



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

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Date: December 12, 2003
From: **Consumer Safety Officer, Division of Dietary Supplement Programs, Office of Nutritional Products, Labeling and Dietary Supplements, HFS-810**
Subject: **75-Day Premarket Notification of New Dietary Ingredients**
To: **Dockets Management Branch, HFA-305**

Subject of the Notification: **Conjugated Linoleic Acid (CLA)**
 Tonalin Brand

Firm: Christopher & Weisberg, P.A.
and Sidney Austin Brown & Wood, LLP for their client Natural ASA

Date Received by FDA: June 17, 2002

90-Day Date: September 15, 2002

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification and related correspondence for the aforementioned substance should be placed on public display in docket number 95S-0316 as soon possible since it is past the 90-day date. Thank you for your assistance.

Victoria L. ...

95S-0316

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MAR 12 2003

Mr. I. Scott Bass, Esq.
Ms. Diane C. McEnroe, Esq.
Sidley Austin Brown & Wood LLP
787 Seventh Avenue
New York, New York 10019

Dear Mr. Bass and Ms. McEnroe:

This is in further response to the June 17, 2002¹ new dietary ingredient notification for conjugated linoleic acids (CLAs) submitted by Jason S. Crush on behalf of your client, Natural ASA, and your supplemental submission of September 13, 2002 concerning the agency's interpretation of section 201(ff)(1) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 321(ff)(1)). On August 29, 2002, my office issued a letter to Mr. Crush in response to the June 2002 new dietary ingredient notification. In that letter, we asserted that synthetically produced CLAs were not a dietary ingredient defined in § 321(ff)(1) and that, therefore, these substances could not lawfully be used as a dietary ingredient in a dietary supplement. In your letter of September 13, 2002, you asserted that our conclusion that synthetic CLAs are not a dietary ingredient under § 321(ff)(1) is incorrect.

We have reconsidered our determination about the status of CLAs under § 321(ff)(1) and now believe that the CLAs described in the June 2002 notification are a dietary ingredient under § 321(ff)(1)(F) and may be lawfully marketed in dietary supplements. We explain the basis for our position below.

CLAs are a group of related polyunsaturated fatty acids that exist as positional and stereoisomers of conjugated dienoic octadecadienoate. Native plant oils do not contain detectable amounts of CLAs. However, CLAs are present in a variety of foods. CLAs are present in meat and dairy products. They also are present in processed vegetable oils and products made from processed vegetable oils (for example, margarines). The absolute and relative amounts of different CLAs present in a particular food are not constant, but vary depending on the characteristics of the raw materials and the processing that they have been subjected to.

¹June 17, 2002 is the date FDA received the notification and is therefore the filing date of the notification under 21 C.F.R. § 190.6(c). The notification is dated June 10, 2002.

The definition of "dietary supplement" is set forth at 21 U.S.C. 321(ff). Among other requirements, a dietary supplement must be intended to supplement the diet and contain 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).

As fatty acids, CLAs are not vitamins, minerals, or amino acids. They are not an herb or other botanical because they are not a plant or a physical part of a plant. They also are not a concentrate, metabolite, constituent, extract, or combination of a vitamin, mineral, amino acid, or of any herb or other botanical. Therefore, to be a dietary ingredient, CLAs would have to qualify as a "dietary substance" under § 321(ff)(1)(E) or as a concentrate, metabolite, constituent, extract, or combination of a dietary substance under § 321(ff)(1)(F).

In my office's August 29, 2002 letter to Mr. Crush, we stated that the information in the June 2002 notification led us to conclude that Natural ASA's CLAs were synthetic and that synthetic CLAs are not a "dietary substance for use by man to supplement the diet by increasing the total dietary intake" under § 321(ff)(1)(E) because, unlike naturally occurring CLAs, they are not commonly used as food or drink by humans. We also stated that synthetic CLAs were not a concentrate, metabolite, constituent, extract, or combination of a "dietary substance" and therefore did not qualify as a dietary ingredient under § 321(ff)(1)(F). We took this position because we were aware of no "dietary substance" that contained synthetic CLAs and, in order for synthetic CLAs to be a "constituent" of a substance, they would need to have been physically a part of that substance in the first place. We therefore concluded that synthetic CLAs were not a dietary ingredient under § 321(ff)(1)(E) or (F).

Neither the June 2002 notification nor the September 2002 supplemental submission contained data showing that synthetic CLAs were components of foods commonly consumed by humans. However, we are now aware of information that provides a basis to conclude that synthetic CLAs are in fact constituents of certain foods that are themselves clearly within the scope of "dietary substance" as defined in § 321(ff)(1)(E). For example, the CLAs in processed vegetable oils are not an inherent component of raw vegetable oils but instead are made as a result of the processing that the oil undergoes;

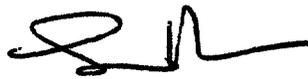
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approximately similar relative amounts to each other) would be a dietary ingredient under § 321(ff)(1)(F) and could lawfully be used in dietary supplements.

