



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: January 30, 2004 6044 '04 FEB -4 P152
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: BioCell Collagen II (Hydrolyzed (denatured) chicken
sternal type II collagen)

Firm: Biocell Technology LLC

Date Received by FDA: May 21, 2003

90-Day Date: August 21, 2003

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 Lutwak

95S-0316

RPT195



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, Maryland 20740

Suhail Ishaq
Vice President
Biocell Technology, LLC
5000 Birch Street
West Tower Suite 4000
Newport Beach, CA 92660

AUG - 5 2003

Dear Mr. Ishaq:

This is to inform you that the notification, dated March 19, 2003, you submitted pursuant to 21 U.S.C. 350b(a)(2) (section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)) was filed by the Food and Drug Administration (FDA) on April 28, 2003. Your notification concerns the substance called "hydrolyzed (denatured) chicken sternal type II collagen (BioCell Collagen II®)" that you intend to market as a new dietary ingredient.

The notification states that the dietary supplements containing BioCell Collagen II® will be marketed in a powder-based tablet or hard-shell capsule, an oil-based soft gelatin capsule, or a liquid-based product. Each capsule, tablet or liquid product will contain up to 3,000 mg of BioCell Collagen II® per serving. According to the notification, the conditions of use of the dietary supplements containing BioCell Collagen II® are "1 to 2 grams daily or as desired." The notification does not indicate the duration of use of the dietary supplements containing BioCell Collagen II®. In addition, the capsule size appears to exceed the daily amount.

Under 21 U.S.C. 350b(a), the manufacturer or distributor of a dietary supplement that contains a new dietary ingredient that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered must 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. Under section 350b(a)(2), there must be a history of use or other evidence of safety establishing that the new dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the dietary supplement is deemed to be adulterated under 21 U.S.C. 342(f)(1)(B) because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or reasonable risk of illness or injury.

FDA has carefully considered the information in your submission, and the agency has significant concerns about the evidence on which you rely to support your conclusion that a dietary supplement containing hydrolyzed (denatured) chicken sternal type II collagen, when used under the conditions recommended or suggested, will reasonably be expected to be safe. FDA has determined that the two published clinical studies (Barnett *et al.*, 1998 and Trentham *et al.*, 1993) that you cite do not provide an adequate basis for a conclusion that the dietary supplement containing BioCell Collagen II® will reasonably be expected to be safe because the information submitted does not relate qualitatively and quantitatively to the BioCell Collagen II®. Specifically, the type II collagen used in the two clinical studies cited is undenatured while your type II collagen is denatured. Furthermore, the highest dose of undenatured type II collagen used in the two clinical trials was thousands of times lower than the recommended dose of your BioCell denatured type II collagen. Clearly this clinical data cannot be used to support the safe use of your product.

Your submission also included the results from a one-day acute oral toxicity study of BioCell Collagen II® in rats that you assert provides a basis to conclude that human consumption of 1 to 2 grams daily of BioCell Collagen II® is reasonably expected to be safe. However, this short-term study is inadequate to establish that BioCell Collagen II is reasonably expected to be safe for long-term use in humans.

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that hydrolyzed (denatured) chicken sternal type II collagen in BioCell Collagen II®, when used under the conditions recommended or suggested in the labeling of your product, will reasonably be expected to be safe. Therefore, your product may be adulterated under 21 U.S.C. 342(f)(1)(B) as a dietary supplement that contains 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. Introduction of such a product into interstate commerce is prohibited under 21 U.S.C. 331(a) and (v).

Your notification will be kept confidential for 90 days after the filing date of April 4, 2003. After the 90-day date, the notification will be placed on public display at FDA's Docket Management Branch in docket number 95S-0316. Prior to that date, you may wish to identify in writing specifically what information you believe is proprietary, trade secret or otherwise confidential for FDA's consideration.

Page 3-Suhail Ishaq

If you have any questions concerning this matter, please contact Victoria Lutwak at (301) 436-1775.

Sincerely yours,

A handwritten signature in black ink, appearing to read 'S. Walker', with a long horizontal line extending to the right.

