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BY ELECTRONIC AND REGULAR MAIL

Mr. William K. Hubbard
Associate Commissioner for Policy and Planning
U.S. Food and Drug Administration (HF-22)
5600 Fishers Lane
Rockville, Maryland 20857

Re: Request for Correction in the Agency Response to the 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

Dear Mr. Hubbard:

We are writing this letter on behalf of our client, Rotta Pharmaceuticals Inc. (Rotta) in response to your October 7, 2004 letter (hereinafter "October 7th letter") containing the agency's conclusions on the above-referenced health claim petition that we submitted on September 17, 2003. We are writing to bring to the agency's attention significant factual errors and mischaracterizations of the underlying science that are found in two different sections of the October 7th letter.

We note at the outset that we continue to believe that we provided sufficient evidence to support the use of the claim proposed in the original health claim petition that "crystalline glucosamine sulfate reduces the risk of osteoarthritis joint deterioration and related joint pain and limitation of function." We, nonetheless, are not challenging the agency position that the clinical studies in patients with osteoarthritis (OA) cannot be used to support a claim that crystalline glucosamine sulfate will reduce the risk of developing OA.

We are bringing to your attention, however, certain statements found in the October 7th letter because the statements that are not supported by the underlying record. As will be discussed in more detail below, the October 7th letter identifies the wrong source of glucosamine that is being evaluated in studies sponsored by the National Institute of Health (NIH). The October 7th letter also

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contains numerous misstatements and mischaracterizations of the underlying evidence in the section that addresses the scientific credibility of the clinical studies that served as the foundation of our petition. Given the importance of having the administrative record contain factually accurate statements, we are asking the agency to include this letter in the administrative record of this rulemaking to ensure that the record accurately reflects our concerns with certain statements found in the October 7th letter.

A. FDA identified the wrong source of glucosamine that is being used in the National Institutes of Health (NIH) sponsored studies as “glucosamine sulfate” instead of “glucosamine hydrochloride.”

We presented extensive data and information in both the testimony before the Food Advisory Committee (FAC) and in the health claim petition establishing the important distinctions between the crystalline glucosamine sulfate that is manufactured and marketed by Rotta and the numerous other dietary sources of glucosamine, such as glucosamine hydrochloride. The information before the agency establishes that most of the clinical evidence available on the effects of glucosamine in osteoarthritis has been obtained with Rotta’s crystalline glucosamine sulfate, including the only two long-term (three-year) clinical trials.¹ These long-term trials establish the efficacy and safety of crystalline glucosamine sulfate in patients with osteoarthritis.

While we recognize that FDA likely considered it unnecessary to draw distinctions between the various sources of glucosamine given the agency conclusion that there is insufficient evidence to support the health claim, the agency should not have mischaracterized the source of glucosamine that is being studied at NIH. The NIH-sponsored clinical studies are using glucosamine hydrochloride and not glucosamine sulfate as stated in the agency letter. The agency specifically states in section I.C.:

[t] here are two ongoing NIH clinical trials using glucosamine. One is the Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT), which is studying the effectiveness of glucosamine sulfate (and chondroitin sulfate) to improve pain and knee function in patients with

¹ Reginster JY, Deroisy R, Rovati LC et al. Long-term effects of glucosamine sulfate on osteoarthritis progression: a randomized, placebo-controlled clinical trial. *Lancet* 2001;357:251-256; Pavelka K, Gatterova J, Olejarova M, Machacek S, Giacovelli G, Rovati LC. Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study. *Arch Intern Med* 2002;162:2113-23.

OA, and the other is studying the absorption and distribution of glucosamine sulfate (and chondroitin sulfate). Both trials use the same dosage of 1500 mg glucosamine sulfate per day either alone or in combination with 1200 mg chondroitin sulfate.

Information on both studies can be accessed on the Clinicaltrials.gov web registry.²

NIH is studying “glucosamine hydrochloride” and not “glucosamine sulfate.” Glucosamine hydrochloride is a different glucosamine salt and its relative bioavailability, pharmacokinetic, efficacy and safety pattern is relatively unknown when compared with the extensive data on Rotta’s crystalline glucosamine sulfate. In addition, the pharmaceutical form and daily dosage schedule are also different. Given the differences in glucosamine sources, it is difficult to predict what relevance the NIH-sponsored studies will have with regard to the efficacy of crystalline glucosamine sulfate, other than to perhaps increase our knowledge about osteoarthritis and glucosamine in general.

