DEPARTMENT OF HEALTH & HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Public Health Service

Memorandum

Date . FEB 25 2000

1505 '00 FEB 28 P2:10

From Senior Regulatory Scientist, Regulatory Branch, Division of Programs & Enforcement Policy (DPEP), Office of Special Nutritionals, HFS-456

Subject 75-day Premarket Notification for New Dietary Ingredient

To Dockets Management Branch, HFA-305

New Dietary Ingredient:	Humifulvate (Humic acid)
Firm:	Corvina Natural Products
Date Received by FDA:	January 11, 2000
90-day Date:	April 9, 2000

In accordance with the requirements of section 413(a)(2) 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 April 9, 2000.

Robert J. Moore, Ph.D.

95S-0316

95S-0316

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC 20204

FEB 25 2000

Andrew G. Pichler, M.D.
President
Corvina Natural Products
6633 Coyle Avenue, #2
Carmichael, California 95608

Dear Dr. Pichler:

This letter is in response to your letter to the Food and Drug Administration (FDA) dated December 30, 1999, 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 the intent of Corvina Natural Products to market a product containing a substance that you assert is a new dietary ingredient, namely, humifulvate. You state that this substance is a form of humic and fulvic acids derived from peat.

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 carefully considered the information in your submission, and the agency has concerns about the evidence on which you rely to support your conclusion that a dietary supplement containing humifulvate will reasonably be expected to be safe. You state in your submission that humifulvate is used in syrups marketed outside the United States and that there have been no adverse effects reported. However, your submission does not provide a quantitative estimate of the typical exposure to this substance based on its history of use elsewhere that would provide a basis to conclude that its history of use is a valid basis for determining that the amount provided by the recommended consumption of it in dietary supplements is reasonably expected to be safe.

Your submission also contained the results of a number of human and animal studies that you assert are adequate to evaluate the safety of ingested humifulvate. The human studies contained in the submission provide little support for concluding that chronic or long-term consumption of dietary supplements containing this ingredient will reasonably be expected to be safe in healthy people. The studies submitted were not designed nor intended to examine the adverse or toxicological effects of humifulvate in healthy people; instead, the studies mostly appear to be designed and intended solely to evaluate its short-term effect in persons

exposed to environmental heavy metals. Such efficacy studies have limited utility for determining whether the long-term use of a substance as an ingredient in dietary supplements is safe.

Most of the animal studies were designed to examine the effect of humifulvate as a chelating agent rather that to evaluate its short-term or long-term safety. Four toxicity/safety studies in rodents appear to be relevant and appropriate to consider the safety of this ingredient[1]. However, these studies are of limited use to evaluating the long-term safety of humifulvate in humans. First, they are of short-term duration and are not therefore, able to provide data relevant to the evaluation of potential complications associated with the regular, long-term use of the ingredient in humans. In at least two studies, possible negative effects on body weight gain of rats fed the highest dosages is unexplained and there appears to be no consideration of the potential relevance of this to longer term oral use of lower doses.

Finally, your submission does not address whether this substance, which is a chelating agent, has any effect on the status of essential minerals in persons consuming it over extended time periods. Chelating agents can deplete body stores of essential elements (for example, zinc, calcium, and so on) resulting in adverse health effects. However, the information in your submission does not in any way address this matter. Evidence that this substance is reasonably expected to be safe as a dietary supplement ingredient should include data from appropriately designed studies that include relevant measures of nutritional and physiological status of essential minerals that are susceptible to chelation and not just measurements of the effect on lead, cadmium, or iron.

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that humifulvate, 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).

Please contact us if you have questions concerning this matter.

Sincerely,

John B. Foret

John B. Foret
Director
Division of Compliance and Enforcement
Office of Nutritional Products, Labeling,
and Dietary Supplements
Center for Food Safety
and Applied Nutrition

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[1]Gachalyi et al., appendix 6 at p. 111; Desi, appendix 6 at p. 54; Kovacs, appendix 6 at p. 24; Antal, appendix 6 at p. 5.

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Notification of New Dietary Ingredient (Humifulvate)
by
Corvina Natural Products, Inc.

Submitted to:

Office of Special Nutritionals (HFS-450)
Center for Food Safety and Applied Nutrition
US Food and Drug Administration
200 C Street, SW
Washington, D.C. 20204

December 30, 1999

VOLUME I OF II

Corvina Natural Products, Inc.

