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PETITION FOR HEALTH CLAIMS:

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- CALCIUM AND KIDNEY STONES.
- CALCIUM AND URINARY STONES.
- CALCIUM AND KIDNEY STONES AND URINARY STONES.

**SUBMITTED TO THE FOOD AND DRUG ADMINISTRATION
OCTOBER 9, 2003**

**PETITIONER:
MARINE BIO USA, INC.**

2004Q-0102

Q17C 1

TABLE OF CONTENTS

Petition for Health Claim: Calcium and Kidney Stones; Urinary Stones; and Kidney Stones and Urinary Stones

Table of Contents.....i

Health Claim Petition

Introduction and Statement of Purpose..... 1

A. Preliminary Requirements4

 1. Calcium meets the definition of 21 C.F.R. § 101.14(b).....4

 a. Calcium is associated with a disease affecting the general U.S. population4

 b. Calcium contributes nutritive value at the levels present in supplements.....5

 c. Calcium is safe and lawful under the FDCA6

B. Summary of Scientific Data Supporting the Proposed Claims.....8

 1. Significant scientific agreement exists to support the amended claim8

 2. Scientific evidence demonstrates the public health benefits of calcium.....8

 3. Scientific summary issues.....8

 a. Is there an optimum level of calcium to be consumed beyond which no benefit would be expected?8

 b. Is there any level at which an adverse effect from the substance or from foods containing the substance occurs for any segment of the population?.....9

 c. Are there certain populations that must receive special consideration?10

d.	What other nutritional or health factors (both positive and negative) are important to consider when consuming the substance?	11
4.	Potential effect of the use of the amended claim on food consumption, including significant alterations in eating habits and corresponding changes in nutrient intakes	11
5.	Prevalence of the disease or health-related condition in the U.S. population and the relevance of the claim in the context of the total daily diet.....	12
6.	Calcium meets the definition of 21 C.F.R. § 101.14(a).....	12
C.	Analytical Method	14
D.	Proposed Model Claims.....	15
E.	Attachments	16
F.	Environmental Impact.....	17
G.	Conclusion and Certification	17

Attachments

Exhibit 1	Scientific Report of Dr. Michael John Glade
Exhibit 2	PDR for Nutritional Supplements, Section on Calcium
Exhibit 3	<u>Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride</u> , Institute of Medicine (National Academy Press 1997).
Exhibit 4	<u>Methods of Analysis for Nutrition Labeling</u> , AOAC International, Chapter 12
Exhibit 5	Scientific References and Medline Research Search Results

October 9, 2003

PETITIONER: Marine Bio USA, Inc.

ADDRESS: c/o Emord & Associates, P.C.
5282 Lyngate Court
Burke, VA 22015

SUBJECT: Petition for Health Claims:

1. Calcium may reduce the risk of kidney stones.
2. Calcium may reduce the risk of urinary stones.
3. Calcium may reduce the risk of kidney stones and urinary stones.

Food and Drug Administration
Office of Nutritional Products, Labeling, and Dietary Supplements
HFS-800
5100 Paint Branch Parkway
College Park, MD 20740

I. Introduction and Statement of Purpose

The undersigned, Marine Bio USA, Inc. (hereinafter "Petitioner"), submits this petition pursuant to section 403(r)(5)(D) of the Federal Food, Drug, and Cosmetic Act ("FDCA")(21 U.S.C. § 343(r)(5)(D)) with respect to calcium and kidney and urinary stones. The proposed claims are contained in Section D below. Attached hereto and constituting a part of this petition is the information necessary to satisfy the requirements specified in 21 C.F.R. § 101.70(f).

This petition presents a logical and valid evaluation of the scientific studies and clinical trials concerning the relationship between calcium and reduction in the risk of kidney stones (nephrolithiasis) and urinary stones (urolithiasis)¹. The attached scientific studies establish that the consumption of calcium may reduce the risk of kidney and urinary stones and justify permitting health claims that link consumption of calcium with reduction in those risks. See Glade Report attached as Exhibit 1.

¹ Nephrolithiasis and urolithiasis produce aggregates of crystals mixed with a protein matrix that cause obstruction of urine flow. The difference between the two is the location of the obstruction of urine flow. In nephrolithiasis, urine flow is blocked in the renal collecting system. In urolithiasis, urine flow is blocked in the ureters or urethra.

