DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: DEC 26 2000

From: 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:	Heme Iron Polypeptide
Firm:	Colorado Biolabs, Inc.
Date Received by FDA:	October 17, 2000
90-Day Date:	January 15, 2001

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 pubic display in docket number 95S-0316 after January 15, 2001.

Felicia B. Satchell

95S-0316

RPT 86

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC

DEC 26 2000

Gary Moore
President
Colorado Biolabs, Inc.
P.O. Box 125
Cozad, Nebraska 69130-0125

Dear Mr. Moore:

This is in response to your letter to the Food and Drug Administration (FDA) dated September 26, 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 (the act)). Your letter notified FDA of your intent to market a dietary supplement product containing the new dietary ingredient heme iron polypeptide (HIP).

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 and injury.

Your notification contains evidence of history of use and other information that you assert is an adequate basis to conclude that the type of dietary supplement product containing the new dietary ingredient will reasonably be expected to be safe. You assert that because HIP is a peptone, it is generally recognized as safe (GRAS) under 21 C.F.R. 184.1553. FDA disagrees that HIP, as produced under the manufacturing method described in your notification, falls within 21 C.F.R. 184.1553. Under 21 C.F.R. 184.1553, peptones are a variable mixture of polypeptides, oligopeptides, and amino acids that are produced by partial hydrolysis of casein, animal tissue, soy protein isolate, gelatin, defatted fatty tissue, egg albumin, or lactalbumin (whey protein). The source of protein in your manufacturing method is Proteins obtained from are different than those obtained from the sources listed in 21 C.F.R. 184.1553 in terms of composition and functionality. The sources for peptones (e.g., gelatin, casein, whey protein, and albumin) do not contain iron nor do they have any known iron-binding properties.

Further, you rely upon 21 C.F.R. 111.50, Packaging of iron-containing dietary supplements, as part of your basis on which you have concluded that a dietary supplement containing HIP will reasonably be expected to be safe. 21 C.F.R. 111.50 requires unit-dose packaging for iron-containing products that contain 30 milligrams (mg) or more of iron per dosage unit. This regulation does not establish the safety of any dosage of iron, as you suggested in your notification, but rather concerns the safe packaging of iron-containing supplements to reduce the risk of accidental iron poisonings of young children.

Although the agency disagrees with some of the statements in your submission, we are not finding at this time that the basis on which you have concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe is inadequate.

Your submission will be kept confidential for 90 days from the date of receipt, October 17, 2000, and after January 15, 2001, 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 any questions concerning this matter.

Sincerely yours,

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

Colorado Biolabs, Inc.
PO Box 125
Cozad, Nebraska
69130-0125

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FAX 308.784.4248
coloradobiolabs.com

September 26, 2000

Ms. Peggy Carlson
Food and Drug Administration
ONPLDS
HFS – Code 820
200 C Street SW
Washington DC 20024

Dear Peggy,

Thank you for taking time to speak with me regarding my original submission. As we discussed, I hope you will be able to expedite the review of our submission.

Enclosed are our papers with the original envelope so that you may see firsthand what happened the first time.

Sincerely,

Gary Moore

Gary Moore
President
Colorado Biolabs, Inc.
Enclosure (1)
GM/tb

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August 31, 3000

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FOOD AND DRUG ADMINISTRATION
200 C STREET, SOUTH WEST
WASHINGTON, D.C. 20204

Dear Sirs,

This letter is intended to constitute a:

NEW DIETARY INGREDIENT NOTIFICATION

NAME AND COMPLETE ADDRESS OF THE MANUFACTURER

Colorado Biolabs, Inc.
404 M Street
P.O. Box 125
Cozad, Nebraska
69130

NAME OF THE NEW DIETARY INGREDIENT

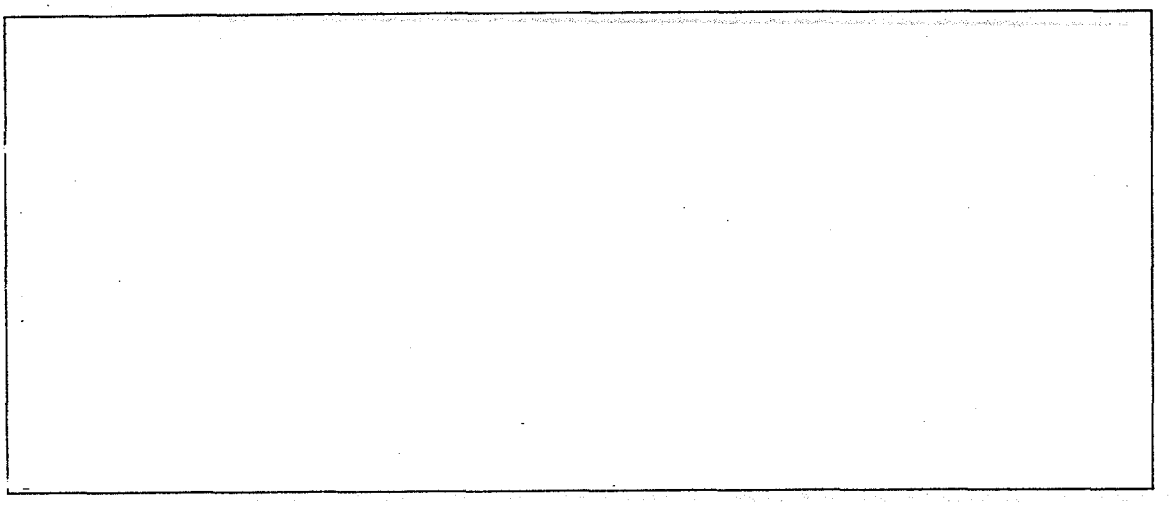
The product may be sold under its generic name: Heme Iron Polypeptide (HIP), or under the branded names: Fenergy, Toraem, or Proferrin

DESCRIPTION OF THE DIETARY SUPPLEMENT

HIP is a peptone: a polypeptide covalently with a tetrapyrole ring containing iron (heme) covalently attached. Average molecular weight is 2750-5500 KiloDaltons. Heme is the moiety inside the hemoglobin molecule present in mammalian blood responsible for carrying oxygen from the lungs to the tissues. Heme iron polypeptide is present in many wide spread food items including meats (beef, pork, and chicken), blood pudding, headcheese, blood sausage.