HUMIC ACID CHEALATED MINERAL SUPPLEMENTS,
HERBALS & VITAMINS

Andrew G. Pichler, M.D.
Exclusive U.S. Distributor for:
Humet Corporation; Budapest Hungary
6633 Coyle Avenue #2, Carmichael, CA 95608
(916) 961-2266 FAX (916) 967-7939

DATE: 12/30/99

Office of Special Nutritionals (HFS-450)
Center for Food Safety and Applied Nutrition
US Food and Drug Administration
200 C Street, SW
Washington, D.C. 20204

Re: Notification of New Dietary Ingredient

Office of Special Nutritionals:

Pursuant to the Dietary Supplement Health and Education Act of 1994 (DSHEA), 21 USC § 350 b(a)(2), and FDA regulations, 21 CFR § 190.6, Corvina Natural Products, Inc., (Corvina) hereby submits this notification and information concerning a new dietary ingredient that Corvina intends to market for use as or in a dietary supplement. Pursuant to the provisions of DHSEA, Corvina will not introduce the ingredient or deliver the ingredient for introduction into interstate commerce until at least 75 days after the date that FDA receives this notification.

The distributor of the new dietary ingredient and the dietary supplement is:

Corvina Natural Products, Inc.
6633 Coyle Avenue #2
Carmichael, CA 95608
Phone: 916-961-2266

The manufacturer of the new dietary ingredient and supplement is:

Humet® Research and Development Company
(formerly called HORIZON-MULTI-PLAN, LTD)
H-1121 Budapest
Konkoly Thege u. 29-33
Hungary
Phone: 011361-160-1828

The manufacturer of other minerals in the supplement is:

SIGMA-ALDRICH Hungary, Ltd.,
Budapest
Hungary

The name of the new dietary ingredient is Humifulvate, which is a unique form of humic and fulvic acids derived from geologically young Hungarian peat. Humifulvate is chemically identifiable humic and fulvic acids derived from Hungarian peat found primarily along the shores of Lake Balaton in Hungary. Humic and fulvic acids are chemically multi-substituted polyaromatic heterocyclic macro- molecules that incorporate cyclic structures joined by aliphatic carbon chains. Those are organic compounds that are found in the human body. Humic and fulvic acids are also extracted from calcium huminate that is found in peat as a by-product of the decomposition of organic matter by lignin. Hungarian peat is geologically 3,000-7,000 years old and yields uniform and high quality humic and fulvic acids. Humifulvate is processed for inclusion in dietary supplements in liquid and solid form.

Humifulvate is a tolpha torf preparate (TTP), a derivative of Hungarian peat. (See Attachment 2 for confirming laboratory analysis.) It is a homogenous-fen type, geologically young, slightly basic (pH 7-8) with a 28-43% ash content. See Attachment 2 at 2-3 for the types, amounts, and ratios of the component parts of Humifulvate that is extracted from Hungarian peat. A schematic rendering of the bio-chemical structure of Humifulvate is attached in Attachment 3. IR spectrological analysis is attached in Attachment 2 at 11-13, 15. A full description of the product is contained in Attachment 4.

The recommended daily use of the dietary supplement is a single daily dose following a main meal. Humet®-R with the Humifulvate type of Hungarian humic acid is sold in 300ml bottles. The recommended daily oral dose of Humet®-R syrup is ten milliliters, which contains 75 mg of Humifulvate, 36 mg potassium, 15 mg magnesium, 14 mg iron, 10 mg zinc, 3 mg maganese, 0.5mg vanadium, 0.2 mg cobalt, 0.17 mg molydenum, and 0.13 mg selenium.

Humifulvate maintains and supports normal absorption and transport of essential nutrients and minerals and the elimination of heavy metals. Humifulvate has been marketed as a component of Humet®-R syrup in Europe since 1993. It is marketed as a dietary supplement for increasing overall vitality and promoting overall health. The Humifulvate found in Humet®-R has been reviewed and approved by the Hungarian National Institute of Pharmacy and Humet®-R is registered in Hungary as a non-prescription preparation, GYI 430/1993. It is sold in Hungary, Russia, Lithuania, Great Britain, Taiwan, Portugal, and the Netherlands. Humet®-R is also registered for sale in the Slovak Republic, Belarus, and the Ukraine. Registration for sale is pending in Canada and the Yeman Republic. The Humifulvate that is the subject of this notification is the same substance that has been tested, analyzed, and approved as a component of Humet®-R (see Attachment 2) and will be manufactured by the Humet®-R manufacturer.

Humifulvate is safe when used as recommended. Humet®-R has been consumed in Hungary since 1993 with no reports of adverse effects associated with its use. HFC is free of pathogens (See Attachment 5 at 10-14). All animal and human studies have used the HFC containing its stated ingredients to affirm its safety. This has been confirmed by independent laboratory analyses, using IR spectroscopy and fingerprinting, which has documented that humifulvate and the minerals and trace elements are in fact present in the HFC and are the same as the product tested in Humet-R® syrup (Attachment 2). No

sign of toxicity or death was noted in single dose toxicity tests in rats. Attachment 6 at 4 and 27. Researchers observed no toxicity in studies where rats were subjected to prolonged feeding. Attachment 6 at 108. Studies in rats and mice revealed no toxicity in doses exceeding 1000mg/kg. The LD_{50} for the Humifulvate has been estimated in verified tests to be more than 600mg/kg, well in excess of any recommended dosage. Attachment 6 contains results of toxicology studies using Humet®-R preparation. Those studies have been reviewed and certified by Dr. László Német of the Hungarian State Control Institute for Veterinary Biologicals, Drugs and Foods. Attachment 6 at 5 is the acute oral LD_{50} by National Insitute of Food and Nutrition Science (OÉTI) in Budapest, Hungary. Attachment 6 at 24 is an acute oral toxicity study conducted in 1996 that observed no lethality of Humet®-R.

