

5826 PETITION FOR HEALTH CLAIMS:

2772 03 MAY 29 16:00

- GLUCOSAMINE AND OSTEOARTHRITIS
- CHONDROITIN SULFATE AND OSTEOARTHRITIS
- GLUCOSAMINE AND CHONDROITIN SULFATE AND OSTEOARTHRITIS
- GLUCOSAMINE AND OSTEOARTHRITIS-RELATED JOINT PAIN, TENDERNESS AND SWELLING
- CHONDROITIN SULFATE AND OSTEOARTHRITIS-RELATED JOINT PAIN, TENDERNESS AND SWELLING
- GLUCOSAMINE AND CHONDROITIN SULFATE AND OSTEOARTHRITIS-RELATED JOINT PAIN, TENDERNESS AND SWELLING
- GLUCOSAMINE AND JOINT DEGENERATION
- CHONDROITIN SULFATE MAY AND JOINT DEGENERATION
- GLUCOSAMINE AND CHONDROITIN SULFATE AND JOINT DEGENERATION
- GLUCOSAMINE AND CARTILAGE DETERIORATION
- CHONDROITIN SULFATE AND CARTILAGE DETERIORATION
- GLUCOSAMINE AND CHONDROITIN SULFATE AND CARTILAGE DETERIORATION

**SUBMITTED TO THE FOOD AND DRUG ADMINISTRATION
MAY 29, 2003**

**PETITIONER:
WEIDER NUTRITION INTERNATIONAL, INC.**

2003Q-0415

CP1

TABLE OF CONTENTS

Petition for Health Claim: Glucosamine and Chondroitin Sulfate and Osteoarthritis

Table of Contentsi

Background of Petitioneriii

Health Claim Petition

- I. Introduction and Statement of Purpose.....1
- II. Preliminary Requirements4
 - A. Glucosamine and chondroitin sulfate meet the definition of 21 C.F.R. 101.14(a).....4
 - B. Glucosamine and chondroitin sulfate meet the definition of 21 C.F.R. 101.14(b)5
 - 1. Glucosamine and chondroitin sulfate are associated with a disease for which the general U.S. population is at risk5
 - 2. Glucosamine and chondroitin sulfate contribute nutritive value at the levels present in supplements7
 - 3. Glucosamine and chondroitin sulfate are safe and lawful under the FDCA8
- III. Summary of Scientific Data Supporting the Proposed Claims12
 - A. Significant scientific agreement exists to support the proposed claims12
 - B. Scientific evidence demonstrates the public health benefits of glucosamine and chondroitin sulfate14
 - 1. Glucosamine studies14
 - 2. Chondroitin sulfate studies15
 - 3. Study comparing effects of glucosamine with chondroitin sulfate16
 - 4. Combination of glucosamine and chondroitin sulfate in supplementation17

C.	Scientific summary issues.....	17
1.	Is there an optimum level of glucosamine and chondroitin sulfate to be consumed beyond which no benefit would be expected?.....	17
2.	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?	18
3.	Are there certain populations that must receive special consideration?	18
4.	What other nutritional or health factors (both positive and negative) are important to consider when consuming the substance?	18
D.	Potential effect of the use of the proposed claims on food consumption, including significant alterations in eating habits and corresponding changes in nutrient intakes	19
E.	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.	19
IV.	Analytical Method	20
V.	Proposed Model Claims.....	20
VI.	Attachments	21
VII.	Environmental Impact.....	22
VIII.	Conclusion and Certification	22

Attachments

Exhibit 1	Report by Dr. Glade
Exhibit 2	National Institutes of Health, <u>Handout on Health: Osteoarthritis</u>
Exhibit 3	PDR for Nutritional Supplements
Exhibit 4	CDC, <u>Targeting Arthritis: The Nation’s Leading Cause of Disability</u>
Exhibit 5	Assay Methods for glucosamine
Exhibit 6	Assay Methods for chondroitin sulfate
Exhibit 7	Scientific Articles

BACKGROUND OF THE PETITIONER

A Utah corporation, Weider Nutrition International, Inc. (“Weider”) is one of the largest suppliers of health, fitness, and wellness products worldwide. Weider manufactures and markets products in the sports nutrition, bottled drink, diet, natural vitamin, and nutritionally based snack bar categories, including some dietary supplements that contain glucosamine and chondroitin sulfate. Weider has been a health, fitness and sports nutrition leader for sixty years since its founding in 1939.

May 29, 2003

PETITIONER: Weider Nutrition International, Inc.

