

**Memorandum**

Date: = DEC 22 2005

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: *Saccharomyces cerevisiae* DIAM-H-04-2

Firm: AIMBR Life Sciences, Inc.

Date Received by FDA: 9/23/05

90-Day Date: 12/22/05

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*\_\_\_\_\_

1995S-0316

RPT 306



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

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

0435 6 JAN 12 P2:34

DEC 6 2005

Alexander G. Schauss, Ph.D. FACN  
Director  
Natural and Medicinal Products Research  
AIBMR Life Sciences, Inc.  
4117 S Meridian  
Puyallup, Washington 98373

Dear Dr. Schauss:

This is to inform you that the notification, dated September 22, 2005 that you submitted on behalf of your client, Embria Health Sciences, 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 September 23, 2005. Your notification concerns the substance that you call "DIAM-H-04-2" that Embria Health Sciences prepares from *Saccharomyces cerevisiae Meyen ex E.C. Hansen var. cerevisiae* and intends to market in a dietary supplement product called "EpiCor™".

According to your notification, "DIAM-H-04-2" will be marketed in as a capsule or tablet containing 500 mg of "DIAM-H-04-2". Your notification states that "The suggested daily intake on the product label will be 500 mg a day, in one serving... The directions for use will be: 'Take one capsule or tablet once a day with or without food.'"

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 21 U.S.C. 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) (section 402(f)(1)(B) of the Act) 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 submission and the agency has concerns about the evidence on which you rely to support your conclusion that "DIAM-H-04-2" will reasonably be expected to be safe.

According to your notification, you recommend a daily intake of 500 mg of "DIAM-H\_04-2". Based on the data and information in your notification, it is unclear to FDA how many viable organisms are present in your recommended daily serving of "DIAM-H\_04-2".

FDA was unable to determine the identity of "DIAM-H-04-2". For example, according to your notification the organism used to produce "DIAM-H-04-2" is *S. cerevisiae*. However, data included in appendix 12 indicates that the viable organisms in your product include lactic acid bacteria and other aerobic, non-yeast organisms. These organisms were not specified in your notification and their presence is inconsistent with the manufacturing process described in appendix 3. Furthermore, while your notification identifies the catalog number of the *S. cerevisiae* product that you purchased from a vendor as the starter culture, it is unclear whether "DIAM-H-04-2" is composed of a specific strain or strains of *S. cerevisiae*.

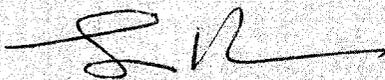
Because the identity of "DIAM-H-04-2" is unclear, it is unclear how your ingredient is qualitatively or quantitatively similar to the substances described in the information that you present as evidence of safety for your new dietary ingredient, or how that information is relevant to evaluating the safe use of your new dietary ingredient under the recommended conditions of use.

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that "DIAM-H-04-2" 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 September 23, 2005. 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.

If you have any questions concerning this matter please contact Dr. Linda Pellicore at (301) 436-2375.

Sincerely yours,

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

Susan J. Walker, M.D.

Director

Division of Dietary Supplement Programs

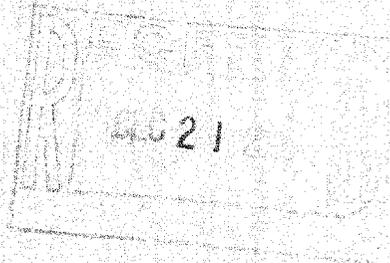
Office of Nutritional Products, Labeling

and Dietary Supplements

Center for Food Safety and Applied Nutrition

# Greenberg Traurig

James R. Prochnow  
Tel. 303.572.6546  
Fax 720.904.7646  
prochnowj@gtlaw.com



December 19, 2005

Dr. Susan Walker, PhD  
Division of Supplement Programs and Compliance,  
Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-820), Center for Food  
Safety and Applied Nutrition (CFSAN),  
Food and Drug Administration  
5100 Paint Branch Parkway  
College Park, MD 20740

Re: New Dietary Ingredient Notification - DIAM-H-04-2

Dear Dr. Walker:

We are representing Embria Health Sciences, LLC ("Embria") in the above referenced matter. Embria received your December 6, 2005 letter which constituted the FDA's response to the 75-day premarket notification filed by Embria through Dr. Alex Schauss for the New Dietary Ingredient DIAM-H-04-2. In your letter, you indicated that the notification would be kept confidential for 90 days after the filing date of September 23, 2005, at which time the notification will be placed on public display at FDA's Docket Management Branch. You further indicated that, prior to that date, Embria could identify, in writing, specifically what information it believes is proprietary, trade secret in nature, or otherwise confidential. Accordingly, as detailed below, I have indicated, on behalf of Embria, those sections of the Premarket Notification which Embria believes are confidential in nature and exempt from publication pursuant to Section 8 of DSHEA.

The "Premarket Notification for DIAM-H-04-2 as a New Dietary Ingredient" filed by Embria consists of 22 pages, plus twenty Appendices attached to the Premarket Notification. I have enclosed a copy of the Premarket Notification with the sections designated by Embria as confidential, proprietary, or trade secrets highlighted for your easy review. I have referenced the highlighted sections below; each of the specified sections, along with all of the Appendices attached to the filed Premarket Notification, is exempt from publication due to the proprietary, trade secret, or confidential nature of the information. These exempt sections are the following:

- Introductory Paragraphs, Page 3,
- Section I. Description, Page 3, Paragraph 1
- Section I. Manufacturing, Page 5, Paragraphs 2-3

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Dr. Susan Walker, PhD  
December 19, 2005  
Page 2

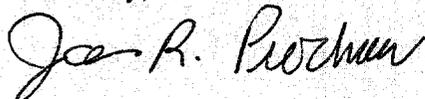
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Section I, i. Chemistry, Pages 6-7, Paragraphs 1-3, 5  
Section II. Stability, Shelf-life, Pesticide Determination, Pages 7-9, (entire section)  
Section III. Toxicology and Safety Studies, Pages 9-17 (entire section)  
Section IV. Summary, Pages 18-19 (entire section)  
Section V., List of Appendices, Pages 20-21 (entire section)

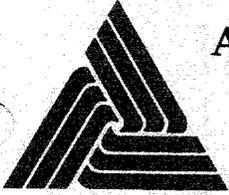
Additionally, as stated above, all of the actual Appendices that accompanied the filed Premarket Notification are proprietary, confidential, or trade secret in nature, and are exempt from publication pursuant to Section 8 of DSHEA.

Please call me if you have any additional questions or comments. Thank you for your attention to this matter.

Sincerely,



James R. Prochnow



**American Institute for Biosocial and Medical Research, Inc.**  
Natural and Medicinal Products Research

P.O. Box 1174  
Tacoma, WA 98401-1174 USA  
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Ph 253-286-2888  
Fx 253-286-2886  
info@aibmr.com

SEP 23 2005  
A.B. / FDA

September 22, 2005

Dr. Susan Walker, PhD  
Division of Supplement Programs and Compliance,  
Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-820), Center for  
Food Safety and Applied Nutrition (CFSAN),  
Food and Drug Administration  
5100 Paint Branch Parkway  
College Park, MD 20740

RECEIVED  
SEP 32 2005

Dear Dr. Walker:

We have been authorized, as evidenced by the attached letter from Embria Health Sciences LLC, ("Embria") Cedar Rapids, Iowa, to submit a premarket New Dietary Ingredient ("NDI") Notification on its behalf, pursuant to Sec. 413(a)(2) of the Federal Food, Drug and Cosmetic Act ("FFDCA") and 21 CFR 190.6. The original and two copies of that Notification are attached in this letter.

Our street mailing address for communications is:

Attention: Alexander G. Schauss, PhD, FACN Director, Natural  
and Medicinal Products Research, AIBMR Life Sciences, Inc.  
4117 S. Meridian,  
Puyallup, WA 98373  
Phone: 253-286-2888  
FAX: 253-286-2451

This NDI Notification presents comprehensive scientific information that is the basis on which Embria has concluded that a dietary supplement containing DIAM-H-04-2, a dried preparation of *Saccharomyces cerevisiae* (to be sold under the tradename EpiCor™), will reasonably be expected to be safe, as required by the statute and regulation identified above. The format of this Notification meets the requirements listed in 21 CFR 190.6 (b) (1 through 5) and follows the numbering system of that regulation.

