DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

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Memorandum

Date

From (Acting) Division Director, Division of Standards and Labeling Regulations, Office of Nutritional Products, Labeling and Dietary Supplements, HFS-820

Subject 75-Day Premarket Notification for New Dietary Ingredients

To Dockets Management Branch, HFA-305

New Dietary Ingredient:	*Phaffia rhodozyma*
Firm:	Igene Biotechnology, Inc.
Date Received by FDA:	May 4, 2000
90-Day Date:	August 1, 2000

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification for the aforementioned new dietary ingredient should be placed on public display in docket number 95S-0316 after August 1, 2000.

Felicia B. Satchell

Felicia B. Satchell

95S-0316

RPT 74

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington DC 20204

JUL 17 2000

Mr. Patrick Monahan
Director of Manufacturing
Igene Biotechnology, Inc.
9110 Red Branch Road
Columbia, Maryland 21045-2024

Dear Mr. Monahan:

This letter is in response to your letter to the Food and Drug Administration (FDA) dated May 4, 2000, making a submission 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). Your letter notified FDA of your intent to market a product containing a new dietary ingredient named *Phaffia rhodozyma*, which you describe as a source of the carotenoid astaxanthin. Your submission was received by FDA on May 4, 2000.

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. Under section 350b(a)(2), there must be a history of use or other evidence of safety establishing that the 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 unreasonable risk of illness or injury.

FDA has evaluated the information in your submission and it appears to provide an adequate basis that a dietary supplement containing *Phaffia rhodozyma* will reasonably be expected to be safe in healthy adults who would consume dietary supplements that provide no more than 250 milligrams of *Phaffia rhodozyma* per day (containing approximately 2 mg astaxanthin) for limited durations of time. However, the studies do not appear to provide a sufficient basis to establish that a dietary supplement containing *Phaffia rhodozyma*, when used under the conditions recommended or suggested in the labeling of your product, will reasonably be expected to be safe for children.

Moreover, the information you submitted does not address the safety of chronic, long-term use of this new dietary ingredient in humans. Therefore, a dietary supplement containing *Phaffia rhodozyma* that is intended for use by children or that is intended for

chronic or long-term use 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 submission will be kept confidential for 90 days from the date of receipt, and after August 1, 2000, your submission will be placed on public display at Dockets Management Branch (Docket No. 95S-0316). Commercial and confidential information in the notification will not be made available to the public.

Please contact us if you have questions concerning this matter.

Sincerely yours,

Felicia B. Satchell

Felicia B. Satchell
(Acting) Division Director
Division of Standards
and Labeling Regulations
Office of Nutritional Products, Labeling
and Dietary Supplements

Igene Biotechnology, Inc.

9110 RED BRANCH ROAD
COLUMBIA, MARYLAND 21045-2024

PHONE: *410-997-2599*
FAX: *410-730-0540*

April 26, 2000

Dr. Robert Moore
Division of Programs and Enforcement Policy
Office of Special Nutritionals HFS-450
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street SW
Washington, DC 20204

RE: New Dietary Ingredient Notification for *Phaffia rhodozyma* as a Source of Astaxanthin

Dear Dr. Moore,

As prescribed by 21 CFR Subpart B 190.6, please be advised of this New Dietary Ingredient Notification for the yeast *Phaffia rhodozyma* as a source of astaxanthin. We plan to market *Phaffia* as a human supplement seventy-five days after the acknowledgement of receipt of this notice, unless otherwise instructed by your Agency. Please find enclosed one original and two copies of this notification. There are three copies of each attachment as well.

(1) We presently produce our product *AstaXin*® at our production facility located in Mexico City. The mailing address is: Fermic, S.A. de C.V., Reforma No. 873 Col. San. N. Tolentino, Iztapalapa, 09850 Mexico, D.F. The facility is a FDA approved plant. The distributor will be Igene Biotechnology, located at 9110 Red Branch Rd., Columbia, Maryland 21045-2024.

