



## PETITION FOR HEALTH CLAIMS:

- CALCIUM AND COLORECTAL CANCER.
- CALCIUM AND COLON CANCER.
- CALCIUM AND RECTAL CANCER.
- CALCIUM AND BREAST CANCER.
- CALCIUM AND PROSTATE CANCER.
- CALCIUM AND COLORECTAL, COLON, RECTAL, BREAST, AND PROSTATE CANCERS.
- CALCIUM AND BREAST AND PROSTATE CANCERS.
- CALCIUM AND COLORECTAL, COLON, AND RECTAL CANCERS.
- CALCIUM AND ANTICARCINOGENIC EFFECTS IN THE COLON, BREAST, AND PROSTATE.
- CALCIUM AND RECURRENT COLON POLYPS.



Date of receipt of  
complete petition  
J.H.K.

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

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

2004Q-0097

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Exhibit 4	“Cancer Facts & Figures—2003,” American Cancer Society
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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 colorectal cancer.
2. Calcium may reduce the risk of colon cancer.
3. Calcium may reduce the risk of rectal cancer.
4. Calcium may reduce the risk of breast cancer.
5. Calcium may reduce the risk of prostate cancer.
6. Calcium may reduce the risk of colorectal, colon, rectal, breast, and prostate cancers.
7. Calcium may reduce the risk of breast and prostate cancers.
8. Calcium may reduce the risk of colorectal, colon, and rectal cancers.
9. Calcium may have anticarcinogenic effects in the colon, breast, and prostate.
10. Calcium may reduce the risk of recurrent colon polyps.

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 colorectal cancer, colon cancer, rectal cancer, breast cancer and prostate cancer. The proposed claims are contained in Section D below. Attached hereto and constituting a part of this petition are the requirements as 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 colorectal, colon, rectal, breast, and prostate cancers. The attached scientific studies establish that the consumption of calcium may reduce the risks of those cancers and justify permitting health claims that link consumption of calcium with reduction in those risks. See Glade Report attached as Exhibit 1.

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. Thus, 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 being anticarcinogenic. Thus, calcium is associated with a disease, cancer, the particular disease that is 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 consistent with generally recognized scientific procedures and principles), there is significant scientific agreement among experts

qualified by scientific training and experience to evaluate such claims that calcium reduces the risk of colorectal, colon, rectal, breast and prostate cancers.

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 major public health concerns in the United States. Colorectal cancer is the third most common life-threatening cancer in the U.S., accounting for 10% of total cancer incidence and total cancer death (2.5% of all deaths among adults in the US). Exh. 1 at 12. Breast cancer ranks second among cancer deaths in women. Exhibit 1 at 28. Lifetime risk for breast cancer in women is 12.5% and increases with age and other factors. Id. Prostate cancer is the second leading cause of cancer in males in the U.S. Exhibit 1 at 30. The probability of a man in the U.S. developing prostate cancer during his lifetime is 16.67%. Id.

NIH estimates overall costs for cancer in the year 2002 to be \$171.6 billion: \$60.9 billion for direct medical costs (total of all health expenditures); \$15.5 billion for indirect morbidity costs (costs of lost productivity due to illness); and \$95.2 billion for indirect mortality costs (costs of lost productivity due to premature death). Exhibit 4 at 3.

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 claims will inform consumers at the point of sale of current scientific evidence concerning means to reduce the risk of colorectal, colon, rectal, breast and prostate cancers.

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 claim proposed does not satisfy its "significant scientific agreement" standard, that the agency authorize the claim or those claims nevertheless, with such succinct and accurate disclaimer or disclaimers as is or 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 risk reduction effects on osteoporosis. 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 six health claims associate calcium with five forms of cancer: colorectal, colon, rectal, breast, and prostate. It is axiomatic that cancer is a disease within the meaning of 21 C.F.R. § 101.14(a)(5). All five diseases and health conditions are ones for which the general U.S. population or a specific subgroup of the U.S. population is at risk. Colorectal cancer, colon cancer, and rectal cancer are diseases and health conditions for which the general population is at risk. Breast cancer is a disease for which the female U.S. population is particularly at risk while prostate cancer is, of course, a disease for which only the male U.S. population is at risk.

