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Martin J. Hahn
Hogan & Hartson, L.L.P.
555 Thirteenth Street, NW
Washington, DC 2004-1109

Dear Mr. Hahn:

This completes our response to your letter dated December 3, 2004 ("December 3 letter") to William K. Hubbard, former Associate Commissioner for Policy and Planning in the Food and Drug Administration (FDA or the agency) concerning FDA's October 7, 2004 letter ("October 7 letter") denying a health claim petition for crystalline glucosamine sulfate and reduced risk of osteoarthritis (OA) submitted by your client, Rotta Pharmaceuticals Inc. By letter dated January 28, 2005, FDA responded to the first point in your December 3 letter, which concerned a factual error about the source of glucosamine that is being evaluated in studies sponsored by the National Institutes of Health (NIH). The following is our response to the remainder of your December 3 letter, in which you argue that FDA misstated and mischaracterized the scientific evidence that served as the foundation of your client's petition.

In the December 3 letter, you state that "FDA mischaracterized the data and made other inaccurate statements when discussing the credibility of the clinical studies supporting the efficacy of crystalline glucosamine sulfate." Specifically, you state that the study on chondroitin sulfate by Conte et al. (1995) should not have been discussed along with the glucosamine studies by Pavelka et al. (2002) and Reginster et al. (2001). Further, you do not agree with FDA's conclusion that the radiographic methodology used in the studies by Pavelka et al. (2002) and Reginster et al. (2001) is not scientifically reliable for assessing the progression of cartilage deterioration (CD).

In the Rotta health claim petition, the study on chondroitin sulfate by Conte et al. (1995) was summarized in section III.B.3, "Clinical trials performed with glucosamine formulations other than crystalline glucosamine sulfate." FDA recognized that the summary of this study in the petition was largely a discussion of the bioavailability and metabolism of chondroitin sulfate. However, the summary ends with the petitioner's conclusion that "[t]he clinical activity reported for chondroitin sulfate in some clinical trials may be similar to that of low dose glucosamine sulfate." Thus, FDA concluded that the petitioner considered the study by Conte et al. (1995) as not only a pharmacokinetic

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study of chondroitin sulfate, but also as indirect evidence for OA risk reduction by crystalline glucosamine sulfate. Therefore, the agency discussed Conte et al. (1995) along with Pavelka et al. (2002) and Reginster et al. (2001) in section II.A.3 of the October 7 letter, which addressed the reliability of specific biomarkers and methods used in these studies to measure CD. Section II.A.3 did not address the substance used in the studies.

The December 3 letter also asserts that FDA mischaracterized a comment by Dr. Felson, an OA expert on the FDA Food Advisory Committee (FAC), who concluded that “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.” You claim that this comment by Dr. Felson was taken out of context because it was made prior to the presentation of the data in these studies by Rotta’s OA expert, Dr. Rovati. Although it is true that Dr. Felson’s comment was made before Dr. Rovati’s presentation, Dr. Felson made his comments after and in response to the presentation by Dr. Bucci, an OA expert for petitioner Weider, that summarized the data from several human clinical studies on glucosamine, including the radiographic data from the studies by Pavelka et al. (2002) and Reginster et al. (2001) (see FAC Transcript, June 7, p. 90).

You further claim that the agency erred in not considering additional comments by Dr. Felson and Dr. Abramson (another OA expert on the FAC) that were made after Dr. Rovati’s presentation to the FAC. In the December 3 letter, you quote two specific comments by Drs. Felson and Abramson that you believe support the reliability of the radiographic methodology used in the studies by Pavelka et al. (2002) and Reginster et al. (2001). In reaching its conclusions, FDA did consider these additional comments quoted in the December 3 letter, along with all of the comments made at the FAC meeting; however, the additional comments by Drs. Felson and Abramson do not specifically address the issue of the reliability of the radiographic methodology. The studies in OA patients by Pavelka et al. (2002) and Reginster et al. (2001) measured the effects of crystalline glucosamine sulfate on indices of joint pain, joint mobility, CD progression using the radiographic method under question, and adverse events. Dr. Felson’s comment (“[I]ovely data-based review with a lot of data . . .”) was about the thoroughness of the data review by your client and did not mention the radiographic methodology. Dr. Abramson’s comment (“interesting studies from Reginster and Pavelka . . . that we can use to extrapolate what looks to be increasingly interesting evidence that the drug does work in the degenerated state”), which may be interpreted as supportive of the efficacy of crystalline glucosamine sulfate in treating OA, does not indicate the outcome(s) he was referring to, whether pain reduction, increased mobility, slower CD progression or all three--any of which could be evidence for efficacy. For these reasons, FDA did not consider the comments by Dr. Abramson and Dr. Felson as endorsements of the reliability of the radiographic methodology used in these studies.