Embria's determination that DIAM-H-04-2 will reasonably be expected to be safe is based on commissioned toxicology studies performed by independent testing laboratories. The enclosed Notification among other things includes a comprehensive Table of Contents and 19 appendices.

This Notification contains trade secrets and confidential commercial information protected from disclosure by the Freedom of Information Act 5 U.S.C. § 552(b)(4) [FOIA] (Exemption 4) and the Federal Trade Secrets Act, 18 U.S.C. § 1905. That protected information appears on pages marked with the heading

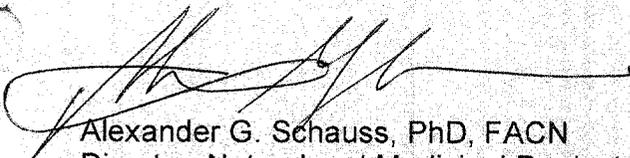
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**This Page Contains Confidential Commercial and Trade Secret Information  
Not for Public Disclosure**

and may not be disclosed to any person not necessary for the review of this notification. As a part of this notification Embria is providing a public version of this Notification for posting on the Docket No. 95S-0316 and public disclosure including, but not limited to, in response to FOIA requests and for the agency's public reading room. On the cover page and each page thereafter the word "PUBLIC" appears in the top margin of the public version of the Notification.

I request that you call me to discuss any concerns or questions that you have about this Notification. I am ready, willing, and able to respond, promptly, to any such communication from you.

Sincerely,



Alexander G. Schauss, PhD, FACN  
Director, Natural and Medicinal Products Research

Enclosures: One original and two copies of the NDI submission



**EMBRIA®**  
Health Sciences

September 9, 2005

Dr. Susan Walker, PhD  
Division of Supplement Programs and Compliance,  
Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-820),  
Center for Food Safety and Applied Nutrition (CFSAN),  
Food and Drug Administration  
5100 Paint Branch Parkway  
College Park, MD 20740

To Whom It May Concern:

Please be advised that Alexander G. Schauss, PhD, FACN, Director, Natural and Medicinal Products Research and his company AIBMR Life Sciences, Inc. have been retained by Embria Health Sciences (EHS) L.L.C. to represent us in the research and filing of a New Dietary Ingredient Notification, as required under 21CFR190.6. Dr. Schauss has full authority to act our behalf in regards to the research and NDI application.

Any questions or concerns related to the research and the New Dietary Ingredient Notification should be directed to:

Attention: Alexander G. Schauss, PhD, FACN  
Director, Natural and Medicinal Products Research,  
AIBMR Life Sciences, Inc.  
4117 S. Meridian,  
Puyallup, WA 98373  
Phone: 253-286-2888  
FAX: 253-286-2451

Sincerely,

Embria Health Sciences

Paul R. Faganel  
President

**Premarket Notification for**

**DIAM-H-04-2**

**as a New Dietary Ingredient**

## **Table of Contents**

- I. Description of DIAM-H-04-2
  - i. Chemistry of DIAM-H-04-2
- II. Stability and Shelf-life Studies of DIAM-H-04-2
- III. Toxicology and Safety Studies of DIAM-H-04-2
- IV. Summary
- V. Appendices (1-20)
- VI. References (1-9) (In a separate 3-ring binder)

The format of this Notification meets the requirements listed in 21 CFR § 190.6 (b) (1 through 5) and follows the numbering system of that regulation.

(b) (1): The name and address of the manufacturer is:

Embria Health Sciences LLC  
838 1<sup>st</sup> Street N.W.  
Cedar Rapids, IA 52405

(b) (2): The name of the dietary supplement that is the subject of the premarket Notification is:

\_\_\_\_\_ *Saccharomyces cerevisiae* Hansen  
(hereinafter called "DIAM-H-04-2") (to be sold under the tradename EpiCor™).

(b) (3): This NDI may be sold for use as a dietary ingredient in a dietary supplement.