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

SUBJECT: Petition for Health Claims: Glucosamine and Chondroitin Sulfate and (1) Osteoarthritis; (2) Osteoarthritis-related joint pain, joint tenderness, and joint swelling; (3) joint degeneration; and (4) cartilage deterioration

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

Weider Nutrition International, Inc. (hereinafter "Petitioner"), pursuant to Section 403(r)(5)(D) of the Federal Food, Drug and Cosmetic Act ("FDCA")(21 U.S.C. § 343(r)(5)(D)), submits this petition for health claims concerning the relationship between the consumption of glucosamine and chondroitin sulfate and reduction in the risk of: osteoarthritis; osteoarthritis – related joint pain, joint tenderness, and joint swelling; joint degeneration; and cartilage deterioration. The proposed claims are contained in section V below. Attached hereto, and constituting a part of this petition, are all of the items 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 glucosamine and chondroitin sulfate and reduction in the risk of: osteoarthritis; osteoarthritis-related joint pain, joint tenderness, and joint swelling; joint degeneration; and cartilage deterioration. The attached scientific studies demonstrate that the consumption of glucosamine and chondroitin sulfate may reduce the risk of osteoarthritis; may reduce the risk of osteoarthritis-related joint pain, joint tenderness, and joint swelling; and may reduce the risk of joint degeneration and cartilage deterioration. The scientific evidence

justifies permitting a health claim that links consumption of glucosamine and chondroitin sulfate with reduction in those risks. See Glade Report attached as Exhibit (Exh.) 1.

The proposed health claims respond to major public health concerns in the United States: osteoarthritis; osteoarthritis-related joint pain, joint tenderness, and joint swelling; and joint degeneration and cartilage deterioration. 21 C.F.R. § 101.75. Osteoarthritis (also known as degenerative joint disease) is a frequent cause of physical disability among adults, affecting more than 20 million Americans. National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Handout on Health: Osteoarthritis, www.niams.nih.gov/hi/topics/arthritis/oahandout.htm (attached as Exhibit 2). It is the most common form of arthritis. Id. In the US, among those aged 15 to 40 years, the incidence of osteoarthritis in at least one joint is 5%; in those over 65 it is over 60%. Exh. 1 at 7. By 2030, 20 percent of Americans—about 70 million people—will have passed their 65th birthday and will be at risk for osteoarthritis. Exh. 2. The prevalence of at least one mildly symptomatic osteoarthritis joint occurs in about 30% of the U.S. population. Exh. 1 at 7.

Glucosamine and chondroitin sulfate are naturally-occurring substances present in cartilage and the extracellular matrix of the articular cartilage of humans and other mammals. Both substances are commonly sold as dietary supplements. As discussed below, both glucosamine and chondroitin sulfate possess properties that help promote and maintain the structure and function of joints in the body and may also have anti-inflammatory activity. PDR for Nutritional Supplements at 94, 187 (attached as Exh. 3). The scientific studies described in this petition directly address the important public health issue of glucosamine and chondroitin sulfate's effects on osteoarthritis; on osteoarthritis-related joint pain, joint tenderness, and joint

swelling; on joint degeneration; and on cartilage deterioration and further national and DHHS policies by identifying low cost means of reducing risks of those diseases and disease conditions.

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 glucosamine and chondroitin sulfate claims will inform consumers at the point of sale of current scientific evidence concerning means to reduce the risk of: osteoarthritis; osteoarthritis-related joint pain, joint tenderness, and joint swelling; joint degeneration; and cartilage deterioration. The petitioned claims will accurately impart to consumers scientific understanding about the relationship between glucosamine and chondroitin sulfate and those diseases and disease conditions.

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, 2002 U.S. Dist. LEXIS 25299 (D.D.C. 2002), the Petitioner respectfully requests that if the agency finds that any of the proposed claims does not satisfy its "significant scientific agreement" standard, that the agency authorize that claim or those claims nevertheless, with such succinct and accurate disclaimers as are reasonably necessary to avoid a potentially misleading connotation. The petitioner will accept any reasonable, succinct, and accurate disclaimers that achieve that objective.

II. Preliminary Requirements

A. Glucosamine and chondroitin sulfate meet the definition of 21 C.F.R. 101.14(a)

The Petitioner seeks FDA approval of the proposed claims for use on dietary supplements containing glucosamine and chondroitin sulfate. Glucosamine and chondroitin sulfate each meet the definition of a “substance” under 21 C.F.R. § 101.14(a): “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. §101.4 (2002). As stated by NIH, both glucosamine and chondroitin sulfate are “nutrients... found in small quantities in food and are components of normal cartilage.” Exh. 2 at 16.

Glucosamine is an amino monosaccharide commonly found in chitin, glycoproteins, and glycosaminoglycans such as hyaluronic acid and heparan sulfate. Exh. 3 at 186. D-Glucosamine is present in all foods containing cartilage or glycoproteins. Exh. 1 at 21. Glucosamine is available commercially as a dietary supplement in three forms: glucosamine hydrochloride or glucosamine HCl, glucosamine sulfate, and N-acetyl-glucosamine. Exh.3 at 187. The type of glucosamine found in supplements is typically derived from marine exoskeletons although synthetic glucosamine is also available. Id. at 187.

