



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Rockville MD 20857

OCT 7 2004

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Re: Health Claim Petition: glucosamine and chondroitin sulfate, and (1) osteoarthritis; (2) joint degeneration; (3) cartilage deterioration; and (4) osteoarthritis-related joint pain, tenderness, and swelling (Docket No. 2004P-0059)

Dear Mr. Emord:

This letter responds to the health claim petition dated May 29, 2003, submitted to the Food and Drug Administration (FDA or the Agency) on behalf of Weider Nutrition International, Inc., (Weider) pursuant to section 403(r)(5)(D) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 343(r)(5)(D)). The petition requested that the Agency authorize health claims characterizing the relationship between the consumption of glucosamine and/or chondroitin sulfate and a reduced risk of: osteoarthritis; osteoarthritis-related joint pain, joint tenderness, and joint swelling; joint degeneration; and cartilage deterioration.

This petition proposed as model health claims for dietary supplements the following claims, which will be referred to by number in the rest of this letter:

1. Glucosamine may reduce the risk of osteoarthritis.
2. Chondroitin sulfate may reduce the risk of osteoarthritis.
3. Glucosamine and chondroitin sulfate may reduce the risk of osteoarthritis.
4. Glucosamine may reduce the risk of joint degeneration.
5. Chondroitin sulfate may reduce the risk of joint degeneration.
6. Glucosamine and chondroitin sulfate may reduce the risk of joint degeneration.
7. Glucosamine may reduce the risk of cartilage deterioration.
8. Chondroitin sulfate may reduce the risk of cartilage deterioration.
9. Glucosamine and chondroitin sulfate may reduce the risk of cartilage deterioration.
10. Glucosamine may reduce the risk of osteoarthritis-related joint pain, tenderness, and swelling.
11. Chondroitin sulfate may reduce the risk of osteoarthritis-related joint pain, tenderness, and swelling.

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12. Glucosamine and chondroitin sulfate may reduce the risk of osteoarthritis-related joint pain, tenderness, and swelling.

The original due date for FDA to file or deny this petition was September 6, 2003 (see 21 CFR 101.70(j)(2)). By mutual agreement, the due date was first extended to September 22, 2003 and then to October 3, 2003. On October 3, 2003, FDA denied the petition. You raised some issues that resulted in FDA reconsidering its denial and filing the petition for comprehensive review on February 13, 2004. By letter dated April 19, 2004, you agreed to FDA review of the petition as a qualified health claim petition. To obtain expert advice on the scientific issues raised by your petition and a health claim petition for crystalline glucosamine sulfate and reduced risk of osteoarthritis from Rotta Pharmaceuticals, FDA held a meeting of the Food Advisory Committee and its Dietary Supplements Subcommittee (collectively, "FAC") on June 7 and 8, 2004. By agreement with you and counsel for Rotta Pharmaceuticals, FDA agreed to issue a decision on claims 1-3 no later than 60 days following the FAC meeting (i.e., by August 6, 2004) and for claims 4-9 no later than 90 days following the FAC meeting (i.e., by September 6, 2004). By mutual agreement, the decision date for this petition was extended to September 10, 2004 and then to October 7, 2004.

FDA did not review claims 10-12 because they are not health claims, as explained in FDA's letters dated October 3, 2003, and February 13, 2004; therefore, the original denial of these claims stands, and they are not addressed in this letter. From this point forward, the remaining claims in your petition (claims 1-9) will be referred to as "the proposed claims" when they are discussed collectively.

In FDA's February 13, 2004 letter, the Agency noted that there was a question as to whether claims 4-9 (the claims about reducing the risk of joint degeneration and cartilage deterioration) are health claims. That question arose for two reasons: (1) uncertainty about whether joint degeneration and cartilage deterioration are diseases or health-related conditions; (2) uncertainty as to whether consumers would interpret these claims as claims to treat OA by reducing the risk of joint degeneration and cartilage deterioration, which are associated with osteoarthritis. As discussed below in section I, FDA has now concluded that cartilage deterioration is a health-related condition. Although the other uncertainties remain, FDA has determined that these issues do not need to be resolved because, even assuming that claims 4-9 qualify as health claims, there is no credible evidence to support them.

Your petition was received before the issuance of the Agency's guidance entitled "Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements" (July 10, 2003)<sup>1</sup>, and therefore this petition was not processed in the manner described in that guidance. In particular, the petition was not posted on the FDA website for a 60-day comment period.

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<sup>1</sup> <http://www.cfsan.fda.gov/~dms/nuttf-e.html>

This letter sets out the basis for FDA's determination that there is no credible scientific evidence to support the proposed health claims and the reasons the Agency is denying this petition for qualified health claims with respect to consumption of glucosamine and chondroitin sulfate and reduced risk of osteoarthritis (OA), joint degeneration (JD), and cartilage deterioration (CD). In brief, the available scientific evidence pertaining to the proposed claims is limited to studies of glucosamine and chondroitin sulfate as treatments for OA, JD, and CD or for conditions associated with existing OA, such as joint pain and swelling. As experts on FDA's Food Advisory Committee--including the three rheumatologists recommended by the petitioners--concluded, there is no basis to extrapolate such treatment evidence to the risk reduction context because the available scientific evidence indicates that normal cells and tissues are genetically and functionally different from osteoarthritic cells and tissues and therefore may respond differently to interventions with exogenous substances. In the case of chondroitin sulfate, there are two studies (Rovetta et al., 2002; Verbruggen et al., 1998) that directly compared the effect of chondroitin sulfate on affected and apparently unaffected finger joints in patients with OA of the hand. These studies found that chondroitin sulfate slowed the progression of OA in affected finger joints but did not prevent OA from developing in the finger joints that appear to be unaffected at the beginning of the study; thus, they not only fail to provide a scientific basis for extrapolating treatment evidence to risk reduction, they actually point to a contrary conclusion.

I. Overview of Data and Eligibility for a Qualified Health Claim

The petition cited 231 publications as support for the proposed claims. These publications consisted of 47 intervention studies, 7 bioavailability studies, 23 studies on the pathology or etiology (including risk factors) of OA and other forms of arthritis, 1 study on estrogen replacement therapy, 35 animal studies, 68 *in vitro/in situ* studies, 39 review articles, 8 meta-analyses<sup>2</sup> and 3 letters to the editor.

You sent a number of letters in support of the petition to FDA's Center for Food Safety and Applied Nutrition (CFSAN) and to the Office of the Chief Counsel while the Agency was reviewing the petition. Some of these letters included supporting information such as comments from scientists retained by the petitioner and citations to additional references. FDA reviewed and considered these letters and supporting information along with the petition. The only letter that contained references not already cited in the petition was your December 2, 2003 letter to Dr. Kathy Ellwood, FDA, enclosing comments from Dr. Michael Orth. The additional references cited in Dr. Orth's comments consisted of 2 case reports, 4 *in vitro/in situ* studies, 1 epidemiology study on OA incidence in the population, 1 animal study and 1 review article. FDA's review of the data and information cited in the petition or submitted with your letters is discussed below in section II.

In addition to the petition and your letters, FDA considered the ongoing National Institutes of Health (NIH) Osteoarthritis Initiative (OAI)<sup>3</sup>. The objective of the OAI is to collect, analyze, and make widely available a large resource of clinical data, radiologic information (images from X-rays and magnetic resonance scans) and biospecimens (blood, urine, DNA) from individuals with early and progressing OA. The goal is to create a public resource to validate imaging and biochemical biomarkers and ensure that validated biomarkers for OA are made widely available. Although the OAI study is now underway, with enrollment having begun spring 2004, the results will not be available for another five years (FAC Transcript, June 7, p. 198).

FDA also considered the deliberations, recommendations and consensus opinions of the experts at the June 7-8, 2004 FAC meeting<sup>4</sup> that specifically addressed issues pertaining to this petition. The members of the FAC included 14 experts from the full food advisory committee; 5 experts from the dietary supplements subcommittee; and 6 experts added as

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<sup>2</sup> A meta-analysis is the process of systematically combining and evaluating the results of clinical trials that have been completed or terminated (Spilker, 1991, p. 793).

<sup>3</sup> The Osteoarthritis Initiative (OAI) is sponsored by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute of Health, Department of Health and Human Services (<http://www.niams.nih.gov/ne/oi/>)

<sup>4</sup> See <http://www.fda.gov/ohrms/dockets/ac/cfsan04.html> for FAC transcripts and other meeting information.

temporary voting members or expert voting consultants<sup>5</sup> because of their expertise in rheumatology, including three experts recommended by the petitioners (i.e., 3 of the 6 experts added).

In a July 1, 2004 letter to FDA, you asserted that 1) the questions posed to the panel revealed bias against the proposed claims and a position inconsistent with the First Amendment standard that governs FDA evaluation of health claims; 2) the key members of the FAC, selected by CFSAN and FDA's Center for Drug Evaluation and Research (CDER), had conflicts of interest and were biased; and 3) you wish the agency to consider revised versions of the claims FDA had rejected (claims 10-12). FDA has already addressed the third issue above in a letter to you dated August 9, 2004. The Agency will address the remaining two issues in a forthcoming letter.

In September 7 and September 14, 2004 letters to FDA, you enclosed a review by Dr. Michael Glade ("Glade FAC review") analyzing the conclusions reached by the FAC at the June 2004 meeting. The scientific concerns raised by the Glade FAC review are addressed in the body of this letter.

