DEPARTMENT OF HEALTH & HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Public Health Service

Memorandum

Date APR 19 1999

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:	evening primrose seed extract
Firm:	Humanetics Corp.
Date Received by FDA:	February 5, 1999
90-day Date:	May 5, 1999

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 May 5, 1999.

Robert J. Moore, Ph.D.

95S-0316

RPT41

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC 20204

APR 19 1999

99 APR 22 A8:08

Mr. Ronald J. Zenk
President and CEO
Humanetics Corporation
600 South Highway 169
Suite 1205
Minneapolis, Minnesota 55426

Dear Mr. Zenk:

This letter is in response to your letter to the Food and Drug Administration (FDA) dated February 2, 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 your intent to market a product named ProenOthera™ containing a new dietary ingredient which consists of a polyphenolic extract from the seeds of the evening primrose plant (*Oenothera biennis*).

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 significant concerns about the evidence on which you rely to support your conclusion that a dietary supplement containing a polyphenolic extract from the seeds of the evening primrose plant (*Oenothera biennis*) will reasonably be expected to be safe. You state in your submission that ProenOthera™ contain various polyphenolic antioxidants that are present in other foods commonly consumed by humans. However, your submission does not provide a quantitative estimate of the typical exposure to these polyphenolic compounds in the human diet that would provide a basis to conclude that the amount of them in the typical diet is a valid basis for determining that the amount provided by the recommended consumption of ProenOthera™ is safe or that the additive exposure to the polyphenols in ProenOthera™ and those in the diet is safe . You also state in your submission that compounds similar to those in ProenOthera™ are present in other products that have a history of human use. However, the submission does not contain information that would establish that exposure to substances related to or similar to, but not the same as, those in ProenOthera™ is a valid basis for determining the safety of your product.

Your submission also contained the results of a study conducted in accordance with Federal Hazardous Substances Act (FHSA). However, the FHSA states that a "[h]azardous substance shall not apply...to foods, drugs, and cosmetics subject to the Federal Food, Drug and Cosmetic Act." Therefore, the FHSA is not the appropriate standard to use to assess the safety or toxicity of food, including dietary supplements. Furthermore, it is difficult to meaningfully apply the results of acute toxicity tests to the chronic exposure to a substance that would result from the use of that substance as a dietary supplement ingredient.

You also state in your submission that "in scientific studies, selected polyphenolic compounds such as those found in ProenOthera™ and mixtures of them have been extensively tested and found to be safe." The evidence cited to support this statement is a statement from a book[1]. The reference states in one declarative sentence that "[c]hronic toxicity tests with dogs indicate that adverse effects would not be produced in man until 35,000 milligrams of Pycnogenol were taken daily for more than six months." But, it is not clear from this statement whether this value represents the actual exposure in the original dog study or an exposure arrived at by adjusting for extrapolation from animals to humans using a uncertainty factor of 100. If the value of 35,000 milligrams/day refers to the exposure in the original study, then the application of an uncertainty factor of 100 would suggest that the potential for adverse effects may be associated with daily exposure to 350 mg/day in humans, an amount in the range or order of magnitude of the recommended intake of ProenOthera™ (i.e., 150-300 mg/day).

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

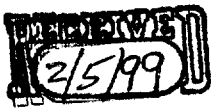
Sincerely,

Lynn A. Larsen, Ph.D.
Director
Division of Programs and Enforcement Policy
Office of Special Nutritionals
Center for Food Safety
and Applied Nutrition

---

[1]Passwater, R.A. and Kandaswami, C. *Pycnogenol: The Super Protector Nutrient*, pp. 101-102, Keats Pub., USA, 1994.

HUMANETICS
CORPORATION



9808 '99 APR 22 A8:08

63590

February 2, 1999

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

Dear Dr. Kahl:

Pursuant to Section 8 of the Dietary Supplement Health and Education Act of 1994, Humanetics Corporation wishes to notify the Food and Drug Administration that it will market a polyphenolic extract from the seeds of the evening primrose plant, *Oenothera biennis*, as a new dietary ingredient under the trade name ProenOthera™. Accordingly, enclosed are two (2) copies of this notification.

The dietary supplement that contains this new dietary ingredient will consist of up to 100 milligrams of ProenOthera™ for ingestion which will be suggested to be taken up to three times per day. ProenOthera™ is currently available for sale as a dietary supplement in New Zealand.