Chondroitin sulfate belongs to a family of heteropolysaccharides called glycosaminoglycans. Id. at 93. Glycosaminoglycans in the form of proteoglycans make up the ground substance in connective tissues’ extracellular matrix. Id. Chondroitin sulfate is found in human, fish, and shark cartilage; skin; heart valves; tendons; and arterial walls. Id. The sources

of chondroitin sulfate used in supplements include bovine trachea, pork byproducts (ears and snout) and shark cartilage. Id. at 94.¹

Because glucosamine and chondroitin sulfate are present as foods and components of foods, they are “substances” as defined by 21 C.F.R. § 101.14(a).

B. Glucosamine and chondroitin sulfate meet the definition of 21 C.F.R. 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.

1. Glucosamine and chondroitin sulfate are associated with a disease for which the general U.S. population is at risk

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

¹ Petitioner’s source of chondroitin sulfate is bovine trachea, exclusively obtained from animals bred and harvested in the United States.

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 proposed health claims associate the substances, glucosamine and chondroitin sulfate, with a disease, osteoarthritis, and with disease or health-related conditions, osteoarthritis-related joint pain, joint tenderness, joint swelling, and joint degeneration and cartilage deterioration.

Osteoarthritis (also known as degenerative joint disease) is the most common form of arthritis, affecting more than 20 million Americans. Exh. 2 at 2. Osteoarthritis is a multifactorial, polygenic disorder involving mechanical, biochemical, environmental, systemic, and genetic factors that contribute to imbalance between synthesis and degradation and deterioration of cartilage matrix. Exh. 1 at 7. It is characterized by focal loss of cartilage and hypertrophic bone spurs. Exh. 1 at 7. While the term osteoarthritis refers to the overgrowth of bone in certain areas of the joint, the disease is marked by net loss of cartilage tissue. Id. Changes in the macromolecular composition of the extracellular matrix of articular cartilage are characteristic of clinically apparent osteoarthritis. Exh. 1 at 6. Those changes cause a chronic degeneration of the extracellular matrix. Id.

The primary complaint in osteoarthritis is pain, particularly concerning use of the affected joint. Id. Pain can be accompanied by varying degrees of joint stiffness, limitation of movement, tenderness and swelling at the joint margins, and loss of function. Id. Radiologically-measured decrease in joint space is significantly correlated with increase in pain severity. Id. at 8.

Each year medical care for arthritis² resulted in 750,000 hospitalizations and 36 million outpatient visits. CDC, Targeting Arthritis: The Nation's Leading Cause of Disability, 2003 attached as Exh. 4 at 2. In 1995, medical care for arthritis cost nearly \$22 billion, and the total cost, including lost productivity, topped \$82 billion, according to estimates from the American Academy of Orthopaedic Surgeons. Id. As discussed supra, the National Institutes of Health have estimated that by 2003 20 percent of Americans will be at risk for osteoarthritis. Exh. 2 at 2. Reduction in the risk of that disease; in the risk of joint pain, tenderness, and swelling associated with that disease; and in the risk of joint degeneration and cartilage deterioration is, thus, an economic and health necessity for the U.S. population.

2. Glucosamine and chondroitin sulfate contribute nutritive value at the levels present in supplements

In accordance with section 101.14(b)(3)(i), glucosamine and chondroitin sulfate contribute nutritive value. While there is no Reference Daily Intake (DRI) for either substance, the nutritive contributions of both are widely recognized. See Exhibit 1 at 12-20; see also, Exh. 3 at 93, 187 (both substances may contribute to the promotion and maintenance of the structure and function of cartilage and may also have anti-inflammatory activity).

Glucosamine is an aminomonosaccharide that serves as a substrate for the biosynthesis of chondroitin sulfate, hyaluronan, and other macromolecules located in the extracellular cartilage matrix. Exh. 1 at 2. Chronic degeneration of the extracellular matrix of articular cartilage is a required precursor to osteoarthritis. Id. at 6. Glucosamine has immunomodulatory, anabolic, and anticatabolic properties that are a result of its interaction with intercellular and intracellular cytokine-based communication systems. Id. at 11.

² These statistics are for all forms of arthritis. Exh. 4(CDC) at 2. Osteoarthritis is the most common form of arthritis. Exh. 2(NIAMS) at 1

Chondroitin sulfate is a glycosaminoglycan. Id. Chondroitin sulfate polymers are secreted into the extracellular matrix of articular cartilage and are covalently bound into proteins, forming protein-polysaccharide complexes called proteoglycans. Id. at 2. Chondroitin sulfate is anticatabolic, significantly stimulates the production of proteoglycans, inhibits the destruction of articular cartilage, and directly protects articular cartilage extracellular matrix macromolecules from elevated degradative enzyme activities characteristic of asymptomatic subclinical cartilage degeneration. Id. at 11-12.

