HEALTH CLAIM PETITION:

DIETARY SUPPLEMENTATION OF CRYSTALLINE GLUCOSAMINE SULFATE (GLUCOSAMINE SULFATE SODIUM CHLORIDE-USP/NF 2003) REDUCES THE RISK OF OSTEOARTHRITS JOINT STRUCTURE DETERIORATION AND RELATED JOINT PAIN AND LIMITATION OF FUNCTION

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September 17, 2003

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SUBJECT: Health Claim Petition: Dietary supplementation of Crystalline Glucosamine Sulfate (Glucosamine Sulfate Sodium Chloride-USP/NF 2003) reduces the risk of osteoarthritis joint deterioration and related joint pain and limitation of function.

I. INTRODUCTION

We submit this Petition on behalf of our client, Rotta Pharmaceuticals Inc. (hereinafter "Petitioner") pursuant to section 403 (r) (5) (D) of the Federal Food, Drug and Cosmetic Act (FFDCA) (21 U.S.C. § 343 (r) (5) (D)) and Food and Drug Administration (FDA) procedures for the review of "qualified health claims" described in Agency guidance for Industry and FDA (68 Fed. Reg. 41387 (July 11, 2003)). The Petitioner respectfully requests that FDA approve for use in the labeling of Crystalline Glucosamine Sulfate (Glucosamine Sulfate Sodium Chloride-USP/NF 2003) a health claim communicating that this substance can reduce the risk of osteoarthritis joint structure deterioration and related joint pain and limitation of function. All of the items specified in 21 C.F.R. § 101.70 (f) are included or attached to this Petition.

The proposed health claim responds to a major public health concern in the United States, osteoarthritis, the most common form of arthritis (1). Osteoarthritis is a serious and degenerative joint disease that generally is characterized by clinical evidence of both joint structural changes and joint pain (1). In the United States, symptomatic osteoarthritis in the knee is estimated to affect six percent of adults aged

30 years and over and symptomatic hip osteoarthritis is estimated to affect roughly three percent (2). Because the prevalence of osteoarthritis increases with age, it is expected that the disease will become even more prevalent as the population ages.

As will be explained more fully below, the Petitioner believes that the proposed health claim is supported by significant scientific agreement within the meaning of section 403(r)(3)(B) of the FFDCA. To the extent 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 agency review the proposed claim as a "qualified health claim," as described in agency guidance of July 11, 2003. In light of the extensive research to date addressing the relationship between crystalline glucosamine sulfate and osteoarthritis, the proposed claims are, at a minimum, "Category B" claims for which the scientific evidence may be described as supportive but not conclusive.

Rotta Pharmaceuticals Inc. is a fully owned subsidiary of the multinational Rotta Research/Rottapharm Group, which developed crystalline glucosamine sulfate for use in osteoarthritis and sponsored many of the clinical trials summarized in this Petition. An overwhelming majority of the published clinical trials evaluating the effect of glucosamine on osteoarthritis have been performed using Rotta Research/Rottapharm Group's source of crystalline glucosamine sulfate. These clinical trials represent the largest body of evidence supporting the use of glucosamine in the prevention of osteoarthritis.

There are limited clinical studies evaluating the effect of other sources of glucosamine on the prevention of osteoarthritis. Other sources of glucosamine do not

share the same quality, pharmacological, and pharmacokinetic properties of crystalline glucosamine sulfate. More importantly, these other sources of glucosamine have not been shown through clinical trials to have the same effect on osteoarthritis as crystalline glucosamine sulfate. Indeed, the scientific literature contains several statements cautioning against the generalization of data on crystalline glucosamine sulfate to support the efficacy of other sources of glucosamine. Simply stated, there are insufficient data to support the inclusion of other sources of glucosamine in the proposed health claim.

Based on our understanding of the agency guidelines on qualified health claims, we believe that there may be sufficient data to support the classification of other sources of crystalline glucosamine sulfate for a "category D" or possibly a "category C" qualified health claim. Because this Petition focuses on crystalline glucosamine sulfate, we do not provide an analysis of whether there are sufficient data to support a qualified health claim for other sources of glucosamine, and if so, whether there are sufficient data to justify placement in "category D" or perhaps "category C."

II. PRELIMINARY REQUIREMENTS

The proposed crystalline glucosamine sulfate/osteoarthritis health claim satisfies all applicable "Preliminary Requirements" under FDA rules, as set forth in 21 C.F.R. §§ 101.70(f) and 101.14(a)-(b). These regulations require that the subject of a health claim be a "substance," as defined in 21 C.F.R. § 101.14(a), the substance be associated with a disease or health-related condition of public health significance, the substance contribute taste, aroma, nutritive value, or certain other technical or functional effects specified by FDA, and the substance be demonstrated to be safe and lawful under the applicable food safety provisions of the Federal Food, Drug, and Cosmetic Act (FFDCA).

A. Crystalline Glucosamine Sulfate Qualifies as a "Substance"

Crystalline glucosamine sulfate is marketed as a dietary supplement and is subject to regulation as a "food" in accordance with section 201(f) of the FFDCA. "Substance" is defined in the FDA regulations as "a specific food or component of food, regardless of whether the food is in conventional food form or a dietary supplement that includes vitamins, minerals, herbs, or other similar nutritional substances" (21 C.F.R. § 101.14(a)). As a lawfully marketed dietary supplement, crystalline glucosamine sulfate falls within the definition of "substance."

B. Crystalline Glucosamine Sulfate is Associated with Osteoarthritis

Crystalline glucosamine sulfate is associated with osteoarthritis, a disease for which the general U.S. population and the elderly (an identified U.S. population subgroup) are at risk. Osteoarthritis is a degenerative joint disease that can potentially

affect all synovial joints (*i.e.,* joints containing a lubricating fluid that is secreted by membranes surrounding the joint). Osteoarthritis involves the degeneration of the articular cartilage, although there may be other contributing factors originating in different joint tissues such as the subchondral bone and the synovium. Surprisingly, the pathogenetic process (biomechanical, biochemical, or other) of this disease is still relatively unknown.

In healthy individuals, articular cartilage is maintained through a dynamic process that balances synthesis and degradation of the cartilage matrix. Degeneration of the articular cartilage is due to an imbalance in this system, which results in a generalized loss of cartilage. Remodelling of the subchondral bone also occurs, as well as mild inflammatory reactive changes in the synovial membrane. These pathological changes of the joint structure can be detected by imaging techniques such as plain radiography, where cartilage loss is usually seen as a decrease in joint space width (joint space narrowing) and by remodelling of the subchondral bone which is evidenced by the presence of osteophytes (bone spurs) and other signs. The degenerative process and the mild synovial inflammation cause joint pain, particularly when the joint is in use, and limit joint function. The scientific evidence in this Petition convincingly establishes that crystalline glucosamine sulfate, when given to individuals diagnosed with osteoarthritis, can prevent further joint degradation, can reverse the symptoms by minimizing the inflammation and restoring articular cartilage, can reduce joint pain and can result in increased joint function. Given the physiological mechanism of action of crystalline glucosamine sulfate and other factors, there also are sufficient data demonstrating the ability of crystalline glucosamine sulfate to be effective in reducing the risk of developing osteoarthritis.

Osteoarthritis is the most common form of arthritis and the most common reason for total hip and total knee replacement (1). Symptomatic disease in the knee is reported to occur in approximately six percent of U.S. adults 30 years of age or older; symptomatic hip osteoarthritis occurs in roughly three percent (2). Because the prevalence of osteoarthritis increases with age, the disease will become even more prevalent as the population ages. Indeed, results of community-based surveys have shown that the general incidence and prevalence of osteoarthritis increase 2- to 10- fold from age 30 to 65 years, with further increases thereafter (3).

Osteoarthritis of the knee is particularly common, with radiographic osteoarthritic changes of the tibiofemoral compartment reported to occur in five percent to 15 percent of people aged 35 to 74 years in the Western world (4). The impact on disability attributable to knee osteoarthritis is similar to that attributed to cardiovascular disease and greater than that caused by any other medical condition in the elderly (5).

C. Crystalline Glucosamine Sulfate Contributes Nutritive Values When Consumed at Levels that are Necessary to Justify the Claim

Crystalline glucosamine sulfate contributes "nutritive value" when consumed at levels necessary to justify the proposed claim and meets the requirement of 21 C.F.R. § 101.14 (b)(3)(i) for substances intended for consumption at other than decreased dietary levels. For purposes of health claims, FDA has defined "nutritive value" to mean "a value in sustaining human existence by such processes as promoting growth, replacing loss of essential nutrients, or providing energy" (21 C.F.R. § 101.14(a)(3)). Crystalline glucosamine sulfate provides nutritive value through its role in the synthesis

of new cartilage and maintenance (through inhibition of catabolic enzymes) of existing cartilage. These functions represent the basis for the clinical effects of crystalline glucosamine sulfate.