Calcium is the subject of an approved health claim for its relationship to osteoporosis. 21 C.F.R. § 101.72. As stated in the final rule for that health claim, ten forms of calcium have been shown to be safe and lawful for use in dietary supplements to FDA's satisfaction in accordance with 101.14. 58 FR 2665, 2670 (Jan. 6, 1993)(calcium carbonate, calcium citrate, calcium glycerophosphate, calcium oxide, calcium pantothenate, calcium phosphate, calcium pyrophosphate, calcium chloride, calcium lactate, and calcium sulfate). Id. citing 56 FR at 60691. Calcium is a safe and lawful substance and contributes nutritive value. 21 C.F.R. § 101.14(b)(i) and (ii). Similarly calcium is a substance within the meaning of 21 C.F.R. § 101.14(a)(2).

As discussed below, calcium possesses properties that have a multitude of beneficial effects in the body including reducing the risk of kidney and urinary stones. Thus, calcium is associated with diseases, nephrolithiasis/ urolithiasis, that are the subject of this petition. 21 C.F.R. § 101.14(b)(i). The scientific report (Exhibit 1), the PDR for Nutritional Supplements chapter on calcium (Exhibit 2), the Institute of Medicine's chapter on calcium (Exhibit 3), and all of the attached scientific articles establish that, based on the totality of publicly available scientific evidence (including evidence from well-designed studies conducted in a manner which is consistent with generally recognized scientific procedures and principles), there is significant scientific agreement among experts qualified by scientific training and experience to evaluate such a claim, that calcium reduces the risk of kidney and urinary stones.

The scientific studies described in this petition directly address the important public health issues of the above-listed diseases and further national and DHHS policies by identifying low cost means of reducing risks of those diseases and disease conditions. The proposed health claims respond to a major public health concern in the United States. Nephrolithiasis/urolithiasis

affects 12% to 20% of men and 5% to 10% of women in the United States. Exh. 1 at 4.

Between 100 and 300 cases occur annually per 100,000 individuals. Id. The risk for a second stone within 6 years is 50%. Id. Annual costs associated with nephrolithiasis in the U.S. exceed \$2 billion. Id.

The Petitioner believes that the truthful and succinct health information conveyed by its proposed health claims will enable consumers to make prudent and effective dietary choices. Labeling dietary supplements with the proposed calcium claim will inform consumers at the point of sale of current scientific evidence concerning means to reduce the risk of kidney and urinary stones.

In accordance with FDA's July 10, 2003 "Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements" and consistent with the decision in Pearson v. Shalala, 164 F.3d. 650 (D.C.Cir. 1999), reh'g denied en banc, 172 F.2d 72 (D.C.Cir. 1999); Pearson v. Shalala, 130 F.Supp.2d 105 (2001), recon. denied, Pearson v. Thompson, 141 F. Supp. 2d 105 (D.D.C. 2001); and Whitaker v. Thompson, 248 F. Supp. 2d 1 (D.D.C. 2002), the Petitioner respectfully requests that if the agency finds that the proposed claims do not satisfy its "significant scientific agreement" standard, that the agency authorize the claims nevertheless, with such succinct and accurate disclaimers as are reasonably necessary to avoid a potentially misleading connotation.

A. Preliminary Requirements

1. Calcium meets the requirements of §101.14(b)

The proposed health claims meet the relevant eligibility requirements of 21 C.F.R. §

101.14(b). Section 101.14(b) requires:

(b) Eligibility. For a substance to be eligible for a health claim:

- (1) the substance must be associated with a disease or health-related condition for which the general U.S. population, or an identified U.S. population subgroup (e.g., the elderly), is at risk, or, alternatively, the petition submitted by the proponent of the claim otherwise explains the prevalence of the disease or health-related condition in the U.S. population and the relevance of the claim in the context of the total daily diet and satisfies the other requirements of this section.
- (2) If the substance is to be consumed as a component of a conventional food at decreased dietary levels, the substance must be a nutrient listed in 21 U.S.C. 343(q)(1)(C) or (q)(1)(D), or one that the Food and Drug Administration (FDA) has required to be included in the label or labeling under 21 U.S.C. 343(q)(2)(A); or
- (3) If the substance is to be consumed at other than decreased dietary levels:
 - (i) The substance must, regardless of whether the food is a conventional food or a dietary supplement, contribute taste, aroma, or nutritive value, or any other technical effect listed in § 170.3(o) of this chapter, to the food and must retain that attribute when consumed at levels that are necessary to justify a claim; and
 - (ii) The substance must be a food or a food ingredient or a component of a food ingredient whose use at the levels necessary to justify a claim has been demonstrated by the proponent of the claim, to FDA's satisfaction, to be safe and lawful under the applicable food safety provisions of the Federal Food, Drug and Cosmetic Act.