The proposed claims do not identify specific intake quantities for glucosamine or chondroitin sulfate. Studies have shown glucosamine supplementation to have nutritive value from 1500 mg to 2000 mg a day. Exh. 1 at 12-15.³ Studies have shown chondroitin sulfate supplementation to have nutritive value from 400 mg to 1500 mg a day. Exh. 1 at 15-19. When combined, glucosamine supplementation is recommended at 1000 mg/day along with 800 mg/day of chondroitin sulfate. Id. at 21.

Glucosamine is typically supplied in solid oral dosage form in capsules containing 500 mg, 550 mg, 750 mg, and 1000 mg; liquid containing 50 mg; and tablets containing 340 mg, 500 mg, and 1000 mg. Exh. 3 at 189. Chondroitin sulfate is typically supplied in solid oral dosage form in capsules containing 250 mg, 400 mg, and 500 mg; and in tablets containing 250 mg, 400 mg, 600 mg. Id. at 96.

3. **Glucosamine and chondroitin sulfate are 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

³ The three forms of commercially-available D-glucosamine vary in molecular size affecting their proportional weights. See Exh. 1 at 8.

what the basis is for the GRAS claim, the food additive status, or prior sanctioned status.” 21 C.F.R. § 101.70(f)(A). In accordance with section 101.13(b)(3)(ii), glucosamine and chondroitin sulfate are both foods and food ingredients and are safe and lawful at the levels necessary to justify the proposed health claims.

As mentioned above, glucosamine is present in all foods containing cartilage or glycoproteins (Exh. 1 at 21) and chondroitin sulfate is present in pork byproducts and other foods. Exh. 3 at 94. The FDCA deems dietary supplements a food under 21 U.S.C. § 321(ff). Accordingly, glucosamine and chondroitin sulfate are both foods and food ingredients under 21 C.F.R. § 101.14(b)(3)(ii).

Glucosamine and chondroitin sulfate are generally recognized as safe and lawful at the levels necessary to justify the proposed health claims. General recognition of safety is based on the views of experts qualified by scientific training and experience to evaluate the safety of substances directly or indirectly added to food. 21 C.F.R. § 170.30(a). The basis for such views may be either (1) scientific procedure or, in the case of a substance used in food prior to January 1, 1958, (2) through experience based on common use in food. Id.

Safe or safety means that there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use. It is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of the use of any substance. Safety may be determined by scientific procedures or by general recognition of safety. In determining safety, the following factors shall be considered:

- (1) the probable consumption of the substance and of any substance formed in or on food because of its use.
- (2) The cumulative effect of the substance in the diet, taking into account any chemically or pharmacologically related substance or substances in such diet.
- (3) Safety factors which, in the opinion of experts qualified by scientific training and experience to evaluate the safety of food and food ingredients, are generally recognized as appropriate.

21 C.F.R. § 170.3.

Glucosamine and chondroitin sulfate have been naturally occurring ingredients in foods consumed in the United States prior to January 1, 1958. There is no evidence that either glucosamine or chondroitin sulfate consumed in foods or as dietary supplements have a cumulative effect in the diet that affects their safety. See Exh. 1 at 21-22 (except that glucosamine may “potentiate active peptic ulcers”); Exh. 3 at 95, 188. There are no known interactions with drugs in clinical practice, except for a general warning that diabetics may need to monitor their blood glucose when taking glucosamine. Id. at 188. Moreover, there are no known harmful interactions with nutritional supplements, except for a general warning that chitosan may decrease the absorption of chondroitin sulfate. Id. at 95. Intake of glucosamine at less than 400 mg a day (for adults) is unlikely to cause adverse reactions. Exh 1 at 21. In an analysis of 16 human studies involving 372 subjects, intake of chondroitin sulfate at less than 800 mg a day did not produce more adverse events than a placebo. Exh. 1 at 22.

The PDR for Nutritional Supplements states that the most frequently reported adverse reactions associated with glucosamine are “mild gastrointestinal complaints such as heartburn, epigastric distress, and diarrhea.” Exh. 1 at 21; Exh. 3 at 188. Similarly, adverse reactions associated with chondroitin sulfate are of the “mild gastrointestinal variety, such as epigastric distress, nausea, and diarrhea.” Id. at 95. The PDR indicates no significant adverse effects for either substance. Exh. 3 at 95 and 188.