Cartilage consists of an extracellular matrix that contains proteoglycans, collagen, and water (6). The proteoglycans are a protein core that contains glycosaminoglycan side chains of varying lengths. Glucosamine is an aminomonosaccharide and is one of the building blocks for the glycosaminoglycans, which can be found in the articular cartilage matrix and synovial fluid. Following oral administration, glucosamine from crystalline glucosamine sulfate is bioavailable to the joint tissues (7) and is preferentially incorporated by the chondrocytes into the components of the glycosaminoglycan chains in the intact cartilage (8). Crystalline glucosamine sulfate stimulates the synthesis of proteoglycans and decreases the activity of catabolic enzymes (9, 10, 11). These activities have been recently related to glucosamine-induced reversal of the negative effects of interleukin-1-stimulated expression of enzymes involved in joint tissue destruction and inflammation, such as metalloproteases, inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2) (12, 13). This cytokine antagonism is achieved through an inhibitory effect of the interleukin-1 intracellular signalling cascade in chondrocytes, and in particular by the suppression of NF-KB activation (13).

The inorganic sulfates found in crystalline glucosamine sulfate are also believed to contribute to the physiological effects. Sulfates control the rate of synthesis of the glycosaminoglycans and proteoglycans that become a part of the cartilage matrix. The sulfate serum levels increase after glucosamine sulfate administration (14). The

importance of sulfate in the cartilage synthesis process provides further support for using a source of glucosamine that provides sulfates.

D. Crystalline Glucosamine Sulfate Use at the Levels Necessary to Justify the Claim is Safe and Lawful

Crystalline glucosamine sulfate is safe and lawful under the applicable food safety provisions of the FFDCA, as required by 21 C.F.R. § 101.14(b)(3)(ii). The FFDCA requires that dietary ingredients and dietary supplements not present a significant or unreasonable risk of injury under the conditions of use recommended or suggested in the product labelling, or if none, under the ordinary conditions of use (FFDCA § 402(f)). As discussed more fully in Section III.D below, the safety of glucosamine is evidenced by clinical trial data, by its physical properties, chemical structure, and metabolic fate, and through experience based on widespread use throughout the world.

III. SUMMARY OF SCIENTIFIC INFORMATION

This section of the Petition summarizes the publicly available randomized controlled clinical trials examining the use of all formulations of glucosamine in the prevention of osteoarthritis-related joint deterioration, joint pain, and limitation of function. We have divided these clinical studies into four separate categories: (1) systematic reviews and meta-analyses, (2) clinical studies conducted prior to 1994, which recognizably are not of the same quality as those published later, (3) clinical studies conducted after 1994, and (4) studies performed with glucosamine formulations other than crystalline glucosamine sulfate.

A. Systematic reviews and meta-analyses

Since 2000, there have been three publications involving major systematic reviews and meta-analyses examining the available literature on glucosamine (all sources) and osteoarthritis. We summarize the systematic reviews in the order of their publication. Please recognize that the first two reviews were conducted prior to the publication of long-term studies in the *Lancet* (2001) (15) and the *Archives of Internal Medicine* (2002) (16).

1. McAlindon T et al. JAMA 2000; 283 :1469-75 (Reference n. 17)

McAlindon et al. combined a meta-analysis with a systematic quality assessment to evaluate the benefit of glucosamine and, separately, chondroitin preparations in relation to osteoarthritis. The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) funded the analysis. The authors limited their search to placebo-controlled trials of at least four weeks duration that had been published prior to June 1999. The authors identified six glucosamine trials for their review (two of which

did not involve oral administration of glucosamine). Of the six trials reviewed, five involved crystalline glucosamine sulfate. The authors noted moderate treatment effect sizes for glucosamine on osteoarthritis symptoms and recognized that effect sizes were larger when treatment exceeded four weeks.

Although the authors concluded that the effects of glucosamine may be exaggerated, due to quality issues and likely publication bias, these findings must be interpreted with caution. The authors did indeed identify the presence of general quality issues for the trials reviewed, but the average quality scores they calculated for the glucosamine trials were similar to the standards reported for peer-reviewed medical journal articles and, admittedly, to that of other agents used in osteoarthritis. The authors also presented asymmetrical funnel plots (*i.e.,* plots of the trials' effect estimates against sample size) for the trials included in the analysis, which they concluded to be suggestive of publication bias, as explained by Egger et al. (18). The authors failed to note the Egger's group finding (18, 19), however, that funnel plot asymmetry is common (*i.e.,* 38 percent), in meta-analyses published in leading medical journals. (As will be discussed below, Cochrane Reviews tend to be more accurate.)

The Egger's group also acknowledged that asymmetry may frequently be due to factors other than bias, such as true heterogeneity (*i.e.,* true difference of effects between trials). True heterogeneity is very probable in osteoarthritis trials due to differences in patient selection, severity stages, and evaluation methods. Furthermore, the authors depicted a combined funnel plot analysis for glucosamine and chondroitin, but asymmetry seems to be much less pronounced for glucosamine. Finally, the authors admitted they were unable to find evidence of unpublished, negative studies, which

would support a finding of likely bias. The Petitioner also is unaware of any such unpublished studies for crystalline glucosamine sulfate.

Notwithstanding the above observations, the authors concluded that glucosamine indeed exhibited moderate to large effects on osteoarthritis symptoms and they noted that glucosamine had a good safety record.

2. **Towheed et al. Cochrane Library, Update Software, Oxford, England; 2001: issue 2 (Reference n. 20)**

Towheed et al. published a more accurate and detailed meta-analysis as a Cochrane Review in early 2001. Towheed covered a similar period as McAlindon (1966 to November 1999), but considered a total of 16 randomized controlled trials, including all placebo-controlled trials examined by McAlindon (17). In addition, the Towheed analysis included 4 clinical trials controlled with a reference medication. The inclusion of trials controlled with a reference medication is of particular importance because the standard pharmacological treatment for osteoarthritis symptoms consists of analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs). The trials in this review used NSAIDs as a reference treatment in the control group.

All trials were randomized and double-blinded, and included a large overall population of 2029 patients (992 assigned to glucosamine and 1037 to comparators). The trials were short-term studies for osteoarthritis symptoms, with a mean trial duration of 6.25 weeks. The oral route was used in the vast majority of trials, at a dose equivalent to 1500 mg/day glucosamine sulfate in most instances. Most trials examined the effects of treatment on the knee.

The authors' quality assessment of these studies, using validated methods, resulted in significantly different comments than those reported previously by McAlindon. Indeed, the authors of this review found that collectively, the glucosamine trials were as good, if not better, than NSAID trials in treating osteoarthritis. The authors assigned the glucosamine trials with a total median quality score of 9 (out of a possible 16). Importantly, there was a strong trend for improvement in quality for more recent trials, with those published in the 1990s having a median scored of 12 while those published in the 1980s had a median score of 7.5.

The authors used Standardized Mean Differences (SMDs) as a measure of effect size and in accordance with the literature, interpreted an effect size of 0.20 as small, 0.50 as moderate, and ≥0.80 as large. The pooled SMD for pain reduction vs. placebo was very large at 1.40. The pooled SMD for function, as measured by the Lequesne index, was moderate at 0.63. The moderate rating corresponded to a difference in the change from baseline vs. placebo of 3.5 points (*i.e.*, a change of over one severity class in the Lequesne's handicap scale (21)).

In the four trials comparing crystalline glucosamine sulfate to NSAIDs (there were no such trials involving other sources of glucosamine), the authors reported that glucosamine was equivalent in two and superior in the other two. The pooled SMD (to measure the effect size vs. NSAIDs) for pain reduction was considered large at 0.86 (3 trials) and small for purposes of joint function as measured by the Lequesne index at 0.32 for the 2 trials. The authors noted therefore a trend for superiority when compared to NSAIDs and suggested that the use of glucosamine represented a possible major breakthrough.

The authors concluded that there was good evidence that glucosamine is both effective and safe in treating osteoarthritis. The authors noted that all but one of the trials used crystalline glucosamine sulfate and that the one trial with glucosamine hydrochloride gave less favourable, or at least more variable results. The authors conclude that the glucosamine formulation and the presence of sulfates, therefore, seem to be important. The safety profile of glucosamine was considered excellent by the authors of this Cochrane Review, although the authors remarked that, at that time, clinical trials to test long-term efficacy and safety were needed. (Such studies have since been performed and published.)

3. **Richy F. et al. Arch. Inter. Med. 2003 ; 163 : 1541-22 (Reference n. 22)**

In the third and most recent meta-analysis, Richy et al. sought to separately evaluate the efficacy and safety of glucosamine sulfate and chondroitin sulfate. The authors restricted their analysis to randomized, double-blind, placebo-controlled trials (thus excluding reference-controlled trials) examining the benefit of oral glucosamine sulfate in knee osteoarthritis, with results expressed by today's state-of-the-art outcomes. These restrictions resulted in only 7 trials with glucosamine sulfate that could be included, only 3 of which had been included in the previous JAMA and Cochrane reviews. Five of the trials involved the Petitioner's crystalline glucosamine sulfate and the remaining two trials involved different formulations of glucosamine sulfate (23, 24).

The Richy meta-analysis has particular merit because it addresses major recommendations noted in the two previous systematic reviews, namely, the need for

(1) further high-quality, large trials and (2) long-term clinical trials. These recommendations have been indeed fulfilled by two independent, high-quality, long-term trials performed with crystalline glucosamine sulfate—one published in the *Lancet* (15) in 2001 and the other in the *Archives of Internal Medicine* in 2002 (16)—that were not available for consideration in the JAMA and Cochrane reviews but were included in this review.

