DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: JUN 17 2004

From: Consumer Safety Officer, Division of Dietary Supplement Programs , Office of Nutritional Products, Labeling and Dietary Supplements, HFS-821

Subject: 75-Day Premarket Notification of New Dietary Ingredients

To: Dockets Management Branch, HFA-305

Subject of the Notification: ZANTHINE Extract Astaxanthin Complex , an extract of the algae, *Haematococcus pluvialis*

Firm: Kleinfeld, Kaplan and Becker, LL,P on behalf of U.S. Nutraceuticals, LLC

Date Received by FDA: _ March 24, 2004_____

90-Day Date: ____June 22, 2004_____

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

Victoria Lutwak

95S-0316

RPT 237

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
5100 Paint Branch Parkway
College Park, Maryland 20740

Anthony L. Young
Kleinfeld, Kaplan and Becker, LLP
1140 Nineteenth Street, N.W.
Washington, D. C. 20036-6606

Dear Mr. Young:

This is to inform you that the notification, dated March 23, 2004, you submitted on behalf of your client, U.S. Nutraceuticals, LLC, 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 March 24, 2004. As stated in your letter dated March 25, 2004, your notification concerns the substance, ZANTHINE Extract Astaxanthin Complex – 10% Standardized, an extract of the algae, *Haematococcus pluvialis* (Flotow em. Wille) that you intend to market as a new dietary ingredient.

You state that the serving level is up to 5 milligrams (mg) (5 mg/day) and that there are no other conditions of use.

Under 21 U.S.C. 350b(a), the manufacturer or distributor of a dietary supplement containing 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 considered 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 unreasonable risk of illness or injury.

FDA has carefully considered the information in your notification and has significant concerns about the evidence on which you rely to support your conclusion that the ingredient, ZANTHINE Extract Astaxanthin Complex – 10% Standardized, will be reasonably expected to be safe.

Your notification failed to adequately identify the relevant test substances in the references you relied on to support your decision that ZANTHINE Extract Astaxanthin Complex – 10% Standardized is reasonably expected to be safe. Based on our telephone conference on May 17, 2004 with you and your client representative, you submitted additional information to clarify the qualitative and quantitative relationship between your product, ZANTHINE Extract Astaxanthin Complex – 10% Standardized, and the test substances in the references submitted in your notification under Tab J. Based on your information, dated May 19, 2004, the isomer composition of ZANTHINE Extract Astaxanthin Complex – 10% Standardized differs significantly from that of the referenced Roche materials. Based on what is stated about the relative isomer compositions of the materials, ZANTHINE Extract Astaxanthin Complex – 10% Standardized would be expected to have significantly more biologic activity than the chemically synthesized Roche materials, which are said to have significantly less of the active 3S-3S' isomer. The appropriate studies with respect to safety are those that use the same material described in the notification as the test articles. Your notification did not provide a reasonable explanation of how the serving level of your product, ZANTHINE Extract Astaxanthin Complex – 10% Standardized, relates qualitatively and quantitatively to the test materials which you relied on to make your decision that ZANTHINE Extract Astaxanthin Complex – 10% Standardized is reasonably expected to be safe

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that ZANTHINE Extract Astaxanthin Complex – 10% Standardized, 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 an 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 March 24, 2004. After the 90-day date, the notification will be placed on public display at FDA's Division of Dockets Management 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.

If you have any questions concerning this matter, please contact Victoria Lutwak at (301) 436-2375.

Sincerely yours,

Susan J. Walker, M.D.
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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RESPONSE TO MAY 17, 2004 DIVISION OF DIETARY SUPPLEMENT PROGRAMS QUESTIONS RE: NEW DIETARY INGREDIENT NOTIFICATION FOR ZANTHIN

Zanthin is a supercritical carbon dioxide extract of *Haematococcus pluvialis* Flotow algae containing at least 9.5% (w/w) astaxanthin. As part of its New Dietary Ingredient Notification for Astaxanthin-rich carotenoid oleoresin (Zanthin), U.S. Nutra referenced various safety studies for synthetic astaxanthin that had been submitted by Roche Vitamins and Fine Chemicals in a feed additive petition. The basis for comparing U.S. Nutra's Zanthin to the Roche material is that the marker compound for both products is the carotenoid astaxanthin, $C_{40}H_{52}O_4$. Accordingly, they are chemically similar, although they appear in the two products in differing concentrations and isomers.

The U.S. Nutra *Haematococcus*-produced supercritical carbon dioxide extract astaxanthin and the Roche-produced synthetic astaxanthin differ in configuational isomeric ratios. Synthetic astaxanthin is typically a racemic mixture of 3S,3'S, 3R,3'R and 3R,3'S configurational isomers in a 1:1:2 ratio, while *Haematococcus* algae biosynthesizes this carotenoid with virtual optical purity in the 3S,3'S form (Turujman et al., 1997). It is therefore reasonable to conclude that the safety of the 3S, 3'S form would be elucidated in the safety studies performed by Roche on its synthetic astaxanthin.