#### A. Substance

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). A substance means a specific food or component of food (21 CFR 101.14(a)(2)). The petition identified glucosamine and chondroitin sulfate as the substances that are the subject of the proposed claims. Glucosamine is purified from the exoskeletons of marine animals used for food (e.g., crab, lobster and shrimp). Chondroitin sulfate is isolated from the cartilage of marine and land animals used for food (e.g., bovine, porcine, fish and shark cartilage). Accordingly, the Agency concludes that glucosamine and chondroitin sulfate are components of food and therefore meet the definition of substance in the health claim regulation (21 CFR 101.14(a)(2)).

#### B. Disease or Health-Related Condition

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 or a state of health leading to such dysfunctioning (21 CFR 101.14(a)(5)). The petition identified OA, JD and CD as the diseases or health-related conditions that are the subjects of the proposed claims.

##### 1. Relationship of Modifiable Risk Factors to Diseases and Health-Related Conditions

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<sup>5</sup> Experts borrowed from another FDA Advisory Committee are referred to as temporary voting members; experts who are not members of an FDA Advisory Committee are referred to as expert voting consultants. Both temporary voting members and expert voting consultants participate fully in advisory committee deliberations and have an equal vote with regular members on recommendations to FDA.

In evaluating whether a condition such as JD or CD is a "health-related condition" within the meaning of 21 CFR 101.14(a)(5) (i.e., a state of health leading to disease), and also in evaluating evidence supplied to demonstrate that a substance reduces the risk of a disease, FDA considers the modifiable risk factors for the disease in question. The term "modifiable risk factor" means a measurement of a variable related to a disease that may serve as an indicator or predictor of that disease and that can be altered by a change in behavior, e.g., changes in diet or activity level. Modifiable risk factors are a type of biomarker. Biomarkers (intermediate or surrogate endpoints) are parameters from which risk of a disease can be inferred, rather than being a measure of the disease itself.<sup>6</sup>

A modifiable risk factor has several characteristics (FAC Transcript, June 7, pp. 50-52): (1) it is associated with disease; (2) it mediates the relationship between intake in healthy people and disease; and (3) its expression is modified by intake of a substance in healthy people. For example, serum LDL cholesterol is a modifiable risk factor for coronary heart disease; thus, intervention studies with a food in healthy subjects that observe decreased serum LDL cholesterol are considered as credible evidence that the food may reduce the risk for coronary heart disease. However, intervention studies with a food that observe decreases in pain, swelling and functionality/mobility do not provide evidence for a reduced risk of a disease because pain, swelling and functionality/mobility do not mediate the relationship between intake of the food in healthy people and disease. Pain, swelling and decreases in functionality/mobility are not in the causal pathway to disease; rather, they are the result of OA or one of many other possible causes (e.g., rheumatoid arthritis, land mine gout, syphilis, injury, overuse, and normal hormonal/physiological changes such as the female menstrual cycle), not all of which are diseases. A substance can effectively treat pain and swelling and improve functionality/mobility even though separate studies demonstrate that the substance does not prevent the disease responsible for the increased pain, increased swelling and decreased functionality/mobility. For example, non-steroidal anti-inflammatory drugs (NSAIDs) do not prevent OA (Brandt, 2002), but NSAIDs can reduce joint pain and swelling, which in turn can improve use of the joint (i.e., improve functionality/mobility).

## 2. Osteoarthritis (Claims 1-3)

OA is a disease, which Stedman's Medical Dictionary defines as arthritis characterized by erosion of articular cartilage, either primary or secondary to trauma or other conditions, which becomes soft, frayed, and thinned with eburnation<sup>7</sup> of subchondral bone and outgrowths of marginal osteophytes<sup>8</sup>.

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<sup>6</sup> Guidance for Industry: Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements, December 22, 1999. <http://www.cfsan.fda.gov/~dms/ssaguide.html>

<sup>7</sup> Eburnation is a change in exposed subchondral bone in degenerative joint disease in which subchondral bone is converted into a dense substance with a smooth surface like ivory (Stedman's Medical Dictionary).

<sup>8</sup> An osteophyte is a bony outgrowth or protuberance (Stedman's Medical Dictionary).

The American College of Rheumatology (ACR)<sup>9</sup> and the OAI<sup>10</sup> use the following diagnostic criteria for OA (FAC Transcript, June 7, p. 253-254; Felson, 2000):

Frequent pain in the joint, plus radiographic evidence of disease in that joint, almost always defined as a definite osteophyte. Above this threshold characterizes an individual as having osteoarthritis. The diagnosis requires a combination of symptoms and radiographic findings.

### 3. Joint Degeneration (Claims 4-6)

At FDA's request, the FAC considered whether JD is a state of health leading to disease, i.e., a modifiable risk factor for OA. The experts at the FAC meeting concluded that JD is not a modifiable risk factor for OA or state of health leading to the disease of OA because it is too nonspecific (FAC Transcript, June 8, pp. 53-54, 134).<sup>11</sup> During the deliberations, a rheumatologist on the FAC characterized the term JD as a "poor choice of words" because it is "too global, too vague." This rheumatologist also noted that JD is not limited to those with OA but can also result from other diseases, including rheumatoid arthritis, land mine gout and syphilis (FAC Transcript, June 8, pp. 9 and 52). Regarding joint degeneration's association with OA, the rheumatologist opined that JD is not a state that leads to OA, but rather "an analogous definition of osteoarthritis" in that it refers to "the net result of osteoarthritis" and "embodies what we see in osteoarthritis" (FAC Transcript, June 8, pp. 9-10). FDA agrees with the experts of the FAC that JD is a non-specific term that is difficult to categorize. JD is closely associated with OA and is the underlying cause of the symptoms of OA, including joint pain and loss of joint function, but not all patients with JD have symptoms of OA.<sup>12</sup> The Agency has concluded that if JD is suitable for a health claim, it is only because JD may be synonymous with OA and therefore, for the purposes of evaluating the evidence in this petition, FDA is considering JD as a synonym for OA. Even if JD is a disease, there is no credible evidence supporting the JD claims, as discussed in section II.

### 4. Cartilage Deterioration (Claims 7-9)

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<sup>9</sup> <http://www.rheumatology.org/public/factsheets/oa.asp?aud=pat>

<sup>10</sup> See the Prospectus of the OA Initiative at <http://www.niams.nih.gov/ne/oi/>

<sup>11</sup> The Glade FAC review asserts that "[t]he FAC did consider joint degeneration to be a modifiable risk factor but not exclusively or uniquely of osteoarthritis," and provide several citations to the FAC transcript to support this assertion. FDA has reviewed the transcript and does not agree with your conclusions that the experts quoted considered JD to be a modifiable risk factor. Specifically, Dr. Cush concluded that JD is not a risk factor for developing OA because it does not lead to OA but rather is "the net result of OA" (FAC Transcript, June 8, p. 9, lines 6-12 and 16-18); Dr. McBride's comment was in response to the preceding discussion about CD (FAC Transcript, pp. 42-45); thus, her comment was referring to CD as a risk factor rather than JD (FAC Transcript, p. 45, lines 10-17); ditto for Dr. Abramson's comment (FAC Transcript, June 8, pp. 46-47); Dr. Miller's comment was from his summary of the FAC's consensus conclusion that JD is not, in fact, a modifiable risk factor for OA (FAC Transcript, June 8, p. 134).

<sup>12</sup> Buckwalter et al. (2000)

The experts at the FAC meeting reached a consensus that CD is a modifiable risk factor for OA (FAC Transcript, June 8, p. 134). FDA concludes that CD is a health-related condition, i.e., a state of health leading to disease, because as a risk factor for OA, CD is a condition that may later develop into OA (FAC Transcript, June 8, p. 53). Notably, although OA/JD is always accompanied by CD (FAC Transcript, June 8, p. 53; Felson, et al., 2000; Buckwalter, et al., 2000), an individual can have CD without developing OA/JD, for example, CD can occur with normal aging of joints (FAC Transcript, June 7, pp. 85-86).

## 5. Summary

The Agency concludes that OA/JD is a disease and CD is a health-related condition under 21 CFR 101.14(a)(5).

## C. Safety Review

Under 21 CFR 101.14(b)(3)(ii), if the substance is to be consumed at other than decreased dietary levels, the substance must be a food or a food ingredient or a component of a food ingredient whose use at levels necessary to justify a claim must be demonstrated by the proponent of the claim, to FDA's satisfaction, to be safe and lawful. FDA evaluates whether the substance is "safe and lawful" under the applicable food safety provisions of the Act. For conventional foods, this evaluation involves considering whether the ingredient that is the source of the substance is generally recognized as safe (GRAS), approved as a food additive, or authorized by a prior sanction issued by FDA (see 21 CFR 101.70(f)). Dietary ingredients in dietary supplements, however, are not subject to the food additive provisions of the act (see section 201(s)(6) of the Act (21 U.S.C. § 321(s)(6)). Rather, they are subject to the adulteration provisions in section 402 of the Act (21 U.S.C. 342) and, if applicable, the new dietary ingredient provisions in section 413 of the Act (21 U.S.C. 350b), which pertain to dietary ingredients that were not marketed in the United States before October 15, 1994. The term "dietary ingredient" is defined in section 201(ff)(1) of the Act and includes vitamins; minerals; herbs and other botanicals; dietary substances for use by man to supplement the diet by increasing the total daily intake; and concentrates, metabolites, constituents, extracts, and combinations of the preceding types of ingredients.