Attached is a summary and reports of the safety studies and other information which establish that this new dietary ingredient, when used under the conditions suggested in the labeling of the dietary supplement, is reasonably expected to be safe. These supporting studies include:

(1) A four-page safety profile summary of ProenOthera™ with reference to published literature.

(2) Fourteen supporting references.

Sincerely,

Ronald J. Zenk
President & CEO

600 South Highway 169 • Suite 1205 • Minneapolis, MN 55426 • (612) 513-9246 • (612) 513-9049 (fax)

ProenOthera™

DSHEA Regulatory Notification

January 1999

ProenOthera™

Basis for concluding this new dietary ingredient will reasonably be expected to be safe

Background

The extract from the seeds of the evening primrose plant, *Oenothera biennis,* which has been named ProenOthera™ is a mixture of polar compounds of which several groups predominate[1,2] (all references are attached). The groups are all polyphenolic compounds including flavonoids, flavonoid oligomers, hydrolyzable and non-hydrolyzable tannins, ellagitannins, gallic acid derivatives and glucogallate esters. ProenOthera™ includes Gallic acid, Catechin, OPC, Procyanidin B3, Ellagic acid and Pentagalloylglucose as given in the table below. About 90% of the compounds present in ProenOthera™ are well known antioxidants with the balance being carbohydrates. ProenOthera™ should not be confused with evening primrose oil. The ProenOthera™ extract contains several other natural compounds found in the primrose plant and seeds. ProenOthera™ is sold as a dietary supplement in New Zealand.

The compounds comprising ProenOthera™ are widespread in nature and have an important role in plant metabolism and mammalian nutrition. The compounds in ProenOthera™ are found in the normal human diet. Major components of ProenOthera™ are found in edible seeds, fruit, vegetables and many traditional herbal medicines[3]. Other polyphenolic extracts, for example pine tree bark and grape seed extracts, that are sold as dietary supplements contain varying proportions of the components found in ProenOthera™, but none have the uniquely broad range of polyphenolic compounds of ProenOthera™.

The compounds in ProenOthera™ contribute to a range of biological activities typical of antioxidants[4]. Recent clinical trials have confirmed that orally ingested antioxidants provide an important dietary role in the human body[5].

Safety Assessments

The compounds comprising ProenOthera™ have been part of the normal human diet for centuries. The compounds are found in numerous dietary seeds, fruits and vegetables. These foods all contain phenolic compounds such as flavonoids, gallates, hydrolyzable and non-hydrolyzable tannis including the oligomeric proanthocyanidins.

Most of the active antioxidants found in the evening primrose plant (gallic acid, catechin, oligomeric proanthocyanidins and procyanidin B3) are also present, in part, in the widely used pine bark, grape seed and green tea extracts. These products have been sold in the USA and many other countries for a number of years as dietary supplements.

The additional active antioxidant compounds present in ProenOthera™ (ellagic acid and pentagalloylgucose) are not in the products above but are present in a number of other widely consumed fruits and plants[6,7] (see table below). Their presence in ProenOthera™ gives it a broader antioxidant activity than other similar products.

Components of ProenOthera™ and Other Products

	Food Source	**ProenOthera™**	**Pine Bark Extract**	**Grape Seed Extract**	**Green Tea Extract**
Gallic acid	Tea	✓	✓	✓	✓
Catechin	Vegetables Tea	✓	✓	✓	✓
OPC	Fruit Vegetables	✓	✓	✓	N/A
Procyanidin B3	Fruit	✓	✓	N/A	N/A
Ellagic acid	Berry Fruit	✓	N/A	N/A	N/A
Pentagalloylglucose	Rhubarb Raspberries	✓	N/A	N/A	N/A

ProenOthera™ was tested and proven not toxic when given orally to rats according to the Federal Hazardous Substances Act Regulations, (16 CFR 1500.3)[8]. This independent study by Consumer Product Testing Co (USA) subjected both male and female albino rats to a dose equivalent to five grams per kilogram body weight (LD_{50}>5g/kg).