B. FDA mischaracterized the data and made other inaccurate statements when discussing the credibility of the clinical studies supporting the efficacy of crystalline glucosamine sulfate.

We also would like to bring to the agency’s attention the numerous mischaracterizations found in section II.A.3., the section of the letter that summarily dismisses the two long-term studies claiming that the studies are so “fundamentally flawed that they are not scientifically credible.” As will be discussed in more detail below, the short discussion in the agency letter mischaracterizes comments made during the FAC meeting, ignores documents that had been included in the original petition and discussed during the FAC meeting, and mischaracterizes the credibility of the long-term studies submitted in the petition.

In this section of the letter the agency identifies a total of nine different clinical studies. The agency divided these nine studies into two groups: a group of six studies and a group of three studies. The agency challenged the credibility of the group with six studies claiming that the studies lacked proper controls and had flawed designs. (See October 7th letter at II.A.1.c. at 12.) Rotta

² The NIH studies can be accessed at <http://www.clinicaltrial.gov/show/NCT00032890> and <http://www.clinicaltrial.gov/show/NCT00086229>.

recognizes that these studies cannot be used to support a prevention claim due to the absence of a placebo or untreated control group. Their credibility in the context of osteoarthritis treatment is not under discussion here. We, nonetheless, included the studies in the petition because we wanted to provide the agency with a complete data package on the studies that have been conducted using glucosamine sulfate for the short-term symptomatic treatment of osteoarthritis.

We do, however, take issue with the agency's dismissal of the second group of studies. The second group of three studies includes the works of Conte, Reginster, and Pavelka. It is unclear why the agency included Conte in this discussion because the Conte study involved chondroitin and we did not use it in support of our health claim. Although our petition referenced the Conte study, we did so merely for the purpose of providing information on the pharmacokinetic properties of chondroitin. Because we did not introduce the Conte study in support of the efficacy of crystalline glucosamine sulfate, the Conte study should not have been included in this grouping of three studies.

The agency criticism of the Pavelka and Reginster studies focuses primarily on the methodology used in those studies to evaluate the progression of osteoarthritis. These studies used the standing, fully extended knee radiographic view to assess joint space narrowing. At the time of these studies, researchers considered this radiographic method the "gold standard" for assessing the progression of OA. It is noteworthy that both of these studies have been published in reputable peer-reviewed journals, *The Lancet* and *Archives of Internal Medicine*. These journals certainly would not have accepted the studies for publication if the study designs used a flawed methodology.

In an attempt to further build its case challenging the radiographic methodology used in the Reginster and Pavelka studies, the agency cites the comments of one of the FAC members, Dr. Felson, who stated, "X-ray films used in the cited studies are no longer used in clinical trials because they are no longer considered reproducible measures over time." (See October 7th Letter at 12-13.) The agency fails to disclose, however, that Dr. Felson made these comments after listening to the presentation and summary of clinical studies submitted by the other petitioner.

The agency letter also fails to disclose that Rotta addressed this very issue in its presentation. Rotta's expert, Dr. Lucio Rovati, made the following comments to the FAC after Dr. Felson made the previously mentioned comments:

the rheumatologists here know that this [crystalline glucosamine sulfate] was the first clinically tested agent that was able possibly to prevent the progression of osteoarthritis joint structure deterioration as determined by radiographic joint space narrowing. We may come back during the discussion on the issue raised previously by Dr. David Felson. Clearly, this was the standardized methodology adopted and the only one available at the time of the trial. It's clearly not the methodology that we will use today, but we've also published validation data that this methodology was not biased by any confounder with respect to the results.

(See FAC Transcript, June 7, 141-142.)

Moreover, Dr. Rovati was eluding to a recently published study that evaluated the methodologies used by Pavelka and Reginster and concluded there is no bias with the radiographic method that might have altered the results in the Pavelka and Reginster studies.³ Although this study was not published when we submitted the petition, we did include an abstract of the study in the health claim petition as reference 39.

Notably, no members of the Food Advisory Committee challenged the credibility of the data presented by Dr. Rovati, including the studies of Pavelka and Reginster. Dr. Felson, who had been critical of the earlier presentation, responded to Dr. Rovati's presentation with the following remark:

Lovely data-based review with a lot of data, which I know you've been very involved in.