U.S. Nutra notes that although its *Haematococcus*-derived extract contains a different configurational isomeric ratio from synthetic astaxanthin, this extract matches more closely the predominant isomer of astaxanthin found in wild salmon salmon species . Astaxanthin, as it is found in wild salmon species, is a common ingredient in food for human consumption. The levels of astaxanthin found in wild salmon species are reported by Turujman et al. (USFDA, Office of Cosmetics and Colors) (1997).

Astaxanthin produced by Haematococcus algae is mono and diesterified with fatty acids, while synthetic astaxanthin listed in the Roche study was produced in a "free" unesterified form. Free astaxanthin is only found in nature in small quantities, with the fatty acid mono and diesters being the predominant forms together with both varying amounts of trans and cis isomeric forms of astaxanthin (Bjerkeng et al., 1997, Renstrom et al., 1981). Astaxanthin esters are cleaved in the body to free astaxanthin.

The Zanthin product contains 9.5% of the astaxanthin carotenoid chemically similar to that tested by Roche. The remaining 90% of the product is solely lipid material and water extracted from the algae. The attached data table (Appendix K) demonstrates the chemical similarity between *Haematococcus pluvialis* algae raw material, and the carbon dioxide extract prepared by U.S. Nutra. The fatty acid composition of the two forms is reasonably similar. Proportions of E, 9Z and 13Z isomers of astaxanthin vary between algae and extract, which is most likely due to isomerization during the extraction process. Similar isomerization of astaxanthin has been seen by other investigators (Yuan and Chen, 1999).

Comparative data of fatty acid and carotenoid content between algae used for extraction by U.S. Nutra (Algatechnologies LTD in the United Kingdom) and Mera Pharmaceuticals (formerly Aquasearch whose premarket notification for *Haematococcus pluvialis* was filed on February 22, 2000 (RPT 65)) is shown in Appendix L.

CTS 87791

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As stated in the attached letter by Dr. Miguel Olaizola (Appendix M), the *Haematococcus pluvialis* raw material used for extraction by U.S. Nutra would have similar phytochemical profile to those produced by other firms, including those listed in New Dietary Ingredient Notifications submitted by Micro Gaia Inc. (RPT 119), Aquasearch Inc. (RPT 65) and Cyanotech Corp. (RPTS 45 and 50) and which were not objected to by FDA.

In summary, I declare that the U.S. Nutra Zanthin product contains only astaxanthin carotenoid that is chemically similar to that presented to FDA in the submitted Roche studies. The astaxanthin carotenoid in Zanthin is present in a carrier lipid that is substantially similar to that found in the *Haematococcus pluvialis* algae product notifications previously submitted to FDA.

I declare under penalty of perjury that the foregoing is true and correct.

Stephen Hill
Technical Services Manager
U.S. Nutra

May 19, 2004
Eustis, Florida

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References:

Bjerkeng, B., M. Følling, S. Lagocki, T. Storebakken, J. Olli and Alsted. 1997. Bioavailability of all-E-astaxanthin and Z-astaxanthin isomers in rainbow trout (*Oncorhynchus mykiss*). *Aquaculture.* 157: 63 - 82.

Renstrom, B., G. Borch, O. Skulberg and S. Liaaen-Jensen. 1981. Optical purity of (3S,3'S) – astaxanthin from *Haematococcus pluvialis. Phytochemistry.* 20: 2561 - 2564.

Yuan, J-P and F. Chen. 1999. Isomerizaion of *trans*-astaxanthin to *cis*-isomers in organic solvents. *J. Agric Food Chem.* 47: 3656-3660.

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Appendix K.
Analytical Comparison of *Haematococcus* Algae Raw Material and CO_2 Extract

