



DEPARTMENT OF HEALTH & HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION


Public Health Service

Memorandum

Date APR 29 1998
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: gamma butyrolactone
Firm: Unique Products Company
Date Received by FDA: February 13, 1998
90-day Date: May 13, 1998

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 13, 1998.


Robert J. Moore, Ph.D.

95S-0316

RPT 25



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

APR 29 1998

Food and Drug Administration
Washington, DC 20204

Mr. Jay L. Caplan
President
Unique Products Company
6312 Ramsgate Court
Brentwood, Tennessee 37027

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Dear Mr. Caplan:

This is in response to your letter to the Food and Drug Administration (FDA) dated February 11, 1998, making a submission pursuant to 21 U.S.C. 350b (section 413 of the Federal Food, Drug, and Cosmetic Act (the Act)) for a new dietary ingredient. Your letter notified FDA of your intent to market a dietary supplement containing a new dietary ingredient, 4-butyrolactone (gamma butyrolactone, herein denoted as GBL).

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 which 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. 343(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 GBL will reasonably be expected to be safe. Your submission states that your product will be marketed to provide a recommended daily dietary exposure to GBL based on the body weight of the user. Your proposed dosage of 20-30 milligrams (mg)/kilogram (kg) body weight, however, is an underestimate of the dosage that would result from a person taking the maximum recommended dosage of 2,500 mg/day (20-40 mg/kg bodyweight in a 60-70 kg adult). In your submission, you cite two lines of evidence purporting to establish that GBL may be safely used as a dietary supplement in humans. However, FDA believes that you have not considered significant limitations of the evidence you cite and findings in the studies cited that point to unresolved, serious health risks associated with the use of GBL as a dietary ingredient. Moreover, your submission ignores unequivocal evidence in the scientific literature of serious health risks from oral consumption of GBL, evidence that precludes a determination that GBL will reasonably be expected to be safe as a dietary ingredient.

1. Normal dietary exposure.

You cite as evidence of safety that GBL is a normal constituent of the diet because it is found in foods such as pineapple, tomato, beer, licorice, wine, vinegar, whey, cooked meat, roasted filberts, coffee, lavender, and apple brandy. However, you provide no data on, nor an estimate of, normal dietary exposure to GBL itself. Thus, no comparisons can be made between typical dietary exposure levels of GBL and the dosages of GBL proposed for your product. Additionally, potential differences in bioavailability and absorption of GBL from foods and encapsulated products were not considered in your submission. Therefore, dietary exposure to GBL is not adequate to support the safety of GBL at the recommended dosages.

2. Studies of GBL exposure in humans.

Your submission cites two studies in humans as evidence that GBL is safe. We disagree that these studies support the safety of long-term exposure to GBL. Neither study was longer than 3 months in duration, which precludes using either one as a basis for concluding that your proposed dosage of GBL is safe for long-term use. Moreover, both studies identified physiological responses that raise doubts about the safety of GBL in dietary supplements. In one study you cited¹, these responses included cardiovascular and respiratory changes, including fluctuations in blood pressure and abnormalities in electroencephalogram (EEG) recordings of patients administered GBL. The authors of this study reported that in EEG recordings “almost all of the normal lines show anomalies,” such as paroxysmal discharges. Also noted were “unexpected occurrence of clonus and psychomotor mechanical movements,” in severe cases and, in one case, an “epileptic crisis.” The authors concluded that the GBL exposure was associated with a “lowered convulsive threshold.”

In the other study cited in your submission as evidence of the safety of GBL², dosages of 10-60 mg per kg body weight produced drowsiness, euphoria, muscle relaxation, dizziness and weakness. Higher dosages of GBL (70-100 mg/kg body weight) produced temporary decreases in heart rate, respiration, and blood pressure and induced hypnotic or deep sleep. These responses were accompanied by side effects such as slow movement, paralytic feelings, twitching and jerking, dizziness, weakness, blurred vision, vomiting, euphoric behavior, and difficulty in communicating. Considering that the dosages proposed for your dietary supplement are approximately 20-40 mg/kg for 60-70 kg persons, the findings from this study reveals a negligible to minimal margin of safety between your suggested dosages and doses associated with significant side effects in humans.

