Minutes of the
FOOD ADVISORY COMMITTEE and DIETARY SUPPLEMENTS SUBCOMMITTEE[1]

GLUCOSAMINE AND CHONDROITIN SULFATE AND OSTEOARTHRITIS

June 7-8, 2004

Bethesda Marriott
Bethesda, MD

Members present—Full Food Advisory Committee:
Douglas L. Archer, Ph.D.; Patrick S. Callery, Ph.D.; Annette Dickinson, Ph.D.; Goulda A. Downer, Ph.D.; Johanna Dwyer, D.Sc., R.D.; Jean M. Halloran; Norman I. Krinsky, Ph.D.; Daryl B. Lund, Ph.D.; Margaret C. McBride, M.D.; Sanford A. Miller, Ph.D.; Mark F. Nelson, Ph.D.; Robert M. Russell, M.D.; Carolyn I. Waslien, Ph.D., RD.

Members present—Dietary Supplements Subcommittee Members:
Edward Blonz, Ph.D.; Edward D. Harris, Ph.D.; Harihara M. Mehendale, Ph.D.; Steven Zeisel, M.D. Ph.D.

Temporary voting members present:
Steven Abramson, M.D.; John J. Cush, M.D.; Luis Espinoza, M.D.; David Felson, M.D., M.P.H.; Scott A. Kale, M.D., J.D., M.S.; Nancy E. Lane, M.D.

Food and Drug Administration representatives:
Robert E. Brackett, Ph.D.; Jeanne Latham; Louisa Nickerson; Linda Reed; J. Craig Rowlands, Ph.D.; Laura M. Tarantino, Ph.D.; James Witter, M.D., Ph.D.

Guest speakers:
Luke R. Bucci, Ph.D., Vice President of Research, Weider Nutrition Group;
Roy D. Altman, M.D., David Geffen School of Medicine, Professor of Medicine and Rheumatology, University of Miami and University of California-Los Angeles;
Lucio C. Rovati, M.D., Executive Medical Director, Rotta Research Laboratorium;
Lee S. Simon, M.D., Harvard Medical School, Associate Clinical Professor of Medicine, Beth Israel Deaconess Medical Center

Public speakers:
Jason Theodasakis, M.D., M.S., M.P.H., FACPM, University of Arizona College of Medicine, Canyon Ranch Medical Department;Gayle Lester, Ph.D., Program Director, Osteoarthritis Initiative & Diagnostic Imaging, NIAMS, NIH, DHHS;
Robert Arnot, M.D., former NBC Special Foreign Correspondent;
Jose Verges, M.D., M.Sc, Ph.D., Clinical Pharmacologist and Scientific Director, Bioiberica S.A.
Todd Henderson, DVM, Executive Vice President, Nutramax Laboratories, Inc.
Chuck Filburn, Ph.D., Director of Research & Development, Nutramax Laboratories, Inc.

Background:

Under the authority of the Federal Food, Drug, and Cosmetic Act, FDA authorizes health claims in the labeling of conventional foods and dietary supplements. Health claims must be reviewed by FDA before they may appear in labeling. In the FDA context, "health claim" does not have its usual broad meaning of any claim about health, rather, for FDA purposes, "health claim" means an express or implied labeling claim about the relationship between a substance (food or food component) and a disease or health-related condition. FDA has defined "disease" by regulation as damage to an organ, part, structure, or system of the body that it does not function properly, except for nutrient deficiency diseases. The agency has interpreted "health-relation condition" to mean a state of health leading to disease.

For the purposes of evaluating proposed health claims involving a disease (e.g. osteoarthritis), FDA has consistently identified two endpoints with which to identify disease risk reduction: a) reduction in incidence of the disease, and; b) beneficial changes in modifiable risk factors/surrogate endpoints for the disease.

FDA also refers to modifiable risk factors/surrogate endpoints for disease as "biomarkers." They are further defined as:

> "a measurement of a variable related to a disease that may serve as an indicator or predictor of that disease. Biomarkers are parameters from which the presence or risk of a disease can be inferred, rather than being a measure of the disease itself. In conducting a health claim review, FDA does not rely on a change in a biomarker as a measurement of the effect of a dietary factor on a disease unless there is evidence that altering the parameter can affect the risk of developing that disease or health-related condition…"

FDA relies primarily on human studies that are primary reports of data collection when attempting to establish a diet-disease relationship.