The petition asserts that glucosamine and chondroitin sulfate are GRAS through experience based on common use in food. According to the petition, glucosamine and chondroitin sulfate have been naturally occurring ingredients in foods consumed in the United States prior to January 1, 1958, and there is no evidence that when glucosamine and chondroitin sulfate are consumed in foods there is a cumulative effect in the diet that is unsafe. The petition further states that there are no known interactions with drugs in clinical practice (except for a general warning that diabetics may need to monitor their blood sugars when taking glucosamine) and there are no known harmful interactions with other dietary supplements (except for a general warning that chitosan may decrease the

absorption of chondroitin sulfate). The petition also states that the most common reported adverse reaction with glucosamine and chondroitin sulfate is mild gastrointestinal distress.

There are no specific intake quantities for glucosamine or chondroitin sulfate proposed in the petition. The petition cites the various supplemental levels used in the scientific literature, which range from 1200-2000 mg glucosamine and from 400-1200 mg chondroitin sulfate when taken separately, and from 1000-1600 mg glucosamine and from 800-1200 mg chondroitin sulfate when taken concurrently. However, the scientific report submitted with the petition as Exhibit 1 does identify a beneficial level for each substance. Those beneficial levels are 1500 mg glucosamine when taken alone, 1000 mg glucosamine when taken concurrently with chondroitin sulfate and 1200 mg chondroitin sulfate when taken separately or concurrently with glucosamine.

The petition concerns the consumption of glucosamine and chondroitin sulfate in dietary supplements. There is no dietary reference intake (DRI) for either glucosamine or chondroitin sulfate. There are two ongoing NIH clinical trials using glucosamine and chondroitin sulfate. One is the Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT)<sup>13</sup>, which is studying the effectiveness of glucosamine and chondroitin sulfate to improve pain and knee function in patients with OA. The other NIH clinical trial is studying the absorption and distribution of glucosamine and chondroitin sulfate<sup>14</sup>. Both trials use the same dosage of 1500 mg glucosamine and 1200 mg chondroitin sulfate per day either alone or in combination. Both trials have received Institutional Review Board (IRB) approval, which includes assessing safety of the dosage.

On the other hand, there are unresolved issues and gaps in the available data concerning glucosamine, such as impact of intake during pregnancy and lactation and in children; long term evaluation of safety (beyond 3 years); details of glucosamine metabolism; and impact in individuals with liver disease or insulin resistance (IOM/FNB, 2004). Furthermore, glucosamine and chondroitin sulfate were nominated to the National Toxicology Program (NTP)<sup>15</sup> for toxicological studies because of widespread long-term use as dietary supplements and inadequate data to assess safety. The NTP studies are under preparation.

Although the information about glucosamine and chondroitin sulfate submitted with the petition and otherwise available to FDA does not raise concerns that would lead the Agency to question the petitioner's assertion that dietary supplements containing these substances at levels cited in the petition are safe and lawful, the Agency did not perform a full safety review and make its own determination on this issue. It was not necessary for

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<sup>13</sup> <http://www.clinicaltrials.gov/show/NCT00032890>

<sup>14</sup> <http://clinicaltrials.gov/show/NCT00086229>

<sup>15</sup> <http://ntp-server.niehs.nih.gov/NomPage/2003Noms.html>

FDA to do so because the Agency is denying the proposed claims for lack of credible evidence, as discussed in section II below.

## II. The Agency's Consideration of Qualified Health Claims

To evaluate proposed health claims about a substance and reduced risk of a disease, FDA looks for evidence that the substance (1) reduces the incidence of the disease, or (2) produces a beneficial change in a modifiable risk factor for the disease.

At FDA's request, the FAC considered whether JD and CD are modifiable risk factors for OA. The FAC concluded that JD is not a modifiable risk factor for OA (FAC Transcript, June 8, p. 134) for the reasons discussed in section I.B.3. FDA agrees.

The FAC further concluded that CD is a modifiable risk factor for OA (FAC Transcript, June 8, p. 134). In discussing the strength of the evidence for this conclusion, however, experts on the FAC commented, for example, that the evidence that CD is a modifiable risk factor is weak (FAC Transcript, June 8, pp. 59-60, 62) and that it is questionable whether modifying CD would reduce the risk of OA (FAC Transcript, June 8, pp. 55, 62-65). The FAC concluded that CD "is and could be used as" a modifiable risk factor (FAC Transcript, June 8, p. 134). FDA agrees that CD could be a modifiable risk factor for OA because CD may proceed to clinical OA, and preventing or slowing CD in individuals without OA may reduce the risk for OA. Further, because FDA is considering JD as a synonym of OA for purposes of your petition, FDA considered CD, the modifiable risk factor for OA, as a modifiable risk factor for JD.

To consider measures of CD, such as biochemical indices of cartilage metabolism<sup>16</sup> and/or catabolism or radiographic changes of cartilage,<sup>17</sup> FDA needs evidence that the proposed measures are considered by the scientific community to be reliable and consistent measures of CD and that the methodology used is valid. Based on current scientific evidence, FDA concludes that none of the measures used in the studies the Agency reviewed in connection with the petition is considered valid for assessing CD (see discussion in section II.A.6 below).

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<sup>16</sup> In the human intervention studies cited by the petitioner, serum, urine, and synovial fluid biochemical measures of cartilage metabolism included keratin sulfate, stromelysin, tissue inhibitor of metalloproteinase (TIMP), cartilage oligometric matrix protein (COMP), pyridinoline, deoxypyridinoline, hyaluronate, protein concentration, collagenolytic activity, phospholipase A2, N-acetylglucosaminidase, sulfated glycosaminoglycans and YKL-40.

<sup>17</sup> Radiographic measures used in human intervention studies cited by the petitioner include extended, weight-bearing x-ray films of the knee joint intended to measure joint space narrowing and x-rays of the finger joints.

## A. Assessment of the Intervention Studies

For its review of the proposed claims, FDA evaluated 18 intervention studies on glucosamine<sup>18</sup>; 20 intervention studies on chondroitin sulfate<sup>19</sup>; 5 intervention studies on glucosamine plus chondroitin sulfate<sup>20</sup>; 2 intervention studies on galactosaminoglucuronoglycan sulfate (GAGGS)<sup>21</sup>; 1 intervention study on glycosamine-glucuron-glycan-sulfate (GGGS)<sup>22</sup>; and 1 intervention study on galactosaminoglycuronglycan (GAG).<sup>23</sup> None of these 47 intervention studies was considered to be relevant to any of the proposed claims for the reasons set forth below. In addition, some of the studies are so flawed in design or execution that they are not scientifically credible and, thus, no conclusions can be drawn from them (as discussed in section II.A.6 below).

### 1. Osteoarthritis (Claims 1-3)

FDA considers human studies that are primary reports<sup>24</sup> of data collection to be the most convincing evidence when attempting to establish a diet-disease relationship. FDA uses two endpoints to evaluate disease risk reduction for purposes of health claim evaluations: a) reduction in incidence of the disease, and b) beneficial changes in modifiable risk factors for the disease. FDA is unaware of any other way to evaluate risk reduction, and the petitioner has not identified any other way.

Of the 47 intervention trials cited in the petition, 45 are not relevant to establishing a relationship between glucosamine and reduced risk of OA in the general healthy population because they were conducted in individuals who already had OA. Thus, these studies cannot and do not supply any direct evidence of reduced OA incidence. FDA also considered whether any observed changes in modifiable risk factors measured in OA patients could be extrapolated to the general population and sought the FAC's opinion on this question. The general consensus of the experts on the FAC was that the available scientific data do not support extrapolating the findings of studies using subjects with

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<sup>18</sup> Bohmer et al., 1982; Braham et al., 2003; Bruyere et al., 2002; Crolle and D'Este, 1980; D'Ambrosio et al., 1981; Drovanti et al., 1980; Houghton et al., 1999; Muller-Fassbender et al., 1994; Noack et al., 1994; Pavelka et al., 2002; Pujalte et al., 1980; Qiu et al., 1998; Reginster et al., 2001; Rindone et al., 2000; Tapadinhas et al., 1982; Thie et al., 2001; Vas, 1982; Vetter, 1969

<sup>19</sup> Alekseeva et al., 2001; Anonymous, 2000; Bourgeois et al., 1998; Charlot et al., 1992; Conrozier and Vignon, 1992; Conrozier, 1998; Conte et al., 1995; Gross, 1983; L'Hirondel, 1992; Leeb et al., 1996; Malaise et al., 1999; Mathieu, 2002; Mazieres et al., 2001; Morreale et al., 1996; Nasonova et al., 2001; Ronca et al., 1998; Rovetta et al., 2002; Thilo, 1977; Uebelhart et al., 1998; Verbruggen et al., 1998

<sup>20</sup> Das, Jr. and Hammad, 2000; Leffler et al., 1999; Nakamura, 2001; Nguyen et al., 2001; Shankland, 1998

<sup>21</sup> Pipitone et al., 1992; Ricciari et al., 1991

<sup>22</sup> Serni et al., 1993

<sup>23</sup> Ricciari et al., 1991

<sup>24</sup> A primary report is the original publication of study results. Examples of non-primary reports are review articles, meta-analyses and commentaries, and letters to the editor.

OA, even those with “mild OA,” to risk reduction in individuals without OA (FAC Transcript, June 8, p. 135; see section II.A.4 below for more discussion on this issue).