This letter supersedes the August 29, 2002 letter to Mr. Crush. The agency does not, at this time, object to the marketing of the CLAs that were the subject of the June 2002 new dietary ingredient notification.

Please contact us if you have further questions on this matter.

Sincerely yours,



**Susan J. Walker, M.D.
Acting Director
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Office of Nutritional Products, Labeling
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September 13, 2002

BY FACSIMILE

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Dear Ms. Satchel:

We respond to your letter dated September 11, 2002. As requested, this response provides substantive support for our position that the agency's legal interpretation of 21 U.S.C. §201(ff)(1)(E) is not correct.

In your recent NDI response letter, you state that the ingredient at issue is neither an herb or botanical nor a dietary ingredient meeting the catch-all definition in Section 201(ff)(1)(E). You further state that an "E" dietary supplement must be "a substance commonly use as human food or drink," relying upon part of a dictionary definition.

For the reasons set forth below, we believe that Congress' intent in clause E is crystal clear. If FDA were correct that "dietary" meant common food or drink, then there would be no "dietary supplements" because people did not commonly eat herbs or concentrates, metabolites or extracts as their daily meals. This new position also contradicts prior agency pronouncements.

I. WHY CLAUSE E EXISTS

Prior to the passage of the Dietary Supplement Health and Education Act ("DSHEA"), FDA took a constricted view of permissible "foods" for sale in supplement form. There was no "dietary supplement" category in the law, and FDA viewed only the

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vitamins and minerals encompassed by Section 411 as legally marketed foods. FDA challenged products other than RDA vitamins and minerals as "unsafe food additives," the theory being that any ingredient added to a capsule or tablet rendered the resulting dietary supplement a food additive. Industry had no defense to those charges.

After 15 years, FDA's food additive theory was reversed in *United States v. Viponte Ltd. Black Currant Oil-Traco Labs, Inc.*, 984 F.2d 814 (7th Cir. 1993) and *United States v. 29 Cartons of ... an Article of Food... Oakmont Investment Co.*, 987 F.2d 33 (1st Cir. 1993). This was during DSHEA negotiations, and industry remained concerned that FDA would challenge future ingredients under other strained theories.¹ Industry thus pushed for an expansive definition of dietary supplement during Congressional hearings.

The "E" definition, as drafted by Congress, was intended explicitly to encompass a large number of substances on the market that were not vitamins, minerals, or amino acids, and that were not found in food or drink. The use of the term "dietary" in subsection E replaced the term "nutritional" in earlier draft bills in order to cover a wider range of products. If Congress had restricted the definition in the way FDA now proposes, there would be a large number of "grandfathered" products that would no longer be legal, despite their long history of use in the United States.

Section 201(ff) thus states, in pertinent part:

•"(ff) The term "dietary supplement" –

(1) means 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

¹ Of particular concern was Coenzyme Q10, a popular supplement at the time, which was both synthetically and naturally derived, that is used for cardiovascular health. Other ingredients that were on the market pre-DSHEA that fall within this catch-all included glucosamine - made from the shells of shellfish - shark cartilage (discussed at pgs. 132-133 of the Dietary Supplement Hearings before a Subcommittee on Appropriations, 103rd Cong., 1st Sess., 1993), shark liver oil, melatonin, and various enzymes, glandulars, and probiotics.

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- (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 in a form described in section 411(c)(1)(B)(i); or
 - (ii) complies with section 411(c)(1)(B)(ii);
 - (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

Except for purposes of section 201(g), a dietary supplement shall be deemed to be a food within the meaning of this Act."

FDA acknowledged the reason for Clause E in its September 23, 1997 publication of the Final Rule regarding *Requirements for Nutrient Content Claims, Health Claims, and Statements of Nutritional Support for Dietary Supplements*, 62 Fed. Reg. at 49859-60:

... 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 S16609 (October 24, 1990). In a discussion between Senators Metzenbaum and Symms before the passage of the 1990 amendments [relating to NLEA], 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 Q10, enzymes such as bromelain and quercetin, amino acids, pollens, propolis, royal jelly, garlic, orotates, calcium-EAP..., glandulars, hydrogen peroxide..., nutritional antioxidants such as superoxid dismutase..., and herbal tinctures" Based upon 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."