(b) (3) (i) and (ii): Level of the NDI in a supplement and conditions of use.

- (1) The suggested daily intake on the product label will be 500 mg a day, in one serving.
- (2) The serving size is one capsule or tablet containing 500 mg of DIAM-H-04-2.
- (3) The directions for use will be: "Take one capsule or tablet once a day with or without food."

## **Section I. Description (Appendices 1-5)**

DIAM-H-04-2 is \_\_\_\_\_ *Saccharomyces cerevisiae*  
Hansen (*S. cerevisiae*) \_\_\_\_\_

DIAM-H-04-2 that may be sold for use as a dietary ingredient in a multi-ingredient dietary supplement or as a sole ingredient dietary supplement.

*S. cerevisiae*, is a species of budding yeast that has been a useful fungus for humans for millennia and has an extensive history of use in the area of food processing. Other names for *S. cerevisiae* are "Brewer's yeast" and "Baker's yeast." It is used to make bourbon whiskey, apple cider, and a fermented rice beverage called "sake", all of which are

consumed world-wide by humans. Brewer's yeast extract is already widely used as a flavor enhancer for soups, soy sauce, sausage, etc., and is also used as a dietary supplement. Brewer's yeast extract is "generally recognized as safe" (GRAS) as a direct food additive (21 CFR §184.1982). A compilation of GRAS affirmed substances listed in 21 CFR part 184 which are derived from microorganisms such as *S. cerevisiae* that are used in foods include protein derived from *S. cerevisiae* (21 CFR §172.325), yeast-malt sprout extract derived from *S. cerevisiae* (21 CFR §172.590), glycan from *S. cerevisiae* (21 CFR §172.898) and dried yeast of *S. cerevisiae* (21 CFR §172.896). *S. cerevisiae* is not among the species of a few genera of yeasts (e.g. *Candida* and *Cryptococcus*) that cause illness in humans or other warm-blooded animals.[Ref. 1]

Despite the fact that yeasts have been used, albeit unknowingly, in the production of human foodstuffs for thousands of years, they were first described by van Leewenhoek in 1680. Pasteur first discovered their real nature in his experiments starting in 1859. Hansen initiated the classification of yeasts in the late 19<sup>th</sup> century and early 20<sup>th</sup> century. Today's modern classification is not dissimilar to his. So it has only been since the late 1800's that the *term Saccharomyces cerevisiae* has been used.[Ref. 2]

The early studies of yeast were concerned mainly with brewing and wine making, and it was from breweries that yeast was first sold as a byproduct, for use in baking, for animal consumption, and for human consumption. This was well established by the late 19<sup>th</sup> century. Work continued in the 20<sup>th</sup> century, with a number of German studies suggesting that yeast would be a useful nutritional supplement for humans and animals.[Ref. 3, 4]

The advent of food shortages during the First World War and again in the latter part of the 20<sup>th</sup> century, when concerns were raised about worldwide food shortages, stimulated a great deal of interest in the use of a variety of yeasts such as *S. cerevisiae* for protein production for both animals and humans (fodder and feed).[Ref. 4]

Hence, there is a long history of thousands of years of consumption of *S. cerevisiae* by humans.

## Manufacturing

Typically, yeast extract hydrolysate from *S. cerevisiae* is autolyzed by raising the temperature of the yeast while in an aqueous suspension and maintaining it at an elevated temperature. This causes the yeast to start digesting itself resulting in the rupturing of the yeast cell wall and release of the yeast cell content. If the suspension is centrifuged, the insoluble cell walls are spun down and the liquid yeast extract is left. That liquid is then concentrated.