Calcium is eligible for a health claim. It currently is the subject of an approved health claim concerning its osteoporosis risk reducing effects. 21 C.F.R. § 101.72.

a. Calcium is associated with a disease affecting the general U.S. population

A "disease or health-related condition" means "damage to an organ, part, structure, or system of the body such that it does not function properly (e.g. cardiovascular disease), or a state of health leading to such dysfunctioning (e.g. hypertension); except that diseases resulting from essential nutrient deficiencies (e.g., scurvy, pellagra) are not included in this definition (claims

pertaining to such diseases are thereby not subject to § 101.13 or § 101.70.” 21 C.F.R. § 101.14(a)(5).

The three health claims associate calcium with kidney stones and urinary stones. Both diseases and health conditions are ones for which the general U.S. population is at risk. As discussed above, nephrolithiasis/urolithiasis affects 12% to 20% of men and 5% to 10% of women in the U.S. Exh. 1 at 4. Between 100 and 300 cases occur annually per 100,000 individuals. Id. Annual costs associated with nephrolithiasis and urolithiasis exceed 2 billion dollars. Id.

b. Calcium contributes nutritive value at the levels present in supplements

In accordance with section 101.14(b)(3)(i), calcium contributes nutritive value. The Reference Daily Intake (RDI) for calcium is 1000 mg. 21 CFR § 101.9(b)(8)(iv).² The nutritive contribution of calcium is widely recognized. See generally, Exhibits 1, 2, and 3. FDA previously recognized calcium’s nutritive value at the levels present in supplements in its final rule on the health claim concerning the relationship between calcium and osteoporosis. 56 FR 60689 at I.D. Calcium is an essential mineral that has a multitude of vital biological roles. Exh. 2 at 74; 56 FR 60689 at I.D. Calcium is, of course, a major constituent of bones and teeth. E.g., Exh. 2 at 74. In addition calcium is necessary for muscle contraction (including heart function), nerve conduction, blood coagulation, glandular secretion, energy production, and immune system function. Id. The mechanism of calcium’s absorption, efficiency, and retention are discussed in detail in Exhibit 1.

² The Institute of Medicine recommends daily calcium intakes of 800 mg (4 through 8 years old), 1300 mg (9 through 18 years old), 1000 mg (19 through 50 years old) and 1200 mg (over 50 years old). Exhibit 1 at 6; Exhibit 3 at 91-117.

As stated in the Glade Report, there is an absolute lack of any reports of clinically-significant adverse reactions attributed to dietary calcium. Exhibit 1 at 7. The report goes on to state that the North American Menopause Society in its 2001 Consensus Opinion stated that the side effect profile from recommended levels of calcium intake is insignificant and that no serious side effects are associated with those levels. *Id.* at 8. Similarly the PDR reports that calcium supplements are generally well tolerated. Exhibit 2 at 77.

Calcium-containing supplements are available in different calcium salts (calcium carbonate, calcium citrate, calcium glycerophosphate, calcium oxide, calcium pantothenate, calcium phosphate, calcium pyrophosphate, calcium chloride, calcium lactate, and calcium sulfate) and in different forms (including capsules, chewable tablets, suspension, tablets, and wafers). 58 FR at 2670; Exhibit 2 at 77-78. Calcium supplements are available in a range of strengths from 150 mg to 1150 mg. Exh. 2 at 77-78.

c. Calcium is safe and lawful under the FDCA

“For each such ingredient listed, the petitioner should state how the ingredient complies with the requirements of § 101.14(b)(3)(ii), e.g., that its use is generally recognized as safe (GRAS), listed as a food additive, or authorized by a prior sanction issued by the agency, and what the basis is for the GRAS claim, the food additive status, or prior sanctioned status.” 21 C.F.R. § 101.70(f)(A). As stated in the final rule for the health claim concerning calcium and osteoporosis, calcium complies with the requirements of § 101.14(b)(3)(ii). Calcium has prior sanctioned status as safe and lawful under the FDCA.

