



**Memorandum**

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Date: OCT 18 2004  
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: Creatine Ethyl Ester HCl  
Firm: Medical Research Institute  
Date Received by FDA: 7/19/2004  
90-Day Date: 10/17/2004

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.

95S-0316

RPT 244



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

Mr. Patrick Noonan  
Warner Center Plaza, Suite 840  
21800 Oxnard Street  
Woodland Hills, California 91367

OCT 1 2004

Dear Mr. Noonan:

This is to inform you that the notification you submitted, dated July 16, 2004, on behalf of your client, Medical Research Institute, 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 July 19, 2004. Your notification concerns the substance called "Creatine Ethyl Ester HCL" (CE2™) that you intend to market as a new dietary ingredient.

The notification informs FDA that Medical Research Institute, Inc. intends to market the new dietary ingredient, "Creatine Ethyl Ester HCL", in 500 mg, 750 mg and 1000 mg capsules, caplets or tablets under the trade name CE2™. The notification further states that "Medical Research Institute will also distribute CE2™ as a bulk raw material powder for incorporation into other nutritional supplement products." The notification states that the "recommended daily dosing of CE2™ shall be 500 milligrams to 5 grams per day, consumed in a single or divided daily dose." The conditions of use of CE2™ as described in your notification include a statement that "Creatine Ethyl Ester HCL" will be recommended for adults only and will not be intended for use by pregnant or lactating women; individuals at risk for renal or hepatic dysfunction; individuals that have been medically prescribed Disulfuram (Antibuse); or individuals with known hypersensitivity to any of the components of "Creatine Ethyl Ester HCL". The targeted population for the dietary ingredient "Creatine Ethyl Ester HCL" is adults and children over the age of eighteen years of age."

Under 21 U.S.C. 350b(a), the manufacturer or distributor of a dietary supplement that contains 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 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.

It is not readily apparent whether the "Creatine Ethyl Ester HCL" that is the subject of your notification is a "dietary ingredient" within the meaning of 21 U.S.C. 321(ff)(1) that may be lawfully used in dietary supplements. The term "dietary supplement" is defined in 21 U.S.C. 321(ff). A dietary supplement means, among other things, a "product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:

- (A) a vitamin;
- (B) a mineral;
- (C) an herb or other botanical;
- (D) an amino acid;
- (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or
- (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E)."

Based on the information in your submission, it is unclear that "Creatine Ethyl Ester HCL" is a "dietary ingredient" within the meaning of 21 U.S.C. 321(ff)(1). Therefore, notwithstanding the discussion below of the information you rely upon as evidence that your product is reasonably expected to be safe, FDA cannot determine, at this time, whether your product contains a dietary ingredient that may lawfully be marketed as a dietary supplement.

Nevertheless, FDA has carefully evaluated the information in your submission and the agency has significant concerns about the evidence upon which you rely to support your conclusion that "Creatine Ethyl Ester HCL" when used under the conditions recommended or suggested in the labeling of your product, will reasonably be expected to be safe. In addition to the history of use claims stated in the notification, the scientific data submitted in appendix 24 of the notification summarize a study of the absorption and biodistribution of CE2™ in a rat model over a 24 hour period. The study concluded that following oral administration of CE2™, CE2™ is rapidly absorbed and dissociates into creatine and ethanol before being bioavailable to the tissues. However, the study failed to provide data showing that creatine levels are increasing as CE2™ dissociates and diffuses from the gut into the blood. This study did not clearly demonstrate the relative concentration of CE2™, creatine, and ethanol between the gut and blood especially during the first three hours after intake. It is unclear to FDA how creatinine levels in the urine could be detected yet there were no recorded measurements for creatine in the blood during the first 190 minutes of the experiment. Therefore, we have concerns about the experimental design of this study and the validity of the conclusion that CE2™ is rapidly absorbed and dissociates into creatine and ethanol before being available to the tissues. In addition, it appears that the long term toxicological effects of doses higher than 3 grams per day are unknown.

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that "Creatine Ethyl Ester Hydrochloride", 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 July 19, 2004. 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 Linda Pellicore, Ph.D. at (301) 436-2375.

Sincerely yours,

*for Robert J. Moore*

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

LAW OFFICES

**W. PATRICK NOONAN**  
A PROFESSIONAL CORPORATION

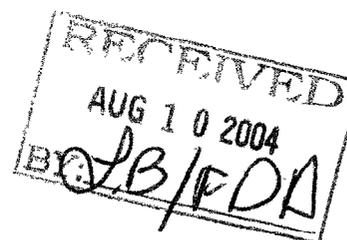
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August 6, 2004

Via Federal Express

Office of Nutritional Products, Labeling,  
And Dietary Supplements (HFS-820)  
Center for Food Safety and Applied Nutrition  
Food and Drug Administration  
5100 Paint Branch Parkway  
College Park, Maryland 20740-3835



Re: New Dietary Ingredient Notification: Creatine Ethyl Ester HCL (CE2™)

Dear Sir or Madam:

It has come to our attention that Attachment Nine in Section Six of the above New Dietary Ingredient Notification, identified as "Kreider RB. Creatine Supplementation: analysis of ergogenic value, medical safety and concerns," did not include Table 1-6 at the end of the article. For that reason, we are providing one original and two copies of that article with Table 1-6 to replace the existing article.

If you should have any questions concerning this matter, please contact me.

Sincerely,

W. Patrick Noonan

Enclosures

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