You also suggest that FDA should have considered the abstract by Pavelka et al. (2002) of a study that reportedly validates the radiographic methodology used by Pavelka et al. (2002) and Reginster et al. (2001). This abstract was submitted in the Rotta health claim

petition and referred to by Dr. Rovati during his presentation at the FAC meeting, but a copy of the complete study, which was published in 2003,¹ had not been submitted to FDA as of October 7, 2004, when the agency made its decision on the petition. As explained in the October 7 decision letter, abstracts do not provide enough information for FDA to determine the relevance of a study to the petitioned health claim, or to determine whether the study is flawed in critical elements such as design, conduct, and data analysis. FDA must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it.

Your letter argues that Dr. Felson's own research supports the reliability of the radiographic method used in Pavelka et al. (2002) and Reginster et al. (2001) (joint space narrowing) by offering an explanation for the variability observed in radiographic studies and showing that cartilage loss measured in radiographic studies correlates well with cartilage loss measured through MRI imaging. The three abstracts of research by Dr. Felson and his group that you cited in the December 3 letter² had not yet been published when FDA made its decision on the Rotta health claim petition. Moreover, even if the abstracts you cite had been available and had been submitted to the docket prior to the decision, as noted above, FDA does not rely on abstracts when reviewing health claim petitions because they do not provide enough information for the agency to evaluate the underlying study.

In reaching its conclusion about the radiographic methodology used in the studies by Pavelka et al. (2002) and Reginster et al. (2001), FDA also considered the conclusions of other panels of OA experts convened to determine the reliability of the radiographic methods used in human clinical studies. As discussed in the October 7 letter, the NIH has created the Osteoarthritis Initiative (OAI) with the goal of creating a public resource to validate imaging and biochemical biomarkers and ensure that validated biomarkers for OA are made widely available. The OA experts on the OAI reached a general consensus that, although the existing radiographic techniques are promising, they are in need of validation before any specific methodology can be considered as reliable (<http://www.niams.nih.gov/ne/oi/prospectus62.htm>). The OAI is currently conducting a five-year longitudinal validation study to determine which radiographic methods are reliable measures of CD over time.

Finally, you assert that the October 7 letter mischaracterized the evidence by stating that FDA "could not find evidence in the petitions, the discussion at the FAC meeting, the OAI or elsewhere" that the radiographic methodology used in the studies by Pavelka et al. (2002) and Reginster et al. (2001) was a reliable measure of CD. FDA agrees that the letter went too far in stating that the agency could not find any evidence that the radiographic methodology used was a reliable measure of CD. However, based on the

¹ Pavelka K, Bruyere O, Rovati LC, Olejarova M, Giacobelli G, Reginster JY. 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 Oct;11(10):730-7.

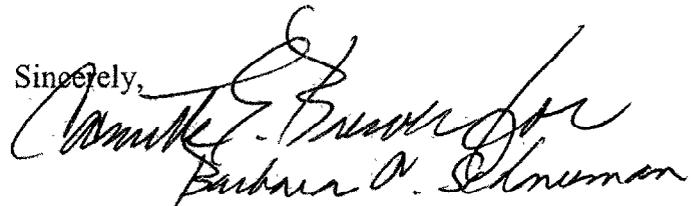
² Hunter et al, *Arthritis Rheum* 2004, 9 Suppl: 1717; Hunter et al, *Arthritis Rheum* 2004, 9 Suppl: 231; Amin et al, *Arthritis Rheum* 2004, 9 Suppl: 563.

totality of the publicly available evidence submitted to FDA, presented at the FAC meeting and identified elsewhere by FDA during its review, the agency reasonably concluded that the radiographic methodology used in the studies by Pavelka et al. (2002) and Reginster et al. (2001) was not a validated methodology and therefore not a scientifically reliable measure of CD over time. FDA did not conclude that the radiographic method used has been determined to be invalid, but rather, that the validity of the method has not been resolved to date, and a determination is therefore dependent upon the results of the validation studies currently underway as part of the OAL. In any event, whether or not these studies assessing CD treatment in OA patients used valid radiographic methodology, their results cannot be extrapolated to show reduction of OA risk in the general healthy population. Therefore, it would have been necessary for FDA to deny the Rotta health claim petition even if the agency had concluded that the radiographic methodology in the studies was valid and reliable.

As you requested, your December 3, 2004 letter has been included in the docket (Docket No. 2004P-0060), where it is identified as LET 11. Our first response to you dated January 28, 2005 has also been included in the docket, and this letter will be placed in the docket as well.

We hope that this is helpful.

Sincerely,

A handwritten signature in cursive script, appearing to read "Barbara O. Schneeman".

Barbara O. Schneeman, PhD
Director
Office of Nutritional Products, Labeling
and Dietary Supplements
Center of Food Safety
and Applied Nutrition