Data were analysed from 1020 patients in glucosamine sulfate trials. The mean quality score of these trials was high: 90 percent according to the scoring method adopted (and significantly higher than in chondroitin trials). The two long-term, three-year, trials of crystalline glucosamine sulfate (15,16) provided consistent results of highly significant evidence of a structural efficacy of crystalline glucosamine sulfate, as assessed by radiographic joint space narrowing. The low to medium effect size on this parameter translated into natural units that expressed a major effect of clinical significance, as explained in detail in the two single study reports (15,16). There were insufficient data to evaluate a possible structural effect of chondroitin.

The global estimators used in this meta-analysis show substantial beneficial effects of crystalline glucosamine sulfate on symptoms of osteoarthritis, whether used in short-term or long-term clinical trials. The corresponding effect sizes tended to be lower than those calculated in the JAMA and Cochrane reviews, because of the more restrictive trial inclusions and the more conservative analysis model, according to the authors. The two studies using other formulations of glucosamine sulfate (23,24) emerged as those with the lowest effect size. Unlike McAlindon's 2000 JAMA meta-

analysis, the authors excluded any effect from possible publication bias on the robustness of the results.

B. Individual clinical trials

Unless otherwise indicated, all individual trials reported in this Petition were randomized, controlled intervention trials. All such trials can be classified or rated as Study Design Type One according to the recent (July 2003) FDA guidance entitled "Interim Evidence-based Ranking System for Scientific Data".

As indicated in the Cochrane Review (20), there is an obvious difference in the quality of the studies performed in the 1980s with those published after 1994, with the later studies being of significantly greater quality. According to the recent FDA guidance document, the earlier studies could be assigned the "?" designator because some uncertainties exist as to whether the studies adequately addressed issues of scientific quality such as inclusion/exclusion, bias, generalizability, and data collection and analysis. The trials published after 1994, however, have adequately addressed these issues and could be assigned the "+" designator.

Our discussion below first summarizes the early clinical trials and then provides a summary of the higher quality studies published after 1994. There is a separate section that summarizes the clinical studies performed on glucosamine formulations other than crystalline glucosamine sulfate. Copies of these clinical studies can be found in Attachment 1, which contains copies of all of the references cited in this Petition.

1. Early clinical trials

a. Placebo-controlled studies

There were four randomized, placebo-controlled, double-blind, parallel-group studies published between 1980 and 1981 (25, 26, 27, 28) that were included in the Cochrane Review (20). Each of these four studies used crystalline glucosamine sulfate at an oral dose equivalent to 1500 mg/day of glucosamine sulfate. At the time of these studies, the pharmacokinetic studies (7) had not yet demonstrated the ability to administer crystalline glucosamine sulfate once per day. These studies involved the administration of a 500 mg dose three times per day.

Two of the studies (25, 26) evaluated oral administration only. Drovanti et al. (25) treated two parallel groups of 40 hospitalized patients (80 total patients) with osteoarthritis at different joint localizations for 4 weeks. Pujalte et al. (26) treated for six to eight weeks two groups with 12 out-patients in each group (24 total patients) that had been diagnosed with osteoarthritis of the knee. The studies used the Likert scale to assess the effects of treatment. Both studies reported a statistically significant decrease in Likert scales scores of the crystalline glucosamine sulfate treated group when compared to the placebo group in joint pain, tenderness, swelling, and movement limitation. In addition, 70-80 percent of the patients in the treated groups showed positive results compared to only 20-40 percent positive results in the placebo groups. Significant clinical improvement was reached in the active group after the second week of treatment. Tolerability was good in both studies with no differences between the treatment and placebo groups. Drovanti (25) also reported no detected abnormalities in fecal occult blood analysis, indicating good tolerance of the gastrointestinal tract for crystalline glucosamine sulfate.

The other two clinical studies (27,28) had identical designs and outcomes and further support the findings of the previous studies. Crolle and D'Este (27) and D'Ambrosio et al. (28) treated two small groups (30 overall in each study) of in-patients with either parenteral crystalline glucosamine sulfate (400 mg/day glucosamine sulfate) or a reference medication for a one-week period that was followed by a two-week treatment with an oral dose of either placebo or 1500 mg/day of glucosamine sulfate. The reports provide little information on the localization of the osteoarthritis in these patients. The studies report that the initial improvement on the usual pain and functional parameters during the parenteral administration was maintained and even increased during the oral treatment with crystalline glucosamine sulfate. These findings further support the efficacy of the glucosamine sulfate 1500 mg/day oral dose. The studies also reported good tolerability for crystalline glucosamine sulfate, which is particularly relevant because the patients in the Crolle and D'Este (27) study had serious concomitant diseases and consequent treatments that were not affected by the crystalline glucosamine sulfate therapy.

b. <u>NSAID-controlled studies</u>

Vaz (29) conducted the first controlled study comparing glucosamine with an NSAID. This randomized, double-blind study had two parallel groups of 20 knee osteoarthritis patients (40 total patients). In this eight-week study, one group received an oral dose of 1500 mg/day of glucosamine sulfate and the other group received 1200 mg/day of ibuprofen. Pain relief tended to be slightly better in the crystalline glucosamine sulfate group than in the group receiving oral ibuprofen. The kinetics of the effect, however, differed. The NSAID group reached its maximum activity within the first two weeks and then remained stable. The crystalline glucosamine sulfate group

attained the same level of efficacy as the ibuprofen group after the third week and showed a trend for a continuous linear improvement. Tolerability also tended to be better for crystalline glucosamine sulfate, although it did not reach statistical significance. Vaz reported no differences at fecal occult blood testing, which was normal in most patients.

c. **Other early clinical studies**

Although not fully relevant to this Petition because it involved the intraarticular route of administration of crystalline glucosamine sulfate, the study by Vajaradul (30) is included in both the JAMA and Cochrane meta-analysis and is therefore briefly reviewed here. A total of 54 patients with knee osteoarthritis (out of 60) completed a 5-week treatment course with weekly intraarticular injections of either glucosamine or placebo. Knee pain decreased to a significantly greater extent and joint function improved in the treatment group. The authors also report good systemic and local safety.

The Cochrane Review also mentions publication of a post-marketing surveillance study by Tapadinhas et al. (31). This study involved 1208 patients with osteoarthritis at different joint localizations that were treated with crystalline glucosamine sulfate in an open fashion by 252 physicians throughout Portugal. The treatment lasted for six to eight weeks with a mean of 50 days and a range from 13 to 99 days. This study is not a randomized, controlled intervention trial. The authors report that a treatment response was obtained in over 90 percent of patients and that, consistent with other published studies, the effects of crystalline glucosamine sulfate persisted after cessation of treatment. The authors also reported good results on the safety of crystalline glucosamine sulfate, which is significant because the study involved patients receiving

previous and concomitant treatments for other diseases. Only 12 percent of patients experienced adverse effects with reactions that were generally mild, reversible, and predominantly affected the gastrointestinal tract.

2. Recent pivotal clinical trials

a. Short-term pivotal trials vs. placebo or vs. NSAIDs

i. Noack W et al. Osteoarthritis Cart 1994; 2: 51-59 (IV.B.10 – Reference n. 32)

In a large randomized, placebo-controlled, double-blind, parallel-group study, Noack et al. evaluated the symptom efficacy and safety of crystalline glucosamine sulfate (equivalent to 1500 mg/day glucosamine sulfate). This study involved two groups of 126 patients (252 total patients) with knee osteoarthritis that received either crystalline glucosamine sulfate or placebo over a 4-week treatment period. The baseline Lequesne index for the patients at the start of the study was between 10 and 11 points, indicating that the symptoms were moderate to severe.

There was a decrease in the Lequesne index by over 3 points after 4 weeks in the patients receiving crystalline glucosamine sulfate ($p<0.05$ vs. placebo), with clinically significant improvement being evident beginning in the second week and continuing thereafter. The responder rate after 4 weeks (calculated as a decrease of at least 3 points in the Lequesne index, together with a positive overall judgment by the investigator) indicated 52 percent of patients responded to crystalline glucosamine sulfate while 37 percent responded to the placebo, in the intent-to-treat population of 126 patients in each group ($p=0.016$).

Tolerability was good and similar between crystalline glucosamine sulfate and placebo, with a six percent incidence of minor adverse events in the crystalline glucosamine sulfate group and ten percent in the placebo group (with four percent and six percent related drop-out incidence, respectively). Routine laboratory tests at entry and study completion did not show any clinically significant modifications.

ii. Müller Fassbender H et al. Osteoarthritis Cart 1994; 2:61-69 – Reference no. 33)

In a twin study to the Noack study (32), Müller et. al. evaluated the same crystalline glucosamine sulfate dosage with ibuprofen at the standard analgesic dose of 1200 mg/day, for 4 weeks. Two hundred patients from a rehabilitation clinic, with knee osteoarthritis and clinical signs of joint flare, were randomized to the active treatments. The Lequesne index (modified by duplicating the pain scores to take into account the bilateral knee involvement in most of the patients) indicated a slightly more severe impairment as compared to the Noack study (32). Nevertheless, no rescue treatment was allowed, with the only exception of a concomitant physical therapy program, for which there were no differences between the two groups.

