



OCT 12 2004

Jonathan W. Emord, Esquire  
Claudia A. Lewis-Eng, Esquire  
Emord & Associates, P.C.  
1800 Alexander Bell Drive  
Suite 200  
Reston, Virginia 20191

Re: Glucosamine and Chondroitin Sulfate/Osteoarthritis Risk Reduction  
Claims; Your Letter Dated July 1, 2004 to Michael M. Landa and Louisa  
T. Nickerson, DHHS/FDA/OC/OCC

Dear Mr. Emord and Ms. Lewis-Eng:

I am responding to the above identified letter (the "July 1 letter") in my capacity as Director of Regulatory Affairs, Center for Food Safety and Applied Nutrition ("CFSAN"), Food and Drug Administration. In the July 1 letter, you assert that the questions posed to the Food Advisory Committee and its Dietary Supplements Subcommittee (collectively, the "FAC") "reveal a pronounced bias against allowance of the claims and a position inconsistent with the First Amendment standard that governs FDA evaluation of health claims." You also assert that "key members of the FAC, selected by CFSAN and FDA's Center for Drug Evaluation and Research ("CDER"), had conflicts of interest and were biased, making their selections plain error and FAC reliance upon them mistaken." In addition, you request FDA to "consider reformed versions" of claims rejected by the agency on the ground that they imply disease treatment. The agency addressed your request in a letter dated August, 9, 2004; hence, this letter will address only your assertions of bias and conflicts of interest.

You characterize the questions posed to the FAC as revealing a "pronounced bias," and complain that FDA did not ask the FAC to apply the "credible evidence" standard or whether "any claim could be made truthfully if properly disclaimed." You concede that the FAC was told that it was not evaluating a drug, but complain that the FAC was "not told that if any credible evidence existed to support the claim, that evidence should be identified as such and not eschewed as undeserving of consideration due to inconclusiveness." You also complain that the FAC was "not told that even preliminary and inconclusive evidence could support a health claim so long as a disclaimer to the claim could be devised to avoid a misleading connotation."

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Your characterization of the questions and your complaints presuppose that (1) FDA sought the FAC's advice or recommendations on the petitions or on the substance-disease or substance-health-related condition relationships claimed in the petitions, and (2) the FAC is the decision-maker in this matter. But the agency did not seek the FAC's advice or recommendations about the regulatory questions before the agency, and FDA, not the FAC, is the decision-maker here. The FAC, after all, does not have any expertise in the evidentiary standards for health claims or in disclaimers. What the FAC does have is scientific expertise. For that reason, the questions FDA posed were intended to elicit from the FAC its views about scientific issues raised by the petitions. As Laura M. Tarantino, Ph.D., then Acting Director of CFSAN's Office of Nutritional Products, Labeling, and Dietary Supplements stated at the outset of the FAC meeting on June 7, 2004 (FAC transcript, p. 24):

[T]he questions that we're asking you to consider are not about health claims per se. Furthermore, as you'll have noted from your background material and the information, the questions are also not about glucosamine and chondroitin sulfate specifically. Rather, what we are asking you and what we're asking your help about is in assessing the science needed to demonstrate reduction in risk of osteoarthritis in healthy people. Health claims have to do with the relationship between a substance and a disease and reduction of risk of a disease in healthy people.

Sanford A. Miller, Ph.D., Chair of the FAC, made this same point about the FAC's role several times during the FAC meeting, on June 7 and June 8 (see, e.g., FAC transcript, June 7, pp. 42, 65, 350-52; June 8, pp. 75-76). On June 7, for example (FAC transcript, pp. 350-52) he stated:

I think that leads me into making a couple of comments before we adjourn for the day. I want to repeat again, the function of this committee is not to evaluate the petitions that were submitted, but the results of the petitions there is to give you some idea, as many of you already well knew, of the methods that were being used in order to support the petition, and the question is: Are these valid methods? Do they predict what they supposedly claim to be predicting? And so on. So while this is a very interesting discussion, it really is not germane to the issue of the work of the committee, and I think it's very important to make that point. Secondly, in order to clarify some of these issues, FDA prepared a statement, again, trying to redefine what the role of the committee is, and I'll just read this to clarify: The committee's task is not to evaluate whether there are sufficient data to conclude that glucosamine and/or chondroitin reduce the risk of osteoarthritis; rather, the committee should address the scientific questions that were provided to it. For the committee's information, the evidentiary standard applied to health claims is different from and weaker than the drug standard. As I indicated this morning, FDA, not the committee, will apply that standard. I think that's important because many of you have experience with drug evaluations,

and that's a different standard than used for foods. I think you have to keep that in mind.