The agency has determined that ten calcium compounds have been demonstrated to be safe and lawful for use in a dietary supplement: calcium carbonate, calcium citrate, calcium glycerophosphate, calcium oxide, calcium pantothenate, calcium phosphate, calcium

pyrophosphate, calcium chloride, calcium lactate, and calcium sulfate. 58 FR at 2670 citing 56 FR at 60691.

In summary, since calcium meets the requirements set forth in 21 C.F.R. § 101.14(b), the preliminary requirements of 21 C.F.R. § 101.70 are fully satisfied.

B. Summary of Scientific Data

1. Significant scientific agreement exists to support the proposed claims

There is significant scientific agreement among experts who study the effect of calcium on kidney and urinary stones that calcium is an effective modifier (reducer) of the risk of those diseases. See Exhibit 1 at 1.

The direct cause of urolith formation is unknown and likely to be multifactorial. Exhibit 1 at 4. There is evidence that essential hypertension and nephrolithiasis may share a similar defect in calcium physiology. Id. (see also Petitioner's simultaneously filed health claims for calcium and essential hypertension, gestational hypertension, and pre-eclampsia (hereinafter "Calcium/Hypertension Petition") for further discussion of studies on point). Nephrolithiasis may be associated with chronic secondary hyperparathyroidism. Id. at 9. Based on the evidence, it is apparent that dietary calcium restriction increases the risk of nephrolithiasis and urolithiasis. Id. Human clinical trials and other scientific evidence are discussed in detail in Exhibit 1 and are summarized in the following section.

2. Scientific evidence demonstrates the public health benefits of calcium

As discussed in detail in Exhibit 1, human studies have shown that adequate calcium nutrition reduces the risk of nephrolithiasis and urolithiasis. Id. at 4. In several studies, daily dietary calcium intake was found to be significantly inversely associated with the risk of symptomatic kidney stone formation. Id. at 5. The human studies on the relationship between calcium and nephrolithiasis and calcium and urolithiasis are amply vetted in the attached scientific report (Exhibit 1).

3. Scientific Summary Issues

- a. Is there an optimum level of the particular substance to be consumed beyond which no benefit would be expected?

Clinical trials have tested daily doses up to 8000 mg of calcium carbonate (up to 3200 mg of elemental calcium) in adults with renal failure, 7800 mg of calcium carbonate and 5200 mg of elemental calcium in young men and women and 3240 mg of calcium carbonate in healthy premenopausal women. Exh. 1 at 7. There is an absolute lack of evidence of clinically-significant reactions that could be attributed to dietary calcium. Id. at 7. Moreover, there are no reports of overdosage. Exh. 2 at 77.

A lowest-observed-adverse-effect level (LOAEL) for calcium in the range of 4 to 5 grams with an uncertainty factor of 2 has been identified for adults, according to the PDR (citing the Food and Nutrition Board of the Institute of Medicine). Id. at 78. Based on that information the tolerable upper intake level for children (1-18 years) and adults (including during pregnancy and lactation) is 2,500 mg/day. Id.; See also, Exh. 1 at 6. The attached scientific report states that reliable and credible scientific literature indicates that daily dietary supplementation of calcium of at least 1200 mg/day of elemental calcium is effective in reducing the risk of nephrolithiasis and urolithiasis. Id. at 9.

- b. Is there any level at which an adverse effect from the substance or from foods containing the substance occurs for any segment of the population?

There is no increased risk for nephrolithiasis among individuals who consume recommended amounts of calcium. See Exhibit 1 The LOAEL for calcium for individuals with a history of nephrolithiasis was calculated to be 1685 mg daily, an amount less than recommendations. Id. FDA has concluded that daily intakes of elemental calcium up to 1800 mg pose no increased risk for kidney stones among the general population. Id. citing 58 FR 2665.

By contrast the PDR states that supplemental calcium taken without food may increase the risk of kidney stones in women and men. Exhibit 2 at 76. The theory is that taking calcium supplements without food limits the opportunity for the beneficial effect that calcium may have in binding oxalate in the intestine. Id. Exhibit 1 and the supporting science show that theory to be incorrect.

The PDR states “calcium supplements are generally well tolerated.” Exhibit 2 at 77. For calcium carbonate, it states that its use may cause gastrointestinal side reactions as constipation, bloating, gas, and flatulence. Id. Prolonged use of doses of calcium carbonate in excess of 12g daily (about 5g of elemental calcium) may lead to milk-alkali syndrome, nephrocalcinosis, and renal insufficiency. Id.

c. Are there certain populations that must receive special consideration?