Humet®-R containing Humifulvate has been subjected to mutagenic studies and under the AMES test criteria exhibits no mutagenic activity. Attachment 6 at 82 contains a copy of the results of two AMES method studies that were conducted in 1992 on Humet®-R containing Humifulvate. Additional testing reveals no mutagenic properties for Humet®-R. Attachment 6 at 69 and 73 contains a copy of the results of mutagenic testing of Humet®-R conducted by Department of Human Genetics of the Medical Research Insitute of Budapest between 1990 and February 1991. The Hungarian National Insitute of Food and Nutrition Science has determined that Humet®-R containing Humifulvate is free of carcinogenic polyaromatic hydrocarbons (PAH) (Attachment 6 at 107).

Multiple animal studies support the safety of Humifulvate (Attachment 6).

- Duda, Nagy and Tubak demonstrated that Humet®-R with Humifulvate type of Hungarian humic acid significantly inhibited tumor growth in mice and produced no toxic effects. Duda E, Nagy T and Tubak V, *Horizon-Multiplan Document* 44-3-11, 1997.

- Pigs of iron deficient sows that were fed Humet®-R and the Humifulvate type of Hungarian humic acid while pregnant exhibited significantly higher hemoglobin levels than did the pigs of iron deficient sows who were given the standard parenteral iron supplement treatment or no treatment. Furthermore, the Humet®-R did not inhibit iron absorption that often accompanies parenteral iron supplementation. Gundel J, et al., *Horizon-Multiplan Document* Humet 037, 1995.

- Pregnant Sprague-Dawley rats fed normal and iron deficient rodent diets exhibited similar hematologic parameter changes to supplementation with Humet®-R as with standard ferrin supplementation without adverse efffect. Szakmári É and Hudák A, *Horizon-Multiplan Document* 42-1-11, 1997.

- The cardiac muscle reperfusion rates were studied in rats that were fed Humet®-R containing Humifulvate for two weeks. In response to ischemic insult, coronary blood flow, aortic blood flow, and left ventricular end

diastolic pressure were improved in those hearts of the rats fed Humet®-R with Humifulvate type of Hungarian humic acid. The results indicate that Humet®-R has a cardioprotective effect that is dose dependent. Ferndinándy P, *Horizon-Multiplan Document* 39-1-08, 1997.

- Adult pigs were fed varying doses of Humet®-R or a control supplement. The pigs were then given a mercury radioisotope. In examining the excretion patterns of the pigs, those animals that were fed Humet®-R with Humifulvate excreted more of the isotope than did the control animals. The results of the study indicate that Humet®-R with Humifulvate is a safe and effective chelator of offending heavy metals while maintaining healthy balances of other metals and minerals.

Clinical trials that examined the safety and efficacy of Humifulvate indicate that it is safe for humans when used as recommended (Attachment 7). Reports of use of Humet®-R as a supplement for patients with serious diseases showed no evidence of toxicity when administered for more than one year (Attachment 7 at 17). Humet®-R has been studied for use in children (Attachment 7 at 21). Those trials involved treatment with Humet®-R preparation for more than six months and showed no evidence of toxicity. Results of the following studies also support the safety of Humifulvate (Attachment 7):

- Gelley, "Retrospective evaluation of the data of patients treated with humic acid metal complex," 1995.

- Csucka, "Retrospective evaluation of the data of patients treated with humic acid metal complex (case reports)," 1991.

- Szuts and Koszo, "The Application of Humet®-R Roborant Syrup in Paediatrics (Open Clinical Test Findings)," 1996.

- Florian, "Treatment of volunteers continually exposed to high dose of lead with Humet®-R syrup," 1995.

- Sallay, "Open-Labeled Prospective Clinical Research on Volunteers Exposed to Lead," 1998, Humet Trade, Research and Development Company: Budapest.

- Miklos, " The study of Humet®-R Syrup's Effect on the Metabolism of Trace Elements in Healthy Volunteers," 1992.

This cover letter containing the notification is available for dissemination to the public. All other materials submitted with this notification, including all attachments, are deemed proprietary and are therefore designated confidential. The enclosed information and scientific studies referenced herein establish that the dietary ingredient, Humifulvate, when used under the conditions suggested, is reasonably expected to be safe.

Respectfully Submitted,

Andrew G. Pickler, M.D.
President
Corvina Natural Products

Enclosures