The responder rate, calculated with a method similar to that of the Noack study (32), was around 50 percent in both groups (48 percent with crystalline glucosamine sulfate and 52 percent with ibuprofen; p=0.67), with a ~40 percent reduction in the Lequesne index after 4 weeks. Consistent with the results reported in earlier studies, the development of the symptomatic effect differed between the two treatments. Ibuprofen induced a faster, although not statistically significant, symptom relief concentrated in the first two weeks while crystalline glucosamine sulfate induced a slower but constant

improvement that was superimposable to that of the NSAIDS from the third week onward.

Crystalline glucosamine sulfate was significantly better tolerated than ibuprofen, with adverse events reported in six percent of patients compared with 35 percent with ibuprofen ($p<0.001$). A related discontinuation rate of only one percent was reported for crystalline glucosamine sulfate while the ibuprofen group had a seven percent rate ($p=0.035$). Adverse events were mainly gastrointestinal in nature, as expected with the mixed COX_1-COX_2 inhibitor ibuprofen. No clinically significant laboratory changes were observed.

iii. Qiu GX et al. Arzneimittelforschung 1998 ; 48 : 469-74 (Reference n. 34)

Qiu also conducted a randomized, double-blind study that compared crystalline glucosamine sulfate (1500 mg glucosamine sulfate/day) with ibuprofen (1200 mg ibuprofen/day). This study confirmed the short-term symptomatic effect of crystalline glucosamine sulfate in knee osteoarthritis in an ethnically distinct population (178 Chinese patients). Knee pain improved with both treatments throughout the four weeks of treatment, with a non-statistically significant difference in favor of crystalline glucosamine sulfate, sustained for the two weeks of follow-up after treatment withdrawal. Also in this case, adverse reactions and related drop-outs were lower with crystalline glucosamine sulfate compared with ibuprofen ($p=0.02$ and $p=0.0017$, respectively).

b. **Long-term pivotal trials**

i. Reginster JY et al. Lancet 2001; 357:251-56 (Reference n.15)

Reginster et al. examined the long-term efficacy and safety of crystalline glucosamine sulfate on the risk of progression of osteoarthritis. A total of 212 patients (mean age 66 years; 76 percent females) with knee osteoarthritis (diagnosed using American College of Rheumatology (ACR) criteria) were randomized to continuous oral treatment with crystalline glucosamine sulfate (equivalent to 1500 mg glucosamine sulfate) once per day or placebo, for three years in a double-blind fashion. Disease severity in terms of symptoms and joint structure changes was mild to moderate. After three years, symptoms had improved to a significantly larger extent in the crystalline glucosamine sulfate group compared with placebo, as evaluated on the WOMAC index subscales of pain and joint function. Percent changes on the global index indicated a ~10 percent worsening with placebo and an improvement with crystalline glucosamine sulfate that was significantly different in both the intention-to-treat population and the per-protocol completers, and as high as 25 percent in the latter.

This study also detected for the first time, a significant joint structure-modifying effect. The primary structural end-point was joint space narrowing evaluated by digital image analysis of the mean joint space width of the medial tibiofemoral joint compartment, as well as by visual inspection (with the aid of a magnifying glass) at the joint's narrowest point. Standardized weight-bearing, antero-posterior radiographs of each knee in full extension were taken at enrollment and after one and three years according to state-of-the-art methodology at the time of study design. Placebo-treated patients suffered a mean joint space narrowing of approximately –0.1 mm/year, which is in line with the structural progression reported in the literature for knee osteoarthritis.

No narrowing occurred on average in the crystalline glucosamine sulfate group and the final differences between groups were significant. Furthermore, 30 percent of patients randomized to placebo presented a severe mean joint space narrowing of more than 0.5 mm, which may predict disability in the future, compared with only 15 percent of patients on crystalline glucosamine sulfate ($p= 0.013$).

There were no significant differences between crystalline glucosamine sulfate and placebo in frequency or pattern of adverse events. Laboratory tests did not show significant abnormalities on system organs or metabolic functions.

The authors of this report openly cautioned against generalizing the results of this study to other sources of glucosamine. Reginster states "[i]n this study glucosamine sulphate was approved as a prescription drug, therefore, our results cannot be generalised to other glucosamine products (or compound mixtures) such as those available in some countries as dietary supplements" (15). In the accompanying editorial to the Reginster study, Dr. Tim McAlindon, Arthritis Center Boston University Medical Center and the principal author of the JAMA meta-analysis (17) notes "since glucosamine is generally self-prescribed, the likely primary beneficiary of this trial will be the nutritional-product industry rather than the pharmaceutical company that sponsored the trial, even though the results may not be generalisable to the highly variable formulations of nutritional products" (35).

In his editorial comments, McAlindon also defined glucosamine for osteoarthritis as the possible dawn of a new era in the treatment of this disease and characterized the Reginster trial as a landmark study in osteoarthritis research (35).

Bruyere et al. published two full reports derived from the trial of Reginster. In the first report (36), a poor correlation between symptoms and radiographic joint structure parameters was observed, as widely described in the scientific literature about osteoarthritis progression. There was, however, a modest significant correlation between knee pain and joint space narrowing. Interestingly, the symptom-modifying effect of crystalline glucosamine sulfate was significantly independent of baseline joint structural damage and its progression. The latter was described in the second report (37): patients with better-preserved joint structure at baseline suffered the most dramatic joint space narrowing after three years when receiving placebo and were those in which the structure-modifying effect of glucosamine was more evident.

ii. Pavelka K et al. Arch Int Med 2002 ;162 : 2113-23 (IV.B.15 – Reference n.16)

This trial independently confirmed the results of Reginster (15) with an almost identical protocol and patient population (202 knee osteoarthritis patients; mean age 62; 78 percent female). Throughout the three years of treatment, symptoms steadily improved with crystalline glucosamine sulfate on the Lequesne index (from mild to moderate baseline values of 8-9 points) over the first year of treatment. This improvement remained constant until the end of the study, with a pattern that differed significantly from placebo. After 3 years, reduction in pain, function limitation, and stiffness was significant for crystalline glucosamine sulfate compared with placebo on the WOMAC index and its subscales, and on the overall Lequesne index, with an effect size that was similar to that observed in the study by Reginster.

This study also reported a striking structure-modifying activity obtained with the same conventional method and similar effect size reported by Reginster (15). Pavelka

reported a progressive joint space narrowing with placebo at each treatment year, while no average loss in joint space width occurred in glucosamine-treated patients. The authors report that 14 percent of the patients on the placebo lost over 0.5 mm joint space width while only five percent receiving crystalline glucosamine sulfate lost 0.5 mm of joint space width (p=0.05). The authors performed an analysis of secondary radiographic features of osteoarthritis and reported a three-fold higher proportion of worsening osteophyte scores (according to a validated radiographic atlas) in the placebo group when compared to the crystalline glucosamine sulfate group. Safety was again similar between crystalline glucosamine sulfate and placebo and is described in detail in the publication.

As did Reginster, Pavelka warns against generalization of the results to other glucosamine preparations other than this original crystalline glucosamine sulfate formulation. Pavelka states

> Glucosamine derivatives are popular dietary supplements in the United States and other countries, exploiting the opportunity provided by the American Dietary Supplement Health and Education Act and the clinical research data obtained with glucosamine sulfate approved as a prescription drug for the treatment of osteoarthritis in Europe and elsewhere. The latter was used in our study and in most of the previous clinical experiences; at present, it is difficult to generalize these results to the highly variable and uncontrolled formulations of the other nutritional products claiming a glucosamine content.

It is interesting to note that the structure-modification findings reported in the Reginster and the Pavelka studies have been questioned because of the use of the conventional standing (full extension) knee radiographic view (38). It has been hypothesized that the major pain relief in the crystalline glucosamine sulfate arm relative to placebo altered the positioning of the knee (favoring a better knee full extension) that might have confounded the estimate of joint space narrowing and exaggerated the differences between treatment groups. The conventional standing (full extension) knee radiographic view was the gold standard at the time of the study design and recommended in scientific guidelines. None of the more recently proposed techniques, such as the new semi-flexed views, have been validated in longitudinal studies (38). Moreover, although this criticism acknowledges the potent and previously unseen (with any other agent) long-term symptom-modifying effect of crystalline glucosamine sulfate, the authors of the two glucosamine long-term trials have elegantly shown that pain relief did not confound the assessment of joint space narrowing. The authors, therefore, have adequately validated their results with respect to structure modification, first in the Pavelka report (published in full after these criticisms were raised) and then in a joint abstract (39).

c. Other recent clinical studies

Two additional studies (40, 41) were included in one or more of the Cochrane (20), JAMA (17), or Richy (22) review articles and meta-analyses, but cannot be considered pivotal for the reasons expressed below. A third study by Förster et al. (42) was not included in any of the meta-analyses, but offers corroborative evidence of the safety and efficacy of crystalline glucosamine sulfate.

Reichelt et al. (40) performed a randomized, placebo-controlled, double-blind trial of glucosamine for six weeks using an intramuscular injection of crystalline glucosamine sulfate. The patients received two injections per week of 400 mg of glucosamine sulfate. This study has limited relevance to the dietary supplementation of crystalline glucosamine sulfate because it involves a different route of administration. Nevertheless, the study is sufficiently large (155 patients with knee osteoarthritis) and well conducted. The authors report a significant decrease in the Lequesne index compared with placebo over the 6 weeks of treatment, which was of comparable magnitude to that observed with oral crystalline glucosamine sulfate. The authors also report that intramuscular injection of crystalline glucosamine sulfate had comparable safety to the placebo.