(2) The name of the new dietary ingredient will be *AstaXin*®. The product is produced by the yeast *Phaffia rhodozyma* which is not a recombinant organism. Attached are references to the first naming of the yeast and the subsequent renaming to *Phaffia* (Appendix 1 & 2).

(3) The description of the dietary supplement *AstaXin*® will contain 2 mg's of astaxanthin and not more than 250mg's of the yeast *Phaffia rhodozyma.* Turujman, (Appendix 3), presents data showing the range of astaxanthin concentration in a variety of wild Salmonid species. The data shows a range of astaxanthin concentration from one to fifty-eight mg/kg. The low level is found in Atlantic Salmon 5.3 mg/kg, to a high of 40.4 mg/kg in Sockeye Salmon. The average human consumption of fish flesh is approximately 0.25 kg in one meal. This equates to a low of 1.3 mg of astaxanthin from Atlantic Salmon, 3.3 mg from the overall average, to 10.1 mg of astaxanthin from Sockeye Salmon. We are proposing a daily consumption of astaxanthin from *Phaffia* of 2.0 mg/day.

In the attached Certificate of Analysis and their chromatograms for our product *AstaXin®*, it can be seen that all the carotenoids present are associated with the natural growth cycle of *Phaffia* (Appendix 4). (Appendix 5) figure 6, page 307, shows the astaxanthin biosynthetic pathway proposed for *Phaffia rhodozyma*. The precursors of *Phaffia*'s astaxanthin are found in natural foods such as: shrimp, krill, tomatoes, leafy green vegetables, pumpkins, broccoli and apricots (Appendix 6), page 3.

The dried powder can be mixed with food grade rosemary oil, or a food grade vegetable oil, and then manufactured into soft gels or capsules. The *Phaffia* dried powder may also be packaged into a tablet. The manufactured soft gels or tablets will be packaged into bottles or blister packs.

The labeling of the package will show the amount of *Phaffia rhodozyma* contained in each capsule, or tablet, the type of oil(s), if added, or any other caking agents, if needed. All current guidelines for labeling will be adhered to. The suggested use of one capsule per day will be on the label, which is equivalent to 250mg's of dried *Phaffia* powder.

(4) The history of use and other evidence of use is attached. This includes references and published information in support of our contention that *Phaffia rhodozyma*, as a source of astaxanthin, will reasonably be expected to be safe when used under the conditions recommended or suggested in the labeling of the new dietary supplement.

Astaxanthin is approved for use in Salmonid feeds at a maximum level of 80mg/kg under CFR section 73.35. The petition was reviewed by the FDA as CAP 7C0211 and includes safety studies with astaxanthin. The acute toxicity of 10 consecutive daily oral doses of astaxanthin in rats was found to be greater than 2000 mg/kg. Information was obtained under the Freedom of Information Act (Appendix 7).

The Carotenoid, astaxanthin, has been legally permitted in foods and feeds by most countries (Appendix 7a). The structural formula for astaxanthin is depicted on page 183 of appendix 7a.

Red Star Specialty Products, *Phaffia rhodozyma,* was tested for mutagenic activity(1994) in the Salmonella/Mammalian-Microsome Reverse Mutation Assay (Ames Assay). The conclusion was *Phaffia* yeast did not cause a positive increase in the number of revertants of any of the tester strains (Appendix 8).

Igene's *Phaffia rhodozyma* (1998) was tested at the University of Maryland Center for Environmental Science at 10X the level normally used in Atlantic Salmon feed. The histopathological data showed the dietary effect of Igene's *Phaffia* did not have a negative impact on the treated fish as compared to the untreated controls (Appendix 9).

The yeast *Phaffia rhodozyma* has been developed as a natural source of astaxanthin for use as an ingredient in feeds for Salmonid fish and other aquatic species being produce by aquaculture. The astaxanthin present in *Phaffia rhodozyma* is in the 3R, 3' R-configuration (Andrews and Starr, 1976). This configuration is present in Salmonid fish because it is widely distributed in the natural foods consumed by Salmonids in the wild (Appendix 10). *Phaffia*

rhodozyma has been "Generally Recognized As Safe (GRAS)" as an ingredient in feed for Salmonid fish (Appendix 11).

