



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

OCT 7 2004

Martin J. Hahn
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555 13th Street NW
Washington, DC 20015

Re: Health claim petition that crystalline glucosamine sulfate reduces the risk of osteoarthritis joint deterioration and related joint pain and limitation of function (Docket No. 2004P-0060)

Dear Mr. Hahn:

This letter responds to the health claim petition dated September 17, 2003, submitted to the Food and Drug Administration (FDA or the Agency), on behalf of Rotta Pharmaceuticals, Inc., 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 a health claim characterizing the relationship between the consumption of crystalline glucosamine sulfate and a reduced risk of osteoarthritis. However, the petition stated that, in the event that the agency disagrees that there is significant scientific agreement in support of the proposed health claim, the petitioner would be willing to have the claim reviewed under the agency's "Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements" (July 10, 2003)¹. This petition proposed as a model health claim for dietary supplements:

Daily dietary supplementation with crystalline glucosamine sulfate reduces the risk of osteoarthritis joint structure deterioration and related joint pain and limitation of function.

The original due date for FDA to file or deny the petition was January 1, 2004. By mutual agreement, the due date was extended to February 2, 2004, and then to February 20, 2004.

In early February 2004, FDA contacted you about the language of your proposed claim, which referred to characteristic signs or symptoms of the disease of osteoarthritis, i.e., joint structure deterioration, related joint pain, and limitation of function. In FDA's view, the inclusion of the term "related" in reference to joint pain and limitation of function further indicated that the proposed claim described signs or symptoms of osteoarthritis in

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

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people who already have that disease. Thus, even though the claim used the phrase "reduces the risk of," the language of the claim indicated that it was aimed at people who have osteoarthritis and who are experiencing and need relief from its symptoms. A claim to relieve symptoms of a disease is a drug claim within the meaning of section 201(g)(1)(B) of the Act, because to relieve symptoms of the disease is to treat or mitigate the disease, and such a claim does not fall within the scope of the health claims provisions in section 403(r) of the Act. Thus, FDA suggested a change in the language of your proposed claim. As stated in a letter to FDA dated February 12, 2004, you agreed to amend the proposed claim language to "Dietary supplementation of crystalline glucosamine sulfate (glucosamine sulfate sodium chloride-USP/NF 2003) reduces the risk of osteoarthritis."

FDA filed the petition on February 13, 2004. To obtain expert advice on the scientific issues raised by your petition and another health claim petition for glucosamine and chondroitin sulfate and reduced risk of osteoarthritis, joint degeneration and cartilage deterioration from Weider Nutrition International, Inc., FDA held a meeting of the Food Advisory Committee and its Dietary Supplements Subcommittee (collectively, "FAC") on June 7 and 8, 2004. By mutual agreement with you and counsel for Weider Nutrition International, Inc., FDA agreed to issue a decision on your claims 60 days following the FAC meeting, i.e., by August 6, 2004. By mutual agreement, the decision date for this petition was extended to September 10, 2004 and then to October 7, 2004.

This letter sets out the basis for FDA's determination that there is no credible scientific evidence to support the proposed health claim, either as an unqualified or as a qualified health claim. In brief, the available scientific evidence pertaining to the proposed claim is limited to studies of glucosamine as a treatment for osteoarthritis, or for conditions associated with existing osteoarthritis, such as joint pain and swelling. As experts on the FAC 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. Thus, the agency is denying this petition for a health claim with respect to consumption of crystalline glucosamine sulfate and a reduced risk of osteoarthritis (OA).

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

The petition cited 58 publications as evidence to support the proposed claim (see attached bibliography). These publications consisted of 25 intervention studies (24 on glucosamine and 1 on chondroitin sulfate), 1 bioavailability study, 2 studies on the pathology or etiology (including risk factors) of OA and other forms of arthritis, 1 animal study, 8 *in vitro/in situ* studies, 12 review articles, 2 meta-analyses, 3 letters to the editor or commentaries, 3 studies on safety, and 1 manufacturer's monograph. FDA's review of the data and information cited in the petition is discussed below in section II.

In addition to the information in the petition, FDA considered the ongoing National Institutes of Health (NIH) Osteoarthritis Initiative (OAI).² 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 meeting³ 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 consultants⁴ because of their expertise in rheumatology, including three experts recommended by the petitioners (i.e., 3 of the 6 experts added).