The second study is of limited value because it is published only in abstract form (41) and is not widely publicly available as a full report. This report is, nonetheless, reviewed in the three meta-analyses (17,20,22) (with very high quality scores in the latter two) and is therefore included here as corroborative evidence. Further information about the study is publicly available from a product monograph (43). In this double-blind study, 319 patients with knee osteoarthritis and moderate to severe symptoms (with baseline Lequesne index mean values around 10-11 points and pain visual analogue scores ≥40 mm out of 100) were randomized to oral crystalline glucosamine sulfate equivalent to 1500 mg glucosamine sulfate once daily), or the conventional NSAID piroxicam (20 mg/day), or the combination of the two agents, or placebo. Treatment was administered for 12 weeks, followed by an eight-week observation period without treatment.

After 4 weeks of treatment, the crystalline glucosamine sulfate symptom-modifying effects were virtually superimposable to those previously described, with a decrease in the Lequesne index of around 3 points in average, similar to that achieved with piroxicam. Thereafter, the improvement continued almost linearly with crystalline glucosamine sulfate. The average decrease exceeded 4 points at the end of the 12 weeks, while it remained around 3 points with piroxicam: both groups displayed significantly better effects than placebo ($p<0.001$), but crystalline glucosamine sulfate tended to be better than the NSAID ($p<0.05$). After withdrawal of the agent administration, the crystalline glucosamine sulfate symptomatic effect was sustained for the 8-week follow-up ($p<0.01$ vs placebo), while the effect was rapidly lost with the piroxicam group. Combination of crystalline glucosamine sulfate with the NSAID tended to show a faster symptom relief over the first 2-4 weeks than each separate agent, but it was afterwards superimposable to crystalline glucosamine sulfate alone.

Patients receiving crystalline glucosamine sulfate had a similar incidence of adverse events than those taking placebo, but significantly less than those in the piroxicam group (15 percent vs 42 percent, $p<0.001$, with 9 percent vs. 33 percent referred to the gastrointestinal tract) with fewer drop outs. Combination of crystalline glucosamine sulfate with the NSAID did not prevent the adverse reactions from the latter.

Finally, Förster et al. recently published, although only in abstract form (42), a randomized, placebo-controlled, double-blind study of the standard crystalline glucosamine sulfate once-daily formulation and dosage, in 160 patients with osteoarthritis of the spine. The substance induced a significant improvement vs.

placebo in most of the pain and functional parameters evaluated over the 6-week treatment course, which was sustained for the 4-week follow-up without treatment. The improvements were apparently more marked in the lumbar spine compared with the cervical spine (not reported). There were no differences between glucosamine and placebo with respect to safety.

3. Clinical trials performed with glucosamine formulations other than crystalline glucosamine sulfate

There are only a few published clinical trials that have evaluated sources of glucosamine other than crystalline glucosamine sulfate. The Petitioner is unaware of any unpublished studies on these other sources of glucosamine. The few published studies that are available, and that are reviewed below, have failed to yield the same consistent results that have been reported in the trials involving crystalline glucosamine sulfate.

Houpt et al. (44) performed a study with glucosamine hydrochloride that is taken into consideration in both the JAMA and Cochrane reviews (but not in the meta-analysis of Richy et al., which deals only with glucosamine sulfate). A total of 101 patients with knee osteoarthritis were randomized and dispensed either glucosamine (as hydrochloride, at a total daily dose of 1500 mg) or placebo for 8 weeks. Houpt used the WOMAC algo-functional index as a primary measure of outcome. With one exception, scores on the remaining 23 WOMAC questions tended to improve with glucosamine compared with placebo. The degree of improvement tended to be greater in the glucosamine group vs. placebo in all WOMAC subscales of pain, function, and stiffness (~20 percent improvement with glucosamine vs less than 10 percent with placebo). However, the difference between groups in the WOMAC score changes failed to reach

statistical significance; a patient daily diary for pain showed a statistically significant pain reduction for glucosamine vs. placebo at some points during the study. Safety was similar between glucosamine and placebo, with 12 percent of subjects in both groups reporting mild gastrointestinal symptom (bloating or cramps).

As discussed in the Cochrane Review, it seems that differences in efficacy may relate to differences between glucosamine sulfate (in appropriate formulations) and hydrochloride salts. As acknowledged by Houpt in their introduction, the efficacy of crystalline glucosamine sulfate is well established while that of glucosamine hydrochloride is only anecdotal. Although detecting a trend for efficacy for glucosamine, the study by Houpt seems to indicate that there may be major differences between the crystalline glucosamine sulfate and the hydrochloride salt that would discourage the translation of efficacy results obtained with the former to preparations containing the latter substance.

Rindone et al. (23) published a small (98 patients), randomized, placebo-controlled, double-blind, parallel-group, 8-week study using an unspecified oral formulation and salt of glucosamine (although the study is considered in the meta-analysis by Richy as being performed with a glucosamine sulfate formulation). To further challenge the poor statistical power of the study, the authors enrolled patients in apparently more severe conditions than in other short-term studies with crystalline glucosamine sulfate. As widely discussed in the paper to explain the study's many limitations, the patients had longer-standing disease, were only men, were heavier, had much more severe disease from the point of view of radiographic staging and, above all, were unresponsive to conventional symptomatic medications (60 percent of patients

were taking NSAIDs or analgesics and were asked not to discontinue them). There were no significant differences between glucosamine and placebo on the symptom evaluations performed. Thirty-four percent of patients taking glucosamine reported mild and self-limiting effects vs. 23 percent with placebo (2 related withdrawals with glucosamine vs. 4 with placebo).

Hughes and Carr (24) recently published a very small (40 patients/group) 6-month, randomized, double-blind, placebo-controlled study of a glucosamine formulation (potassium chloride glucosamine sulfate, plus vitamin C, calcium carbonate and manganese) not tested previously in any clinical trial to the knowledge of the Petitioner. The study was considered in the recent meta-analysis by Richy (22). The authors described the trial design as pragmatic in that they enrolled patients with a wide range of pain and other symptom severity and included all grades of radiological severity, which is contrary to the standard practice in osteoarthritis clinical trials. The patient population varied in terms of osteoarthritis severity with 10 percent of the population classified as a Kellgren and Lawrence radiological grade 1 (doubtful osteoarthritis), and over 20 percent presented with a grade 4 (severe osteoarthritis); patients on these extreme ends of the Kellgren and Lawrence radiological grade are usually excluded from clinical trials. To further complicate matters, almost 50 percent of patients were on NSAIDs and were asked not to discontinue them, making it difficult to assess the treatment efficacy and the rescue analgesic consumption. Indeed, there were no significant differences between glucosamine and placebo in any of the validated symptom end-points of the study. The placebo effect was classified to be strong by the authors. Indeed the authors report elsewhere that most of the patients misunderstood the study information and thought that everyone in the study was

receiving glucosamine (45), which might have seriously biased the study. It is very difficult to draw any conclusion on the efficacy of this glucosamine sulfate preparation based on this trial. Also in this case, safety was similar to that of placebo.

In a preliminary study, Thie et al. (46) described a similar efficacy between a glucosamine sulfate formulation and ibuprofen in a small group of patients with osteoarthritis of the temporomandibular joint.

In a small (34 patients with degenerative joint disease), 16-week, randomized, placebo-controlled, cross-over trial, Leffler et al. (47) reported a significant benefit on knee osteoarthritis symptoms with a combination of glucosamine hydrochloride, chondroitin sulfate, and manganese ascorbate. Similar results were recently described by Das and Hammad (48) in a slightly larger group (93 patients only) of knee osteoarthritis subjects treated for 6 months. Although these are two favorable studies, there may be reservations on the relevance of such a small sample size for generalizability of the results. In addition, caution appears to be in order due to the likely metabolism of chondroitin sulfate.

Chondroitin sulfate is a glycosaminoglycan normally present in the cartilage matrix and consisting of a high molecular weight, long chain of repeating units of differently sulfated residues of glucuronic acid and N-acetyl galactosamine, obtained with extraction processes from animal tissues. It is used in some countries for the treatment of osteoarthritis under the rationale that it is speculatively similar to that of glucosamine sulfate. The rationale is difficult to understand given the major differences in physico-chemical properties between the two (*i.e.*, a macromolecular tissue extract

compared to a low molecular weight pure glucosamine sulfate). Actually, oral absorption of high molecular mass polymers is questionable. Pharmacokinetic studies (49) have shown that after oral administration the largest peak consists of one of the constituent monomers, N-acetyl-galactosamine, which is probably responsible for the beneficial activity, although absorption of a small fraction of high molecular weight chondroitin sulfate cannot be excluded. Very early studies had shown that N-acetyl-galactosamine might induce metabolic activities similar to that of its precursor glucosamine, although with a lower potency (50). It may be speculated, therefore, that the clinical activity reported for chondroitin sulfate in some clinical trials may be similar to that of low dose glucosamine sulfate.