¹Benda P, Deshaies G, Perles R et al. First clinical trial of butyrolactone. *Ann Medicopsychol*; 1960; 118: 770-6.

²Tanaka Z, Mukai A, Takayanagi Y et al. Clinical application of 4-hydroxybutyrate sodium and 4-butyrolactone in neuropsychiatric patients. *Folia Psychiatrica et Neurologica Japonica*; 1966; 20:9-16+.

3. Evidence not considered in the submission.

There is substantial and compelling evidence from case reports of accidental poisonings resulting from the oral consumption of GBL-containing products (such as nail polish remover and glue remover) by humans and from experimental studies in animals that preclude making a determination that GBL will reasonably be expected to be safe.

First, studies in rodents demonstrate that GBL is toxic. GBL administered by oral gavage to male and female rats (1,200 mg/kg body weight) resulted in the death of all of the animals³ within 3 days. In a 13 week study, all male rats administered an average daily dose of 640 mg GBL/kg bodyweight (by gavage) died during the study³. The lethality effects in rats occur at doses only 16 to 30 fold greater than the suggested human dosage proposed in your submission. Typically, safety assessments use safety factors to extrapolate animal data to humans. Generally, safety factors of 100 to 1000 are used, depending on the nature of the data utilized in the safety assessment. To arrive at a margin of safety, safety factors are typically applied to the no observable adverse effect level (NOAEL) or lowest observable adverse effect level (LOAEL) of the most sensitive toxicological end point for the substance (i.e., the physiological system or effect most sensitive to the substance). These NOAEL and LOAEL effect levels would be at a dose below the dose that causes death. Thus, in this case, the margin of safety between the suggested GBL dose for humans in your submission and the GBL dose that causes toxic effects in animals is even less than 16-30 fold. Your submission ignores the serious hazards of GBL exposure as evidenced by these rodent studies.

Second, orally administered GBL, once absorbed, is rapidly converted to 4-hydroxybutyrate (gamma hydroxybutyrate, herein denoted as GHB). GHB readily crosses the blood-brain barrier and results in neuropharmacological responses characteristic of central nervous system (CNS) depression. Under controlled clinical conditions, a progression of signs and symptoms occur in response to GHB doses from 10-60 mg/kg body weight⁴. Physiological responses to GHB include depressed cardiac and respiratory function, abrupt somnolence, unconsciousness, seizures, coma, and other adverse effects. Numerous case reports of GHB-

³National Toxicology Program. Toxicology and carcinogenesis studies of gamma-butyrolactone in F344/N rats and B6C3F1 mice (gavage). Research Triangle Park, NC: US Department of Health and Human Services, Public Health Service, National Institute of Health (NIH), NIH Publication No. 92-3137, Technical Report Series No. 406, 1992.

⁴Metcalf DR, Emde RN, Stripe JT. An EEG-behavioral study of sodium hydroxybutyrate in humans. *Electroenceph Clin Neurophysiol* 1966; 20:506-12; Mamelak M. Gammahydroxybutyrate: an endogenous regulator of energy metabolism. *Neurosci Biobehav Rev* 1989; 13:187-98; Lapierre D, Monplaisir J, Lamarre M et al. The effect of gamma-hydroxybutyrate on nocturnal and diurnal sleep of normal subjects: Further considerations on REM sleep-triggering mechanisms. *Sleep* 1990; 13:24-30; Vickers MD. Gamma hydroxybutyric acid. *Int Anesth Clin* 1969; 7:75-89.

induced toxicity in humans have been published in recent years⁵. The onset of symptoms can occur as early as 15-60 minutes after exposure, and most cases require required emergency medical attention and supportive care. Recovery typically occurs within 7-10 hours, although recovery may require as much as 4-5 days⁶. Dyer (see footnote 5) reviewed 16 cases of acute GHB poisoning and found symptoms to occur at intakes as low as 1/4 teaspoon (estimated dosage range of 10 - 30 mg/kg body weight for a 70 kg adult). His data, and that of others, suggest that the acute toxicological effects of GHB are associated with a steep dose-response curve.