**i. Chemistry of DIAM-H-04-2 (Appendices 6-9).**

In 21 CFR §172.896 (Ref. 4), it states that " Dried yeast (*Saccharomyces cerevisiae* and *Saccharomyces fragilis*) and dried torula yeast (*Candida utilis*) may be safely used in food provided the total folic acid content of the yeast does not exceed 0.04 milligrams per gram of yeast (approximately 0.008 milligram of pteroylglutamic acid per gram of yeast)".[Ref. 6]



**Section II. Stability, Shelf-life, Pesticide Determination  
of DIAM-H-04-2 (Appendices 10-13).**

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TRADE SECRET  
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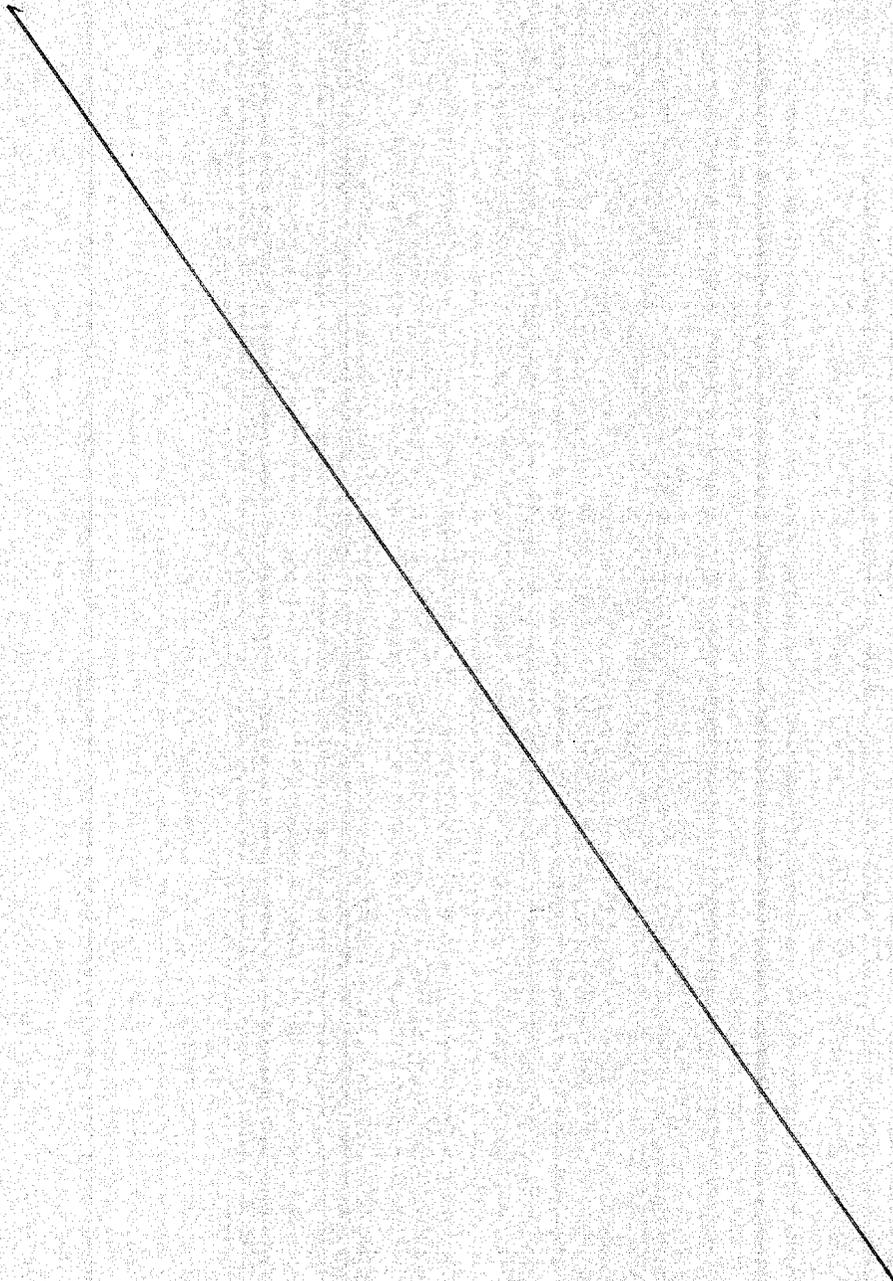
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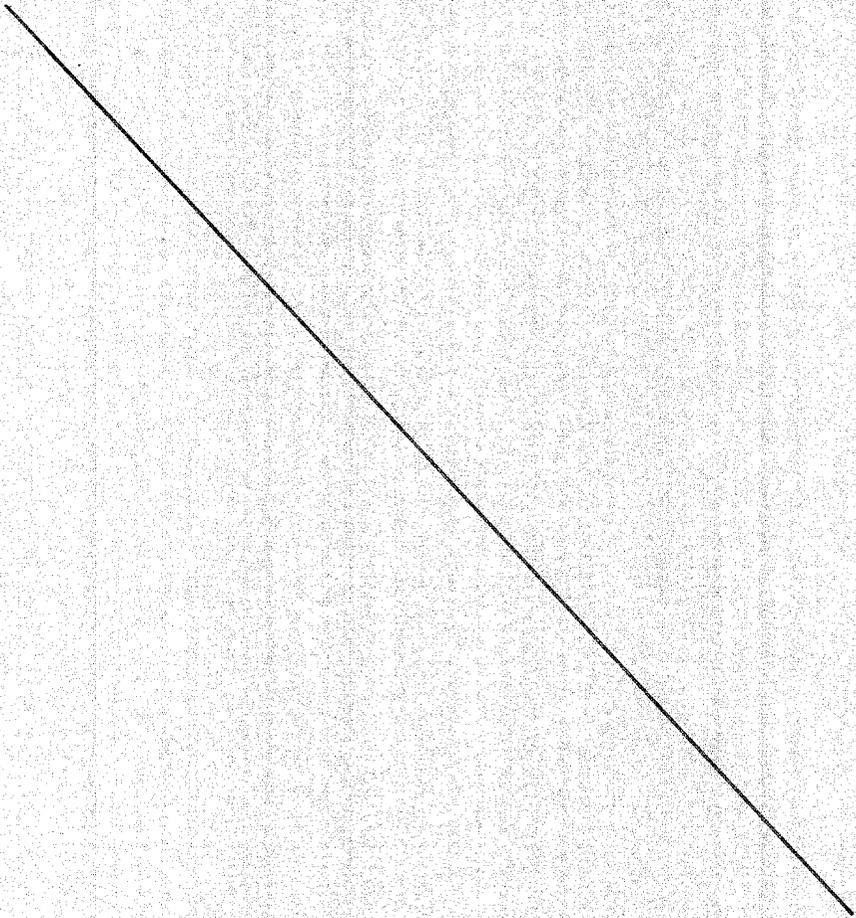
**Section III. Toxicology and Safety Studies of DIAM-H-04-2 (Appendices 14-20)**