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 crystalline glucosamine sulfate as the substance that is the subject of the proposed claim. Glucosamine is purified from the exoskeletons of marine animals used for food (e.g., crab, lobster and shrimp). Accordingly, the Agency concludes that crystalline glucosamine sulfate is a component of food and therefore meets 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 as the disease or health-related condition that is the subject of the proposed claim.

² 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/>)

³ See <http://www.fda.gov/ohrms/dockets/ac/cfsan04.html> for FAC transcripts and other meeting information.

⁴ 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.

1. Osteoarthritis

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 eburnation⁵ of subchondral bone and outgrowths of marginal osteophytes⁶.

Notably, although OA is always accompanied by cartilage deterioration (CD) (FAC Transcript, June 8, p. 53; Felson, et al., 2000; Buckwalter, et al., 2000), an individual can have CD without developing OA; for example, CD can occur with normal aging of joints (FAC Transcript, June 7, pp. 85-86).

The American College of Rheumatology (ACR)⁷ and the OAI at the National Institutes of Health (NIH) 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.

The Agency concludes that OA is a disease 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

⁵ 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).

⁶ An osteophyte is a bony outgrowth or protuberance (Stedman's Medical Dictionary).

⁷ <http://www.rheumatology.org/public/factsheets/oa.asp?aud=pat>

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 the safety of glucosamine is evidenced by clinical trial data showing a low rate of adverse events; by its physical properties, chemical structure, and metabolic fate; and by experience based on widespread use as a dietary supplement in the United States and as a prescription drug in more than 40 countries of the world. According to the petition, the scientific community agrees that glucosamine supplementation presents no significant or unreasonable risk of illness or injury. The petition states that the mechanism of action (through inhibition of catabolic enzymes) of glucosamine does not account for any particular toxicity pattern of crystalline glucosamine sulfate. The petition states that there is a low potential for drug interactions and that adverse events that are attributed to glucosamine are generally mild and transient, and often relate to gastrointestinal concerns. The petition also states that clinical studies have failed to report any findings establishing a concern with administering crystalline glucosamine sulfate to diabetics, although data are relatively scarce. Furthermore, the petition states that the safety of glucosamine is supported by its extensive history of use in the U.S., where it is one of the most widely marketed dietary supplements, and in other countries where it has been available as a prescription drug for more than two decades. According to the petition, pharmacovigilance monitoring systems in Europe and elsewhere have not identified any safety issues with glucosamine. The petition considers 1500 mg/day glucosamine sulfate, which corresponds to 1884 mg of crystalline glucosamine sulfate, an optimal level of intake beyond which the health benefits have not been clinically demonstrated.

The petition concerns the consumption of crystalline glucosamine sulfate as a dietary supplement. There is no dietary reference intake (DRI) for glucosamine. There are two ongoing NIH clinical trials using glucosamine. One is the Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT)⁸, which is studying the effectiveness of glucosamine sulfate (and chondroitin sulfate) to improve pain and knee function in patients with OA, and the other is studying the absorption and distribution of glucosamine sulfate (and chondroitin sulfate)⁹. Both trials use the same dosage of 1500 mg glucosamine sulfate per day either alone or in combination with 1200 mg chondroitin sulfate. 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/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).

⁸ <http://www.clinicaltrials.gov/show/NCT00032890>

⁹ <http://clinicaltrials.gov/show/NCT00086229>

Furthermore, glucosamine was nominated to the National Toxicology Program (NTP)¹⁰ for toxicological studies because of widespread long-term use as a dietary supplement and inadequate data to assess safety. The NTP study is under preparation.

Although the information about glucosamine 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 this substance 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 claim for lack of credible evidence, as discussed in section II below.

II. The Agency's Consideration of a Health Claim

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.

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.¹¹

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

¹⁰ <http://ntp-server.niehs.nih.gov/NomPage/2003Noms.html>

¹¹ 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>

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).

At FDA's request, the FAC considered whether joint degeneration (JD) and CD are modifiable risk factors for OA. The experts at the FAC meeting reached a consensus that JD is not a modifiable risk factor for OA because it is too nonspecific (FAC Transcript, June 8, pp. 53-54, 134). During the deliberations, a rheumatologist on the FAC characterized the term as a "poor choice of words" because it is "too global, too vague." Regarding joint degeneration's association with OA, this 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). The 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). FDA agrees with the experts of the FAC that JD is not a modifiable risk factor for OA..