Based on anecdotal evidence, it is sometimes claimed that a combination of dietary supplements containing chondroitin sulfate and glucosamine-derivatives may offer added value in the treatment of osteoarthritis. However, there is no scientific proof for this claim and, on the basis of the discussion above, the rationale of such a combination is also weak because adding chondroitin to glucosamine would presumably only slightly increase the dose of glucosamine. The two very small clinical trials reviewed here (47,48) do not allow one to distinguish between the effects of glucosamine alone or of the combination. It seems, therefore, that combinations of glucosamine and chondroitin sulfate cannot benefit from the claims proposed for crystalline glucosamine sulfate.

C. Level of crystalline glucosamine sulfate needed to justify the claim

As is described in the above summary of scientific evidence, the clinical studies consistently used 1500 mg/day of glucosamine sulfate, corresponding to 1884 mg of

crystalline glucosamine sulfate. The Petitioner considers this to be the optimum level of intake beyond which the health benefits of crystalline glucosamine sulfate have not been demonstrated clinically and thus are not to be expected. The Petitioner is unaware of any level at which an adverse effect from crystalline glucosamine sulfate would be expected to occur. The Petitioner is aware that certain populations, namely, individuals with diabetes, may need to receive careful monitoring while taking crystalline glucosamine sulfate, as it has been suggested—but not established—that crystalline glucosamine sulfate may increase insulin resistance.

In the United States, crystalline glucosamine sulfate is available as caplets of 750 mg glucosamine sulfate and as sachets of powder for oral solution, dosed for once-daily administration of 1884 mg crystalline glucosamine sulfate (1500 mg glucosamine sulfate). This latter formulation is particularly relevant because it is the formulation used in the latest clinical trials, including the long-term studies.

D. Global analysis of safety

The safety of glucosamine for use as a dietary supplement is supported by the numerous clinical trials, by its physical properties, chemical structure, and metabolic fate, and by experience based on widespread use in the United States and throughout the world. The safety of crystalline glucosamine sulfate is also acknowledged by the three systematic reviews and meta-analyses that have published.

1. Clinical trial data

Several recent clinical trials and the meta-analysis publications in prestigious clinical journals (e.g., *Lancet*, *Journal of the American Medical Association*, *Archives of Internal Medicine*, *Cochrane Library*) provide a coherent scientific assessment about

the efficacy and safety of glucosamine. These publications reflect agreement in the scientific community that glucosamine supplementation presents no significant or unreasonable risk of illness or injury.

In the pivotal short-term clinical trials for crystalline glucosamine sulfate (32,33,34), the incidence of patients reporting adverse events on glucosamine ranged between six and 12 percent with drop-outs due to adverse events in less than four percent of the patients. Importantly, none of the studies reported statistically or clinically significant differences between crystalline glucosamine sulfate and placebo in the incidence of adverse events or safety related drop-outs. In the trials comparing crystalline glucosamine sulfate with NSAIDs, the NSAID groups consistently had a significantly higher incidence of adverse events and safety related drop-outs than the group receiving crystalline glucosame sulfate. In those rare instances when patients reported adverse events, they generally involved mild and transient reactions associated with the gastrointestinal system such as abdominal pain or discomfort, nausea, diarrhea, constipation, and/or meteorism. Other reported adverse events include headache, dizziness and minor allergic reactions such as cutaneous rashes with erythema and itching. This pattern of adverse events was similar between crystalline glucosamine sulfate and placebo in all trials.

The pattern of adverse events described in the short-term pivotal clinical trials is similar to that described in all of the other short-term trials (40,41,42,43). No study reported more than 15 percent of patients in the glucosamine groups experiencing adverse events.

The long-term pivotal trials are particularly important, as they allow the assessment of continued safety during prolonged use, which is seldom, if ever, described for agents used in osteoarthritis. In both the Reginster (15) and the Pavelka (16) trials, the safety of crystalline glucosamine sulfate was similar to that of placebo. Because these studies involved long-term administration of crystalline glucosamine sulfate in elderly patients, it is not surprising that most of the patients in the Reginster study reported at least one adverse event with crystalline glucosamine sulfate or placebo, 94 percent and 93 percent, respectively. The patients in the Pavelka study had a slightly lower rate of adverse events in the crystalline glucosamine sulfate and placebo groups of 66 and 64 percent, respectively. The adverse events, however, involved mild to moderate and transient events in the crystalline glucosamine sulfate and placebo groups consisting of abdominal discomfort or pain, dyspepsia and nausea, or disturbed defecation. Musculoskeletal adverse events were likely related to osteoarthritis; treatment-unrelated cardiovascular events were also common in this elderly population, as were urinary infections and seasonal respiratory tract infections. Few and sporadic serious events were also reported in both the crystalline glucosamine sulfate and placebo groups, with no "signal" for any toxicity being detected with the active treatment.

In all short-term and long-term clinical trials, there were no modifications of routine laboratory tests during treatment with crystalline glucosamine sulfate.

2. Properties and Metabolic Fate

The mechanism of action of glucosamine, briefly reviewed in section II of this Petition, does not account for any particular toxicity pattern of crystalline glucosamine

sulfate. Unlike NSAIDs, glucosamine does not inhibit type 1 cyclooxygenase (COX-1), which explains the significantly better safety pattern at the gastrointestinal level.

Osteoarthritis is a chronic disease that involves a majority of elderly patients, who frequently receive treatments for concomitant diseases. Glucosamine does not compete for absorption mechanisms and, after absorption, does not bind to plasma proteins. The metabolic fate of this endogenous substance is mainly the incorporation in proteoglycans or degradation independently of the cytochrome enzyme system. The physicochemical, pharmacokinetic, and metabolic properties of glucosamine suggest a low potential for adverse effects and a low potential for drug interactions. With regard to the latter, the clinical studies have found no evidence of any drug interactions.

Recent animal experimental studies with suprapharmacological intravenous doses of glucosamine suggested that the compound might increase insulin resistance through a complex interaction with the so-called hexosamine pathway (one of the alternative routes of glucose metabolism) (51). Two recent human studies using extremely high intravenous (52) or even intraarterial (53) glucosamine doses indicated that such a mechanism is probably not operating in humans. These studies did not detect an effect on insulin sensitivity, secretion or action by glucosamine administration. Indeed, a recent report (54) clarified that fasting plasma glucose levels were not modified by the short-term crystalline glucosamine sulfate administration, even in patients with hyperglycaemia at baseline, nor in the long-term pivotal trial by Reginster (15), where fasting blood glucose even tended to decrease, on average. In the long-term study by Pavelka (16), four patients developed diabetes during the study, but three were on placebo and only one on crystalline glucosamine sulfate.

A very recent report (55) evaluated a small group of 26 elderly patients with type 2 diabetes, receiving daily supplementation for 90 days with a combination of 1500 mg glucosamine hydrochloride and 1200 mg chondroitin sulfate or placebo (in a randomized, double-blind setting). No patient had any change in their diabetes management during the study. There were no significant differences between groups in post-treatment haemoglobin A_{1c} concentrations, nor were there any significant differences within groups before and after treatment. Although this report is reassuring, given the differences between crystalline glucosamine sulfate and glucosamine hydrochloride, the results of this study should not be generalized to crystalline glucosamine sulfate.

The clinical studies published to date have failed to report any findings establishing concern with the administration of crystalline glucosamine sulfate to diabetics. The data in this patient population, however, is recognizably relatively scarce.

3. <u>Experience based on use</u>

The extensive use of glucosamine products throughout the world also supports its safe use. In the United States, glucosamine products are among the most widely marketed dietary supplements. In one recent U.S. market analysis, glucosamine was ranked as the 11th best selling supplement in the United States; in a dietary supplement use survey, glucosamine was ranked as the fourth most common supplement among a randomly selected sample of 2590 adult men and women (National Academy of Sciences, Institute of Medicine, Safety Review: Draft Prototype Monograph on Glucosamine (Jan. 2003)). Although widely consumed as a dietary supplement, the

published literature contains few reports of adverse events. Adverse events that are attributed to glucosamine are generally mild and transient, and often relate to gastrointestinal concerns.

Although crystalline glucosamine sulfate is regulated as a dietary supplement in the United States, it has been available as a prescription drug in over 40 countries of the world for over two decades. Among the countries in which glucosamine is regulated as a drug are seven countries within the European Community-EC (Finland, Germany, Greece, Ireland, Italy, Portugal and Spain) and several other European countries (Baltic countries, Bulgaria, Czech Republic, Hungary, Poland, Rumania, Russia, Slovak Republic). The substance has been extensively used in practice (as evident from market data) on a wide geographical basis throughout the world, but no safety issues have been raised through the pharmacovigilance monitoring system in Europe and in other countries where the substance has a prescription drug status.

IV. HIGH RANKING FOR THE STRENGTH OF THE EVIDENCE FOR THE PROPOSED HEALTH CLAIM FOR CRYSTALLINE GLUCOSAMINE SULFATE

The Petitioner has evaluated the strength of the total body of evidence that supports the proposed claim for crystalline glucosamine sulfate according to the FDA guidance regarding significant scientific agreement (*Guidance for Industry: Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements*) and recent guidelines concerning the review of so-called "qualified health claims" (*Interim Evidence-based Ranking System for Scientific Data*). In the opinion of the Petitioner, available evidence reflects significant scientific agreement among qualified experts that crystalline glucosamine sulfate reduces the risk of osteoarthritis-related joint deterioration, joint pain, and limitation of function. Should FDA disagree, however, the Petitioner would be willing to consider review of the proposed claim as a "qualified health claim," as described in agency guidance of July 11, 2003. In light of the extensive research to date addressing the relationship between crystalline glucosamine sulfate and osteoarthritis, the proposed claim is, at a minimum, a "Category B" claim for which the scientific evidence may be described as supportive but not conclusive.