Colorectal cancer is the third most common life-threatening cancer in the U.S., accounting for 10% of total cancer incidence and total cancer death (2.5% of all deaths among adults in the US). Exh. 1 at 12. Breast cancer ranks second among cancer deaths in women. Exhibit 1 at 28. Lifetime risk for breast cancer in women is 12.5% and increases with age and other factors. Id. Prostate cancer is the second leading cause of cancer in males in the U.S. Exhibit 1 at 30. The probability of a man in the U.S. developing prostate cancer during his lifetime is 16.67%. 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).<sup>1</sup> 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

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<sup>1</sup> 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 51; Exhibit 3 at 91-117.

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. In addition to its anti-osteoporotic activity calcium has anticarcinogenic activity. See Exh. 1 generally; Exh. 2 at 74-75; Exh. 3 at 89-91.

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 33. 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. Similarly the PDR reports that calcium supplements are generally well tolerated. Exhibit 2 at 77.

Calcium-containing dietary 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 cancer, particularly colorectal cancer, colon cancer, rectal cancer, breast cancer, and prostate cancer, that calcium is an effective modifier (reducer) of the risk of those cancers. See Exhibit 1 at 1; Exhibit 2 at 75-76. The scientific literature shows that calcium has anticarcinogenic effects. See Exhibit 1; Exhibit 2 at 74.

The mechanism of action of calcium on colorectal cancer, colon and rectal cancers is fairly well understood as is the pathogenesis of those diseases. Exhibit 1 at 4 - 27. The mechanism of action of calcium on breast cancer is not well understood nor is the pathogenesis of that disease, although it is multifactorial. Exhibit 1 at 28 - 29. Similarly the mechanism of action of calcium on prostate cancer and the pathogenesis of that disease are not well understood. Exhibit 1 at 30-31. However, calcium has been shown to produce beneficial physiological and biochemical effects such as normalizing the rate of colorectal mucosal epithelial proliferation, inhibiting aberrant crypt foci within the colorectal mucosa, inhibiting secondary bile acid production, and inhibiting the biosynthesis of polyamines in breast tissue. See Exhibit 1. As discussed in Exhibit 1 those beneficial effects may reduce the risk of colorectal, colon, rectal, breast and prostate cancers, respectively. Relevant 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**

#### **Colorectal Cancer**

As discussed in detail in Exhibit 1, the intestinal epithelium is in a constant state of renewal with a continuous high rate of cell proliferation, differentiation, and apoptotic cell death.

Id. at 4. Colorectal carcinogenesis is a complex, multistep process involving initiation, promotion, expansion, and progression stages that are not necessarily discrete or well-defined. Id. at 5-6. It is believed that mutations in the adenomatous polyposis coli (APC) gene may be the initiating event in the development of most or all colorectal neoplasia. Id. at 6. In normal colorectal mucosa, exposure to carcinogenic compounds produces damage to the epithelium; however, in cells with the mutated APC gene unrestrained hyperproliferation produces aberrant crypt foci. Id. Aberrant crypt foci are preneoplastic lesions predictive of increased risk of colon cancer. Exhibit 1 at 6. Other factors contributing to the initiation or promotion of colorectal cancer are discussed in further detail in Exhibit 1 at 5-10.

As stated in the conclusion section of Exhibit 1, maintenance of normal healthy colorectal epithelium is dependent upon the ability of colonocytes to sustain elevated intracellular calcium concentrations (which are partially dependent upon the local availability of calcium ions). Id. at 35. Moreover, locally available calcium ions are effective in the prevention of the early hyperproliferative phase of colorectal carcinogenesis. Id. at 36.

Secondary bile acids stimulate hyperproliferation of the colorectal mucosa and are endogenous colorectal carcinogens. Id. at 36. A high-fat diet is a major risk factor for colorectal cancer and may promote colorectal cancer by increasing the amounts of long-chain fatty acids and bile acids present within the lumen of the colon. Id. at 10. Calcium decreases the exposure of the human colorectal epithelium to secondary bile acids. Id.

Extensive research in animals has demonstrated the antineoplastic effect of calcium in the large bowel. Id. at 13-16. Animal studies on calcium and colorectal cancer are discussed in Exhibit 1 at 13-16.

