



AUG 29 2002

Jason S. Crush
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Dear Mr. Crush:

This letter is in response to your notification, dated June 10, 2002, submitted to the Food and Drug Administration (FDA) for a new dietary ingredient pursuant to 21 U.S.C. 350b(a)(2) [section 413 (a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)]. FDA received your submission on June 17, 2002. Your letter notified FDA that your client, Natural ASA (and its affiliates) has been marketing conjugated linoleic acid (CLA) products in the United States (U.S.) since 1998, and at the time of introduction into the U.S. market in 1998, no pre-market notification letter was submitted to FDA. Your letter also stated that no pre-market notification letter was submitted because at that time Natural ASA formed the opinion that the CLA contained in its products was not a new dietary ingredient as defined by 350b of the Act.

Your notification further stated that CLA is a naturally occurring ingredient, which is available in meat and dairy products, and chemically equivalent to the CLA in Natural ASA's products and therefore makes a pre-market notification letter not required.

However, your notification also stated that the products marketed by Natural ASA contain CLA that is isolated and purified from safflower oil and contain higher concentrations of CLA than those found in meat and dairy products. Your notification stated that this is the basis for the present notification, and to be in full compliance with regulations in view of possible differing opinions as to the status of CLA as a new dietary ingredient.

21 U.S.C. 350b(a)(2) requires that a manufacturer or distributor of a dietary supplement that contains a new dietary ingredient submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion.

CLA is a term that refers to a group of polyunsaturated fatty acids that exist as positional and stereoisomers of conjugated dienoic octadecadienoate. Plant oils do not contain significant amounts of CLA. However, CLA can be produced synthetically by exposing plant oils rich in linoleic

acid, such as safflower and soybean, to base and heat.¹ The CLA product produced in this manner contains predominantly the cis-9, trans-11, and the trans-10, cis-12 isomers.^{2,3} The isomeric ratio and profile of synthetic preparations of CLA vary significantly from the naturally occurring CLA of meat and dairy products.³ Additionally, human consumption of linoleic acid from sources such as safflower and soybean does not convert it to CLA.⁴ Your notification contains, among other things, technical data on the CLA that your client produces. Your client's CLA product contains the cis-9, trans-11, and the trans-10, cis-12 isomers in amounts that are typical of synthetic preparations.⁵

FDA has carefully evaluated your submission and has concerns about the evidence on which you rely to support your conclusion that CLA is a new dietary ingredient and conforms to the statutory definition of a dietary supplement. The CLA that your client produces is not a dietary ingredient under section 21 U.S.C. 321 (ff)(1) of the Act.

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).

The CLA that is produced by your client is not a vitamin, mineral, or amino acid under 21 U.S.C. 321 (ff)(1) (A), (B), or (D). Because it is not a plant or a physical part of a plant (e.g., a leaf, stem, or root) it is not an herb or other botanical under 21 U.S.C. 321 (ff)(1)(C). Nor does FDA believe that this chemical is a "dietary substance for use by man to supplement the diet by increasing the total dietary intake" under 21 U.S.C. 321(ff)(1)(E). The term "dietary substance" is not defined in the Act. FDA interprets it with its common or usual meaning. Webster's II New Riverside University Dictionary defines "dietary" as "of or pertaining to the diet" and "diet" as "an organism's usual food or drink." Therefore, a "dietary substance" means a substance that is commonly used as human food or drink. The statutory language "for use by man to supplement the diet by increasing the total dietary intake" supports this interpretation; and one cannot increase the total dietary intake of something that is not customarily part of the diet in the first place. Humans do not commonly use chemically manufactured or synthetic CLA as food or drink.

Moreover, synthetic CLA is not a dietary ingredient as defined by 21 U.S.C. 321 (ff)(1)(F) because it is not a concentrate, metabolite, constituent, extract, or combination of any of the other types of

¹ Natural Medicines Comprehensive Database; Conjugated Linoleic Acid Monograph (2002).

² Johnson, LW. Integrative Medicine Consult 3(3): 17,21 (2001).

³ Belury, M.A. Annu. Rev. Nutr. 22:505-531 (2002).

⁴ Herbel BK, McGuire MK, McGuire MA, Shultz TD. Am J Clin Nutr. 67:332-337 (1998).

⁵ Exhibit A: Natural Tonalin, the essential supplement Product Specification Natural Tonalin, the essential supplement Technical Data-Bulk Oil Natural Tonalin, the essential supplement Technical Data – Bulk Capsules.

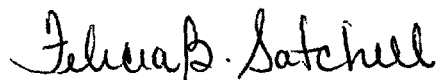
dietary ingredients. This synthetic group of compounds cannot be obtained by concentrating, metabolizing, or combining vitamins, minerals, amino acids, botanicals, or dietary substances. Nor is the substance in question a constituent or extract of any other type of dietary ingredient. Some CLA compounds are constituents of meats and dairy products, they are metabolic intermediates that occur in low amounts and therefore extraction of these compounds from the natural sources are cost prohibitive.³ Although some forms of synthetic CLA compounds may be chemically indistinguishable from naturally occurring CLA compounds, a substance that has never been physically a part of a whole cannot be a constituent or an extract of that whole, irrespective of the starting material as the source.

Further, synthetic CLA is not a constituent of a dietary substance because it is not an inherent component of anything commonly used as human food or drink. Likewise, it is not an extract of any dietary substance. Therefore, synthetically produced CLA is not a dietary ingredient under 21 U.S.C. 321 (ff)(1).

In summary, a product like yours does not appear to be a dietary ingredient or a dietary supplement as defined in 21 U.S.C. 321 (ff). For the reasons discussed above, the Agency concludes that synthetic CLA or Tonalin™ does not meet the definition of a dietary supplement. Introduction of such a product into interstate commerce is prohibited under 21 U.S.C. 331 (a). In addition, because the Agency concluded that the subject of your notification cannot be marketed as a dietary supplement, FDA did not review the evidence of safety information you submitted on CLA or Tonalin™.

Your submission will be kept confidential for 90 days from the date of receipt, and after September 15, 2002, your notification will be placed on public display at FDA's Docket Management Branch (Docket No. 95S-0316). Commercial and confidential information will not be disclosed to the public.

Sincerely yours,



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