The clinical studies convincingly establish that an oral dose of crystalline glucosamine sulfate (1500 mg of glucosamine sulfate/day) is an effective therapy for patients with mild, moderate and even severe osteoarthritis by reducing joint deterioration and accompanying joint pain and limitation of function. Indeed, existing clinical practice guidelines for osteoarthritis published by major scientific organizations support the use of crystalline glucosamine sulfate in osteoarthritis. The two most

important recommendations are those released by the American College of Rheumatology (ACR) and by the European League Against Rheumatism (EULAR). These organizations published their most recent guidelines in 2000, (56, 4), prior to the publication of the Cochrane review (20), the meta-analysis by Richy (22) and the long-term pivotal trials by Reginster (15) and by Pavelka (16).

The 2000 EULAR guidelines (4), in their evidence-based assessment, support the short-term efficacy of glucosamine on pain reduction and improved function. The guidelines acknowledge the potential for disease modification by placing crystalline glucosamine sulfate in category 1B—indicating a "high category of evidence" in support of the recommendation. The highest category of evidence is 1A and at the time of the 2000 publication, the EULAR placed only NSAIDs and patient education in the 1A category. The EULAR has since evaluated the new data on crystalline glucosamine sulfate and has updated its practice guidelines (Osteoarthritis Task Force: EULAR recommendations for treatment of knee osteoarthritis – 2003 Version, presented during the Annual European Congress of Rheumatology – Lisbon, Portugal, 18-21 June 2003 – Full report publication due in the fall of 2003). Glucosamine sulfate has now been placed in category 1A indicating that there is the highest level of evidence with a very large effect size and very high quality clinical trials supporting its efficacy in this patient population.

A four-member ACR subcommittee issued a consensus guideline in 2000 (56) that recognized glucosamine among the agents under investigation and stated that "while a number of studies support the efficacy . . . for palliation of joint pain . . . the subcommittee believes that it is premature to make specific recommendations . . . ."

The ACR has not yet updated these guidelines to consider the compelling data on crystalline glucosamine sulfate published since this earlier review. Hochberg, one of the four members of the ACR subcommittee did publish an "informal update" of the ACR guidelines in 2001 with a paper entitled "What a difference a year makes: reflections on the ACR recommendations for the medical management of osteoarthritis" (57). In this paper, Hochberg reviews the new evidence appearing in the year following the ACR guideline publication that stress, among others, the recommendation for the use of glucosamine. Hochberg acknowledges the different evidence-based perspective of the EULAR guidelines and, especially the appearance in early 2001 of the glucosamine Cochrane Review and the long-term trial by Reginster. With a particular emphasis on the original crystalline glucosamine sulfate preparation, Hochberg's analysis encourages the U.S. medical community "to reassess the use of glucosamine as a first-line agent at least for patients with knee osteoarthritis who have mild-to-moderate pain".

Hochberg's focus on patients with mild-to-moderate osteoarthritis derives from the emphasis placed on Reginster's long-term study, later reinforced by Pavelka's study. Although this focus is definitely correct for the reduction in the risk of osteoarthritis joint structure deterioration, Reginster's group has shown that symptoms are relieved by glucosamine irrespectively of baseline disease severity. In addition, the short-term trials reviewed here indicate the symptomatic effect of crystalline glucosamine sulfate also in moderate-to-severe patients.

The slightly different recommendations coming out of these European and U.S. expert bodies is not surprising. There are major differences in the perception of the role

of glucosamine for osteoarthritis in the United States and in Europe. While crystalline glucosamine sulfate is regulated in much of Europe as a prescription drug, it and other forms of glucosamine are regulated as a dietary supplement in the United States. The tepid recommendation from the ACR consensus guideline may very well reflect the concern in the U.S. medical community that patients with osteoarthritis will try to self-medicate without first seeking the intervention of a medical professional. In addition, most patients lack the sophistication to distinguish the various sources of glucosamine and may chose a formulation other than crystalline glucosamine sulfate which is the standardized formulation with robust clinical data supportive of its use. Regardless of the reason for the different recommendations, Hochberg's "informal update" of the 2000 ACR consensus guidelines does recommend the use of crystalline glucosamine sulfate in osteoarthritis patients with mild to moderate pain.

While we recognize that data in this Petition convincingly establish that crystalline glucosamine sulfate has been proven to be an effective therapy for individuals with osteoarthritis, the data also establish that crystalline glucosamine sulfate is effective at reducing the risk of developing osteoarthritis joint structure degradation, pain, and limitation of function. FDA has previously recognized that it is appropriate to consider clinical studies involving a diseased population to support a health claim for a reduced risk of developing a disease. Perhaps most relevant are the extensive data supporting the cardiovascular benefits of omega-3 fatty acids in patients with cardiovascular disease.

When issuing the qualified health claim for dietary supplements of omega-3 fatty acids, the agency specifically recognized that "the evidence from interventional

trials with CHD as an endpoint is strongly favourable in a diseased population showing that omega-3 fatty acid intake is related to reduced risk of CHD" and "that there is suggestive evidence that the benefit on CHD reported in diseased populations will carry over to the general population because omega-3 fatty acids have similar physiological effects in both diseased and general populations" (Letter from Christine J. Lewis, Ph.D., to Jonathan W. Emord, Esq. (Oct. 31, 2000)). Although the agency cited the absence of controlled studies in the healthy population as one of the factors preventing a finding of significant scientific agreement for omega-3 fatty acids, the Petitioner believes that the clinical studies on crystalline glucosamine sulfate provide an even more compelling case than those studies with omega-3 fatty acids.

The physiological effect of crystalline glucosamine sulfate is well characterized. Crystalline glucosamine sulfate not only provides one of the building blocks for cartilage synthesis, but it suppresses those enzymes, that in patients with osteoarthritis, create an imbalance by breaking down cartilage at a faster rate than it is synthesized. Crystalline glucosamine sulfate will have the same physiological impact in the healthy population, as determined by clinical studies of patients with "mild osteoarthritis," a patient population quite similar to the general population.

The clinical studies are supportive of the use of crystalline glucosamine sulfate in osteoarthritis prevention, particularly those studies that evaluated patients with a mild form of the disease. Indeed, Hochberg (57) specifically recommends the use of crystalline glucosamine sulfate in patients with mild osteoarthritis. The long-term study of Reginster (15) further supports the ability of crystalline glucosamine sulfate to reduce the risk of developing osteoarthritis. Reginster demonstrated that the protective effects

on joint structure are dramatic in those patients that started the trial with a better-preserved joint (37). Reginster classified certain patients as having "mild osteoarthritis" based on the radiographic joint space width at the beginning of the trial. The preventative effects of crystalline glucosamine sulfate in this patient population with "mild osteoarthritis," a patient population very similar to the "healthy population," combined with the well-known mechanism of action for crystalline glucosamine sulfate support the ability of crystalline glucosamine sulfate to be effective in preventing the onset of osteoarthritis.

The Petitioner believes that the evidence in this Petition establishes that there is significant scientific agreement among qualified experts to support the proposed health claim for crystalline glucosamine sulfate (*i.e.*, a "high level of comfort" that is not likely to be reversed by new and emerging evidence). Accordingly, it is the opinion of Petitioner that the proposed claim should be allowed as a First Level Scientific Ranking and FDA Category A health claim. To the extent that FDA disagrees with this assessment, Petitioner would accept classification of the evidence into FDA Category B and the appropriate qualifying language that would need to accompany such a health claim (*i.e.*, "although there is scientific evidence supporting the claim, the evidence is not conclusive").

V. GLUCOSAMINE FORMULATIONS OTHER THAN CRYSTALLINE GLUCOSAMINE SULFATE DO NOT HAVE THE SAME BODY OF EVIDENCE TO SUPPORT ANY CLAIM

Although several forms of glucosamine are presently marketed for dietary supplement use in the United States, crystalline glucosamine sulfate is the only form of glucosamine that has been studied extensively. Crystalline glucosamine sulfate was recently referred to in the USP/NF 2003 as Glucosamine Sulfate Sodium Chloride (crystalline glucosamine sulfate) that, when dissolved in water, gives a solution containing glucosamine, sulfate, sodium and chloride ions in stoichimetric ratios of 2:1:2:2. For simplicity, this specific substance is referred to in the clinical and other scientific literature as glucosamine sulfate. Other forms of glucosamine include glucosamine hydrochloride, or N-acetyl-glucosamine or other, sometimes unspecified "glucosamine sulfate" formulations.

These other forms of glucosamine (*i.e.*, glucosamine hydrochloride, N-acetyl-glucosamine, or other "glucosamine sulfate" formulations) may not share the same quality, pharmacological, pharmacokinetic and, especially, clinical properties of crystalline glucosamine sulfate. The publicly available data establish that the same degree of confidence applicable to crystalline glucosamine sulfate does not apply to any other glucosamine formulations. There are few clinical trials performed with formulations other than crystalline glucosamine sulfate and those studies that have been conducted generally feature small sample sizes with less consistency in results when compared to the studies with crystalline glucosamine sulfate.