The PDR for Nutritional Supplements states that persons who form calcium-containing kidney stones are advised against taking supplemental calcium. Id. at 77. Persons with achlorhydria should take calcium carbonate with food. Id. Calcium supplementation is contraindicated in persons with hypercalcemia (hypercalcemia is caused by sarcoidosis, hyperparathyroidism, hypervitaminosis D, and cancer). Id. at 76. However only with daily intakes of over 4,000 mg of calcium may there be an increased risk for the development of hypercalcemia, particularly if accompanied by equivalently large amounts (over 6,000 mg) of carbonate. Exh. 1 at 7.

Conditions that produce lower levels of circulating estrogen alter calcium homeostasis. The 1997 DRI chapter on calcium states that young women with amenorrhea resulting from anorexia nervosa have reduced net calcium absorption, higher urinary calcium excretion, and a

lower rate of bone formation. Exh. 3 at 76. Exercise-induced amenorrhea also results in reduced calcium retention and lower bone mass. Id.

- d. What other nutritional or health factors (both positive and negative) are important to consider when consuming the substance?

According to the PDR, concomitant use of calcium with biophosphonates, levothyroxine (only calcium carbonate), quinolones, and tetracycline may decrease absorption of those drugs. Exh. 2 at 77. Concomitant use of calcium with H2 blockers and proton pump inhibitors may decrease absorption of calcium. Id. Concomitant use with vitamin D analogues may increase absorption of calcium. Id.

4. Potential effect of the use of the proposed claims on food consumption, including significant alterations in eating habits and corresponding changes in nutrient intakes.

Daily calcium consumption meets or exceeds the RDI only in a small fraction of the population. Exh. 1 at 6. Only half of children 4 to 8 years old consume at least 800 mg of calcium daily; less than 25% of boys 9 to 13 years old consume at least 1300 mg of calcium daily; less than 50% of boys 14 to 18 years old consume at least 1300 mg of calcium daily; only about 5% of adolescent girls consume at least 1300 mg of calcium daily; less than 50% of adult men and only about 10% of adult women consume at least 1000 mg of calcium daily; and less than 10% of the population over 50 years old consumes at least 1200 mg of calcium daily. Id. The Institute of Medicine has suggested that “some seemingly healthy individuals may require higher calcium intakes” and that for individuals at risk for dietary calcium intakes below recommendations, “use of calcium supplements may be desirable in order to meet [recommendations].” Exhibit 1 at 6. The PDR for Nutritional Supplements states that about 25% of women in the U.S. take calcium supplements. Id. at 74.

The proposed claims may increase use of oral calcium supplements among the general population, including populations at risk of nephrolithiasis and urolithiasis. The Petitioner does not anticipate substantial dietary changes in the general population but does expect there to be some increase in consumer preferences for calcium-containing supplements. The effect on such people is expected to be beneficial, reducing the risk of nephrolithiasis and urolithiasis.

5. Prevalence of the disease or health-related condition in the U.S. population and the relevance of the claims in the context of the total daily diet.

As discussed above, nephrolithiasis/urolithiasis affects 12% to 20% of men and 5% to 10% of women in the United States. Exh. 1 at 4. Between 100 and 300 cases occur annually per 100,000 individuals. Id. The risk for a second stone within 6 years is 50%. Id. Annual costs associated with nephrolithiasis in the U.S. exceed \$2 billion. Id.

As discussed in the preceding section, calcium consumption meets or exceeds the RDI in only a small fraction of the population. Exh. 1 at 6. In the context of the daily diet, supplementation represents the most efficient method for the population to meet the RDI and the best calcium source for consumers to avoid the high fat content of dairy products. Moreover, claims appearing at the point of sale help guide consumers in making healthful choices.