**Susan J. Walker, M.D.
Acting Division Director
Division of Dietary Supplement Programs
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition**

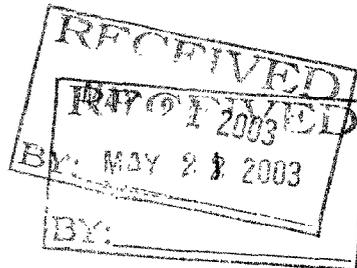
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Wednesday, March 19, 2003

Office of Nutritional Products
Labeling and Dietary Supplements (HFS-800)
Food and Drug Administration
200 C Street, S.W.
Washington, D.C. 20204



TO WHOM IT MAY CONCERN:

While two New Dietary Ingredient Notification submissions have already been made to the FDA and posted on public display at FDA's Document Management Branch for the ingredient "Chicken Type II Collagen", we are submitting the following information as notification of a dietary ingredient because our product is manufactured using a different process. The previous notifications made by Chicken Cart Inc. on March 9, 1999 and Autoimmune, Inc. on November 14, 2000 were put on public display by the FDA on February 18, 2001. You will find confirmation of this on FDA's website on New Dietary Ingredients (<http://www.cfsan.fda.gov/~dms/ds-ingrd.html>), Report Nos. 44 and 88. According to the website, the notifications for both ingredients were filed without comment. This information is provided to show that the intended use of this material is as a dietary ingredient, not a drug ingredient.

1. Manufacturer's Name and Address:

BioCell Technology, LLC
5000 Birch St. West Tower, Suite #3000
Newport Beach, CA 92660

2. Name of dietary ingredient:

Hydrolyzed (Denatured) Chicken Sternal Type II Collagen (BioCell Collagen II® Brand)

The new dietary ingredient is BioCell Collagen II, which is prepared from chicken sternal cartilage. Type II collagen is the predominant form of collagen in the sternal cartilage and accounts for approximately half of the dry weight of the sternal cartilage, the remaining portion of the cartilage is made up of Gycosaminoglycans predominately Chondroitin Sulfate and Hyaluronic Acid.

To obtain the new dietary ingredient BioCell Collagen II®, the method involves separating sternal cartilage from chicken carcasses, hydrolyzing the cartilage using natural enzymes, sterilizing the hydrolyzed material using temperature, drying the material to form a powder and packaging it in a drum with a plastic liner. The finished powder is water soluble.

3. DESCRIPTION OF THE DIETARY SUPPLEMENT THAT WILL CONTAIN THE NEW DIETARY INGREDIENT

The dietary supplement that will contain BioCell Collagen II® in a formulation is a powder based tablet or hard-shell capsule, an oil based soft gelatin capsule, or liquid based product. The supplement will be packaged in an appropriate package for the dosage form.

- (i) The level of the New Dietary ingredient in the Dietary Supplement
Each capsule, tablet, soft gel or liquid formulation will contain up to 3,000 mg of BioCell Collagen II per serving.

- (ii) The Conditions of Use Recommended or Suggested in the Labeling of the Dietary Supplement

The recommended dosage of this product is 1 to 2 grams daily or as desired.

4. HISTORY OR USE OR OTHER EVIDENCE OF SAFETY ESTABLISHING THAT THE DIETARY INGREDIENT, WHEN USED UNDER THE CONDITIONS RECOMMENDED, WILL REASONABLY BE EXPECTED TO BE SAFE

Dietary Component-

Chicken sternal cartilage, the raw material source of BioCell Collagen II®, is found in the normal diet as the "soft white bone" of chicken sternum cartilage, which is located in the breast cut of chicken food. This cartilage, along with other selected structural tissue is typically incorporated as an ingredient in home made chicken soup, but is also consumed directly by individuals who enjoy its chewy texture and distinct taste. This collagen is typically eaten in a denatured state as a result of the cooking process, which is very similar because BioCell Collagen II undergoes a thorough heat cooking period in which it hydrolyzed or denatured. Amino acids are constituents of chicken sternal cartilage and are common to the food supply.

Safety Study on BioCell Collagen II®-

As an added measure to confirm the safety of BioCell Collagen II®, an Acute Oral Toxicity Study in Rats was performed by Convince Laboratories and is enclosed with this notification for your review.

US PATENTS-

BioCell Collagen II® is manufactured and licensed in accordance with two U.S. Patents that cover the use of this ingredient as a dietary supplement.