FDA agrees with the FAC. The Agency notes that, absent data that provide a basis to extrapolate results from OA patients to risk reduction in healthy individuals, there is no more reason to suppose that glucosamine or chondroitin sulfate will reduce the risk of OA than there is to suppose that an analgesic, such as ibuprofen, used to treat the pain and inflammation associated with OA will prevent OA.<sup>25</sup> The fact that a product treats, mitigates, or cures a disease does not necessarily mean that it will reduce the risk of the disease.

The two other intervention studies are also not relevant, albeit for different reasons. In Braham et al. (2003) the authors stated that the subjects in this study had “regular knee pain, most likely due to previous articular cartilage damage, and possibly osteoarthritis,” and that “[r]adiological assessments were not made mandatory in this study due to time and monetary constraints.” This study is not relevant because the endpoints measured (joint pain and functionality) are not modifiable risk factors for OA, as discussed in section I.B.1. Further, the subjects in this study were not properly examined for the presence or absence of OA/JD; if the subjects had OA/JD, this study would not be relevant for the additional reason that the results from OA/JD patients cannot be extrapolated to risk reduction in healthy individuals without OA/JD (FAC Transcript, June 8, p. 135). Thus, FDA did not consider this study in the current review because it is not relevant. In Bohmer et al. (1982) the patients had chondropathia patellae.<sup>26</sup> This study is not relevant because the endpoint measured (joint pain) is not a modifiable risk factor for OA/JD. Further, this study is so flawed in design that conclusions cannot be drawn from it because the study did not include a control group and there was no statistical analysis of the data. Thus, FDA did not consider this study in the current review because it is not relevant or scientifically credible.

Some of the 47 intervention studies were not relevant to your proposed claims or could not be evaluated for other reasons, including the following: 1) 34 studies<sup>27</sup> measured OA/JD symptoms (e.g., joint pain, swelling, mobility) rather than OA/JD incidence or

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<sup>25</sup> Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID). NSAIDs are a class of analgesics used to treat the symptoms of OA. NSAIDs do not prevent the development of OA in humans, even though they do so in rodent models of OA (Brandt, 2002).

<sup>26</sup> Chondropathia patellae is a disease of the cartilage and patella (Stedman’s Medical Dictionary and Dorland’s Illustrated Medical Dictionary). The patella is a bone in the knee commonly referred to as the kneecap.

<sup>27</sup> Bohmer et al., 1982; Bourgeois et al., 1998; Braham et al., 2003; Brandt et al., 2004; Bruyere et al., 2003; Charlot et al., 1992; Conrozier and Vignon, 1992; Crolle and D’Este, 1980; D’Ambrosio et al., 1981; Das, Jr. and Hammad, 2000; Drovanti et al., 1980; Gross, 1983; Houpt et al., 1999; L’Hirondel, 1992; Leeb et al., 1996; Leffler et al., 1999; Mazieres et al., 2001; Morreale et al., 1996; Muller-Fassbender et al., 1994; Nakamura, 2001; Nasonova et al., 2001; Nguyen et al., 2001; Noack et al., 1994; Pipitone et al., 1992; Pujalte et al., 1980; Qu et al., 1998; Riccieri et al., 1991; Rindone et al., 2000; Shankland, 1998; Tapadinhas et al., 1982; Thie et al., 2001; Thilo, 1977; Vas, 1982; Vetter, 1969

changes in the OA/JD modifiable risk factor of CD; 2) 1 study<sup>28</sup> was submitted as an abstract, which does not provide enough information for FDA to determine the relevance of the study based on factors such as the study population characteristics or the composition of the product (e.g., food, dietary supplement) used in the study<sup>29</sup>; 3) 3 studies<sup>30</sup> were on substances other than glucosamine and chondroitin sulfate; 4) in 3 studies<sup>31</sup> the patients were injected with glucosamine sulfate into the muscle, intravenously, or into the joint rather than given glucosamine sulfate by the oral route. The biological effects of glucosamine when ingested cannot be determined from studies that use another route of administration without additional studies evaluating the effect of the difference in route of administration. The petition did not provide data demonstrating that injection of glucosamine sulfate does not alter its biological effects by bypassing the chemical alterations that occur during digestion, absorption and first-pass metabolism following oral administration. Absent data demonstrating that the biologically active form of glucosamine sulfate at the target site is the same when it is injected compared to when it is ingested, FDA does not consider studies that inject glucosamine sulfate relevant for determining risk reduction from consumption of glucosamine as a dietary supplement.

## 2. Joint Degeneration (Claims 4-6)

FDA considered the 47 intervention trials cited in the petition for evidence of a reduced risk for JD in the general healthy population. As discussed in section I, for purposes of this health claim petition, FDA is considering JD as a synonym for OA. Therefore, the analysis of intervention studies for OA in section II.A.1 also applies to JD. As discussed for OA in section II.A.1 above, FDA has concluded that these studies are not relevant to establishing a relationship between glucosamine and chondroitin sulfate and a reduced risk of OA/JD in the general healthy population because they were conducted in individuals with OA/JD and (1) there is no evidence of reduced OA/JD incidence, and (2) any observed changes in modifiable risk factors measured in OA/JD patients cannot be extrapolated to the general population (FAC Transcript, June 8, p. 135; see discussion below in section II.A.4).

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<sup>28</sup> Nakamura et al., 2001

<sup>29</sup> In addition, abstracts do not contain sufficient information for FDA to determine whether the study is flawed in critical elements such as its design, execution, and data analysis. FDA must review the scientific quality of a study to determine whether credible conclusions can be drawn from it.

<sup>30</sup> Galactosaminoglucuronoglycan sulfate (GAGGS) (Pipitone et al., 1992; Riccieri et al., 1991), glycosamine-glucuron-glycan-sulfate (GGGS) (Serni et al., 1993) and galactosaminoglycuronglycan (GAG) (Riccieri et al., 1991)

<sup>31</sup> Crolle and D'Este, 1980; D'Ambrosio et al., 1981; Vetter, 1969

### 3. Cartilage Deterioration (Claims 7-9)

FDA considered 11 intervention trials<sup>32</sup> that attempted to measure CD. FDA has concluded that these studies are not relevant to establishing a relationship between glucosamine and chondroitin sulfate and a reduced risk of CD in the general healthy population because they were conducted in individuals with CD, and (1) there is no evidence of reduced CD incidence, and (2) any observed changes measured in subjects with CD cannot be extrapolated to the general population, as discussed below in section II.A.4.

### 4. Results from Patients with OA/JD and CD Cannot be Extrapolated to Predicting Reduced Risk of OA/JD and CD in the General Healthy Population

#### a. The risk factors for developing OA/JD are not the same as those for progression of OA/JD

There are differences in the risk factors associated with healthy individuals developing OA/JD versus the risk factors associated with the worsening of existing OA/JD (i.e., OA/JD progression) (FAC Transcript, June 7, pp. 67-68, 239; FAC Transcript, June 8, 21-22). Therefore, it would not be reasonable to conclude from the available evidence that substances that treat OA/JD will also reduce the risk of OA/JD (FAC Transcript, June 7, p. 68; FAC Transcript, June 8, p. 82). A major goal of the NIH sponsored OAI is to identify exactly what will trigger the onset of OA/JD in high-risk individuals, which is unknown at this time (FAC Transcript, June 8, p. 83). The evidence provided in the petition was gathered from OA/JD patients and measures effects of glucosamine and chondroitin sulfate on changes associated with OA/JD worsening (i.e., progression). This treatment evidence is not relevant to predicting the effects of glucosamine and chondroitin sulfate on developing OA/JD in healthy individuals (i.e., OA/JD risk reduction) (FAC Transcript, June 8, p. 135).

#### b. Cells from patients with OA/JD and CD are not the same as cells from healthy individuals

Although it is difficult to pinpoint exactly when pre-OA/JD ends and clinical OA/JD begins, osteoarthritic chondrocytes<sup>33</sup> and tissues (cartilage) are different than non-OA/JD cells and tissues and therefore may respond differently to interventions and treatments (FAC Transcript, June 8, p. 68). A normal chondrocyte and an early OA/JD chondrocyte are different, and an early OA/JD chondrocyte is different from an established OA/JD chondrocyte (FAC Transcript, June 7, p. 130). For example, normal chondrocytes,

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<sup>32</sup> Anonymous, 2000; Conrozier, 1998; Conte et al., 1995; Malaise et al., 1999; Mathieu, 2002; Pavelka et al., 2002; Reginster et al., 2001; Ronca et al., 1998; Rovetta et al., 2002; Uebelhart et al., 1998; Verbruggen et al., 1998

<sup>33</sup> A chondrocyte is a non-dividing cartilage cell occupying a lacuna (i.e., small space or cavity) within the cartilage matrix (Stedman's Medical Dictionary).

hypertrophic chondrocytes<sup>34</sup> and diseased chondrocytes have very different gene expression profiles<sup>35</sup> relative to each other (FAC Transcript, June 7, p. 130). Moreover, there are functional differences between normal chondrocytes and OA/JD chondrocytes. For example, as a normal chondrocyte becomes an OA chondrocyte, the proteoglycan (a component of cartilage) that the OA chondrocyte makes is not normal and does not work as well as normal proteoglycan (FAC Transcript, June 7, pp. 123-124). Although glucosamine and chondroitin sulfate are reported to stimulate OA chondrocytes to make new proteoglycan in OA patients, proteoglycan synthesized by OA chondrocytes is not normal and does not function normally. Moreover, there is no evidence from clinical studies in people without OA that glucosamine and chondroitin sulfate stimulate normal chondrocytes to make normal proteoglycan that functions normally (FAC Transcript, June 7, pp. 124-125),<sup>36</sup> which would be necessary to reduce OA risk.