Human studies on the antineoplastic effect of calcium in the large bowel are discussed in Exhibit 1 at 16-27. The human studies are numerous and varied. They are fully vetted in the attached scientific report. Id. Overall, the studies show that daily calcium supplementation at amounts equal to or in excess of the IOM Daily Recommended Intake levels have an anticarcinogenic effect on colorectal cancer. Id. Among those studies are clinical trials showing that daily calcium supplementation has a direct reduction effect on development of crypt cell proliferation rates, a precursor to colorectal cancer. Exhibit 1 at 16-19. Numerous other human studies (including case-control, observational, and epidemiological studies) show that daily dietary supplementation with calcium reduces the incidence of colorectal cancer. Id. Thus, the evidence shows that there is significant scientific agreement that calcium reduces the risk of colorectal, colon and rectal cancers thus providing a public health benefit.

### **Breast Cancer**

The scientific evidence demonstrates that calcium has public health benefits in relation to its effects on breast cancer incidence. While the pathogenesis of breast cancer is multifactorial and understood incompletely, the continued biosynthesis of polyamines is required for cellular proliferation in the breast. The rate limiting enzyme in polyamine synthesis is ornithine decarboxylase (ODC) and the overexpression of ODC is associated with increased malignant potential of human mammary epithelial cells. Exhibit 1 at 28-29. Dietary supplementation with calcium has significantly decreased ODC activity in the rectal epithelial mucosa of humans suggesting the calcium-induced inhibition of ODC-sensitive characteristics of epithelial cells also will be chemopreventive and chemoprotective in the breast.

Two large prospective epidemiologic studies support the conclusion that adequate daily intakes of calcium may be chemopreventive against human breast cancer. Id. at 29. In one, the

Nurses Health Study (of the 88,691 women participating only about 15% consumed the current IOM recommendations for calcium), the relative risk for breast cancer was found to be significantly decreased by intakes of calcium from dairy products in excess of 800 mg daily in premenopausal women. Id. at 29. One retrospective case-controlled study indicated that the multivariate-adjusted odds for breast cancer were reduced by calcium intakes at 871 mg or greater. Id. Another retrospective case-controlled study saw multivariate odds for breast cancer significantly reduced among women who consumed the highest quartile of calcium daily compared to the women in the study who consumed the lowest quartile of calcium daily. Id. Additional studies on breast cancer are discussed further in Exhibit 1 at 28-30. The evidence shows that there is significant scientific agreement that calcium reduces the risk of breast cancer, thus providing a public health benefit.

### **Prostate Cancer**

The scientific evidence demonstrates that calcium benefits public health by reducing prostate cancer incidence. Carcinogenesis in the prostate resembles carcinogenesis in other calcium-responsive epithelial tissues such as colorectal and breast tissues. Exhibit 1 at 30. Rats consuming supplemental dietary calcium have exhibited significantly increased resistance to the prostate cancer-promoting effects of a high-fat, low-calcium diet. Id. While retrospective and prospective observational studies concluded that prostate cancer was independent of calcium intake, a prospective case-control epidemiologic study found that the risk for histologically confirmed prostate cancer was significantly decreased (by about two-thirds) in men who consumed the most calcium on a routine daily basis. Id. at 30-31. The results of two prospective observational studies have been mistakenly interpreted as providing evidence that dietary calcium paradoxically increases risk for prostate cancer. Id. at 31. In fact, the studies confirm

the cancer-promoting properties of dairy-type fats. Id. Similarly, a retrospective case-control observational study confirmed that when calcium and dairy product intakes are correlated with a correlation coefficient (r) of 0.90, both will appear to increase risk for prostate cancer but the appearance is mistaken because the high fat content of dairy products increases the risk of cancer masking the cancer risk reducing effects of calcium. Id. Thus, the evidence shows that there is significant scientific agreement that calcium reduces the risk of prostate cancer, thus providing a public health benefit.

### 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 health premenopausal women. Exh. 1 at 33. That report notes that all the studies cited in it share the characteristic of an absolute lack of evidence of clinically-significant reactions that could be attributed to dietary calcium. Id. at 33. 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 52. The attached scientific report states that reliable and credible scientific literature reveals daily dietary supplementation of at least



1200 mg/day of elemental calcium is effective in reducing the risk of colorectal, colon, rectal, breast, and prostate cancers. Id. at 35.