As you know, the FAC concluded, and FDA agreed, that the intervention studies on treatment of osteoarthritis are not evidence of a risk reduction effect and that animal and in vitro studies are not sufficient to demonstrate a risk reduction effect in the absence of clinical data. Thus, assuming for the sake of argument that your complaints about the questions posed to the FAC, the evidentiary standard allegedly employed by the FAC, and the failure of the FAC to consider disclaimers, had any merit (and they do not), the absence of supporting evidence for your claims means that your complaints are beside the point.

FDA decided to seek expert advice on specific scientific issues on osteoarthritis, including its etiology, its modifiable risk factors, and relevant models after the agency had reconsidered an initial decision denying the petition submitted by your client. Neither the Food Advisory Committee nor its Dietary Supplements Subcommittee had members with the requisite expertise in rheumatology. For this reason, FDA decided to add physicians with expertise in osteoarthritis and other joint diseases as temporary voting members (in the case of experts borrowed from another FDA Advisory Committee, such as the Arthritis Advisory Committee) or expert voting consultants (in the case of experts who are not members of an FDA Advisory Committee), and sought recommendations for qualified experts from each of the petitioners. FDA focused on identifying the best scientific expertise available and on identifying conflicts of interest.

The FAC included 13 members from the Food Advisory Committee, 4 members from the Dietary Supplements Subcommittee of the Food Advisory Committee, and 6 experts FDA added to the FAC as temporary voting members or expert voting consultants because of their expertise in rheumatology. These six included one expert (Scott A. Kale, M.D.) recommended by your client and two experts (Nancy E. Lane, M.D. and Luis Espinoza, M.D.) recommended by the other petitioner. You assert that the other three experts -- Steven B. Abramson, M.D., John J. Cush, M.D., and David T. Felson, M.D., MPH -- should not have been added because, you claim, they had a conflict of interest. In the case of Dr. Cush, the alleged conflict was his past acceptance of funding from "pharmaceutical companies that sell non-steroidal anti-inflammatory drugs used in the treatment of . . . symptoms of osteoarthritis"; in the case of Dr. Abramson and Dr. Felson, the alleged conflict was that they have in the past accepted or are now accepting funding from the National Institutes of Health (NIH) in connection with a "study devoted to learning more about osteoarthritis through the identification and analysis of biomarkers in joint, bone, and synovial tissue."

Dr. Cush is currently Chief of the Division of Rheumatology and Clinical Immunology, Medical Director of the Arthritis Center of Presbyterian Hospital of Dallas and is a Clinical Professor of Internal Medicine at the University of Texas Southwestern Medical School. In 1996 and 1998 he was voted to the "Best Doctors In America" list by his peers. Dr. Cush has remained active with his alma mater and is on the Board of Trustees and Academic Board of St. Georges University where he continues as a teacher and

advisor. He serves on the Arthritis Advisory Committee, CDER. Dr. Cush has authored a rheumatology textbook entitled, "Rheumatology: Diagnosis and Therapeutics" that was released by Lippincott, Williams & Wilkins in November 1998. He has nearly 70 publications on a variety of topics including rheumatoid arthritis, RA immunopathogenesis, drug-induced lupus, spondyloarthropathies, immunotherapy, and adult-onset Still's disease. He has been co-editor of the American College of Rheumatology Hotlines since 1999.