In addition, some cellular processes reportedly affected by glucosamine and chondroitin sulfate in OA/JD chondrocytes are controlled differently in OA/JD chondrocytes than in normal chondrocytes and are more important in the late stages of the disease process than early on. For example, the pathology of OA/JD involves inflamed catabolic chondrocytes brought about through activation of pathways such as NF-kappa B that are mediated by cytokines (e.g., IL-1).<sup>37</sup> This activity in turn increases catabolic inflammatory processes and production of enzymes such as metalloproteinase. Studies of glucosamine and chondroitin suggest that they may be effective in blocking these inflammatory processes and metalloproteinase production by beneficially influencing the cytokines and thereby preventing the NF-kappa B pathway from being activated. However, activated NF-kappa B and the resulting increase in catabolic inflammatory processes and metalloproteinase production are not typical of normal chondrocytes (FAC Transcript, June 8, pp. 84-85). Therefore, if the effect of glucosamine and chondroitin sulfate in OA/JD is through blocking the activation of cytokine pathways (as suggested in the petitions and FAC meeting; FAC Transcript, June 7, pp. 101, 186),<sup>38</sup> then the

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<sup>34</sup> A hypertrophic chondrocyte is an enlarged chondrocyte that may be in the early stages of disease.

<sup>35</sup> A gene expression profile is a measure of the number and/or level of genes that are expressed ("turned on") at a given moment in time. Although nearly all the cells in our bodies have the same number of genes, not all the same genes in each cell type are expressed at the same time or at the same levels. For example, if two cells, cell A and cell B, each have 1000 genes, and cell A expresses 500 of these genes, but cell B expresses only 250 of the genes, then these two cells are said to have different gene expression profiles. The existence of different gene expression profiles between cells indicates that there are significant differences in the cells and suggests that the cells will respond differently to treatments.

<sup>36</sup> See especially the conclusion of Luke Bucci, Ph.D., a scientist employed by Weider who made a presentation at the FAC meeting in support of Weider's petition (FAC Transcript, June 7, p. 125, lines 2-4).

<sup>37</sup> A cytokine is a generic term for nonantibody proteins released by one cell population on contact with specific antigen, which act as intercellular mediators, as in the generation of an immune response (Dorland's Illustrated Medical Dictionary).

<sup>38</sup> The Glade FAC review asserts that the FAC "ignored or misinterpreted a large body of evidence" demonstrating that the biochemical and structural differences between normal cartilage and OA cartilage do not correspond to differences in how normal chondrocytes and osteoarthritic chondrocytes respond to glucosamine, chondroitin, or other stimuli. Although it is impossible to determine what each FAC member

evidence indicates that glucosamine and chondroitin sulfate will not beneficially affect normal chondrocytes where these cytokine-mediated catabolic pathways are not activated. Furthermore, there is no evidence that modifying these processes in normal chondrocytes will prevent them from becoming OA/JD chondrocytes (FAC Transcript, June 8, pp. 84-85). In sum, because of these genetic and functional differences between normal chondrocytes and OA chondrocytes, there is no basis to conclude that whatever effects glucosamine and chondroitin sulfate may have on early or established OA/JD chondrocytes in the context of disease treatment or mitigation are relevant to reduction of risk in non-OA/JD cells.

It is not uncommon for diseased cells and normal cells to respond differently to treatments or exogenous substances, and these differences must be considered when drawing conclusions. For example, effectively treating a cancer cell with a chemotherapy drug is not evidence that the chemotherapy drug will prevent a normal cell from becoming a cancer cell. Chemotherapy drugs work by taking advantage of the differences that exist in cancer cells compared to normal cells.

c. Studies in patients with unilateral knee or hand OA/JD do not support risk reduction in the general healthy population

Experts who presented at the FAC meeting on behalf of the petitioners suggested that results from “unaffected” knees in studies of OA/JD patients with unilateral knee OA/JD,<sup>39</sup> where patients have been diagnosed with OA/JD in one knee, was evidence that glucosamine and chondroitin sulfate reduced the risk of OA/JD in healthy individuals. However, following a closer examination of these data, it became clear that most or all of these patients also had some degree of OA/JD in the other (contralateral) knee (FAC Transcript, June 8, pp. 71, 76-77, 79, 179-180). The contralateral knees of most of the patients in these studies had radiographic disease,<sup>40</sup> which is a fairly late structural

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did or did not consider in reaching their respective opinions, the FAC Transcript indicates that cellular and mechanistic data regarding normal and osteoarthritic chondrocytes were discussed. For example, Luke R. Bucci, Ph.D., a scientist employed by Weider, and Roy D. Altman, M.D., a physician scientist representing Rotta Pharmaceuticals, who made presentations at the FAC meeting in support of Weider’s and Rotta Pharmaceuticals’ petitions, respectively, discussed cellular and mechanistic data extensively throughout their presentations (FAC Transcript, June 7, pp. 69-105, 156-165), and the FAC members asked questions and commented on these data (FAC Transcript, June 7, pp. 111-115, 123-126, 129-130, 186, 269-287; FAC Transcript, June 8, 84-85). Moreover, FDA provided the FAC members with your client’s petition, including the scientific review at Exhibit 1 that the Glade FAC review cites as part of the evidence that the FAC allegedly ignored. Therefore, the FAC members were aware of this evidence, and much of it was discussed at the FAC meeting. Even so, the consensus of the FAC members was that the *in vitro* studies on normal and OA chondrocytes summarized in the Glade FAC review and in Exhibit 1 of your petition were not sufficient to show risk reduction absent confirmation with human data from clinical studies (FAC Transcript, June 8, p. 135). The FAC did not ignore the available data; they merely disagreed with your conclusions about the significance of these data.

<sup>39</sup> Reginster et al., 2001; Pavelka et al., 2002.

<sup>40</sup> Radiographic disease means that evidence of OA/JD can be detected on X-rays, which is a diagnostic criterion for OA/JD (see section I.B.1).

finding of OA/JD (FAC Transcript, June 7, p. 180) indicating that there was existent disease in both knees (FAC Transcript, June 7, pp. 179-180). A similar conclusion was reached by the investigators of a clinical trial presented at the American College of Rheumatology (Brandt et al., 2004). These investigators stated that they had a difficult time identifying “unaffected” contralateral knees, and upon closer examination the contralateral knees all had some measure of OA/JD (FAC Transcript, June 7, pp. 180-181). Thus, in patients diagnosed with unilateral knee OA/JD, the evidence so far indicates that the contralateral knee also has OA/JD and therefore is not a “healthy” knee. The evidence indicates that knee OA/JD is a bilateral and often systemic process, and that the presence of clinical disease in one knee joint is either a harbinger of or goes along with clinical disease in its contralateral partner, and therefore, the contralateral knee is not the same as a normal knee (FAC Transcript, June 7, pp. 189-190, 225). For this reason, findings of changes in the contralateral knee in patients diagnosed with OA/JD who supplement their diet with glucosamine or chondroitin sulfate are not a sufficient surrogate for a risk reduction effect from such supplementation in the general healthy population without OA/JD. When commenting on the glucosamine studies, Dr. Lucio Rovati, a scientist employed by Rotta Pharmaceuticals who made a presentation to the FAC in support of Rotta’s petition, recognized that “[t]here is no study of [OA/JD] prevention” with glucosamine (FAC Transcript, June 7, p. 173).

Further, studies on chondroitin sulfate and hand OA/JD do not demonstrate OA/JD risk reduction measured by changes in CD. Given that OA/JD appears to be a systemic disease (FAC Transcript, June 7, pp. 189-190, 225), the appearance of OA/JD in some finger joints likely indicates that all the finger joints are affected to some extent (FAC Transcript, June 7, pp. 229-230). Thus, as with studies in knee OA/JD patients, the findings of studies of hand OA/JD patients are likely not a valid surrogate for risk reduction in individuals without OA/JD (FAC Transcript, June 8, p.89). However, even if one could demonstrate that the finger joints that appeared to be normal at the start of the hand OA/JD studies truly were unaffected by OA/JD, the results of these studies do not indicate any benefit to these unaffected or less affected joints. Consumption of chondroitin sulfate for three years did not prevent development of OA/JD in finger joints that appeared to be normal at the start of the study, even though it slowed progression of CD in joints known to be affected at the start of the study (Verbruggen et al., 1998). Similarly, chondroitin sulfate plus naproxen<sup>41</sup> did not prevent development of OA/JD in finger joints that appeared to be unaffected at the start of the study, even though a treatment effect on CD was observed in the affected joints (Rovetta et al., 2002). Thus, in patients with hand OA/JD, chondroitin sulfate may have treated or mitigated OA/JD and CD by slowing its progression, but chondroitin sulfate did not prevent OA/JD and CD from developing in finger joints that appeared to be normal at the start of the study (FAC Transcript, June 8, p. 73).

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<sup>41</sup> Naproxen (e.g., Aleve®) belongs to a class of drugs called non-steroidal anti-inflammatory drugs (NSAIDs). Other members of this class include ibuprofen (Motrin®), indomethacin (Indocin®), nabumetone (Relafen®) and several others. These drugs are used for the management of mild to moderate pain, fever, and inflammation.