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.

To consider measures of CD, such as biochemical indices of cartilage metabolism and/or catabolism¹² or radiographic changes of cartilage,¹³ 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.3 below).

¹² In human intervention studies cited by the petitioner, synovial fluid biochemical measures of cartilage metabolism and/or catabolism included N-acetylglucosaminidase (NAG), sulfated glycosaminoglycans (SGAG) and hyaluronic acid (HA).

¹³ 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

FDA considers human studies that are primary reports¹⁴ 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.

All 25 of the intervention trials¹⁵ cited in the petition 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 do not and cannot supply any direct evidence of reduced OA incidence. FDA also considered whether studies in OA patients that observed changes in CD¹⁶, a modifiable risk factor for OA, 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 patients with OA as the subjects, even those with "mild OA," to risk reduction in individuals without OA (FAC Transcript, June 8, p. 135; see section II.A.1 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 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.¹⁷ The fact that a product treats, mitigates, or cures a disease does not necessarily mean that it will reduce the risk of the disease.

Some of the 25 intervention studies were not relevant to your proposed claims or could not be evaluated for other reasons, including the following: 1) 14 studies¹⁸ measured OA symptoms (e.g., joint pain, swelling, mobility) rather than OA incidence or changes in the OA modifiable risk factor of CD; 2) 3 studies¹⁹ were submitted as abstracts, which do not

¹⁴ 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.

¹⁵ Bruyere et al., 2002; Bruyere et al., 2003; Conte et al., 1995; Crolle and D'Este, 1980; D'Ambrosio et al., 1981; Das, Jr. and Hammad, 2000; Drovanti et al., 1980; Foerster et al., 2000; Houpt et al., 1999; Hughes and Carr, 2002; Leffler et al., 1999; Muller-Fassbender et al., 1994; Noack et al., 1994; Pavelka et al., 2002a; Pujalte et al., 1980; Qiu et al., 1998; Reginster et al., 2001; Reichelt et al., 1994; Rindone et al., 2000; Rovati, 1997; Tapadinhas et al., 1982; Thie et al., 2001; Vajjaradul, 1981; Vas, 1982.

¹⁶ Conte et al., 1995; Pavelka et al., 2002; Reginster et al., 2001.

¹⁷ Ibuprofen is an NSAID, which is 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).

¹⁸ Crolle and D'Este, 1980; D'Ambrosio et al., 1981; Das, Jr. and Hammad, 2000; Drovanti et al., 1980; Houpt et al., 1999; Leffler et al., 1999; Muller-Fassbender et al., 1994; Noack et al., 1994; Pujalte et al., 1980; Qiu et al., 1998; Rindone et al., 2000; Tapadinhas et al., 1982; Thie et al., 2001; Vas, 1982

¹⁹ Foerster et al., 2000; Pavelka et al., 2002b; Rovati, 1997.

provide enough information for FDA to determine the relevance of the studies based on factors such as the study population characteristics or the composition of the products (e.g., foods, dietary supplements) used in the studies²⁰; 3) 1 study²¹ was on a substance other than glucosamine sulfate; 4) in 4 studies²² 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 sulfate 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 sulfate as a dietary supplement.

1. Results from Patients with OA Cannot be Extrapolated to Predicting Reduced Risk of OA in the General Healthy Population

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

There are differences in the risk factors associated with healthy individuals developing OA versus the risk factors associated with the worsening of existing OA (i.e., OA 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 will also reduce the risk of OA (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 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 patients and measures effects of glucosamine on changes associated with OA worsening (i.e., progression). This treatment evidence is not relevant to predicting the effects of glucosamine on developing OA in healthy individuals (i.e., OA risk reduction) (FAC Transcript, June 8, p. 135).

²⁰ 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.

²¹ Conte, et al., 1995

²² Crolle and D'Este, 1980; D'Ambrosio et al., 1981; Reichelt, et al., 1994; Vajradul, 1981

b. Cells from patients with OA are not the same as cells from healthy individuals

Although it is difficult to pinpoint exactly when pre-OA ends and clinical OA begins, osteoarthritic chondrocytes²³ and tissues (cartilage) are different than non-OA 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 chondrocyte are different, and an early OA chondrocyte is different from an established OA chondrocyte (FAC Transcript, June 7, p. 130). For example, normal chondrocytes, hypertrophic chondrocytes²⁴ and diseased chondrocytes have very different gene expression profiles²⁵ relative to each other (FAC Transcript, June 7, p. 130). Moreover, there are functional differences between normal chondrocytes and OA 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 is 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 stimulate normal chondrocytes to make normal proteoglycan that functions normally (FAC Transcript, June 7, pp. 124-125),²⁶ which would be necessary to reduce OA risk.