Meeting Summary:

The meeting convened on Monday, June 7 at 8 a.m.

Dr. Sanford A. Miller, Chairman of the Food Advisory Committee welcomed the committee and introduced the members.

Linda Reed, Acting Executive Secretary for the Food Advisory Committee shared some rules of the road and read the conflict of interest statement into the record.

Dr. Robert Brackett, Director of the Center for Food Safety and Applied Nutrition (FDA) welcomed everyone and provided opening remarks.

Background and Questions to the Committee:
Laura M. Tarantino, Ph.D., former Acting Director, Office of Nutritional Products, Labeling and Dietary Supplements (ONPLDS), Center for Food Safety and Applied Nutrition (CFSAN)

Dr. Tarantino briefed the committee concerning the charge before them. She emphasized that the questions being asked are not about a health claim, per se, or about glucosamine or chondroitin sulfate. FDA sought input concerning the etiology of osteoarthritis (OA), potential modifiable risk factors and the relevance of certain types of scientific studies used to substantiate the substance-disease relationship.

The questions before the committee:

1) a. Is joint degeneration a state of health leading to disease, i.e. a modifiable risk factor/surrogate endpoint (as discussed above) for OA risk reduction? What are the strengths and limitations of the scientific evidence on this issue?

   b. Is cartilage deterioration a state of health leading to disease, i.e. a modifiable risk factor/surrogate end point for OA risk reduction? What are the strengths and limitations of the scientific evidence on this issue?

2) a. If we assume that joint degeneration is a modifiable risk factor/surrogate endpoint for OA risk reduction and we assume that research demonstrates that a dietary substance treats, mitigates or slows joint degeneration (cartilage deterioration) in patients diagnosed with OA, is it scientifically valid to use such research to suggest a reduced risk of OA in the general health population (i.e., individuals without OA) from consumption of the dietary substance?

   b. If we assume that cartilage deterioration is a modifiable risk factor/surrogate endpoint for OA risk reduction and we assume that research demonstrates that a dietary substance treats, mitigates or slows joint degeneration (cartilage deterioration) in patients diagnosed with OA, is it scientifically valid to use such research to suggest

a reduced risk of OA in the general health population (i.e., individuals without OA) from consumption of the dietary substance?

3) If human data are absent, can the results from animal and *in vitro* models of OA be used to demonstrate risk reduction of OA in humans?
    a. To the extent that animal or *in vitro* models of OA may be useful, what animal models, types of evidence, and endpoints should be used to assess risk reduction of OA in humans?
    b. If limited human data are available, what data should be based on human studies and what data could be based on animal and *in vitro* studies to determine whether the overall data are useful in assessing a reduced risk of OA in humans?

Dr. Tarantino acknowledged there is incomplete knowledge available to answer these questions. But, she said, based on what we know today, which way does the needle point?

Overview of Legal Framework:
Louisa Nickerson, Food and Drug Division, HHS Office of the General Counsel

Ms. Nickerson briefed the committee concerning the legal framework for the Food Advisory Committee and the legal differences between drugs and dietary supplements. If the product is intended to treat, mitigate or cure disease, FDA regulates it as a drug. Health claims, on the other hand, are about reducing the risk of a disease or health-related condition—not treating, mitigating or curing diseases.

Overview of Petitions:
J. Craig Rowlands, Ph.D., Nutrition Programs and Labeling Staff, ONPLDS, CFSAN

Dr. Rowlands provided a summary of:

- ?? The scientific evidence submitted
- ?? Petitioners' conclusions
- ?? FDA's evaluation of the evidence
- ?? Questions and objectives facing the committee

As summarized by Dr. Rowlands, the petition submitted by Weider Nutrition International, Inc. claims that:

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

The petition submitted by Rotta Pharmaceutical, Inc. claims that crystalline glucosamine sulfate may reduce the risk of osteoarthritis.