THE FOLLOWING INFORMATION ENCLOSED INSIDE THE BOX(S) MUST BE CONSIDERED SECRET AND CONFIDENTIAL AND IS NOT FOR PUBLIC DISCLOSURE

Heme iron polypeptide is extracted from by the following method:



The dried material may be encapsulated or tableted for consumption and packaged in bottles containing any number of pills (e.g. 15, 20, 30, 60, 90, 120, etc...).

THE LEVEL OF THE NEW DIETARY INGREDIENT IN THE DIETARY SUPPLEMENT

The capsules/tablets may contain 6, 7.2, 9, 12, or 15 milligrams of elemental iron.

THE CONDITIONS OF USE RECOMMENDED OR SUGGESTED IN THE LABELING

The recommended daily intake of the product may be:

1 tablet/capsule per day or as recommended by a physician
1 to 3 tablets/capsules per day or as recommended by a physician, or
3 tablets/capsules per day or as recommended by a physician

HISTORY OF USE AND EVIDENCE OF SAFETY

Upon ingestion of raw or rare meats the human body routinely encounters heme iron polypeptide during the digestion process as proteolytic enzymes degrade hemoglobin and myoglobin. Humans have been consuming meat since the dawn of time.

Since HIP is a peptone it is already Generally Recognized As Safe (GRAS):

21CFR, Subpart B - LISTING OF SPECIFIC SUBSTANCES AFFIRMED AS "GRAS"

Sec. 184.1553 Peptones.

(a) Peptones are a variable mixture of polypeptides, oligopeptides, and amino acids that are produced by partial hydrolysis of casein, animal tissue, soy protein isolate, gelatin, defatted fatty tissue, egg albumin, or lactalbumin (whey protein). Peptones are produced from these proteins using proteolytic enzymes that either are considered to be generally recognized as safe (GRAS) or are regulated as food additives. Peptones are also produced by denaturing any of the proteins listed in this paragraph with safe and suitable acids or heat.

(b) FDA is developing food-grade specifications for peptones in cooperation with the National Academy of Sciences. In the interim, these ingredients must be of a purity suitable for their intended use.

(c) In accordance with Sec. 184.1(b)(1), these ingredients are used in food with no limitation other than current good manufacturing practice. The affirmation of these ingredients as GRAS as direct human food ingredients is based upon the following current good manufacturing practice conditions of use:

(1) These ingredients are used as nutrient supplements as defined in Sec. 170.3(o)(20) of this chapter; as processing aids as defined in Sec. 170.3(o)(24) of [[Page 522]] this chapter; and as surface-active agents as defined in Sec. 170.3(o)(29) of this chapter.

(2) These ingredients are used in food at levels not to exceed current good manufacturing practice.

(d) Prior sanctions for these ingredients different from the uses established in this section do not exist or have been waived. [49 FR 25430, June 21, 1984, as amended at 50 FR 49536, Dec. 3, 1985]

Heme iron polypeptide has been on the market in Japan since 1991- Sold by Asahi Chemical Industry Company of Tokyo, Foods Division. The product is currently consumed on the Japanese market at the rate of approximately 15 metric tons per year. To date, Asahi has had no adverse effects reported.

Asahi sells the product as tablets, and formulated into foods including chocolate drinks, prune jellies, sesame and other flavored biscuits, hard candies, and condiments for flavoring steamed rice.

Heme iron polypeptide is accepted by the Japanese government under the FOSHU regulations and is recognized as a highly bioavailable form of iron for the human diet.

Asahi has performed LD_{50} studies in mice to determine the toxicity of the product. They determined that for 1% elemental iron heme iron polypeptide, the estimated LD_{50} of the product is 20 grams per kilogram. **This value is more than 5 times that of NaCL**. This dosage level corresponds to a dose of 0.75 kilograms (2% Fe) for a 75 kilogram man. If a person were to take the maximum recommended dose: 3 tablets per day each containing 15 milligrams of 2% elemental iron, they would be consuming approximately 1/333rd of the LD_{50}.

Currently "The use of **iron** and iron salts as iron sources in dietary supplements offered in solid oral dosage form (e.g. tablets or capsules), and containing 30 milligrams or more of iron per dosage unit, is safe" **21CFR 1, §111.50.** Keep in mind that the dosage forms of heme iron polypeptide are between 6 and 15 milligrams per solid unit dosage form - lower than in this citation.

Colorado Biolabs has performed clinical evaluations on normal healthy subjects with total doses between 20 and 60 milligrams per day with minimal side effects.

All lots of product for formulation into dietary supplements are subjected to routing microbiological analysis for potential food borne pathogens including *S. aureaus*, Staphylococcus spp, coliforms, and yeasts and molds and are certified to be in compliance with FDA guidelines for each before fabricated into market ready forms.

Currently in the US, many people experiencing iron deficiency anemia, for which iron is obviously indicated may receive doses or iron between 100 and 200 milligrams per day (1,2,3,4). These doses are far more than the recommended use expressed on the labels for heme iron polypeptide.

This concludes the current notification.

Sincerely,

Gary M. Moore
President - Colorado Biolabs, Inc.
(308) 784-2444