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July 1, 2004

VIA UPS NEXT DAY AIR
AND FACSIMILE

Michael M. Landa
Louisa T. Nickerson
DHHS/FDA/OC/OCC
Building PKLN
Mail Stop GCF-1
Rockville, MD 20857

Re: Glucosamine and Chondroitin Sulfate/Osteoarthritis Risk Reduction Claims

Dear Mike and Louisa:

We understand that within sixty days of the Food Advisory Committee's issuance of its recommendations, the Center for Food Safety and Applied Nutrition will supply you with its conclusions. As stated in our letter of June 4, 2004, we believe CFSAN erred by issuing tentative conclusions in advance of the meeting. We also believe the questions posed to the panel 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. We further believe that key members of the FAC, selected by CFSAN and CDER, had conflicts of interest and were biased, making their selections plain error and FAC reliance upon them mistaken.

In particular, the first question posed to the panel asked whether joint degeneration and cartilage deterioration were "modifiable risk factors/surrogate endpoints" for osteoarthritis risk reduction? That question frames the issue in unduly narrow terms. So long as there is credible evidence that consumption of glucosamine and chondroitin sulfate does affect the tissue in question in a way that may reduce osteoarthritis risk, it does not matter whether there has been a definitive determination as to whether joint degeneration or cartilage deterioration have been found, or are generally recognized, as modifiable risk factors or surrogate endpoints within FDA's definition of those terms. Despite repeated urging from CFSAN staff, the panel appears not to have understood the agency's meaning of those terms and, instead, appears to have understood

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the terms in a manner consistent with the First Amendment standard. That is, the panel appeared to accept that if an intervention affected cartilage deterioration, it would necessarily affect the risk of osteoarthritis and, so, voted in favor of that proposition.

The second and third questions ask whether if joint degeneration and cartilage deterioration are assumed to be modifiable risk factors or surrogate endpoints for osteoarthritis, and if a dietary substance operates in a drug-like fashion (i.e., treats, mitigates, or slows degeneration or deterioration), it would be "scientifically valid" to use that treatment evidence to suggest a reduced osteoarthritis risk in the general population. There are several problems with those questions. They effectively ask the panel to consider the dietary substance to be the equivalent of a drug. It is therefore entirely unsurprising that the panel engaged in extensive colloquy on the extent to which proof existed to a near certain degree that chondroitin sulfate and glucosamine prevented osteoarthritis in healthy individuals. Extrapolation from the clinical trials to the prevention context depends upon the standard for review. Proof to a near certain degree is not the standard for assessing dietary supplement claims; credible evidence is. The panel did not evaluate the evidence under the proper standard. The panel was never instructed by FDA of that standard. While informed that they were not evaluating a drug, they were 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. Credible evidence permits logical inferences. Logic dictates that a substance known by clinical trial evidence, in vitro evidence, and animal studies to build cartilage matrix will necessarily reduce risk of osteoarthritis because that condition is defined as a progressive loss of that cartilage resulting ultimately in eburnation. The panel members were 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. Consequently, while it is entirely logical to extrapolate from evidence revealing cartilage matrix construction in diseased populations consuming chondroitin sulfate and glucosamine (including those in the earliest stages, some prediagnostic, and those followed after treatment cessation) and from the in vitro and animal data, the panel found that doing so would be inconsistent with the level of proof they believed to be needed to establish a scientifically "valid" proof of effectiveness in the general healthy population. The panel thus did not perform its function in a manner consistent with the First Amendment standard applied to this agency's health claim reviews. It never answered whether credible evidence existed to support the claims. It never considered whether any claim could be made truthfully if properly disclaimed. It instead determined whether proof existed to a near certain degree not to support the claims but to support use of glucosamine and chondroitin sulfate as drugs in the prevention and treatment of osteoarthritis. That assessment is the wrong one.

The fourth question is likewise skewed. It asks the panel to consider animal and in vitro data alone and to assess whether it "demonstrate[s] risk reduction of OA in humans." The panel should have considered the totality of the evidence, not a subset, for any ultimate determination. The panel was not instructed that it need only determine whether the evidence was credible. Instead, it was asked to assess whether the evidence

demonstrated the result. That begs for proof to a near certain degree, which again, is erroneous because the credible evidence standard is not the drug standard.