## 5. The Intervention Studies Do Not Provide Evidence of Risk Reduction

Based on these studies and the other scientific evidence discussed above, FDA concludes that none of the intervention studies provides relevant scientific evidence for the relationship in the proposed claims because the studies used subjects diagnosed with OA/JD and CD.<sup>42</sup> Thus, there is no evidence of reduced OA/JD or CD incidence. Moreover, the results of the treatment studies on CD in OA/JD patients (11 studies<sup>43</sup>) cannot be extrapolated to show reduction of OA/JD or CD risk in the general healthy population. In addition, as discussed below, a number of the intervention studies are so flawed in design, execution, or analysis that they are not scientifically credible.

## 6. Some of the Intervention Studies Are Not Scientifically Credible Because of Serious Flaws in Design, Execution, or Analysis

FDA concluded that, in addition to not being relevant for reasons discussed above, 28 of the intervention studies are so flawed that credible scientific conclusions cannot be drawn from them for the following reasons: 1) 16 studies<sup>44</sup> lacked a control group or did not report a statistical analysis against the control group (Spilker, 1991, pp. 59-64); 2) 5 studies<sup>45</sup> did not identify the statistical tests used or no statistical analysis was performed (Spilker, 1991, pp. 498); 3) 11 studies<sup>46</sup> attempted to assess changes in CD in OA/JD patients based on biochemical and/or radiographic evidence using unreliable methods for measuring CD (FAC Transcript, June 7, pp. 117, 231<sup>47</sup>; June 8, p. 37). Relying on biochemical markers of cartilage metabolism collected in the serum (a component of blood), urine, and synovium (a thin membrane lining the joint space), as was done in the cited studies, is not reliable because these markers reflect (serum, urine), or may reflect (synovium), systemic changes rather than joint-specific changes and are therefore not specific indicators of changes in the affected tissues (FAC Transcript, June 7, pp. 234-239). The X-ray film methods<sup>48</sup> used in the cited studies are no longer used in

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<sup>42</sup> 45 of 47 intervention studies were conducted in OA patients. The remaining 2 studies were not relevant for other reasons. See section II.A.1.

<sup>43</sup> See footnote 32.

<sup>44</sup> Bohmer et al., 1982; Conte et al., 1995; Gross, 1983; Leeb et al., 1996; ; Malaise et al., 1999; Morreale et al., 1996; Muller-Fassbender et al., 1994; Nakamura, 2001; Qiu et al., 1998; Riccieri et al., 1991; Ronca et al., 1998; Shankland, 1998; Tapadinhas et al., 1982; Thie et al., 2001; Thilo, 1977; Vas, 1982

<sup>45</sup> Bohmer et al., 1982; Gross, 1983; Nasonova et al., 2001; Semi et al., 1993; Vetter, 1969

<sup>46</sup> See footnote 32

<sup>47</sup> The citations from the June 7 FAC transcripts use the term "cartilage loss." Based on review of the FAC transcript as a whole, FDA concludes that the FAC used the terms "cartilage loss" and "cartilage deterioration" interchangeably to mean reduced cartilage mass and/or integrity.

<sup>48</sup> Radiographic views of the standing, fully extended knee (referred to in the FAC transcript as "extended, weight-bearing films") cannot be controlled to assure that the same view is obtained at each data point and therefore, are no longer used in clinical trials to evaluate joint space loss because they are no longer considered reproducible measures over time (FAC, June 7, p. 117). An additional problem with the radiographic method is that it may actually be measuring pseudo-widening of the joint, rather than joint space loss, and it is not known whether pseudo-widening measures improvement in cartilage (FAC Transcript, June 7, pp. 119-120). Further, joint space loss is non-linear and difficult to predict, which

clinical trials to evaluate joint space loss because they are no longer considered reproducible measures over time (FAC Transcript, June 7, p. 117). FDA could not find any evidence in the petitions, the discussions at the FAC meeting, the OAI or elsewhere that any of the biochemical and radiographic markers of CD used in the cited studies are considered valid for measuring CD; rather, the available evidence indicates that these markers are not scientifically reliable as measures of CD. Therefore, FDA has concluded that these studies<sup>49</sup> are so flawed that they are not scientifically credible and could not be used to draw conclusions about OA/JD and CD risk reduction even if they had been conducted in the general healthy population rather than in people who already had these conditions.

#### B. Assessment of Observational Studies

For its review of the proposed claims, FDA evaluated two case reports<sup>50</sup> submitted with your December 2, 2003 letter. Neither of these case reports is relevant to establishing a relationship between glucosamine and chondroitin sulfate and a reduced risk of OA/JD or CD in the general healthy population. The case report by Van Blitterswijk et al. (2003) is not relevant because the one patient treated had OA/JD and CD of the spine; therefore, the treatment results cannot be extrapolated to OA/JD and CD risk reduction in the general healthy population (FAC Transcript, June 8, p. 135). Further, case reports cannot be used to draw conclusions about substance-disease relationships in the absence of other clinical data because case reports do not include a control group or a statistical analysis of the data.

The case report by Schenck et al. (2000) of a female basketball player, who had a rare articular impaction injury involving the femoral head (i.e., hip joint), is not relevant because the study was about healing an injury, not reducing OA/JD or CD risk. Although a history of joint injury is a risk factor for OA, that risk factor does not go away when the injury is healed or the symptoms from the injury are resolved. There is no evidence provided in this case report or in the December 2, 2003 letter that if glucosamine and chondroitin sulfate stimulated healing of the joint, it did so in a way that caused the joint to be resistant to future development of OA/JD and CD. Further, this case report by Schenck et al. (2000) is subject to the same limitations as all case reports, as discussed above, and therefore cannot be used to draw conclusions about substance-disease relationships in the absence of other clinical data. Thus, because of the relevance problems with these case reports and their inherent limitations as scientific evidence, FDA did not consider them to be credible evidence supporting the proposed claims.

#### C. Assessment of Other Information Submitted By the Petitioner

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creates many problems for its quantification and assessment even in well constructed trials (FAC, June 7, p. 231; June 8, p. 37).

<sup>49</sup> See footnote 32.

<sup>50</sup> A case report is a publication where observations of one or a few patients are described in detail.

The 36 animal studies and 72 *in vitro/in situ* studies were considered as background information that is useful to understanding scientific issues about the substance-disease relationships in the proposed claims. The general consensus of the FAC was that, in the absence of relevant human studies, animal and *in vitro* studies are not sufficient to predict human OA/JD and CD risk reduction. “[A]nimal studies and *in vitro* studies cannot replace human studies ... the value of animal studies is in hypothesis generation and in getting a better understanding of the mechanisms that might be involved in interaction between various materials and the processing of OA [or JD]” (FAC Transcript, June 8, p. 135 (concluding remarks of FAC chair summarizing FAC’s answers to the questions posed by FDA)).

Humans walk on two legs, while the most commonly used laboratory animal models of disease (including the ones used in the animal studies cited in the petition) walk on four. There is a biomechanical aspect of human OA/JD and CD that cannot be reproduced in four legged animals because of the weighting of the joints that can set off inflammation, which in humans tends to be more intense than in animals that distribute their weight over four legs (FAC Transcript, June 8, pp. 102-103). The physiology of animals is different from that of humans. Because the etiology of OA/JD and CD is poorly understood, these differences make it impossible to measure how well any animal model of OA/JD and CD mimics OA/JD and CD in humans. Thus, because of the differences between animal and human physiology and the lack of understanding of OA/JD and CD pathology, there is no assurance that any effect measured in animals has any relevance to the human disease or can be repeated in humans. Extrapolating to humans at risk of OA/JD and CD is even more problematic with *in vitro* models of OA/JD and CD. *In vitro* experiments are conducted in an artificial environment that cannot mimic human physiology, which may affect the development of OA/JD and CD or the body’s response to consumption of glucosamine and chondroitin sulfate.

In the absence of human data suggesting a reduced risk of OA/JD or CD from consumption of glucosamine and chondroitin sulfate, FDA has concluded that animal studies cited in the petition do not provide credible support for the proposed claims due to the differences in the physiology of humans and animals, the differences in the biomechanical forces in two legged humans versus four legged animals used in the studies cited in the petition, and the inability to determine whether the pathology of OA/JD and CD in animal models mimics the pathology of human OA/JD and CD. Further, FDA has concluded that *in vitro* studies of OA/JD and CD also do not provide credible support for the proposed claims because *in vitro* models cannot reproduce the physiological and biomechanical processes involved in the development of OA/JD and CD, nor can they reproduce the normal physiological responses to consumption of glucosamine and chondroitin sulfate.

The remaining studies cited in the petition were not primary reports<sup>51</sup> on the effects of glucosamine and chondroitin sulfate on the incidence of OA/JD and CD or changes in modifiable risk factors for OA/JD and were therefore only considered as background information for understanding scientific issues about the substance-disease relationship. These remaining studies include 7 bioavailability studies,<sup>52</sup> 24 studies on the pathology or etiology (including risk factors) of OA/JD and other forms of arthritis,<sup>53</sup> 1 study on estrogen replacement therapy,<sup>54</sup> 40 review articles,<sup>55</sup> 8 meta-analyses,<sup>56</sup> and 3 letters to the editor.<sup>57</sup>

#### D. Other Data and Information

The FAC met on June 7-8, 2004. The purpose of this meeting was to gather information and to receive advice and recommendations relating to the etiology of OA, its modifiable risk factors (if any), and the relevance of scientific studies cited in the petitions to substantiate the proposed risk reduction claims. FDA gave the FAC questions to answer, and the FAC, including all three of the rheumatologists recommended by the petitioners, reached the following consensus opinions:

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<sup>51</sup> See footnote 24.