(See FAC Transcript, June 7, 178-179.) In addition, one of the other rheumatologists on the FAC, Dr. Abramson, stated "some interesting studies from Reginster and Pavelka in patients that we can use to extrapolate what looks to be increasingly interesting evidence that the drug does work in the degenerated state." (See FAC Transcript, June 8, 85.) These and other comments made during the FAC are at odds with an agency position that the Pavelka and Reginster studies are lacking in credibility.

³ Pavelka K, Bruyere O., Rovati L.C., Olejarova, Giacobelli G., Reginster J.Y. Relief in mild-to-moderate pain is not a confounder in joint space narrowing assessment of full extension knee radiographs in recent osteoarthritis structure-modifying drug trials. *Osteoarthritis Cartilage* 2003;11:730-737 (Copy Attached).

Although Rotta presented data in its original petition and before the FAC validating the radiographic method used in the Pavelka and Reginster studies, the agency states in its October 7th letter:

FDA could not find evidence in the petitions, the discussion at the FAC meeting, the OAI or elsewhere that any of the biochemical and radiographic markers of CD used in the cited studies [*i.e.*, Pavelka, Reginster and Conte] are considered valid for measuring CD; rather the available scientifically credible evidence indicates that these markers are not scientifically reliable as measures of CD.

(See October 7th Letter at 12.) There simply is no basis for this FDA statement because (1) the Pavelka and Reginster studies measured radiographic joint space narrowing (JSN), a methodology recognized by experts as appropriate for measuring CD (although other imaging techniques may be more appropriate if they are validated in the future), (2) Rotta did present evidence in its petition and before the FAC validating the methodology used in these two long-term studies, and (3) there is other research that validates the use of radiographic methods for assessing JSN.

A review of the research published by Dr. Felson, one of the FAC members, further supports the validity of JSN for evaluating CD. Dr. Felson noted during the FAC that the meniscus in the knee, rather than the articular cartilage, is playing an important role in joint space narrowing measured radiographically. (See FAC Transcript, June 7, 117-118.) Dr. Felson's group is convincingly showing through MRI imaging that position and degeneration of the meniscus may account for a great part of the variability in JSN. Nevertheless, the research notes that cartilage loss contributes at least 40%⁴ and that meniscal changes have potent effects on cartilage loss.⁵ Perhaps more important, Dr. Felson's group has reported that cartilage loss on MRI and JSN are well correlated.⁶ Dr. Felson's findings establish that, while MRI or other techniques may replace radiography in future studies in OA, radiographic measures of JSN are still valid techniques for measuring OA and CD.

We recognize that today's research involves the use of semi-flexed knee methods that are more efficient than the radiographic methods used by Pavelka and Reginster.⁷ It is not uncommon, particularly in emerging fields like OA research,

⁴ Hunter et al, Arthritis Rheum 2004, 9 Suppl: 1717.

⁵ Hunter et al, Arthritis Rheum 2004, 9 Suppl: 231.

⁶ Amin et al, Arthritis Rheum 2004, 9 Suppl: 563.

⁷There are at least three semi-flexed radiographic view methods, but there is no agreement on which is the most efficient in prospective and randomised clinical trials. Omeract/OARSI convened a panel

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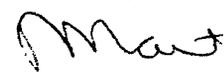
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for methodologies to develop and change over time. As new methods are developed, the results from studies using earlier methods are not summarily dismissed in the absence of bias or some other evidence that would call into question the results of the study. The Pavelka and Reginster studies have been critically evaluated and the results have been validated, thus, substantiating the credibility of the study results.

In conclusion, our review of Section II.A.3. of the October 7th letter has uncovered numerous mischaracterizations of the underlying data and other statements that are not supported by the data before the agency. Given the nature of our concerns, we ask the agency to include this letter as part of the administrative record for this rulemaking.

We thank you in advance for your consideration of this request. If you have any questions or comments, please contact us.

Sincerely,



Martin J. Hahn

Attachment

cc: Kathy Ellwood, Ph.D.

of OA experts in Bethesda, Maryland in December 2002 for the purpose of reaching consensus on the method that should be used. Many of the experts at this workshop also attended the FAC (*i.e.*, Dr. Altman, Dr. Felson, Dr. Simon, and Dr. Rovati). The results from the workshop entitled, Omeract/OARSI Workshop for Consensus in OA Imaging, have never been published because the group could not reach consensus.