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FDA also spoke to the issue as part of its participation in the Interagency Committee on Human Research document entitled "Definition of Human Research":

36. Dietary Supplements: Nutrient Ingredients. (Includes all essential and non-essential nutrients and other food constituents that are typically described in standard nutrition reference texts or that fall within the review parameters of the Food and Nutrition Board. National Academy of Sciences in consideration of Dietary Reference Intakes (DRI's). Thus, this category would include substances recognized as essential nutrients - i.e., iron, vitamin C, essential amino acids, etc. - and substances not generally recognized as being essential but that have or may have a dietary or nutrient role in humans).

37. Dietary Supplements: Botanical and Other Non-Nutrient Ingredients. (Includes all plant-derived materials whether fresh, preserved, or dried full plants, plant parts, plant species mixtures, plant extracts, "herbs" or "herbal products," regardless of whether they meet the dictionary definition of herb or that are comprised of parts, extracts, or preparations of woody plants will be included as botanical ingredients. Other Dietary Substances comprise a broad and diverse group of substances that are neither of plant origin nor alone could be viewed as "nutrients" within the common-sense meaning of the term. For example, such substances could include animal or plant metabolites or constituents, microorganisms and certain of their constituents, etc. The substances subject to inclusion in this category are limited by the statutory definition of "dietary supplement" in the DSHEA - i.e., not an approved or investigational drug, not a conventional food or meal replacement, and intended to be used to supplement the diet, etc.)

This year, the Institute of Medicine ("IOM"), in its Proposed Framework for Evaluating the Safety of Dietary Supplements ("IOM Proposal"), written pursuant to a referral from FDA, emphasized the "broad spectrum of products that qualify as dietary supplements" under DSHEA, categorizing them as "vitamins, minerals, herbs or other botanicals, amino acids, animal-derived products, hormones and hormone analogs, enzymes, and concentrates, metabolites, constituents, or extracts of these. Within each of these categories, products may be pure single entities of known or unknown chemical

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components, mixtures in which all or some components are known or mixtures of unknown chemical components." IOM Proposal, pg. 14.²

In short, neither FDA nor any other authoritative body has limited the plain meaning of clause E to a redundant definition of food.

II. THE SAFEGUARD SURROUNDING THE CLAUSE E CATCH-ALL

Congress placed limitations on this broad definition of dietary supplement to provide assurances against unsafe dietary supplements being introduced to the market.

First, DSHEA restricts the definition by permitting dietary supplements only in special forms (capsule, tablet, powder, liquid). It also requires that they be ingested. Subsection (ff)(2)(A). This latter provision prevents against the marketing of dietary supplements as nasal sprays, parenterals, creams or sublinguals.

Second, and more critical, is the new safety section. Section 402(f) added a new dietary ingredient adulteration clause, a new "unreasonable risk of illness or injury" standard for dietary supplements that is more rigorous than the prior section 402(a) standard, and a section providing emergency HHS powers for dangerous products.

The first safety screen is thus the 75-day pre-market notification. FDA has the ability to evaluate new substances under Section 413 and 402(f)(1):

[a product is adulterated if it] "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."

The second screen is the higher safety standard in the 402(f) adulteration standard for dietary supplements:

[a product is adulterated if it is a] "dietary supplement or contains a dietary ingredient that presents a significant or unreasonable risk of illness or injury under (i) conditions of use recommended or suggested in labeling, or (ii) if no

² Indeed, two of the six ingredients selected for the IOM prototype reviews include products which would not meet FDA's proposed definition of dietary supplement. Glucosamine, one of the top 25 dietary supplements sold in 2001, which was on the market in 1994 is made from the shells of shellfish.

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conditions of use are suggested or recommended in the labeling, under ordinary conditions of use."

Underscoring Congress' awareness of the safety underpinnings of the clause E/402(f) interrelationship is this testimony by then FDA Commissioner Kessler:

Mr. Chairman, I don't have a problem if someone wants to sell those products as long as there is no problem with safety, and as long as they don't make a claim that can't be supported. If someone wants to put sawdust in a bottle and sell it for \$14, it is okay with me as long as they don't put a claim that it is useful to prevent cancer, heart disease, diabetes, or arthritis. That is where I draw the line. When supplements are really being sold as drugs in disguise promoted to treat serious disease, then I believe we have a problem. Dietary Supplement Hearings before a Subcommittee of the House Appropriations Committee, 103rd Congress, 1st Sess., pg. 82 (1993).

The third safety screen is Section 201(ff)(3), which states that a product cannot be a dietary supplement if it was first marketed as a new drug or biologic³ (or subject to a substantial, publicized IND). That provision is bolstered by point one of the official legislative history⁴, which once again reflects Congress' awareness that non-foods could be dietary supplements.