GBL is readily absorbed and converted to GHB *in vivo*. Orally administered GBL produces cerebral and plasma concentrations of GHB that are higher than those achieved by oral administration of GHB⁷. Evidence on the physiological effects of oral doses of GBL obtained from case reports of poisonings⁸ in humans and from the animal and human studies discussed above demonstrate that the effects are consistent with the responses known to result from oral doses of GHB. GHB toxicity is well characterized and has been associated with the use of products that provide doses at a similar level of magnitude as those you propose to recommend for your product⁵.

Based on the information in your submission and other scientific literature the agency has reviewed, FDA disagrees with your conclusion that GBL, when used under the conditions recommended or suggested in the labeling of your product, will reasonably be expected to be safe. Therefore, your product is adulterated under 21 U.S.C. 343(f)(1)(B) because it contains

⁵MMWR, Morbidity and Mortality Weekly Report. Gamma hydroxy butyrate use - New York and Texas, 1995-1996. 1997; 46(13):281-3; MMWR, Morbidity and Mortality Weekly Report. Multistate outbreak of poisonings associated with the use of gamma hydroxy butyrate. 1991; 39:861-3; Friedman J, Westlock R, Furman M. Grievous bodily harm: gamma hydroxybutyrate abuse leading to a Wernicke-Korsakoff syndrome. *Neurology* 1996; 46:469-71; Dyer JE. gamma-hydroxybutyrate: a health-food product producing coma and seizure like activity. *Am J Emer Med* 1991; 9:321-4.

⁶MMWR, Morbidity and Mortality Weekly Report. Gamma hydroxy butyrate use - New York and Texas, 1995-1996. 7; 46(13):281-3; Suner S, Szlatenyi CS, Wang RY. Pediatric gamma hydroxybutyrate intoxication. *Pediatric GHB Toxicity* 1997; 4:1041-5.

⁷Guidotti A, Ballotti PL. Relationship between pharmacological effects and blood and brain levels of gamma-butyrolactone and gamma-hydroxybutyrate. *Biochem Pharmacol* 1970; 19:883-94.

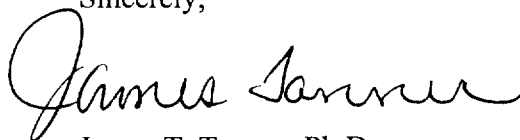
⁸Rambourg-Schepens M-O, Buffet M, Durak C, Mathieu-Nolf M. Gamma butyrolactone poisoning and its similarities to gamma hydroxybutyric acid: two case reports. *Vet Human Toxicol* 1997; 39:234-5.

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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 this product into interstate commerce is prohibited under 21 U.S.C. 331(a) and (v).

Please contact us if you have any questions concerning this matter.

Sincerely,

A handwritten signature in cursive script that reads "James Tanner". The signature is written in black ink and is positioned above the printed name and title.

James T. Tanner, Ph.D.
Acting Director
Division of Programs and Enforcement Policy
Office of Special Nutritionals
Center for Food Safety
and Applied Nutrition

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Rec'd
2/13/98

UNIQUE PRODUCTS COMPANY

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Pursuant to 21 C.F.R. § 20.61 and 21 U.S.C. § 331(j)

February 11, 1998

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

Re: New Dietary Ingredient Notification

To whom it may concern:

Unique Products Company ("Unique Products") hereby submits the following notification for a new dietary ingredient pursuant to 21 C.F.R. § 190.6 (1997). We request that the FDA acknowledge receipt of this submission pursuant to 21 C.F.R. §190.6(c) (1997).

Unique Products is the manufacturer of the proposed new dietary supplement. The company is located at the address indicated on the top of this letter. Jay L. Caplan is Unique Products' designated representative for providing information and answering questions related to this product. He may be reached at the above listed address and telephone number.

The new dietary ingredient that is the subject of this notification is 4-butyrolactone. It is also known as gamma-butyrolactone, 4-butanolide, dihydro-2(3H)-furanone, oxanolone-2, tetrahydro-2-furanone, butyryl lactone, or 4-deoxytetric acid (hereinafter referred to as "gamma-butyrolactone").