Health claims, Dr. Rowlands said, are about a substance-disease relationship—specifically, about risk reduction in healthy populations, not disease treatment or mitigation of a disease. For the purposes of health claims, FDA considers healthy individuals as being those that do not have the diagnosed disease that is the subject of the health claim. As a result, a key question facing the committee is defining what is healthy and what constitutes a diagnosed condition.

Using Stedman's Medical Dictionary, Dr. Rowlands noted that osteoarthritis (OA) is "arthritis characterized by erosion of articular cartilage, either primary or secondary to trauma or other conditions, which becomes soft, frayed, and thinned with eburnation of subchondral bone and outgrowths of marginal osteophytes."

Characterized risk factors for OA include: genetic predisposition, trauma, anatomic/postural abnormalities, and obesity. Based on the petitions, the literature and consultation with the experts, there are currently no biomarkers that are valid modifiable risk factors/surrogate endpoints for OA.

The scientific evidence summarized in the petitions included:

- ?? *In vitro* mechanistic studies
- ?? Animal studies
- ?? Human clinical studies in OA patients.

The petitioners concluded that:

- ?? Human clinical intervention studies in OA patients support OA risk reduction in healthy populations.
- ?? Joint degeneration and cartilage deterioration are valid modifiable risk factors/surrogate endpoints for OA.
- ?? Animal and *in vitro* models of OA are relevant to OA risk reduction in humans.

FDA's evaluation of the evidence focused on three issues:

- ?? Relevance of OA treatment studies to OA risk reduction in the healthy population
- ?? Validity of joint degeneration and cartilage deterioration as modifiable risk factors/surrogate endpoints for OA
- ?? Relevance of animal and *in vitro* models to OA in humans.

In evaluating the petitions, FDA noted that the strongest evidence for a relationship would be glucosamine and chondroitin sulfate intervention studies in healthy subjects demonstrating a reduced incidence of OA. Alternatively, a relationship could be established from studies demonstrating that glucosamine and chondroitin sulfate produced beneficial changes in valid modifiable risk factors for OA.

However, for these petitions, all of the human clinical intervention studies were conducted in OA patients. No intervention or observational studies were conducted in healthy people demonstrating OA risk reduction.

In addition, FDA has not identified any validated and accepted modifiable risk factors/surrogate endpoints for OA. FDA has tentatively concluded that, to date, there are no validated biochemical biomarkers that can be used as risk factors/surrogate endpoints for OA. Degenerative structural changes (e.g., joint degeneration and cartilage deterioration) are associated with OA. There is considerable interest in determining whether these degenerative structural changes, based on radiographic or biochemical evidence, may also cause OA—a major goal of the NIH sponsored Osteoarthris Initiative.

FDA has found no intervention studies with any substance in healthy people that measured both joint degeneration or cartilage deterioration and OA incidence. We don't know, Dr. Rowlands said, if joint degeneration and cartilage deterioration can be modified by intake of a substance in healthy people.

Concerning animal and *in vitro* models, Dr. Rowlands pointed out that animals have a different physiology and that the etiology of OA is poorly understood. For instance, he said, non-steroidal anti-inflammatory drugs (NSAIDs) inhibit OA in rodents but not humans.

Dr. Rowlands returned to and reiterated the questions facing the committee. The objective is to seek the committee's recommendations concerning:

- ?? The science needed to demonstrate risk reduction, not disease treatment or mitigation
- ?? The etiology of OA, valid modifiable risk factors/surrogate endpoints for OA, and relevant models of OA.

Dr. Rowlands noted that the issue at hand is not glucosamine and chondroitin sulfate, but current understanding of the etiology of OA and its modifiable risk factors/surrogate endpoints, which is necessary to assess substance-OA relationships.

Petitioner:
Weider Nutrition International, Inc.
Luke R. Bucci, Ph.D., Vice President of Research, Weider Nutrition Group

Dr Bucci's presentation:

- ?? Reviewed the need for reducing the risk of OA
- ?? Summarized the proposed health claims
- ?? Reviewed the roles of glucosamine and chondroitin sulfate in reducing OA risk
- ?? Explained credible evidence supporting the claims.