In short, the panel was led to its conclusions through use of questions that beg for near conclusive proof, rather than credible evidence. Moreover, the panel was not instructed on the credible evidence standard and was not instructed on the role of disclaimers in assuring truthful dissemination of accurate scientific information. Their role should not have been to determine whether proof existed to a near certain degree but, rather, whether the proof that did exist could be accurately conveyed to the public via the claims that existed and via use of disclaimers. From the start, the instructions and questions to this panel ensured a biased, negative conclusion.

That bias is further reflected in CFSAN's choice of certain key temporary voting members who suffer from a conflict of interest and bias. We note that the temporary voting members who were the most influential, the ones the chairman of the panel and others deferred to repeatedly to explain the meaning of the scientific evidence, are ones selected by CFSAN and CDER. That alone is not enough to suggest a conflict or bias, but the following facts make the existence of conflict and bias obvious. Those individuals should never have been selected to serve on the panel in light of their conflicts of interest and bias.

As explained on the FDA's website, a conflict of interest arises when "an employee participates in an official matter and there is a direct and predictable link between the matters in which the Federal employee participates and the employee's financial interests." ("Policies and Procedures for Handling Conflicts of Interest with FDA Advisory Committee Members, Consultants, and Experts," website last viewed on 06/14/2004). Where the potential exists for an officer or employee of the U.S. government, or of any independent agency, including special government employees (such as appointed members of the Food Advisory Committee) to behave in a manner that directly affects their own or a related party's pecuniary interest, a conflict of interest is said to arise, and, according to the law, such an individual should be excluded from participating unless a waiver or exemption is granted. Where it is shown that such an employee has a financial interest in the matter upon which he/she has been asked to analyze, judge, critique or comment, the potential for bias or impartiality exists, and steps should be taken to remove that bias or limit its influence in the decision making process.

A conflict of interest can develop without there being a direct ascertainable pecuniary interest to an employee. Actions that result in a financial benefit to a spouse, partner or organization, or the maintenance of one's own current or future position may rise to the level of bias or impartiality. For example, where a decision is made or action taken to preserve future funding, guarantee future employment or protect one's current status and financial position, a conflict of interest may exist, and action should be taken to eliminate its effects.

Examining the background, research and funding of some of the Temporary Voting Members of the FDA's Food Advisory Committee who had de facto greatest

suasion over all other members leads one to conclude that there existed a conflict of interest that affected the outcome of the Food Advisory Committee's consideration of the scientific evidence concerning Glucosamine and Chondroitin Sulfate and its relationship to osteoarthritis. A number of the committee's members have received funding from organizations and corporations having aims that differ significantly from those of the petitioner, Weider Nutrition International, Inc.

The following are specific examples of lack of impartiality that should have resulted in exclusion from committee membership but did not. John J. Cush, M.D., Chief of the Division of Rheumatology and Clinical Immunology and Director of the Arthritis Consultation Center at Presbyterian Hospital of Dallas, has in the past accepted research funding and grants from (and has served as a consultant to) a number of large pharmaceutical companies that sell non-steroidal anti-inflammatory drugs used in the treatment of joint pain and other symptoms of osteoarthritis, including Amgen/Wyeth¹, Novartis Pharmaceutical Corp.² and Pfizer Inc.³. Financially, a large number, if not all of these companies, would be adversely affected if the Committee made recommendations in favor of the proposed claims because reduction in the risk of osteoarthritis will result in lower demand for NSAIDS used in the treatment of osteoarthritis. Considering his source of research funding, Dr. Cush could not be considered unbiased or impartial and should have been excluded from committee membership.