In addition, some cellular processes reportedly affected by glucosamine in OA chondrocytes are controlled differently in OA 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 involves inflamed catabolic chondrocytes brought about through activation of pathways such as NF-kappa B that are mediated by cytokines (e.g., IL-1).²⁷ This activity in turn increases catabolic inflammatory processes and production of enzymes such as metalloproteinase. Studies of glucosamine suggest that it 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

²³ 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).

²⁴ A hypertrophic chondrocyte is an enlarged chondrocyte that may be in the early stages of disease.

²⁵ 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.

²⁶ 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).

²⁷ 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).

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 in OA is through blocking the activation of cytokine pathways (as suggested in the petitions and FAC meeting; FAC Transcript, June 7, pp. 101, 186), then the 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 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 chondrocytes in the context of disease treatment or mitigation are relevant to reduction of risk in non-OA 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 OA 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 patients with unilateral knee OA,²⁸ where patients have been diagnosed with OA in one knee, was evidence that glucosamine and chondroitin sulfate reduced the risk of OA 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 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,²⁹ which is a fairly late structural finding of OA (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 (FAC Transcript, June 7, pp. 180-181). Thus, in patients diagnosed with unilateral knee OA, the evidence so far indicates that the contralateral knee also has OA and therefore is not a “healthy” knee. The evidence indicates that knee OA is a bilateral and often systemic process, and that the presence of clinical disease in

²⁸ Reginster et al., 2001 and Pavelka et al., 2002.

²⁹ Radiographic disease means that evidence of OA can be detected on X-rays, which is a diagnostic criterion for OA (see section I.B.1).

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 who supplement their diet with glucosamine are not a sufficient surrogate for a risk reduction effect from such supplementation in the general healthy population without OA (FAC Transcript, June 8, p. 89). Indeed, your own expert, Dr. Lucio Rovati, recognized that "[t]here is no study of [OA] prevention" with glucosamine (FAC Transcript, June 7, p. 173).

2. 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. Thus, there is no evidence of reduced OA incidence. Moreover, the results of the treatment studies on CD in OA patients (3 studies³⁰) cannot be extrapolated to show reduction of OA 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.

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

FDA concludes that, in addition to not being relevant for reasons discussed above, 9 of the intervention studies are so flawed that credible scientific conclusions cannot be drawn from them for the following reasons: 1) 6 studies³¹ lacked a placebo or untreated control group or did not report a statistical analysis against the control group (Spilker, 1991, pp. 59-64); 2) 3 studies³² attempted to assess changes in CD in OA patients based on biochemical and radiographic evidence using unreliable methods for measuring CD (FAC Transcript, June 7, pp. 117, 231³³; June 8, p. 37). Relying on biochemical markers of cartilage metabolism collected in the synovium (a thin membrane lining the joint space), as was done in the cited study, is not reliable because these markers may reflect 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 methods³⁴ used in the cited studies are no longer used in clinical trials to

³⁰ See footnote 16.

³¹ Conte et al., 1995; Muller-Fassbender et al., 1994; Qiu et al., 1998; Tapadinhas et al., 1982; Thie et al., 2001; Vas, 1982

³² See footnote 16.

³³ The citations from the June 7 FAC transcript uses 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.

³⁴ 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

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 studies³⁵ are so flawed that they are not scientifically credible and could not be used to draw conclusions about OA risk reduction even if they had been conducted in the general healthy population rather than in people who already had OA.

B. Assessment of Observational Studies

The petition cited no observational studies³⁶ on glucosamine and OA incidence or changes in CD, the modifiable risk factor for OA.

C. Assessment of Other Information Submitted with the Petition

The 1 animal study and 8 *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 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” (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 study cited in the petition) walk on four. There is a biomechanical aspect of human OA 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 and CD is poorly understood, these differences make it impossible to measure how well any animal model of OA and CD mimics OA and CD in humans. Thus, because of the differences between animal and

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

³⁵ See footnote 16.