- 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. Exh. 1 at 33 (see Exh. 1 at 33 and the petitioner's simultaneously filed health claims for calcium and kidney stones (hereinafter "Calcium/Kidney Stone Petition") for further discussion of studies on point). 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. The Calcium/Kidney Stone Petition reveals 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 53.

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 31. 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 32. 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 dietary supplements among the general population, including populations at risk of colorectal cancer, breast cancer and prostate cancer. 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 those diseases and health conditions.

**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 previously, breast cancer is the second most frequent cause of death from cancer among women. Prostate cancer is the second most frequent cause of death from cancer among men. For both sexes, colorectal cancer is the third most frequent cause of death from cancer. Thus, all three diseases are significant diseases in the U.S. population.

Breast cancer is the most frequently diagnosed non-skin cancer in women. Exhibit 4 at 9. An estimated 211,300 new cases of invasive breast cancer are expected to occur among women

in the U.S. during 2003. *Id.* About 1,300 new cases of breast cancer are expected in men in 2003. *Id.* In addition about 55,700 new cases of *in situ* breast cancer are expected among women this year. An estimated 40,200 deaths (39,800 women and 400 men) are anticipated from breast cancer this year. *Id.*

Prostate cancer is the second leading cause of cancer in males in the U.S. Exhibit 1 at 30; Exhibit 4 at 16. An estimated 220,900 new cases of prostate cancer will occur in the U.S. during 2003. Exhibit 4 at 16. About 189,000 new cases of prostate cancer were diagnosed in the U.S. in 2002 while over 30,000 men in the U.S. died from that disease that year. Exhibit 1 at 30. The probability of a man in the U.S. developing prostate cancer during his lifetime is 16.67%. *Id.* Combining all stages of prostate cancer, the five-year relative survival rate is 96%, 10-year survival is 75%, and the 15-year survival is 54%. *Id.*

The incidence of colorectal cancer in the U.S. is about 60 cases per 100,000 adults, occurring with nearly equal frequency in both men and women. Exhibit 1 at 4. In 2002 there were approximately 148,000 new diagnoses and about 57,000 deaths in the United States. *Id.* In 2003 it is estimated that 105,500 colon and 42,000 rectal cancer cases are expected in the U.S. Exhibit 4 at 11. Five-year survival following diagnosis is between 10% and 90%, depending on the stage of disease at first diagnosis. Exhibit 1 at 4.

As discussed in the preceding section, calcium consumption meets or exceeds the RDI in only a small fraction of the population. Exhibit 1 at 51. 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 daily sources. Moreover, claims appearing at the point of sale provide consumers indispensable guidance in making informed choices in the market.

**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. However, as discussed in the Glade Report, the fat in dairy products may increase the risk of cancer. Exhibit 1 at 30; 31. 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 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 by the method attached as Exhibit 5.

**D. Model Health Claims**

Petitioner proposes the following model claims for calcium:

**Calcium may reduce the risk of colorectal cancer.**

**Calcium may reduce the risk of colon cancer.**

**Calcium may reduce the risk of rectal cancer.**

**Calcium may reduce the risk of breast cancer.**

**Calcium may reduce the risk of prostate cancer.**

**Calcium may reduce the risk of colorectal, colon, rectal, breast, and prostate cancers.**

**Calcium may reduce the risk of breast and prostate cancers.**

**Calcium may reduce the risk of colorectal, colon, and rectal cancers.**

**Calcium may have anticarcinogenic effects in the colon, breast, and prostate.**

**Calcium may reduce the risk of recurrent colon polyps**

As discussed above, multiple studies have shown that oral supplementation with calcium significantly reduces the risk of the above diseases. 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 in 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**

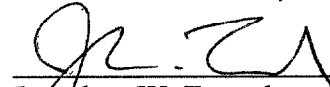
For the foregoing reasons, the Petitioner requests that FDA approve the proposed health claims. The Petitioner looks forward to working with FDA in promulgating a regulation authorizing the use of dietary supplement health claims concerning the association with calcium and colorectal cancer, colon cancer, rectal cancer, breast cancer, and prostate cancer.

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