The maximum (safe) daily intake of both glucosamine and chondroitin sulfate is well above the amount reasonably required to accomplish the intended nutritive effect. 21 C.F.R. § 172.5. The safe upper limits for glucosamine and chondroitin sulfate have not been established. See Exh. 1 at 21-22; Exh. 3 at 95-96, 188-189. No deaths have occurred in mice and rats from glucosamine intakes of up to 5000 mg/kg body weight. Exh. 1 at 21. Dietary supplementation

with glucosamine for up to three years did not produce an increase in the incidence or severity of side effects in placebo-controlled human studies. Id. Oral supplementation in rats and rabbits with chondroitin sulfate polymers at 1 g/kg body weight daily produced no effects on mutagenesis or reproductive function. Id. at 22. Dietary supplementation with chondroitin sulfate polymers for up to two years did not produce any increase in the incidence or severity of side effects in placebo-controlled human studies. Id.

The nutritive effect in reducing the risk of osteoarthritis; osteoarthritis-related joint pain, joint tenderness, and joint swelling; joint degeneration and cartilage deterioration has been recorded in daily doses ranging from 1200 mg to 2000 mg (glucosamine) and from 400 mg to 1200 mg (chondroitin sulfate) when taken separately, and from 1000 mg to 1600 mg (glucosamine) and from 800 mg to 1200 mg (chondroitin sulfate) when taken concurrently. Id. The proposed health claims thus comply with the safety and lawfulness requirements of 21 C.F.R. § 101.14(b)(3)(ii).

In summary, since glucosamine and chondroitin sulfate meet 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.

III. Summary of Scientific Data Supporting the Proposed Claims

A. Significant scientific agreement exists to support the proposed claims

There is significant scientific agreement among experts who study in the field of osteoarthritis that glucosamine and chondroitin sulfate are effective modifiers of the risk of osteoarthritis; the risk of osteoarthritis-related joint pain, joint tenderness, and joint swelling; and the risk of joint degeneration and cartilage deterioration. See Exh. 1 at 1. The scientific literature shows that dietary supplementation with glucosamine and chondroitin sulfate contributes to the preservation of articular cartilage, inhibits the initiation of osteoarthritic change in articular cartilage, and inhibits the progression of osteoarthritic change to symptomatic osteoarthritis. Id. at 23. Dietary supplementation with glucosamine and chondroitin sulfate is an effective modifier of osteoarthritic change and reduces the risk for osteoarthritis and of osteoarthritis-related joint pain, joint tenderness, and joint swelling. Id.

Although the mechanism of glucosamine and chondroitin sulfate's preservation and reparation effects is not entirely understood, much is known about the biochemistry and physiology of the molecules containing both substances. See Exh. 1 at 1-3, 6-12; Exh. 3 at 94, 187. Glucosamine is involved in glycoprotein metabolism. Exh. 1 at 1-2, 9-11; Exh. 3 at 187. Specifically, glucosamine appears to act by interrupting message transduction. Exh. 1 at 10. Its immunomodulatory, anabolic and anticatabolic properties result at least in part from interaction with intercellular and intracellular cytokine-based communication systems. Id. at 11.

Chondroitin sulfate appears to stimulate increases in the secretion of proteoglycans in nonosteoarthritic cartilage tissue and by embryonic articular cartilage chondrocytes in cell culture. Id. at 11. Further, chondroitin sulfate may play a role in the direct protection of articular

cartilage extracellular matrix macromolecules from the elevated degradative enzyme activities characteristic of asymptomatic subclinical cartilage degeneration. Id. at 12.

Glycoproteins, or proteoglycans, form the ground substance in the extra-cellular matrix of connective tissue. Id. The polysaccharide groups in proteoglycans are called glycosaminoglycans (GAGs) which include, among other substances, chondroitin sulfate. Id. All the GAGs contain derivatives of glucosamine. Id. GAG chains are fundamental components of aggrecan found in articular cartilage, which gives that cartilage its shock-absorbing properties. Id. In later stages of joint degeneration, aggrecan biosynthesis is decreased, leading to the loss of cartilage resiliency that accompanies osteoarthritis. Exh. 1 at 6-8; Exh. 3 at 187.

Within the cartilage matrix, constituents such as proteoglycans undergo a distinct turnover process during which the catabolism and removal of molecules from the extracellular matrix is in balance with the synthesis and deposition of new molecules. Exh. 1 at 1-2. A chronic imbalance in matrix macromolecule turnover producing net loss of articular tissue is a required precursor to the development of osteoarthritis and joint pain. Id. at 4. Studies have shown that glucosamine added to a culture mixture of chondrocytes harvested from osteoarthritic human articular tissue inhibited the inherent and IL-1 β -induced catabolic activity of metalloproteases secreted by chondrocytes and stimulated the synthesis of physiologically-relevant proteoglycans similar to proteoglycans synthesized by chondrocytes harvested from nonosteoarthritic human articular cartilage. Id. at 10. In addition, studies have also shown that when added to a culture media of chondrocytes harvested from osteoarthritic human articular cartilage, in which adhesion of chondrocytes to fibronectin and overall protein synthesis is significantly inhibited while extracellular collagenase activity is significantly increased, glucosamine restored the adhesive properties of the chondrocytes, significantly reduced

extracellular collagenase activity and significantly increased the rate of protein syntheses. Id. at 10. Thus, glucosamine aids in the synthesis of proteoglycans and inhibits catabolic activity in the extracellular matrix of cartilage, helping to maintain the proper balance essential to cartilage health. Id. at 10-11.