Owing to a growing understanding of the association between free radicals and biological systems, there has been intense interest in safe and functional natural antioxidants[9]. Thus in scientific studies, selected polyphenolic compounds such as those found in ProenOthera™ and mixtures of them have been extensively tested and found to be safe, for example in dogs, at levels of 35 grams per day for more than six months[10].

Polyphenol extracts from pine bark and grape seed have been commercialized and sold as dietary supplements. The principal constituents of these extracts are oligomeric procyanidins, which are also present in ProenOthera™[11]. Other antioxidant compounds identified in ProenOthera™ have also been identified in traditional herbal products[12]. Preparations from plants that contain flavonoids as the principal physiologically functional constituents have been used for centuries to benefit human health[12,13]. Over 500 varieties of flavonoids are known and most of them are present in the human diet.

Dose Considerations

The recommended dietary supplement dose of ProenOthera™ is 50 to 100 mg taken one to three times daily.

As demonstrated by the above table, ProenOthera™ is a mixture of polyphenolic antioxidant compounds that are found in fruits and vegetables that comprise part of the normal human diet. Owing to the recognized health benefits of fruit and vegetables, health authorities

recommend that at least five helpings per day of fruit and vegetables be taken, in part, to provide adequate intake of polyphenolic compounds. It is estimated that the average American's daily intake of one group of polyphenolic compounds, the flavonoids, is up to 1 gram[14]. Thus, dietary supplementation with polyphenolic compounds found in fruits and vegetables may be recommended to help maintain efficient bodily function. Based on their history of use in dietary supplements, the fact that antioxidant compounds of ProenOthera™ are present in fruits and vegetables consumed in the normal daily diet, the fact that the antioxidant compounds of ProenOthera™ are present in similar antioxidants sold and used for years in many countries, and by the demonstration of an oral LD_{50} greater than 5 grams/kilogram (rats), a wide safety confidence margin exists for the doses recommended of ProenOthera™.

References

1. Lu, F. and Foo, L.Y. "Phenolic antioxidant components of evening primrose." *Nutrition, Lipids, Health and Disease*, Ong. A.S.H., Niki, E. and Packer, L., (Eds.), Ch. 7, pp. 86-95, AOCS Press, 1995.

2. Shahidi F., et. al. "Antioxidant activity of phenolic extracts of evening primrose (Oenothera biennis): a preliminary study," *J. Food Lipids*, 4, pp. 75-86, 1997.

3. Hemel P.B., et. al. "Cherokee plants," Slyva, N.C., pp. 33, Herald Pub. Co., 1975; Herrick, J.W. "Iroquois medical botany," University Microfilms International, Ann Arbor, pp. 91-92, 175-176, 1977.

4. See ref. 1.

5. Rice-Evans, C.A., Miller, N.J., and Paganga, G. "Antioxidant properties of phenolic compounds," *Trends in Plant Science*, 2(4), pp. 152-159, 1997.

6. Maas, J.L., Galletta, G.J., and Stoner, G.D. "Ellagic acid, an anticarcenogen in fruits, especially in strawberries," *HortScience*, 26(1), January, 1991.

7. Goto, H., et. al., "Endotherlium-dependent vasodilator effect of extract prepared from the roots of *Paeonia lactifora* on isolated rat arorta," *Planta Medica*, 62, pp. 436-439, 1996; *The Pharmacopoeia of Japan*, 12th edition, pp. 697-698, 1991.

8. Consumer Product Testing Co. Final Report Summary, April 29, 1998.

9. Frankel, E.N. "Natural and biological antioxidants in foods and biological systems. Their mechanism of action, applications and implications," *Lipid Technology*, July, pp. 77-80, 1995.

10. Passwater, R.A., and Kandaswami, C. *"Pycnogenol: The Super Protector Nutrient"*, pp. 101-102, Keats Pub., USA, 1994.

11. Foo, L.Y. Industrial Research Ltd., New Zealand, correspondence, 1995.

12. Haslam, E., et. al. "Traditional herbal medicines – the role of polyphenolics," *Planta Medica*, 55, 1, 1989.

13. Havsteen, B. "Flavonoids, a class of natural products of high pharmacological potency," *Biochemical Pharmacology*, 12(7), pp. 1141-1148, 1983.

14. Huang, M.T. and Ferraro, T. "Phenolic compounds in food and cancer prevention." *Phenolic compounds in food and their effects on health II*, ACS Symposium Series, 507.