Dr. Bucci noted that OA is the leading cause of disability in the US and results in 9,500 deaths and $51 billion in medical costs.

Weider Nutrition's proposed health claim would state that glucosamine may reduce the risk of OA, joint degeneration and cartilage deterioration. It would also state that chondroitin sulfate may reduce the risk of OA, joint degeneration and cartilage deterioration.

Dr. Bucci pointed to human supplementation trials in OA to demonstrate their applicability to risk reduction. Cartilage tissue, he said, is not an "inert Teflon washer as the public sometimes perceives." Cartilage tissue is subject to wear and tear and produces degraded fragments constantly.

Joint tissues, he said, can only maintain themselves and resist degradation by biosynthesis of more matrix. The only way joint tissues can make more matrix is to utilize glucosamine and manufacture more chondroitin sulfate. The biosynthesis of chondroitin sulfate is essential to maintenance and thus, prevention of joint deterioration, he said.

In addition, he said, the same biochemical, regulatory, cellular, biosynthetic, anabolic, catabolic and metabolic mechanisms are operative in cartilage whether the condition is perfect health or OA. "The cartilage," he said, "is unaware of the label of disease." There is an unbroken continuum of events in cartilage from health to degenerative disease. Therefore, he said, there is no agreed upon threshold or marker that clearly defines the onset of OA. My argument, he said, is that the same type and extent of imbalance between matrix component synthesis and degradation can be seen in "healthy" and OA subjects.

OA, he went on to say, results from an imbalance of normal anabolic and catabolic activities in cartilage and is a deficiency of normal regulation of cartilage maintenance. Both glucosamine and chondroitin sulfate help regulate and normalize cartilage maintenance and thus reduce risk of OA.

Dr. Bucci went on to discuss biomarkers affected by glucosamine, including inhibition of cartilage breakdown and degradative enzymes as well as its anti-inflammatory effects (it works by regulatory cells to stop the problem, but is not an anti-inflammatory). He also reviewed biomarkers affected by chondroitin sulfate, including inhibition of cartilage breakdown and degradative enzymes as well as biosynthesis of hyaluronic acid, glycosaminoglycans, proteoglycans, and collagen in joints.

In summary, Dr. Bucci said, "normal people would be benefited" by glucosamine and chondroitin sulfate, just as OA patients are benefited. You can safely treat people, he said, and prevent problems and reduce risk and economic burden.

In human studies of OA, both glucosamine and chondroitin sulfate prevented the loss of cartilage over time. Both glucosamine and chondroitin sulfate affect many biomarkers known to cause, promote or exacerbate joint degeneration. And, animal models of OA as well as *in vitro* studies demonstrate their applicability to prevention and support human clinical findings.

The "result is inescapable," he said. Glucosamine and chondroitin sulfate reduce risk of OA.

Questions and Discussion:

Questions from committee members included: whether or not joint degeneration is a surrogate endpoint for OA or whether it defines OA, the difference between OA and normal tissue, and whether health claims would be applicable to early changes. In the view of a number of committee members, OA and normal tissue are not the same. Dr. Mehendele pointed out new processes occur in the joint and joint tissues once disease occurs. Dr. Abramson also said that he did not agree that normal chondrocytes are the same as diseased (OA) chondrocytes.

Dr. Felson noted the data are not that convincing and pointed to a new trial to be conducted by NIH concerning glucosamine, osteoarthritis and biomarkers for the disease. While the preponderance of the evidence is supportive, he said, "the jury is still out."

Dr. Cush said, "I don't feel you have connected the dots…we have to make leaps of faith." He did not feel sure, he explained, that the conclusions had been proven.

Petitioner:
Rotta Pharmaceutical, Inc.
Roy D. Altman, M.D., Professor of Medicine and Rheumatology, University of Miami and University of California-Los Angeles
Lucio C. Rovati, M.D., Executive Medical Director, Rotta Research Laboratorium

Dr. Altman explained that their presentation would cover:

- ?? An introduction of crystalline glucosamine sulfate (CGS)
- ?? Clinical trail evidence of CGS in OA
- ?? Why long-term therapeutic trials of CGS support the claim of disease prevention
- ?? Effects in prophylactic animal models of OA
- ?? Mechanism of action
- ?? Why glucosamine formulations other than CGS do not have the same body of evidence to support any claim
- ?? Scientific agreement on the use of CGS for OA.