³⁶ An observational study records specific events that are occurring in a defined population without any intervention by the researcher (Spilker, 1991, p. 47).

human physiology and the lack of understanding of OA 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 is even more problematic with *in vitro* models of OA and CD. *In vitro* experiments are conducted in an artificial environment that cannot mimic human physiology, which may affect the development of OA and CD or the human body's response to consumption of glucosamine.

In the absence of human data suggesting a reduced risk of OA from consumption of glucosamine, FDA has concluded that animal studies cited in the petition do not provide credible support for the proposed claim 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 study cited in the petition, and the inability to determine whether the pathology of OA and CD in animal models correctly mimics the pathology of human OA and CD. Further, FDA has concluded that *in vitro* studies of OA and CD also do not provide credible support for the proposed claim because *in vitro* models cannot reproduce the physiological and biomechanical processes involved in the development of OA and CD, nor can they reproduce the normal physiological responses to consumption of glucosamine.

The remaining studies cited in the petition were not primary reports³⁷ on the effects of glucosamine on the incidence of OA or changes in modifiable risk factors for OA and were therefore only considered as background information for understanding scientific issues about the substance-disease relationship. These studies included 1 bioavailability study,³⁸ 2 studies on the pathology or etiology (including risk factors) of OA and other forms of arthritis,³⁹ 12 review articles,⁴⁰ 2 meta-analyses,⁴¹ 3 letters to the editor or commentaries,⁴² 3 studies on safety and 1 manufacturer's monograph.⁴³

³⁷ See footnote 14.

³⁸ 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.

³⁹ 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.

⁴⁰ 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).

⁴¹ 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.

⁴² Commentaries and letters to the editor focus on a particular issue or issues from a study, presentation at a meeting etc. Commentaries and letters to the editor do not present the detailed results, execution, design, or other features of a study. FDA uses commentaries and letters to the editor to identify relevant primary reports, which the Agency then evaluates. FDA also uses commentaries and letters to the editor to identify information that is useful to understand the scientific issues about the substance-disease relationship (i.e., background information).

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:

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 document⁴⁴]) 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

⁴³ Product monographs are prepared by the manufacturer to convey specific information about a product such as its specifications. FDA uses product monographs to identify information that is useful to understand the scientific issues about the substance-disease relationship (i.e., background information).

⁴⁴ The background section of the FAC questions document (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 the discussion of modifiable risk factors in the introduction to section II.

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 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).

E. Comparison to Past Health Claim Petitions

Your petition states that studies in OA 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 (<http://www.cfsan.fda.gov/~dms/ds-ltr11.html>)⁴⁵, 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

⁴⁵ <http://www.cfsan.fda.gov/~dms/ds-ltr11.html>

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 nor any intervention studies demonstrating similar physiological effects of glucosamine 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 claim. There were no intervention studies that could demonstrate a reduced incidence of OA because the subjects in the cited studies already had OA at the beginning of the study. Further, all three of the human intervention studies measuring CD⁴⁶ were conducted in OA patients and, therefore, are not relevant to establishing OA 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 sulfate and OA incidence or changes in CD, the modifiable risk factor for OA. Further, animal and *in vitro* models of OA and CD, such as those cited in the petition or presented at the FAC meeting, cannot be used to substantiate OA risk reduction in the absence of human data.

In summary, there are no intervention studies in healthy populations or observational studies reporting reduced OA incidence with consumption of glucosamine, and the glucosamine human intervention studies in OA patients are not relevant to predicting OA risk reduction in healthy individuals (FAC Transcript, June 8, p. 135). In the absence of human data, animal and *in vitro* studies are not sufficient to predict OA risk reduction in humans (FAC Transcript, June 8, p. 135). Review articles, commentaries, letters to the editor, meta-analyses, bioavailability studies, and studies identifying OA risk factors, though useful for understanding issues related to OA, 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 claim.

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

⁴⁶ See footnote 16.

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 may reduce the risk of OA, a qualifying statement to the effect that although there is some evidence that glucosamine treats or mitigates OA, evidence that glucosamine 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 labeling [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 either an unqualified or a qualified health claim for crystalline glucosamine sulfate and reduced risk of OA. Thus, FDA is denying your petition for the following proposed health claim:

Dietary supplementation of crystalline glucosamine sulfate (glucosamine sulfate sodium chloride-USP/NF 2003) reduces the risk of osteoarthritis.

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,



William K. Hubbard
Associate Commissioner for Policy and Planning

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