Peak	Fatty Acid		CO_2 Extract[1] % of FA total	Algae[2] % of FA total
1	12:0	Lauric	0.07	0.05
2	13:0	Tridecanoic	0.10	0.09
3	14:0	Myristic	0.51	0.52
4	15:0	Pentadecanoic	0.03	0.03
5	16:0	Palmitic	12.21	13.14
6	16:1 n-7	*cis*-9-Palmitoleic	0.32	0.24
7	17:0	Heptadecanoic	0.11	0.10
8	17:1	*cis*-10-Heptadecenoic	1.87	1.76
9	18:0	Stearic	0.79	0.77
10	18:1 n-9 *c/t*	*cis*-9-Oleic and/or *trans*-9-Elaidic	24.14	24.37
11	18:2 n-6 *c/t*	*cis*-9,12-Linoleic and/or *trans*-9,12-Linolelaidic	30.68	30.30
12	20:0	Arachidic	1.77	1.86
13	18:3 n-6	γ-Linolenic	14.83	14.15
14	20:1	*cis*-11-Eicosenoic	0.25	0.26
15	18:3 n-3	Linolenic	0.18	0.18
16	21:0	Heneicosanoic	1.65	1.15
17	20:2	*cis*-11,14-Eicosadienoic	0.48	0.53
18	22:0	Behenic	0.06	0.06
19	20:3 n-6	*cis*-8,11,14-Eicosatrienoic	1.34	1.40
20	22:1 n-9	*cis*-13-Erucic	0.06	0.07
21	20:3 n-3	*cis*-11,14,17-Eicosatrienoic	8.37	8.81
22	20:4 n-6	*cis*-5,8,11,14-Arachidonic	0.12	0.12
23	20:5 n-3	*cis*-5,8,11,14,17-Eicosapentaenoic	0.06	0.05

Cartenoid	CO_2 Extract[1] % w/w extract	Algae[2] % w/w algae
E-Astaxanthin	5.92	2.88
9Z-Astaxanthin	1.48	0.48
13Z-Astaxanthin	2.58	0.68
β-Carotene	0.03	0.01
Lutein	0.07	0.04
Canthaxanthin	0.03	0.01

[1] USN manufactured product, lot #: 031029-HAOR, lab ID: U0221-1

[2] Algatechnologies Lot #: AST10203

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Appendix L. Analytical Comparison of *Haematococcus* Algae Materials

Fatty Acid		Algatechnologies n=2, r=3		Mera Pharma n=2,r=2	
		% of total	σ_n	% of total	σ_n
14:0	Myristic	0.38	0.008	0.36	0.008
15:0	Pentadecanoic	0.44	0.018	0.45	0.002
15:1	Pentadecenoic	-	-	0.43	0.047
16:0	Palmitic	11.82	0.064	24.13	0.204
16:1 n-7	*cis*-9-Palmitoleic	0.28	0.008	0.45	0.008
17:0	Heptadecanoic	2.14	0.021	1.18	0.032
17:1	*cis*-10-Heptadecenoic	5.42	0.032	4.40	0.157
18:0	Stearic	0.58	0.010	1.29	0.036
18:1 n-9 *c/t*	*cis*-9-Oleic and/or *trans*-9-Elaidic	21.11	0.056	23.93	0.450
18:2 n-6 *c/t*	*cis*-9,12-Linoleic and/or *trans*-9,12-Linolelaidic	30.47	0.053	19.57	0.034
20:0	Arachidic	2.03	0.015	1.42	0.023
18:3 n-6	γ-Linolenic	14.42	0.020	14.04	0.320
20:1	*cis*-11-Eicosenoic	0.22	0.006	0.36	0.010
18:3 n-3	Linolenic	0.13	0.008	0.16	0.011
21:0	Heneicosanoic	1.08	0.019	0.79	0.048
20:2	*cis*-11,14-Eicosadienoic	0.52	0.010	-	-
20:3 n-6	*cis*-8,11,14-Eicosatrienoic	1.34	0.017	0.76	0.031
22:1 n-9	*cis*-13-Erucic	0.23	0.009	-	-
20:3 n-3	*cis*-11,14,17-Eicosatrienoic	0.63	0.007	0.61	0.016
20:4 n-6	*cis*-5,8,11,14-Arachidonic	6.76	0.100	5.68	0.100
23:0	Tricosanoic	-	-	0.22	0.011

Carotenoid	Algatechnologies			Mera Pharma		
	% w/w	σ_n	% of total	% w/w	σ_n	% of total
E-Astaxanthin	2.60	0.090	78	1.96	0.045	60
9Z-Astaxanthin	0.07	0.012	2	0.70	0.018	21
13Z-Astaxanthin	0.49	0.085	15	0.51	0.014	16
Total Astaxanthins	3.16		94	3.17		97
β-Carotene	0.136	0.004	4	0.089	0.012	3
Lutein	0.043	0.001	1	0.004	< 0.001	< 1
Canthaxanthin	0.009	0.003	< 1	0.001	< 0.001	< 1
Total Other Carotenoids	0.188			0.094		
Total Carotenoids	3.35			3.26		

Legend:

Algatechnologies: Algae Lots: 304, 404, 504, 604 and 704, USN lab ID U0264-1;
704, 804, 904, USN lab ID U0264-2
2 samples, 3 replicates = total 6 data sets

Mera Pharma: Algae Lots: DB1-040309, USN lab ID U0280-1; DB2-040308, USN lab ID U0280-2
(Formerly Aquasearch) 2 samples, 2 replicates = total 4 data sets