III. THE AUGUST 29, 2002 INTERPRETATION OF CLAUSE E READS DSHEA OUT OF THE LAW AND ELIMINATES A MAJOR SEGMENT OF THE EXISTING MARKET

DSHEA added a new category to the FFCDA. The definition of "dietary supplement" is, as FDA recognized in its 1997 Federal Register publication, an explication – not a delimitation. Were FDA's current theory correct, then "dietary supplement" could not include any product meeting clauses C-F of Section 201(ff). People have not traditionally "commonly" consumed botanical metabolites or synthetically derived isolated amino acids for meals.

Section 201(f), the definition of "food," existed since 1938 and covered commonly used food or drink. That is precisely why, after FDA refused to recognize

³ Note that Congress implicitly included biologics as potential dietary ingredients (as well as synthetic drugs).

⁴ Congressional Record October 6, 1994 at H1180. See also Congressional Record August 13, 1994 at S11709.

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dietary supplements other than RDA vitamins and minerals as "food," DSHEA was necessary. The products covered by clauses C-F are precisely things other than commonly-used food or drink.

In addition, subsection (2)(B) states that a dietary ingredient cannot be "represented as a conventional food or as a sole item of a meal or the diet". If it cannot be a conventional food, but must, as FDA suggests, be from commonly-used food or drink, then it can only be a "concentrate, metabolite, constituent, extract or some derivative" of a food or drink. If that is the case, Congress would have combined this concept with subsection F, because E would have been superfluous.

Finally, the last clause in the definition of "dietary supplement" states that, with the exception of the use of the term "foods" in the definition of drugs, supplements are foods. There would be no need to say that a dietary supplement is a food or drink twice. Subsection E becomes superfluous. Subsection E means what it says: "other dietary ingredients" - "those that are intended to supplement the diet by increasing total dietary intake".

Other Products

FDA's current position is inconsistent with positions it has taken on a number of other NDI's, the most telling being plant stanols/sterols. Despite the use of the term "plant" in plant stanols/sterols, these products are tall oil, which is derived as a by-product of the kraft paper pulping process - not something commonly used for food or drink, but a waste product. Docket Nos. OOP-1275 and OOP-1276. Phytosterols are not vitamins, minerals, herbs or botanicals, amino acids, or a concentrate, metabolite, constituent, extract or combination of any of these. Yet, FDA voiced no objection to the NDI filings for these substances. Humifulvate, a byproduct of Hungarian peat, fared similarly. (Docket No. 95S-0316).

The phytosterol example is strikingly similar to the product at issue here. This substance is not constructed from other chemicals or modified by adding chemical moieties or substituents. It is derived from an edible oil consumed as food, which is structurally altered by exposure to a set of conditions. It is also found in other food forms at varying concentrations. It has known functional effects in the body, and humans consume it regularly.

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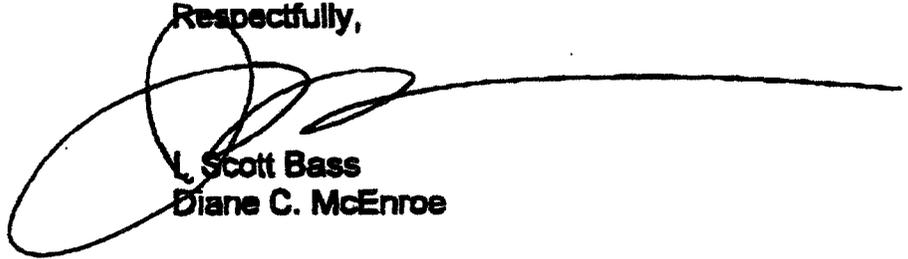
Examples of other dietary ingredients accepted as dietary supplements and relevant to this analysis are:

- Melatonin, found in animal tissue but produced synthetically
- Zeaxanthin, a carotenoid found in fruits and vegetables but produced synthetically
- Arachidonic acid and tocosahexaonic acid, present in fish oil, but manufactured through a fermentation process
- Coenzyme Q10, found in meat but manufactured synthetically
- Shark cartilage, discussed earlier
- Glucosamine, derived from the shells of shellfish
- Glandular extracts

CONCLUSION

We respectfully submit that this submission meets the "substantive" requirement set forth in your September 11th letter. As we discussed with FDA, we hope to follow up with: (a) a meeting with the Office of Chief Counsel and three industry attorneys; (b) a possible meeting with ONPLDS and representatives of our client to discuss the scientific statements in your recent NDI letter.

Respectfully,



L. Scott Bass
Diane C. McEnroe

ISB:dmp

cc: **Christine Lewis Taylor, Ph.D.**
Daniel Troy, Esq.