Studies have shown that chondroitin sulfate stimulated significant increases in the secretion of proteoglycans in nonosteoarthritic cartilage tissue. Id. at 12. Studies with rabbits have also shown that supplementation with chondroitin sulfate significantly inhibited the destruction of articular cartilage following a collagen injection and significantly inhibited the depletion of proteoglycans in articular cartilage following subsequent injection of bradykinin. Id. at 13. Those studies suggest that chondroitin sulfate also increases the rate of protein synthesis essential to cartilage function and also suggest a role in the direct protection of articular cartilage extracellular matrix macromolecules from the elevated degradative enzyme activities characteristic of asymptomatic subclinical cartilage degeneration. Id. at 13. Human clinical trials and epidemiological studies are discussed in the following section.

B. Scientific evidence demonstrates the public health benefits of glucosamine and chondroitin sulfate

Numerous clinical trials have evaluated the effects of glucosamine and chondroitin sulfate (separately and in combination) on the risk of, and pain, tenderness, and swelling associated with, osteoarthritis, as well as the risk of joint degeneration and cartilage deterioration.

1) Glucosamine studies

In two randomized, double-blind, placebo-controlled clinical studies, compared to the effects of placebo, dietary supplementation of subjects with mild to severe femorotibial osteoarthritis with crystalline D-glucosamine sulfate for 1 month produced significantly greater

reductions in articular pain, tenderness, swelling, and restriction of movement. Exh. 1 at 13. In a recent long-term, randomized, double-blind study, 3 years of glucosamine supplementation by subjects with mild to severe femorotibial osteoarthritis produced significantly greater reductions in the mean rate of femorotibial joint space narrowing, of the WOMAC total pain score, of the WOMAC indices of total knee health, pain, function, and stiffness, of the Lequesne functional index, and of pain assessed by a visual analog scale. Id. In a far-ranging multicenter open-label study, 1208 evaluable subjects were supplemented with glucosamine for 13 to 99 days. Physician ratings of subject responses were highly favorable (“Good”- 58%; “Sufficient”-36%). Id. at 14.

Meta-analyses of available scientific studies have concluded that supplementation of glucosamine produced significantly greater reductions in the severity of osteoarthritic pain in a variety of locations, resulting in a lower level of voluntary consumption of NSAIDs (nonsteroidal anti-inflammatory drugs). Id. Numerous other studies and results are included in the scientific reported as Exh. 1. Additional studies are attached as Exhibit 7.

2) Chondroitin sulfate studies

As indicated in the enclosed scientific report and supporting science, in randomized, double-blind, placebo-controlled studies of subjects with femorotibial osteoarthritis ranging from mild to severe, dietary supplementation with chondroitin sulfate consistently produced significantly greater decreases in the Lequesne Index of functional impairment and in the severity of spontaneous joint pain assessed using a visual scale. Exh. 1 at 15. In a randomized, double-blind, placebo-controlled study of subjects with osteoarthritis of the interphalangeal joints, daily supplementation with chondroitin sulfate produced a significantly greater decrease in the number of subjects whose osteoarthritis had progressed. Id. at 16. In another randomized,

double-blind, placebo-controlled study, 2 years of dietary supplementation with chondroitin sulfate produced significantly greater decreases in the severity of spontaneous joint pain and subjects reported decreased voluntary use of NSAIDs for rescue from pain. Id. In yet another controlled study of subjects with early mild femorotibial osteoarthritis, 330 days of chondroitin sulfate supplementation produced significantly greater decreases in the severity of: spontaneous joint pain assessed using a visual analog scale, pain on passive movement, pain on active movement, pain in the evening; significantly greater increases in joint mobility and ambulation; and a significantly smaller decrease in mean articular cartilage thickness. Id. Further, in several studies, the effectiveness of chondroitin sulfate in reducing pain associated with osteoarthritis has been compared directly to the effectiveness of NSAIDs. Id. at 17.

Investigators applying meta-analyses of chondroitin sulfate supplementation studies have concluded that dietary supplementation with chondroitin sulfate for at least 120 days produced significantly greater reductions in the Lequesne Index of function impairment and in the severity of pain assessed using a visual analog scale than did placebo. Id. at 18. Other investigators concluded that dietary supplementation with chondroitin sulfate by individuals with osteoarthritis consistently produced significant decreases in joint pain and significant increases in joint function of small-to-moderate magnitude and that supplementation is “probably effective in osteoarthritis in reducing pain and in improving joint function.” Id. at 18-19. Numerous other studies are analyzed in the scientific report attached as Exhibit 1 and additional studies are attached as Exhibit 7.