PAGES 10 THROUGH 17

REDACTED IN ITS  
ENTIRETY  
CONTAINS  
TRADE SECRET  
CONFIDENTIAL  
COMMERICAL  
INFORMATION

#### **IV. Summary**





In summary, the studies presented in this Notification are an adequate basis upon which Embria has concluded that DIAM-H-04-2, when used under the conditions recommended or suggested in the labeling of its dietary supplement product, will reasonably be expected to be safe.

## **V. List of Appendices**

Appendix 1.

Appendix 2.

Appendix 3.

Appendix 4.

Appendix 5.

Appendix 6.

Appendix 7.

Appendix 8.

Appendix 9.

Appendix 10.

Appendix 11.

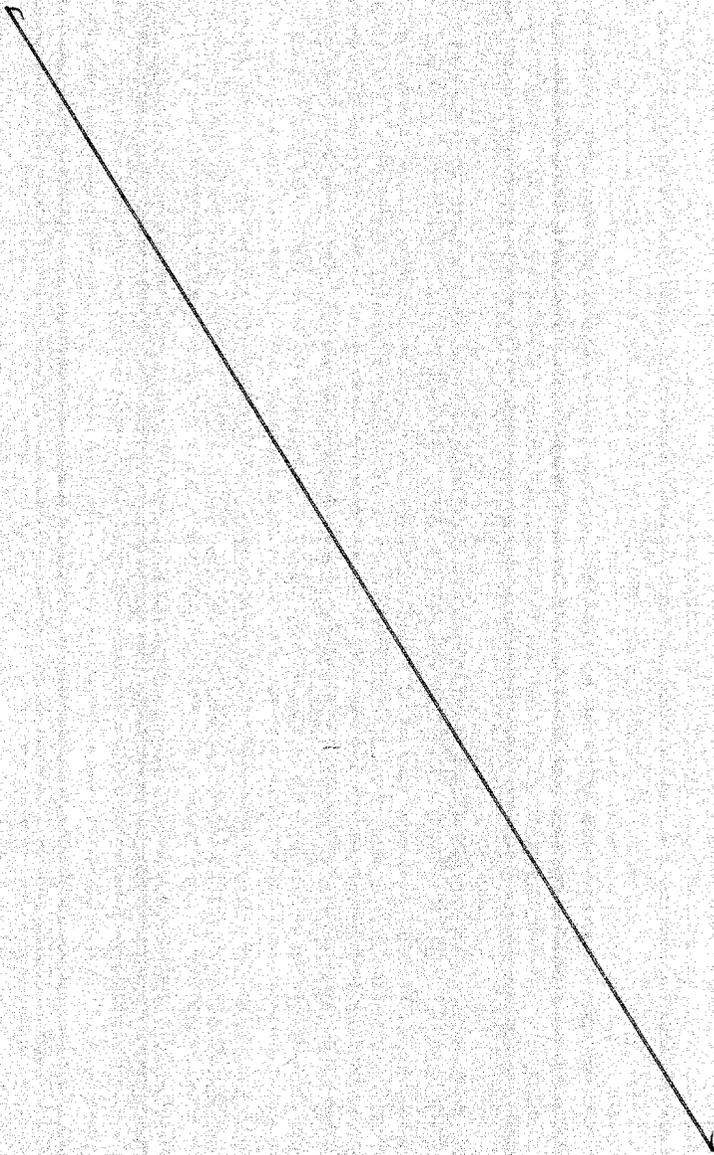
Appendix 12.

Appendix 13.

Appendix 14.

Appendix 15.

Appendix 16.



Appendix 17.

Appendix 18.

Appendix 19.

Appendix 20.

## VI. References (In a Separate 3-Ring Binder)

1. Partial list of microorganisms and microbial-derived ingredients that are used in foods. Office of Food Additive Safety, Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration, July 2001, obtained from <http://www.cfsan.fda.gov/~dms/opa-micr.html>, obtained September 7, 2005.
2. Reed G. and Pepler HJ. *Yeast Technology*. AVI Publishing: Westport, CT, 1973, p. 10.
3. Rose AH and Vijayalakshmi G. *Baker's Yeasts*. In: *The Yeasts: Volume 5, Second Edition*. Rose AH and Harrison JS [eds.] Academic Press: New York, 1993, pp. 357-360,
4. Harrison, JS. Food and fodder yeasts. In: *The Yeasts: Volume 5, Second Edition*. Rose AH and Harrison JS [eds.] Academic Press: New York, 1993, pp. 399-433.
5. Adamson GE, Lazarus SA, Mitchell AE, Prior RL, et al. HPLC method for the quantification of procyanidins in cocoa and chocolate samples and correlation to total antioxidant capacity. *J Agric Food Chem*, 1999; 47: 4184-4188
6. 21 CFR 172.986, Dried yeasts permitted for direct addition to food for human consumption.

7. Mouse lymphoma thymidine kinase gene mutation assay. *Toxicological Principles for the Safety Assessment of Food Ingredients* (Redbook 2000), Office of Food Additive Safety, U.S. Food and Drug Administration, October 2001, from: <http://www.cfsan.fda.gov/~redbook/redivc1c.html>, obtained September 22, 2005.
8. Dooley DC, Oppenlander BK, Xiao M. Analysis of primitive CD34- and CD34+ hematopoietic cells from adults: gain and loss of CD34 antigen by undifferentiated cells are closely linked to proliferative status in culture. *Stem Cells*, 2004; 22:556-69.
9. Mills JB, Rose KA, Sadagopan N, Sahi J, and de Moraes, SMF. Induction of drug metabolism enzymes and MDR1 using a novel human hepatocyte cell line. *J Pharmacol Exp Therap*, 2004; 309: 303-309.

**Premarket Notification for**  
**DIAM-H-04-2**  
**as a New Dietary Ingredient**

**(REFERENCES)**