The results from the studies on crystalline glucosamine sulfate cannot be generalized to other forms of glucosamine. There are important chemical and physiological differences between the various sources of glucosamine. As stated throughout this Petition, these differences include the following:

- Other sources of glucosamine have not been shown to be bioequivalent with the crystalline glucosamine sulfate formulations used in clinical trials.
- The clinical trials conducted on other sources of glucosamine have yielded less consistent results than those with crystalline glucosamine sulfate.
- The inorganic sulfates found in crystalline glucosamine sulfate are also believed to contribute to its physiological effects. These inorganic sulfates are not found in other sources of glucosamine. Sulfates control the rate of synethsis of the glycosaminoglycan and proteoglycan that become a part of the cartilage matrix. The sulfate serum levels increase after glucosamine sulfate administration (14). The importance of sulfate in the cartilage synthesis process provides further support for using a source of glucosamine that provides sulfates.

The published literature also is replete with statements cautioning against the generalization of the results from studies involving crystalline glucosamine sulfate to other sources of glucosamine. We repeat below many of the concerns that have been expressed in the scientific literature:

- The authors of the Cochrane review (20) noted that all but one of the trials used crystalline glucosamine sulfate and that the one trial with glucosamine hydrochloride gave less favourable, or at least more variable results. The authors conclude that the glucosamine formulation and the presence of sulfates, therefore, seem to be important.
- The meta-analysis peformed by Richey (22) noted that the two studies using other formulations of glucosamine sulfate (23, 24) emerged as those with the lowest effect size.
- Reginster states "[i]n this study glucosamine sulphate was approved as a prescription drug, therefore, our results cannot be generalised to other glucosamine products (or compound mixtures) such as those available in some countries as dietary supplements" (15).
- In the accompanying editorial to the Reginster study, Dr. Tim McAlindon, Arthritis Center Boston University Medical Center and the principal author of the JAMA review (17) notes "since glucosamine is generally self-prescribed, the likely primary beneficiary of this trial will be the nutritional-product industry rather than the pharmaceutical company that sponsored the trial, even though the results may not be generalisable to the highly variable formulations of nutritional products" (35).
- Pavelka (16) states "[g]lucosamine derivatives are popular dietary supplements in the United States and other countries, exploiting the opportunity provided by the American Dietary Supplement Health and Education Act and the clinical research data obtained with glucosamine sulfate approved as a prescription drug for the treatment of osteoarthritis

in Europe and elsewhere. The latter was used in our study and in most of the previous clinical experiences; at present, it is difficult to generalize these results to the highly variable and uncontrolled formulations of the other nutritional products claiming a glucosamine content."

- Houpt (44) notes in the introductory remarks on his study of glucosamine hydrochloride that efficacy of crystalline glucosamine sulfate is well established, while that of glucosamine hydrochloride is only anecdotal.

Given the concerns expressed in the scientific community and the differences between crystalline glucosamine sulfate and other forms of glucosamine, it simply is not possible to generalize the findings in the crystalline glucosamine sulfate clinical studies to other sources of glucosamine.

Limitation of the proposed health claim to crystalline glucosamine sulfate is consistent with the accepted principle that health claim eligibility must be restricted to the specific substances for which the claimed health benefit has been demonstrated by credible scientific evidence. In the case of health claims regarding specific types of soluble fiber and coronary heart disease (CHD), for example, FDA determined that soluble fiber is a family of heterogeneous substances that differ significantly in their effect on CHD risk. In the final rule that established the health claim regulation (21 C.F.R. § 101.81), the agency decided to authorize the claim for one type of soluble fiber only—beta-glucan from whole oats—for which the available data demonstrated a beneficial effect on CHD risk (62 Fed. Reg. 3583, 3587-88 (Jan. 23, 1997). FDA encouraged manufacturers to Petition for a claim for additional soluble fibers if there was evidence to demonstrate a beneficial effect of such fibers on serum lipid levels and

thus, risk of heart disease. (*Id.*) Indeed, FDA intentionally structured the initial health claim regulation to facilitate its subsequent amendment as evidence became available to support extension of the claim to other sources of soluble fiber. As anticipated, FDA later amended the health claim regulation to include soluble fiber from psyllium seed husk and oatrim—a beta-glucan soluble fiber fraction that is produced from alpha-amylase hydrolyzed oat bran or whole oat flour.

The same case-by-case approach is warranted for health claims regarding crystalline glucosamine sulfate and osteoarthritis risk. As with the soluble fiber, there are physiological differences in the various sources of glucosamine that require the health claim to be specific to each source of glucosamine. Moreover, the precedent established by the soluble fiber health claim establishes that manufacturers of other sources of glucosamine must develop the data and Petition FDA for inclusion of their substance in the health claim. A similar approach is warranted here.

In addition to the absence of clinical studies supporting the efficacy of other sources of glucosamine in the prevention of osteoarthritis, there also is a concern with the variability in glucosamine content of these other products (58). The amount of glucosamine sulfate in the Petitioner's product can be precisely detected by suitable potentiometric methods (Attachment 2). The methods proposed are validated for specificity, linearity, accuracy and precision. Unlike manufacturers of other dietary supplements, the Petitioner does not use the high-performance liquid chromatography method described in the USP 26, NF 21. Surprisingly, this method does not detect "glucosamine" but only the chloride ions present in glucosamine hydrochloride or glucosamine sulfate sodium chloride (crystalline glucosamine sulfate). By using this

USP method it would be possible to detect a content of glucosamine of 100 percent when there is no glucosamine in the dietary supplement (provided, of course, that chloride ions are present in the dietary supplement) (see also Petitioner's comments under Attachment 3).

VI. PROPOSED MODEL CLAIM

The Petitioner believes that the scientific information publicly available and summarized in this Petition, supports the following proposed model health claim claim:

> **Daily dietary supplementation with Crystalline Glucosamine Sulfate reduces the risk of osteoarthritis joint structure deterioration and related joint pain and limitation of function.**

This model claim captures the information presented in this Petition by informing the consumer that crystalline glucosamine sulfate can reduce the risk of osteoarthritis-related joint deterioration, joint pain, and limitation of function. The claim is intended to assist in the prevention of the major health-related conditions that are associated with osteoarthritis.

The Petitioner is willing to consider alternative health claim language that may accurately characterize the nature and weight of the substantiating scientific evidence concerning the benefits of crystalline glucosamine sulfate in osteoarthritis. The claim should not, however, be extended to any other glucosamine formulation or combination product.

VII. POTENTIAL EFFECT OF THE CLAIM ON TOTAL INTAKES OF THE SUBSTANCE

Dietary supplements claiming a glucosamine content are widely used in the United States. Approval of this health claim may further increase the consumption of glucosamine containing supplements, particularly those containing crystalline glucosamine sulfate. The increased consumption of crystalline glucosamine sulfate is expected to have a beneficial impact in that it would reduce the incidence of osteoarthritis. No adverse or beneficial changes in other dietary practices are expected.

VIII. DESCRIPTION OF ATTACHMENTS

All reports from clinical trials that are publicly available are included under Attachment 1, together with all scientific references cited here, in order of appearance in the text of this Petition. To the best of Petitioner's knowledge, all non-clinical studies relied upon in this Petition were conducted in compliance with the good laboratory practices regulations set forth in 21 C.F.R. Part 58 and all clinical studies were either conducted in accordance with the requirements for institutional review set forth at 21 C.F.R. Part 56 or were not subject to such requirements in accordance with 21 C.F.R. § 56.104 or § 56.105, and were conducted in compliance with the requirements for informed consent set forth in 21 C.F.R. Part 50.

Attachment 2 includes the description of the assay of for glucosamine in crystalline glucosamine sulfate.

Attachment 3 includes the Petitioner's comments on the HPLC determination of glucosamine in raw material and tablets described in the USP 26 NF 21 (see section V for Attachments 2 and 3).

Attachment 4 contains the results from a Medline search of the terms "glucosamine and osteoarthritis" and includes articles with and without abstracts. The search has been updated and includes all articles already indexed in Medline at the end of August 2003. Not surprisingly, this search identified numerous publications that have limited relevance for purposes of this Petition. This Petition summarizes only those articles that are of sufficient quality and relevance to provide meaningful input on

the relationship between glucosamine and osteoarthritis. The Petition also includes relevant abstracts that cannot be searched in Medline and other articles related to this topic.

IX. ENVIRONMENTAL IMPACT

Pursuant to 21 C.F.R. § 25.32(p), the requested health claim approval sought in this Petition is categorically excluded from any requirement to prepare an environmental assessment or environmental impact statement.

X. CONCLUSION AND CERTIFICATION

For the foregoing reasons, the Petitioner requests that FDA approves the proposed health claim.

On behalf of Petitioner, and pursuant to 21 C.F.R. § 101.70(h), the undersigned certifies that, to the best of Petitioner's knowledge, the Petition includes all information and views on which Petitioner relies and is a representative and balanced submission that includes all favorable as well as unfavorable information known by Petitioner to be pertinent to the evaluation of the proposed health claim.

Yours very truly,

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