3) Study comparing effects of glucosamine with chondroitin sulfate

In an open label trial, subjects with femorotibial osteoarthritis consumed either glucosamine or chondroitin sulfate. After 3 months, there were no significant differences

between the groups of subjects—72% assessed their improvement as “good” without side effects. Id. at 19

4) Combination of glucosamine and chondroitin sulfate in supplementation

In one randomized, double-blind, placebo-controlled clinical trial, subjects with mild to moderate femorotibial osteoarthritis supplemented their diets with either a combination of glucosamine and chondroitin sulfate or a placebo. After 6 months, the supplementation was associated with significantly greater decreases in the Lequesne index of functional impairment. Id. at 20. In another controlled trial, dietary supplementation with a combination of glucosamine and chondroitin sulfate was compared with a placebo in subjects with painful osteoarthritis of the temporomandibular joint. Id. at 20. After 12 weeks, those supplemented with the combination exhibited significantly greater decreases in temporomandibular joint tenderness and sounds and in voluntary consumption of pain relieving medications without the production of side effects. Id. Other studies are included in the scientific report attached as Exhibit 1. Additional studies are attached as Exhibit 7.

C. **Scientific summary issues**

1. Is there an optimum level of glucosamine and chondroitin sulfate to be consumed beyond which no benefit would be expected?

Clinical trials have tested daily doses ranging from 1500 mg to 2000 mg (glucosamine) and 400 mg to 1200 mg (chondroitin) when taken separately, and 1000 mg to 1600 mg (glucosamine) and 800 mg to 1200 mg (chondroitin) when taken concurrently. Exh. 1 at 20-21; see also Exh. 2. The attached scientific report states that reliable and credible scientific literature indicates that daily dietary supplementation of D-glucosamine at 1000 mg/day is effective in reducing the risk of and joint pain, tenderness and swelling associated with osteoarthritis when taken with at least 800 mg/day of chondroitin sulfate. Id. at 21. There is no evidence of an

optimum level of either substance to be consumed beyond which no benefit is expected.

Moreover, there are no reports of overdosage. Exh. 3 at 95, 188.

2. 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 are no levels identified at which adverse events occur for any segment of the population. Exh. 3 at 95, 188. There is a lack of reports of adverse reactions in the published scientific literature and the safety of oral supplementation with glucosamine and chondroitin sulfate have been documented in detail by several investigators. Exh. 1 at 14.

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

The PDR for Nutritional Supplements cautions that because of insufficient safety data, pregnant women and nursing mothers should avoid using glucosamine, and those with type 2 diabetes and those who are overweight who also have problems with glucose tolerance should have their blood sugars carefully monitored. Exh. 3 at 188. The PDR also cautions that because of insufficient safety data, pregnant women and nursing mothers should avoid using chondroitin sulfate, and caution should be exercised by those taking warfarin and those with hemophilia because of “the theoretical possibility of chondroitin sulfate’s antithrombotic activity.” Exh. 3 at 95.

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

There are no harmful interactions with drugs for either substance. Id. at 95, 188. Glucosamine may increase insulin resistance and consequently affect glucose tolerance. Id. at 188. Thus, the PDR suggests that diabetics who decide to use glucosamine supplements will need to monitor their blood sugar and may need to adjust the dosage of the medications they take

to control blood glucose levels. Id. The PDR also states that chitosan supplementation may decrease the absorption of chondroitin sulfates if taken concurrently. Id. at 95.

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

The proposed claims may increase use of oral glucosamine and chondroitin sulfate supplements among the general population, including populations at risk of osteoarthritis. The Petitioner does not anticipate substantial dietary changes in the general population but does expect there to be some increase in consumer preferences for glucosamine and chondroitin sulfate-containing supplements. The effect on such people is expected to be beneficial, reducing the risk: of osteoarthritis; of osteoarthritis-related joint pain, tenderness and swelling; and of joint degeneration and cartilage deterioration.

E. 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, the proposed health claims respond to a major public health concern in the United States: osteoarthritis; osteoarthritis-related joint pain, tenderness and swelling; and joint degeneration and cartilage deterioration. Osteoarthritis is one of the most frequent causes of physical disability among adults, affecting more than 20 million Americans. National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Handout on Health: Osteoarthritis, (attached as Exhibit 2). It is the most common form of arthritis. Id. Before age 45, osteoarthritis occurs more frequently in males. After age 45, osteoarthritis occurs more frequently in females. Id. By 2030, 20 percent of Americans—about 70 million people—will have passed their 65th birthday and will be at risk for osteoarthritis. Id.