Gamma-butyrolactone is found in the following food or food items : pineapple, tomato, lavender, beer, licorice, apple brandy, wine, vinegar, whey, cooked meat, roasted filberts, and coffee. The attached studies and papers provide the proof we

are relying on to state that the new dietary ingredient is found in all of the above listed product. See World Health Organization - International Agency for Research on Cancer, "Gamma-Butyrolactone", Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Vol. 11 page 231 (1975); PhytochemDB, Assay : Lavandula angustifolia #1, <http://probe.nal.usda.gov:8300/> ; PhytochemDB, Assay : Ananas comosus #1, <http://probe.nal.usda.gov:8300/> ; PhytochemDB, Assay : Lycopersicon esculentum #1, <http://probe.nal.usda.gov:8300/> ; PhytochemDB, Assay : Glycyrrhiza glabra #1, <http://probe.nal.usda.gov:8300/> .

The proposed new dietary supplement will consist of gamma-butyrolactone sealed in soft gel capsules. Each capsule will contain between 325 mg and 500 mg of gamma-butyrolactone. The product will be packaged in such a manner that a minimum of four and a maximum of five soft gel capsules will be sealed within a single pouch. The maximum dosage of the new ingredient within each pouch is thus two and one-half grams, or 5 capsules at 500 mg each. The pouch is constructed of a heat sealed paper/polyethylene/foil/polyethylene laminate. Pouches may then be packaged in cartons and each carton will contain between five and thirty pouches.

The new dietary supplement is intended to support relaxation, normal sleep, and the release of growth hormone in the body. The recommended dose will vary by weight of the individual. Recommended dosage levels will be given in number of capsules. The maximum recommended dosage is one pouch, or a maximum of 5 capsules. Lower doses will be identified as appropriate for smaller individuals.

The packaging will clearly identify the recommended doses. It will also identify that the product should only be taken once a day, on an empty stomach and only before bedtime.

The packaging will also contain a complete set of warnings as to what activity should be avoided when using this product. The packaging will contain warnings that the product should not be used in conjunction with either alcohol or central nervous system depressants. Consumers further will be warned not to use the product prior to driving or to operating machinery. The packaging will identify that this product should not be used by individuals with the following conditions: epilepsy, convulsions, seizures, brachycardia, high blood pressure or cardiovascular disease, Cushing's syndrome, or hyperprolactinemia. Pregnant or lactating women and persons under the age of 18 should also not use the product.

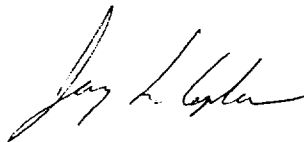
We have included the studies and reports upon which we have relied to determine that the new dietary ingredient is safe for the uses identified. The WHO Monograph mentioned above shows that gamma-butyrolactone did not cause cancer in mice or rats orally fed the product. In that study, the rats and mice were given oral doses exceeding 800 mg/kg. The dietary supplement dosage is approximately 20 mg/kg to 30 mg/kg. A second carcinogenesis study is also included: Toxicology and Carcinogenesis Studies of Gamma-Butyrolactone (CAS No. 96-48-0) in F344/N Rats and B6C3F1 Mice (Gavage Studies), <http://ntp-server.niehs.nih.gov>

We have also included two clinical studies which examined the use of gamma-butyrolactone. One study showed that an oral dose of 1.5 grams of gamma-butyrolactone elicited relaxation and induced sleep. P. Benda et. al., First Clinical Trial of Butyrolactone, Ann. Medicopsychol. Vol. 118 pp. 770-776 (Nov, 1960). This study is provided in the original French and with an English translation.

The second study describes the use of gamma-butyrolactone in varying doses with 9 normal male patients and 288 neuropsychiatric patients. Dr. Z. Tanaka et. al., Clinical Application of 4-Hydroxybutyrate Sodium and 4-Butyrolactone in Neuropsychiatric Patients, 20 Folia Psychiatric et Neurologic Japonica, Vol. 20, No.1 (1966). No serious side effects were noted over a two year period. Laboratory examinations of liver, kidney and heart revealed no significant abnormal findings. The study did note that gamma-butyrolactone could induce relaxation.

Please let us know if you have any questions or comments about this information.

Sincerely,



Jay L. Caplan
President

pr

cc: Geoffrey Levitt-Venable ; fdaapp/4

enc: 2 carc. reports, 2 clin. studies with translation, 3 USDA analyses

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