Hazleton Labs, now Covance Labs, in Madison, Wisconsin, conducted a 13-week Dietary Toxicity Study with *Phaffia* in Rats. I have submitted only the text and the conclusions of the study (Appendix 12). The actual study is several hundred pages. The results show the administration of *Phaffia* yeast to male and female Crl : CD (SD) BR rats for at least 13 weeks resulted in no adverse effects at levels up to, and including, 10.0% (W/W). Information obtained under the Freedom of Information Act.

The yeast *Phaffia rhodozyma* has been evaluated as an astaxanthin source in Salmonid diets for over twenty years (Appendix 13). Arcadian Processors (Palmetto, LA) markets an astaxanthin extract from crustaceans into the United States marketplace. In Japan Itano Refrigerated Food Co. Ltd. markets astaxanthin from Antarctic krill as a human supplement. This is distributed by the US company, Optipure, as "Astax-1700".

We contend that our product, *AstaXin*, as a new Dietary Ingredient, when used under the conditions recommended, and/or suggested, in the labeling will reasonably be expected to be safe. We have included citations to published articles, actual test data on our product, as well as data from similar products, as evidence that our product will reasonably be expected to be safe. Our product is manufactured under GMP conditions at a FDA licensed and approved facility in Mexico City.

I can be reached at 410.997.2599 for additional information at your convenience during regular business hours.

Sincerely,

Patrick Monahan

Patrick Monahan
Director of Manufacturing
Igene Biotechnology, Inc.
9110 Red Branch Road
Columbia, Maryland 21045-2024
Fax. 410.730.0540

CC: Dr. Stephen Hiu, President Igene Biotechnology

APPENDIX LIST

APPENDIX 1	A Comparative Study of the Yeast Florae Associated with Trees on the Japanese Islands and on the West Coast of North America. 1972. Herman J. Phaff, et al.
APPENDIX 2	Phaffia, a New Yeast Genus in the Deuteromycotina (Blastomycetes). 1976. Miller, M. W., et al.
APPENDIX 3	Rapid Liquid Chromatographic Method to Distinguish Wild Salmon from Aquacultured Salmon Fed Synthetic Astaxanthin. 1997. Turujman, Saleh A., et al.
APPENDIX 4	Certificates of Analysis - AstaXin® - Igene Biotechnology, Inc.
APPENDIX 5	Astaxanthin from Microbial Sources. 1991. Johnson, Eric A., and Gil-Hwan An.
APPENDIX 6	Carotenoids - Continuing Education Module, By: Eric Yarnell N.D.
APPENDIX 7	Roche Vitamins and Fine Chemicals, Astaxanthin as a Pigmenter in Salmon Feed.
APPENDIX 7.A.	A Review. Microbial Sources of Carotenoid Pigments Used in Foods and Feeds. 1991. Nelis, H.J. and A.P. De Leenheer.
APPENDIX 8	Red Star Specialty Products - Mutagenic Activity test in the Salmonella/Mammalian-Microsome Reverse Mutation Assay - 1994.
APPENDIX 9	Study "Effect of Dietary Phaffia rhodozyma on Atlantic Salmon Performance". 1998. Maryland Industrial Partnerships (MIPS) Report performed at the University of Maryland Center for Environmental Science, Horn Point.
APPENDIX 10	The Value of Phaffia Yeast as a Feed Ingredient for Salmonid Fish. Gary W. Sanderson and Setsuko O. Jolly.
APPENDIX 11	GRAS Status of Phaffia rhodozyma Yeast as a Feed Ingredient for Salmonids. 1992. Gary W. Sanderson.
APPENDIX 12	13-Week Dietary Toxicity Study with Red Star® Phaffia Yeast in Rats. 1995. Hazleton Wisconsin, Inc. Labs.
APPENDIX 13	Phaffia Rhodozyma as an Astaxanthin Source in Salmonid Diets. 1980. Johnson, Eric A., et al.