Additionally, a number of the temporary committee members have in the past or are currently receiving funding from the National Institutes of Health. Specifically, Steven Abramson, M.D., Professor of Medicine and Director of NYC's Department of Rheumatology, and David Felson, M.D., Boston University Professor of Medicine and Director of the school's NIH-funded Clinical Research Training Grant, are current participants in a four year study funded by the NIH devoted to learning more about osteoarthritis through the identification and analysis of biomarkers in joint, bone and synovial tissue. Initiated in February 2004, the five participating institutions, two of which have research teams directed by the above noted doctors, will share \$4.6 million over the next five years. The questions posed to the panel create a conflict for Drs. Abramson and Felson because to answer any of the questions posed affirmatively would cause them to admit that some of their research into the existence of biomarkers has been effectively answered in prior published studies, thus calling into question at least some of the bases for government funding of the studies. They thus have a direct and substantial interest in finding all questions posed unanswered until their own NIH study is completed. The conflict is obvious and substantial. Their participation in (and their scientific and financial commitment to) the study, for this and other reasons,⁴ reveals bias

¹ Amgen/Wyeth markets and sells the following NSAIDs: Duract, Lodine, Lodine XL, Naparelan, Orudis and Oruvail.

² Seller of Voltaren and Voltaren-XR.

³ Seller of Feldene.

⁴ The claim of discovery is one of palpable prestige and economic benefit to scientists engaged in public and private research. If the sum of extant scientific research already answers some of the questions said to be unanswered that are the subject of federally funded research, the scientists involved would experience a loss of prestige and fewer economic benefits.

and a lack of impartiality that should have caused them to be excluded from committee membership.

The bias of Drs. Cush, Abramson, and Felson is particularly damaging to the integrity of the FAC's work because repeated statements by other committee members, particularly at the close of the FAC meeting, reveals substantial reliance on their opinions as a basis for decision.

We also find bias present in the process that led to their selection. CFSAN and CDER revealed opposition to the proposed claims at meetings held with Weider on November 24, 2003 in the offices of Chief Counsel. CFSAN and CDER are responsible for the selection of Drs. Cush, Abramson, and Felson to serve on the panel. That selection is tainted by an appearance of bias and in fact resulted in the selection of individuals who suffered either a conflict of interest or bias.

We are aware that the agency met with representatives of Rotta Pharmaceuticals and reached an accommodation with them whereby Rotta withdrew the original claims it sought and had the agency consider a new one, i.e., an osteoarthritis risk reduction claim. While Weider continues to believe the risk reduction claims entirely appropriate under the apposite standard, FDA's tentative conclusions reveal that the agency is predisposed against those claims.

The agency needs to be mindful of the fact that Weider's claims include ones that are not tied to osteoarthritis. The following three petitioned claims concern joint degeneration and cartilage deterioration, regardless of its source:

- Glucosamine may reduce the risk of joint degeneration.
- Chondroitin sulfate may reduce the risk of joint degeneration.
- Glucosamine and chondroitin sulfate may reduce the risk of joint degeneration.
- Glucosamine may reduce the risk of cartilage deterioration.
- Chondroitin sulfate may reduce the risk of cartilage deterioration.
- Glucosamine and chondroitin sulfate may reduce the risk of cartilage deterioration.

Neither the tentative conclusions nor any of the FAC's deliberations directly addressed those questions, albeit no one on the panel appeared to quarrel with the evidence supporting the role of the dietary substances in building cartilage matrix and thereby reducing the risk of cartilage deterioration.

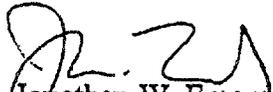
Weider also wishes for the agency to consider reformed versions of the claims FDA has rejected (due to the agency's view that they imply disease treatment). Like Rotta, Weider too wishes to reform those claims to comport with FDA's wishes. In particular, Weider asks FDA to consider the following in lieu of the three claims FDA has rejected as treatment claims:

Glucosamine may reduce the risk of joint-related pain.
Chondroitin sulfate may reduce the risk of joint-related pain.
Glucosamine and chondroitin sulfate may reduce the risk of joint-related pain.

The evidence of pain reduction in the record is substantial and follows logically from proof of construction of cartilage matrix. Weider will soon supply the FDA with a supplemental scientific evaluation of the existing evidence on this point to aid in the assessment of these three revised claims.

We will be in touch with you soon to discuss these matters in greater detail.

Sincerely,



Jonathan W. Emord
Claudia A. Lewis-Eng
Counsel to Weider Nutrition International, Inc.