6. Calcium conforms to the definition of the term “substance” in 21 C.F.R. §101.14(a)(2).

“Substance means a specific food or component of food, regardless of whether the food is in conventional food form or a dietary supplement that includes vitamins, minerals, herbs, or other similar nutritional substances.” 21 C.F.R. §101.14(a). Calcium is a substance within the meaning of Section 101.14(a). Calcium is an essential mineral and an alkaline earth metal. Exhibit 2 at 74. Calcium accounts for one to two percent of adult human body weight. Exhibit 3 at 71 and Exhibit 2 at 74. It is a major constituent of bones and teeth, where 99% of total body

calcium is present. Exhibit 2 at 74 and Exhibit 3 at 71. The remainder of body calcium is present in blood, extracellular fluid, muscle, and other tissues where it plays a role in mediating vascular contraction and vasodilation, muscle contraction, the beating of the heart, blood coagulation, the production of energy, maintenance of immune function, nerve transmission, and glandular secretion. *Id.* Milk products such as milk and cheese are the most calcium-dense foods and are the major food sources of calcium in North American diets. Exhibit 3 at 73. Other foods rich in calcium include collard greens, Chinese cabbage, mustard greens, broccoli, bok choy, tofu, and sardines with bones. Exhibit 2 at 74 and Exhibit 3 at 73. Grains and beans (particularly soybeans) are also sources of calcium. Exhibit 3 at 73. One source of calcium used in manufacturing supplements is calcium from coral which contains both calcium carbonate and calcium oxide.

Calcium dietary supplements are available in several different salts, dosage forms, and dosage amounts. Calcium supplements include the salts calcium carbonate, calcium citrate, calcium phosphate, calcium lactate, and calcium gluconate. Exhibit 2 at 77. Dosage forms include capsules, chewable tablets, liquids, powders, suspensions, tablets and wafers. Exhibit 2 at 78. Dosage amounts range from 150 mg (capsule) to 1.8 G/5ml (syrup) with typical tablets and capsules having 250 or 500 mg amounts. *Id.*

C. Analytical Data

The amount of calcium contained in dietary supplements that bear the petitioner's health claims may be ascertained by the same methods used by FDA to determine the amount of calcium contained in dietary supplements bearing the calcium and osteoporosis health claim approved in 21 C.F.R. § 101.72. That section and the final rule implementing that regulation do not identify the analytical method for that determination. See, 21 C.F.R. § 101.72 and 58 FR 2665. According to the Association of Analytical Chemists (AOAC), the amount of calcium contained in a dietary supplement that may be a candidate for bearing the health claims can be ascertained the method attached as Exhibit 4.

D. Model Health Claims

Petitioner proposes the following model claim for calcium:

Calcium may reduce the risk of kidney stones.

Calcium may reduce the risk of urinary stones.

Calcium may reduce the risk of kidney stones and urinary stones.

As discussed above, multiple studies have shown that oral supplementation with calcium significantly reduces the risk of the above disease. Moreover, clinical trials and the long history of daily use have proven the safety of calcium supplements for the general population.

E. Attachments

Attached are copies of the scientific studies (Exhibit 1) and other information referenced in, and constituting the basis for, this Petition. To the best of Petitioner's knowledge, all non-clinical studies relied upon were conducted in compliance with the good laboratory practices regulations set forth in 21 C.F.R. Part 58, and all clinical or other human investigations relied upon were either conducted in accordance with the requirements for institutional review set forth at 21 C.F.R. Part 56 or were not subject to such requirements in accordance with 21 C.F.R. § 56.104 or 56.105, and were conducted in conformance with the requirements for informed consent set forth in 21 C.F.R. § 50 et seq. See generally, 21 C.F.R. § 101.7 (c)-(d).

F. Exclusion from Environmental Assessment

The requested health claim approvals sought in this petition are categorically excluded from the environmental impact statement requirements under 21 C.F.R. § 25.24.

G. Conclusion and Certification

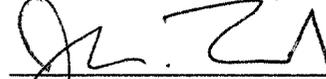
For the foregoing reasons, the Petitioner requests that FDA approve the proposed health claims. The Petitioner looks forward to working with FDA in promulgating a regulation authorizing the use of dietary supplement health claims concerning the association between calcium and kidney stones and calcium and urinary stones.

Any questions concerning this Petition may be directed to Jonathan W. Emord, Esq., Emord & Associates, P.C. See below for his contact information.

The undersigned certify on behalf of the Petitioner that to the best of the Petitioner's knowledge this petition is a representative and balanced submission that includes unfavorable information as well as favorable information, known to it to be pertinent to the evaluation of the proposed health claims.

Respectfully submitted,

MARINE BIO USA, INC.,



Jonathan W. Emord
Claudia A. Lewis-Eng
Andrea G. Ferrenz
Jonathan R. Goodman
Kathryn E. Balmford
Its Counsel

Emord & Associates, P.C.
5282 Lyngate Court
Burke VA 22015
Phone: (202) 466-6937
Fax: (202) 466-6938
jemord@emord.com