<sup>52</sup> A bioavailability study measures how well a substance is absorbed and distributed throughout the body. A bioavailability study does not measure whether a substance reduces the incidence of disease or affects a surrogate endpoint.

<sup>53</sup> The pathology and etiology studies identify changes and factors that are associated with OA and the development of OA but do not measure the effects of glucosamine and chondroitin sulfate on the incidence of OA or changes in surrogate endpoints for OA.

<sup>54</sup> The study on estrogen replacement therapy is not relevant because estrogen replacement is not the subject of this petition.

<sup>55</sup> Review articles summarize the findings of primary reports. FDA uses review articles to identify relevant primary reports, which the Agency then evaluates. FDA also uses review articles to identify information that is useful to understand the scientific issues about the substance-disease relationship (i.e., background information).

<sup>56</sup> A meta-analysis is the process of systematically combining and evaluating the results of clinical trials that have been completed or terminated (i.e., primary reports) (Spilker, 1991, p. 793). FDA uses meta-analysis to identify relevant primary reports, which the Agency then evaluates.

<sup>57</sup> Letters to the editor focus on a particular issue or issues from a study, presentation at a meeting, etc. Letters to the editor do not present the detailed results, execution, design, or other features of a study. FDA uses letters to the editor to identify relevant primary reports, which the Agency then evaluates. FDA also uses letters to the editor to identify information that is useful to understand the scientific issues about the substance-disease relationship (i.e., background information).

Question #1

a) Is joint degeneration a state of health leading to disease, i.e., a modifiable risk factor/surrogate endpoint (as discussed above [in the background section of the questions document<sup>58</sup>]) for OA risk reduction? What are the strengths and limitations of the scientific evidence on this issue?

Answer: Joint degeneration is not a modifiable risk factor for OA (FAC Transcript, June 8, pp. 134-135).

b) Is cartilage deterioration a state of health leading to disease, i.e., a modifiable risk factor/surrogate endpoint (as discussed above) for OA risk reduction? What are the strengths and limitations of the scientific evidence on this issue?

Answer: Cartilage deterioration “is and could be used as” a modifiable risk factor for OA. Although it is possible to define a non-affected population, currently there are not enough data to distinguish people who are subject to OA from those who are not (FAC Transcript, June 8, pp. 134-135).

Question #2

a) If we assume that joint degeneration is a modifiable risk factor/surrogate endpoint for OA risk reduction and we assume that research demonstrates that a dietary substance treats, mitigates or slows joint degeneration in patients diagnosed with OA, is it scientifically valid to use such research to suggest a reduced risk of OA in the general healthy population (i.e., individuals without OA) from consumption of the dietary substance?

b) If we assume that cartilage deterioration is a modifiable risk factor/surrogate endpoint for OA risk reduction and we assume that research demonstrates that a dietary substance treats, mitigates or slows cartilage deterioration in patients diagnosed with OA, is it scientifically valid to use such research to suggest a reduced risk of OA in the general healthy population (i.e., individuals without OA) from consumption of the dietary substance?

Answer to a) and b): The data do not support the idea of using information gathered in experiments on OA patients to interpolate the effect of glucosamine and

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<sup>58</sup> The background section of the FAC questions document ([http://www.fda.gov/ohrms/dockets/ac/04/briefing/4045b1\\_06\\_a\\_Questions%20Revised.pdf](http://www.fda.gov/ohrms/dockets/ac/04/briefing/4045b1_06_a_Questions%20Revised.pdf)) stated that FDA also refers to modifiable risk factors/surrogate endpoints for disease as “biomarkers” and further explained, in part, that a biomarker is “a measurement of a variable related to a disease that may serve as an indicator or predictor of that disease. Biomarkers are parameters from which the presence or risk of a disease can be inferred, rather than being a measure of the disease itself. In conducting a health claim review, FDA does not rely on a change in a biomarker as a measurement of the effect of a dietary factor on a disease unless there is evidence that altering the parameter can affect the risk of developing that disease or health-related condition.” See also section I.B.1.

chondroitin sulfate in a healthy population of individuals without OA (FAC Transcript, June 8, p. 135).

Question # 3

If human data are absent, can the results from animal and *in vitro* models of OA be used to demonstrate risk reduction of OA in humans?

a) To the extent that animal or *in vitro* models of OA may be useful, what animal models, types of evidence, and endpoints should be used to assess risk reduction of OA in humans?

b) If limited human data are available, what data should be based on human studies and what data could be based on animal and *in vitro* studies to determine whether the overall data are useful in assessing a reduced risk of OA in humans?

Answer to a) and b): In general, animal studies and *in vitro* studies cannot replace human studies. The value of animal studies is in hypothesis generation and in getting a better understanding of the mechanisms that might be involved in interaction between various materials and the processing of OA (FAC Transcript, June 8, p. 135).<sup>59</sup>

E. Comparison to Past Health Claim Petitions

In your December 3, 2003 letter to FDA Chief Counsel Daniel E. Troy, you argued that extrapolating treatment data to the risk reduction context is scientifically accepted and consistent with FDA's practice in reviewing past health claim petitions. You stated that the scientific evidence supporting qualified health claims for phosphatidylserine and reduced risk of dementia and for phosphatidylserine and reduced risk of cognitive dysfunction came from treatment studies in patients suffering from Alzheimer's,

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<sup>59</sup> Regarding the questions about animal and *in vitro* studies, the Glade FAC review asserts that “[s]everal members of the FAC repeatedly expressed concerns that the nature of these combined questions was inherently misleading in its attempt to preclude the requisite consideration of the totality of the available evidence when assessing the potential of a dietary substance to exhibit disease risk reduction potential.” This assessment of the FAC members’ comments is clearly wrong. Nowhere in the FAC Transcript did any member state that the questions about the animal and *in vitro* studies were “misleading.” You cite comments from Dr. Krinsky (FAC Transcript, June 8, p. 128, lines 5-6) and Dr. Miller (FAC Transcript, June 8, p. 133, lines 16-22) to support your assertions. However, taken in the context of his other remarks, Dr. Krinsky’s comment was in agreement with the general consensus that although animal and *in vitro* studies contribute to the totality of the evidence, they cannot replace human clinical studies (see FAC Transcript, June 8, p. 128, lines 3-17). Similarly, Dr. Miller’s statement (which, incidentally, was intended to summarize the consensus of the FAC as a whole) drew the same conclusion that animal and *in vitro* studies are useful “in a supportive sense” but that “the basic credibility of the relationship must be based on human studies” (FAC Transcript, June 8, p. 133, lines 16-20). FDA agrees that animal and *in vitro* studies can provide useful information, e.g. with regard to the safety of a substance and its potential mechanism of action, but in the case of OA, animal and *in vitro* studies cannot replace human clinical studies for evaluating a possible risk reduction effect.

dementia, and senility. Although FDA characterized the studies submitted with your petition as mitigation studies in a diseased population (i.e., studies of whether phosphatidylserine could treat dementia or cognitive dysfunction by reducing their symptoms), the Agency erred in stating that all of the studies were mitigation studies. In fact, four studies were conducted in subjects without diagnosed dementia or cognitive dysfunction, aged 50 years or more, who were at risk of dementia beyond what occurs with the normal aging process.<sup>60</sup> Three of the four credible studies in this group demonstrated a significant benefit in reducing the risk of dementia and cognitive dysfunction with the intake of phosphatidylserine. FDA was also in error in concluding that mitigation studies in diseased populations alone constituted credible evidence to substantiate the proposed claims, when in fact, for mitigation studies to be considered relevant, additional evidence from non-diseased populations is needed to demonstrate that the mechanisms for the mitigation effects measured in the diseased populations are the same as the mechanisms for risk reduction effects in non-diseased populations. In the case of phosphatidylserine, because there were studies conducted in non-diseased populations, there was some credible evidence for a substance-disease relationship. In the near future, FDA intends to issue a letter correcting its analysis of the scientific evidence for the qualified health claims for phosphatidylserine and reduced risk of dementia and for phosphatidylserine and reduced risk of cognitive dysfunction.

Your December 3, 2003 letter also asserted that a "centerpiece" of FDA's argument to the district court in support of the Agency's denial of the antioxidant vitamin/cancer health claim petition was that there were no studies documenting that antioxidants interfered with cancer progression in diseased populations studied. This characterization of FDA's position is incorrect. In fact, the populations studied in the antioxidant intervention studies did not have cancer (i.e., no identifiable malignant mass), but instead were considered to be at high risk for developing cancer, e.g. because they smoked or had a non-cancerous lesion from which cancer is known to develop, such as a colon polyp. Furthermore, the data considered as part of the health claim petition for antioxidant vitamins and reduced risk of cancer included observational studies that measured the incidence of various cancers as a function of antioxidant vitamin consumption as well as antioxidant vitamin intervention studies that measured as the endpoint either cancer incidence or a valid modifiable risk factor for cancer. In contrast, your petition for claims about glucosamine and chondroitin sulfate and reduced risk of OA/JD and CD does not include observational studies that showed reduced incidence of OA/JD or CD with consumption of glucosamine or chondroitin sulfate, nor does it include intervention studies of glucosamine or chondroitin sulfate showing either reduced incidence of OA/JD or CD or a beneficial effect on a modifiable risk factor for any of these conditions. Thus, in the phosphatidylserine and dementia/cognitive dysfunction claim and the antioxidant vitamin and cancer claim, evidence for substantiation of the claims was provided, in whole or in part, from populations that did not have the diseases that were the subject of the claims, but rather were healthy or at-risk populations. Moreover, to

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<sup>60</sup> Crook et al., 1991; Jorissen et al., 2001; Palmeri et al., 1987; Villardita et al., 1987.

date, every other health claim for which FDA has issued an authorizing regulation or an enforcement discretion letter was based in whole or in part on evidence from studies conducted in healthy or high risk human populations demonstrating that a substance reduced the incidence of a disease and/or produced beneficial changes in a modifiable risk factor for a disease. This is not the case with the evidence for your proposed claims.

