (a carotenoid found in fruits and vegetables, but generally produced synthetically);
- coenzyme Q 10 (a substance found in meat, but manufactured synthetically, as noted above).¹⁷

Several examples illustrate that FDA recognizes the equivalence of naturally extracted sources and synthetic sources of dietary ingredients. For example, FDA has affirmed as GRAS both natural and synthetic riboflavin;¹⁸ vitamin A;¹⁹ and vitamin D.²⁰ Similarly, FDA approved the food additive Vitamin D3 in both natural and synthetic forms.²¹

Most significantly, FDA's nutrition labeling regulation states that a food would be deemed misbranded if its labeling states or implies "[t]hat a natural vitamin in a food is superior to an added or synthetic vitamin."²² This prohibition dates back to the late 1960s, when the agency vigorously defended its position on this issue during two years of public hearings on special dietary food restrictions.²³ As recently as the late 1990s, FDA reaffirmed the validity of the prohibition, stating that it was "aware of nothing that establishes that a claim of difference between the natural and synthetic version of the same form of a nutrient is not misleading."²⁴ This longstanding agency position would make no sense if FDA began to deny the validity of synthetic ingredients as dietary ingredients or suggest a material distinction between synthetic and natural versions of identical ingredients.

Finally, FDA has long maintained that the method of a product's manufacture is not a material fact unless it renders a substantive change in the finished product itself. FDA

¹⁷ Letter from L. Scott Bass and Diane C. McEnroe to Felicia B. Satchell, Director, Division of Standards and Labeling Regulations, Office of Nutritional Products, Labeling and Dietary Supplements, Center for Food Safety and Applied Nutrition, Food and Drug Administration, at 8 (Sept. 13, 2002).

¹⁸ 21 C.F.R. § 184.1695(a)

¹⁹ 21 C.F.R. § 184.1930(a)

²⁰ 21 C.F.R. § 184.1950.

²¹ 21 C.F.R. § 172.380 (a).

²² 21 C.F.R. § 101.9(k)(4).

²³ These hearings took place between 1968 and 1970. See 38 Fed. Reg. 2143, 2147, 2150 (Jan. 19, 1973) (summarizing FDA's conclusions based on the hearings, including its finding that "[t]here is no nutritional difference between a vitamin provided by a synthetic source and the same vitamin provided by a natural source....").

²⁴ 62 Fed. Reg. 49826, 49841 (Sept. 23, 1997).

articulated this position most clearly and vigorously in the domain of genetically engineered foods. Despite receiving many comments from stakeholders requesting that the agency impose mandatory disclosure requirements for foods or food ingredients that came from bioengineered sources, the agency stated that it was “not aware of any information showing that foods derived by these new methods differ from other foods in any meaningful or uniform way, or that, as a class, foods developed by the new techniques present any different or greater safety concern than foods developed by traditional plant breeding.”²⁵ Even in this controversial domain, FDA clearly found the manner of manufacture not to be “material” within the meaning of the FDCA, and therefore concluded that the agency lacked statutory authority to require any special labeling for genetically engineered foods.²⁶

Simply stated, FDA’s erroneous and restrictive approach toward the evaluation of synthetically derived nature-identical new dietary ingredients and those without a history of use for supplementing the diet has the potential for drastic negative consequences for human health and the environment. The agency’s approach finds no support in the plain language or the Congressional intent of DSHEA and stands in contrast to FDA’s own approach to synthetically produced materials in other comparable areas.

IV. Conclusion

CRN urges FDA to consider these comments as it develops its NDI notification guidance and evaluates future NDI notifications. The public interest will best be served if the agency reconsiders its interpretation of the dietary ingredient definition in light of the plain language and clear underlying intent of DSHEA.

Respectfully submitted,



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²⁵ 57 Fed. Reg. 22984, 22991 (May 29, 1992). The agency reaffirmed this belief in developing its 2001 guidance on this same topic. See Draft Guidance for Industry: Voluntary Labeling Indicating Whether Foods Have or Have Not Been Developed Using Bioengineering (January 2001) (stating that “[t]he agency is still not aware of any data or other information that would form a basis for concluding that the fact that a food or its ingredients was produced using bioengineering is a material fact that must be disclosed under sections 403(a) and 201(n) of the act.”).

²⁶ FDA’s position has been upheld in court. See, e.g., *Alliance for Bio-Integrity v. Shalala*, 116 F. Supp. 2d 166 (D.D.C. 2000) (rejecting a direct challenge to FDA’s 1992 Statement of Policy regarding the labeling of bioengineered foods); *Stauber v. Shalala*, 895 F. Supp. 1178 (W.D. Wis. 1995) (finding that FDA did not act arbitrarily and capriciously in not requiring the labeling of dairy products derived from cows treated with Bovine Somatotropin (BST)).