The presence of glucosamine and chondroitin sulfate in the cartilage of fish and animals has not been measured as a part of the daily diet. Supplementation is the most effective method

to achieve the levels of glucosamine and chondroitin sulfate in order to have nutritive effect. As the attached scientific report indicates, the reliable and credible scientific literature indicates that daily dietary supplementation with 1500 mg of D-glucosamine sulfate is effective in reducing the risk of, and joint pain, tenderness and swelling associated with, osteoarthritis when taken alone, and 1000 mg a day when combined with chondroitin sulfate. Id. at 21. The reliable and credible scientific literature indicates that daily dietary supplementation with 1200 mg of chondroitin sulfate, consumed alone or with glucosamine is effective in reducing the risk of osteoarthritis and of joint pain, tenderness, and swelling associated with osteoarthritis. Id. Thus, both substances offer a safe, inexpensive, and readily accessible means for reducing the risk of osteoarthritis; osteoarthritis-related joint pain, tenderness, and swelling; and joint degeneration and cartilage deterioration.

IV. Analytical Method

The amount of glucosamine contained in a dietary supplement that may be a candidate for bearing the health claims can be ascertained by High-Performance Liquid Chromatography (HPLC) according to the Petitioner, Weider Nutrition International, the Institute for Nutraceutical Advancement, and the University of Alberta, Edmonton, Alberta, Canada, as well as by Glucosamine Rapid Assay, according to the Department of Microbiology and Immunology, University of British Columbia. See Exh. 5. The amount of chondroitin sulfate contained in a dietary supplement that may be a candidate for bearing the health claims can be ascertained by the Cetylpyridinium Chloride (CPC) Titration Method according to the Petitioner and the Institute for Nutraceutical Advancement. See Exh. 6.

V. Proposed Model Claims

Petitioner proposes the follow model claims for glucosamine and chondroitin sulfate:

- **Glucosamine may reduce the risk of osteoarthritis.**
- **Chondroitin sulfate may reduce the risk of osteoarthritis.**
- **Glucosamine and chondroitin sulfate may reduce the risk of osteoarthritis.**
- **Glucosamine may reduce the risk of osteoarthritis-related joint pain, tenderness and swelling.**
- **Chondroitin sulfate may reduce the risk of osteoarthritis-related joint pain, tenderness and swelling.**
- **Glucosamine and chondroitin sulfate may reduce the risk of osteoarthritis-related joint pain, tenderness and swelling.**
- **Glucosamine may reduce the risk of joint degeneration.**
- **Chondroitin sulfate may reduce the risk of joint degeneration.**
- **Glucosamine and chondroitin sulfate may reduce the risk of joint degeneration.**
- **Glucosamine may reduce the risk of cartilage deterioration.**
- **Chondroitin sulfate may reduce the risk of cartilage deterioration.**
- **Glucosamine and chondroitin sulfate may reduce the risk of cartilage deterioration.**

Multiple studies have shown that oral supplementation with glucosamine and chondroitin sulfate significantly reduces the risk of osteoarthritis; osteoarthritis-related pain, tenderness, and swelling; joint degeneration; and cartilage deterioration. Moreover, clinical trials have proven the safety of those substances for the general population.

VI. Attachments

Attached are copies of the scientific studies and other information referenced in, and constituting the basis for, this petition. To the best of the 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 eq seq. See generally, 21 C.F.R. § 101.7 (c)-(d).

VII. Environmental Impact

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.

VIII. Conclusion and Certification

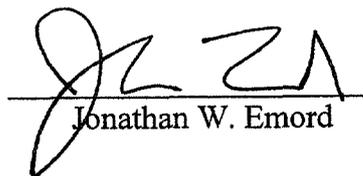
For the foregoing reasons, the Petitioner requests that the FDA approve the proposed health claims. The Petitioner looks forward to working with the FDA in promulgating a regulation authorizing the use of dietary supplement health claims concerning the association between glucosamine and chondroitin sulfate and the risk of osteoarthritis; of osteoarthritis-related pain, tenderness, and swelling; and of joint degeneration and cartilage deterioration.

Any questions concerning this Petition may be directed to Jonathan W. Emord, Esq. or to Claudia A. Lewis-Eng, Esq., Emord & Associates, P.C., 5282 Lyngate Court, Burke, VA 22015 (202) 466-6937.

The undersigned certify on behalf of the Petitioner that to the best of Petitioner's knowledge and belief, the Petition includes all information and views on which the Petitioner relies and is a representative and balanced submission that includes unfavorable information as

well as favorable information known by the Petitioner to be pertinent to evaluation of the proposed health claims.

Sincerely,


Jonathan W. Emord


Claudia A. Lewis-Eng

Andrea G. Ferrenz
Jonathan R. Goodman
Kathryn E. Balmford

Counsel to

Weider Nutrition International, Inc.

Emord & Associates, P.C.
5282 Lyngate Court
Burke, VA 22015
P: (202) 466-6937
F: (202) 466-4938
Email: jemord@emord.com; clewis-eng@emord.com
Date submitted: May 29, 2003