Food

Letter Regarding 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(Docket No. 2004P-0059)

October 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.
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)[(1)], 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.

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[(2)] 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) [(3)]. 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[(4)] 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 temporary voting members or expert voting consultants[(5)] 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**

   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.[(6)]

   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[(7)] of subchondral bone and outgrowths of marginal osteophytes[(8)].

   The American College of Rheumatology (ACR)[(9)] and the OAI[(10)] 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).[(11)] 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.[(12)] 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)**

   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)[(13)], 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[(14)]. 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)[(15)] 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 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[(16)] and/or catabolism or radiographic changes of cartilage,[(17)] 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).

A. Assessment of the Intervention Studies

For its review of the proposed claims, FDA evaluated 18 intervention studies on glucosamine[(18)]; 20 intervention studies on chondroitin sulfate[(19)]; 5 intervention studies on glucosamine plus chondroitin sulfate[(20)]; 2 intervention studies on galactosaminoglucuronoglycan sulfate (GAGGS)[(21)]; 1 intervention study on glycosamine-glucuron-glycan-sulfate (GGGS)[(22)]; and 1 intervention study on galactosaminoglycuronglycan (GAG).[(23)] 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[(24)] 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 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.[(25)] 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.[(26)] 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[(27)] measured OA/JD symptoms (e.g., joint pain, swelling, mobility) rather than OA/JD incidence or changes in the OA/JD modifiable risk factor of CD; 2) 1 study[(28)] 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[29]; 3) 3 studies[30] were on substances other than glucosamine and chondroitin sulfate; 4) in 3 studies[31] 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 a 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 populatior 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).

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

   FDA considered 11 intervention trials[32] 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**

   1. 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).

   2. 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[33] anc 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 earl OA/JD chondrocyte is different from an established OA/JD chondrocyte (FAC Transcript, June 7, p. 130). For example, norma chondrocytes, hypertrophic chondrocytes[34] and diseased chondrocytes have very different gene expression profiles[35] 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 proteoglycar (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),[36] 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).[37] 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 glucosamin 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),[38] then the evidence indicates that glucosamine and chondroitin sulfat 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.