The Rotta Pharmaceuticals petition asserts that studies in OA/JD patients are relevant because FDA has previously recognized that it is appropriate to consider clinical studies involving diseased populations, specifically the data supporting the cardiovascular benefits of omega-3 fatty acids in patients with a prior history of cardiovascular disease (CHD patients). However, in the 2000 enforcement discretion letter for the omega-3 fatty acids and CHD claim<sup>61</sup>, FDA concluded that the intervention studies in diseased populations could not be used by themselves as evidence for an effect in the general population, but that there was sufficient suggestive evidence that the benefit reported in CHD patients (i.e., secondary risk reduction) could be extrapolated to the general population because of (1) the primary CHD risk reduction in the general population associated with EPA and DHA consumption from fish in observational studies, and (2) intervention studies demonstrating similar physiological effects of EPA and DHA in both the diseased and general populations. Unlike the evidence considered in the 2000 omega-3 fatty acids and CHD review, the current petition cites neither observational studies showing evidence of primary risk reduction in the general population with consumption of glucosamine or chondroitin sulfate nor any intervention studies demonstrating similar physiological effects of glucosamine or chondroitin sulfate in both the diseased and general populations.

#### F. Strength of the Scientific Evidence

FDA considered the totality of the publicly available evidence and determined that there is no credible evidence to support the proposed claims. There were no intervention studies that could demonstrate a reduced incidence of OA/JD or CD because the subjects in all but two of the cited studies already had OA/JD and CD at the beginning of the study,<sup>62</sup> and the remaining two studies measured endpoints that are not risk factors for OA/JD or CD. Further, all 11 of the human intervention studies measuring CD<sup>63</sup> were conducted in OA/JD patients with CD and therefore are not relevant to establishing OA/JD or CD risk reduction in the general healthy population (FAC Transcript, June 7, p. 173). In addition, the validity of the radiographic and biochemical markers for CD used in these studies has not been established, and experts in the field consider these markers scientifically unreliable (FAC Transcript, June 7, pp. 177, 234-239). There were no observational studies in the general population on glucosamine or chondroitin sulfate and OA/JD incidence, CD incidence, or changes in CD, the modifiable risk factor for OA/JD.

<sup>61</sup> <http://www.cfsan.fda.gov/~dms/ds-ltr11.html>

<sup>62</sup> As discussed in section I.B.4, OA/JD is always accompanied by CD (FAC Transcript, June 8, p. 53; Felson, et al., 2000; Buckwalter, et al., 2000).

<sup>63</sup> See footnote 32.

Two case reports submitted with your December 2, 2003 letter to FDA did not support your proposed claims because they concerned treatment of OA/JD and CD or treatment of an articular impaction injury to a joint. Further, studies of animal and *in vitro* models of OA/JD and CD, such as those cited in the petition, cannot be used to substantiate OA/JD and CD risk reduction in the absence of human data.

In summary, there are no intervention studies in healthy populations or observational studies reporting reduced OA/JD or CD incidence with consumption of glucosamine or chondroitin sulfate, and the glucosamine and chondroitin sulfate human intervention studies in OA/JD patients are not relevant to predicting OA/JD and CD risk reduction in people who do not have these conditions (FAC Transcript, June 8, p. 135). In the absence of human data, animal and *in vitro* studies are not sufficient to predict OA/JD and CD risk reduction in humans (FAC Transcript, June 8, p. 135). Finally, review articles, letters to the editor, meta-analyses, bioavailability studies, and studies identifying OA/JD risk factors are background information that cannot establish a substance-disease relationship without credible evidence from primary reports. Therefore, FDA has concluded that there is no credible scientific evidence supporting the proposed claims.

#### G. Agency's Consideration of Disclaimers or Qualifying Language

We considered but rejected use of a disclaimer or qualifying language to accompany the proposed claims. We concluded that neither a disclaimer nor qualifying language would suffice to prevent consumer deception here, where there is no credible evidence to support any of the claims. Adding a disclaimer or incorporating qualifying language that effectively characterizes the claim as baseless is not a viable regulatory alternative because neither the disclaimer nor the qualifying language can rectify the false message conveyed by the unsubstantiated claim. *See, e.g., In re Warner-Lambert Co.*, 86 F.T.C. 1398, 1414 (1975), *aff'd*, 562 F.2d 749 (D.C. Cir. 1977) (pro forma statements of no absolute prevention followed by promises of fewer colds did not cure or correct the false message that Listerine will prevent colds); *Novartis Consumer Health, Inc. v. Johnson & Johnson-Merck Consumer Pharms. Co.*, 290 F.3d 578, 598 (3d Cir. 2002) ("We do not believe that a disclaimer can rectify a product name that necessarily conveys a false message to the consumer."). In such a situation, adding a disclaimer or qualifying language does not provide additional information to help consumer understanding but merely contradicts the claim. *Resort Car Rental System, Inc. v. FTC*, 518 F.2d 962, 964 (9th Cir.) (per curiam) (upholding FTC order to excise "Dollar a Day" trade name as deceptive because "by its nature [it] has decisive connotation for which qualifying language would result in contradiction in terms."), *cert denied*, 423 U.S. 827 (1975); *Continental Wax Corp. v. FTC*, 330 F.2d 475, 480 (2d Cir. 1964) (same); *Pasadena Research Labs v. United States*, 169 F.2d 375 (9th Cir. 1948) (discussing "self-contradictory labels"). In the FDA context, courts have repeatedly found such disclaimers ineffective. *See, e.g., United States v. Millpax, Inc.*, 313 F.2d 152, 154 & n.1 (7th Cir. 1963) (disclaimer stating that "no claim is made that the product cures anything, either by the writer or the manufacturer" was ineffective where testimonials in a

magazine article promoted the product as a cancer cure); *United States v. Kasz Enters., Inc.*, 855 F. Supp. 534, 543 (D.R.I.) ("The intent and effect of the FDCA in protecting consumers from . . . claims that have not been supported by competent scientific proof cannot be circumvented by linguistic game-playing."), *judgment amended on other grounds*, 862 F. Supp. 717 (1994).

In the context of a claim that glucosamine and/or chondroitin sulfate may reduce the risk of OA, a qualifying statement to the effect that although there is some evidence that glucosamine and/or chondroitin sulfate treat or mitigate OA, evidence that glucosamine and/or chondroitin sulfate may reduce the risk of OA is entirely lacking, would inevitably convey a treatment or mitigation claim. Such a claim is a drug claim rather than a health claim, see *Whitaker v. Thompson*, 353 F.3d 947 (D.C. Cir. 2004), and could not itself be disclaimed. See, e.g., *United States v. Undetermined Quantities . . . "Exachol,"* 716 F. Supp. 787, 791 (S.D.N.Y. 1989) ("An article intended to be used as a drug will be regulated as a drug . . . even if the product's labelling [sic] states that it is not a drug."); *United States v. Storage Spaces Designated Nos. 8 and 49*, 777 F.2d 1363, 1366 n. 5 (9th Cir. 1985) ) (products promoted in manner suggesting they were synthetic cocaine substitutes were drugs despite labeling stating that products were "incense" and "not for drug use"); *United States v. 3 Cartons . . . "No. 26 Formula GM,"* 132 F. Supp. 569, 574 (S.D. Cal 1952) ("Where a person has set in motion forces that result in creating an impression that an article has value in the treatment of disease, he cannot avoid the legal consequences of such action by a disclaimer in the labeling asserting there is no scientific evidence that the article has therapeutic value.").

### III. Conclusions

Based on FDA's consideration of the scientific evidence submitted with your petition and other pertinent scientific evidence, FDA concludes that there is no credible evidence to support qualified health claims for glucosamine or chondroitin sulfate and reduced risk of OA, JD or CD. Thus, FDA is denying your petition for qualified claims based on the following proposed health claims:

1. Glucosamine may reduce the risk of osteoarthritis.
2. Chondroitin sulfate may reduce the risk of osteoarthritis.
3. Glucosamine and chondroitin sulfate may reduce the risk of osteoarthritis.
4. Glucosamine may reduce the risk of joint degeneration.
5. Chondroitin sulfate may reduce the risk of joint degeneration.
6. Glucosamine and chondroitin sulfate may reduce the risk of joint degeneration.
7. Glucosamine may reduce the risk of cartilage deterioration.
8. Chondroitin sulfate may reduce the risk of cartilage deterioration.
9. Glucosamine and chondroitin sulfate may reduce the risk of cartilage deterioration.

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Please note that scientific information is subject to change. FDA intends to evaluate new information that becomes available to determine whether it necessitates a change in this decision. For example, scientific evidence may become available that will support the use of a qualified health claim or that will support significant scientific agreement.

Sincerely,

A handwritten signature in black ink, appearing to read "W. Hubbard", written over a horizontal line.

William K. Hubbard

Associate Commissioner for Policy and Planning