Dr. Abramson is Professor of Medicine and Pathology at the New York University School of Medicine where he is Director of the Division of Rheumatology. He is also Physician-in-Chief and Chairman of the Department of Rheumatology and Medicine at the Hospital for Joint Diseases. Dr. Abramson graduated from Dartmouth College and earned his medical degree from Harvard Medical School. He completed his internship and residency at the New York University Medical Center-Bellevue Hospital where he also pursued a fellowship in rheumatology. Dr. Abramson is currently a member of the Board of Trustees of the National Arthritis Foundation. He has served as Chairman of the Arthritis Advisory Committee, CDER, and continues as an active consultant to the Committee. Dr. Abramson has also served on various committees and organized various symposia at the American College of Rheumatology and is on the Board of Directors of the Osteoarthritis Research Society International. He has published more than 170 articles and book chapters. He has served on the Editorial Board of several journals and is currently Associate Editor for Arthritis and Rheumatism. Dr. Abramson is known internationally for his research contributions to the basic understanding of inflammation and immunologically induced tissue injury. In recent years, Dr. Abramson's research interests include inflammatory mediators produced by articular cartilage, particularly the role of chondrocyte-derived nitric oxide, PGE and inflammatory cytokines in promoting the catabolic state that characterizes progressive joint damage in osteoarthritis.

Dr. Felson is Professor of Medicine and Public Health and Principal Investigator of the NIH-funded Boston University Multipurpose Arthritis and Musculoskeletal Diseases Center and the Boston University Multidisciplinary Research Center. Ongoing projects include the study of osteoarthritis of the knees and hands in Framingham cohort and offspring study groups and the newly constituted Framingham Omni Cohort which is a sample of minority, middle-aged and elderly subjects in Framingham. Dr. Felson is the principal investigator of the Beijing Osteoarthritis Study, a study of the prevalence of knee, hand and hip osteoarthritis in a population-based sample of Beijing residents 60 years and over. His research has consistently focused on musculoskeletal diseases highly prevalent in the elderly, and he has written extensively on the epidemiology of osteoarthritis. Dr. Felson has also been the chairperson of a committee to develop outcome measures in rheumatoid arthritis trials and has been similarly involved in developing definitions of outcome for trials and other musculoskeletal diseases. He has served as a consultant to the Arthritis Advisory Committee, CDER, and serves on the Steering Group of the NIH Osteoarthritis Initiative.

Drs. Abramson, Cush and Felson's unique understanding and thorough knowledge of osteoarthritis qualified them to provide critical expert advice on the FAC.

Before selecting Drs. Abramson, Cush, and Felson, FDA did conclude that they each had a financial conflict of interest within the meaning of 21 U.S.C. 208(a).<sup>1</sup> The agency also concluded, however, that the "need for [each of these experts'] services, with respect to particular matters of general applicability, outweighs the potential for a conflict of interest created by any personal or imputed financial interest that he may have in particular matters of general applicability," and issued each expert a waiver under 21 U.S.C. 208(b)(3) in accordance with its terms. Given the expertise of Drs. Abramson, Cush, and Felson, FDA's decision to grant the waivers was reasonable and consistent with past decisions to grant waivers under similar circumstances.

You should also know that the experts recommended by the petitioners - - Drs. Kale, Lane, and Espinoza -- had a financial conflict of interest within the meaning of 21 U.S.C. 208(a), and that FDA also issued each expert a waiver under 21 U.S.C. 208(b)(3).

Conflicts of interest and waivers on the FAC are not unusual, because the world-renowned experts FDA seeks for its advisory committee are of course also much sought after by the private sector and by other government agencies. The law recognizes this tension and resolves it by providing for waivers; if a conflict of interest were sufficient to make a possible candidate for advisory committee membership ineligible for service without the possibility of a waiver, FDA would be unable to obtain the outside expertise it needs. Not surprisingly, then, FDA issued waivers to 11 of the other 17 members of the FAC.

Sincerely yours,



Michael M. Landa  
Director of Regulatory Affairs  
Center for Food Safety and Applied Nutrition

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<sup>1</sup> None of the potential conflicts FDA identified, however, was related to your allegations, which concern matters far afield (Dr. Cush's past funding from pharmaceutical companies that market non-steroidal anti-inflammatory drugs) or matters as to which there is agreement in the scientific community that further research is needed (Dr. Abramson and Dr. Felson's NIH-funded research concerning biomarkers.) Indeed, Roy D. Altman, M.D., one of the other petitioner's experts, is a member of the Steering Group of NIH's Osteoarthritis Initiative, which funded the \$4.6 million grant to which you refer.