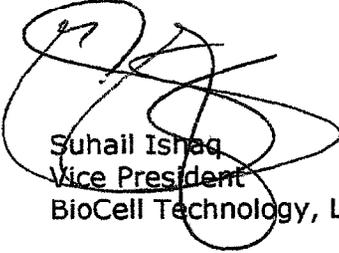
US PATENT NO. 6,025,327 (Enclosed)- Hydrolyzed collagen type II and use thereof... Hydrolyzed collagen type II powder compositions, method of preparing the compositions and use of the compositions in treating cartilage defects. The compositions are orally administered to an individual in need of cartilage augmentation in a daily dosage of between about 2,000 and 3,000 mg per day.

US PATENT NO. 6,323,319 (Enclosed)- Method of making hydrolyzed collagen type II... Hydrolyzed collagen type II powder compositions, method of preparing the compositions and use of the compositions in treating cartilage defects. The

compositions are orally administered to an individual in need of cartilage augmentation in a daily dosage of between about 2,000 and 3,000 mg per day.

We trust this New Dietary Ingredient Notification submission provides the information that FDA requires. If there are any questions concerning this submission, please contact me.

Sincerely yours,



Suhail Isnaq
Vice President
BioCell Technology, LLC

REFERENCES

1. Knauper et al. "Biochemical characterization of human collagenase-3," *J. Biol. Chem.* 271:1544-1550 (1996).
2. Alkayali, A. Biocell Technology, LLC. "Hydrolyzed collagen type II and use thereof," US Patent # 6,025, 327. February 15, 2000.
3. Bedi et al. "Purification and characterization of a collagen-degrading protease from *Porphyromonas ginivalis*," *J. Biol. Chem.* 269:599-606 (1994).
4. Alkayali, A. Biocell Technology, LLC. "Method of making hydrolyzed collagen type II," US Patent # 6,323,319. February 15, 2000.
5. M. Barinaga, "Treating Arthritis With Tolerance," *Science* 261:1669-1670 (1993).
6. M.A. Cremer, et al., "Collagen-Induced Arthritis In Rats: Antigen-Specific Suppression of Arthritis and Immunity By Intravenously Injected Native Type II Collagen," *The Journal of Immun.* 131(6): 2995-3000 (1983).
7. M.E. Englert, et al., "Suppression of Type II Collagen-Induced Arthritis by the Intravenous Administration of Type II Collagen or Its Constituent Peptide .alpha..sub.1 (II) CB.sub.10," *Cellular Immunology* 87:357-365 (1984).
8. D.E. Trentham, et al., "Autoimmunity to Type II Collagen: An Experimental Model of Arthritis," *The Journal of Experimental Medicine* 146:857-868 (1977).
9. D.E. Trentham, et al., "Effects of Oral Administration of Type II Collagen on Rheumatoid Arthritis," *Science* 261:1727-1730 (1993).
10. Brucknet et al. 'p-HMW-Collagen, a minor collgen obtained form chick embryo cartilage without proteolytic treatment of the tissue', *Eur. J. Biochem.* 136 : 333-339 (1983).
11. Trentham et al. 'Autoimmunity of Type II Collagen: An Experimental Model of Arthritis', *J. of Exp. Medicine.* 146 : 857-868 (1977).
12. Barnett, ML, et al., "Treatment of rheumatoid arthritis with oral type II collagen. Results of a multicenter, double-blind, placebo controlled trial," *Arthritis Rheum* 41 (2) : 290-297 (1998).
13. Ronca F, et al., "Anti-inflammatory activity of chondroitin sulfate," *Osteoarthritis Cartilage* suppl. 6 (A) : 14-21 (1998).
14. Moskowitz RW. "Hyaluronic acid supplementation," *Curr Rheumatol Rep* 2(6):466-71 (2000).
15. Anderson I. "The properties of hyaluronan and its role in wound healing," *Prof Nurse* 17(4):232-5 (2001).
16. Greco RM, et al., "Hyaluronic acid stimulates human fibroblast proliferation within a collagen matrix," *J Cell Physiol* 177(3):465-73 (1998).
18. Ghersetich I, et al, "Hyaluronic acid in cutaneous intrinsic aging," *Int J Dermatology* 33 (2): 119-122 (1994).
19. Moskowitz RW. "Role of collagen hydrolysate in bone and joint disease," *Semin Arthritis Rheum* 30(2):87-99,(2000)
20. Glaza, SM, "Acute oral toxicity study of BioCell collagen II™ in rats," Covance Laboratories. November 16, 2001.