Dr. Rovati summarized systematic reviews and meta-analyses of randomized controlled trials, as well as new long-term clinical studies of glucosamine sulfate for disease modification in OA.

He pointed to joint degeneration/cartilage deterioration as modifiable risk factors/surrogate endpoints for OA risk reduction. Joint degeneration is an

indicator/predictor of OA. He noted that cartilage deterioration is the most widely accepted surrogate of joint degeneration and that it can be indirectly assessed by plain radiography, measuring changes in joint space width (JSW). And, he noted, JSW is accepted by all scientific and regulatory guidelines, including FDA and European Medicines Agency (EMEA), to assess progression of OA.

He presented data concerning the prevention of joint structure impairment by glucosamine sulfate, 1500 mg/day for three years in two long-term studies. Assessment of JSW was the primary outcome measure of joint degeneration in long-term human studies with CGS and was linked with an improvement in symptoms that lead to patient disability and, in the long run, in prevention of joint surgery.

Dr. Rovati also presented data concerning clinical research performed in patients diagnosed with knee OA and suggesting a reduced risk of OA in the general healthy population from consumption of CGS. As noted in his presentation: "The contra lateral knees of patients in the two long-term studies had baseline JSW values that are hard to differentiate from those of the general population. Nevertheless, the trend for the prevention of JSN [joint space narrowing] was similar to that observed in the signal [diseased] joint."

Dr. Rovati summarized information from a 5-year follow-up study of 3-year treatment with CGS for the prevention of knee OA. He pointed to reduced need for lower limb joint surgery as well as significantly slower progression in joint structure changes and long-lasting symptomatic effect.

Effects in prophylactic animal models also support a preventive role for the substance, according to Dr. Rovati.

Dr. Altman expanded on the effects of CGS in prophylactic animal models and noted that there were two animal models to support the idea. He provided details of work concerning CGS in the prevention of canine experimental OA lesions and rabbit OA.

Dr. Altman also discussed *in vitro* studies with crystalline glucosamine sulfate in human OA chondrocytes.

He addressed the anti-inflammatory effects of crystalline glucosamine sulfate which:

- ?? Does not inhibit cycloxygenase activity
- ?? Inhibits moderately the release of proteolytic enzymes
- ?? Inhibits lysosomal enzymes
- ?? Inhibits the generation of aggressive superoxide radicals
- ?? Inhibits the synthesis of inducible nitric oxide.

Finally, he explained the physiological mechanism of action of CGS and why glucosamine formulations other than CGS do not have the same body of evidence to support any claim.

In the conclusions to his presentation, Dr. Rovati stated that "we recognize that there is no study of prevention, and perhaps this will be difficult to obtain with anything in the near future. But there are several hints from the data published that suggest that the substance may prevent osteoarthritis…"

The Rotta Pharmaceutical petition summary, found on pages 5 and 45 of the petition, concludes 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." The petition summary goes on to say that sufficient data exists demonstrating the ability of CGS to be effective in reducing the risk of developing OA. They conclude that the preventative effects of CGS in a patient population with mild OA is very similar to the "healthy population" and supports the ability of CGS "to be effective in preventing the onset of osteoarthritis."

Questions and Discussion:

Considerable discussion ensued concerning the implications of studies concerning contra lateral knees in patients with OA and the application of those studies to healthy populations. This discussion focused on the issue of trying to define a healthy population versus a population with OA. Committee members discussed the significance of joint space width and joint space narrowing, with Dr. Cush noting that joint space narrowing may not be related to symptoms.

"The big argument is what constitutes the base line," Dr. Miller stated, and added, "what is the kind of data that would be needed to demonstrate that a prevention claim can be made."

Dr. Abramson pointed out that the NIH 5-year study would attempt to address these very issues. "How do we pretend to know the answer today," he asked, when we won't know for 5 years?"

Dr. Miller reiterated the charge to the committee to assess whether there is sufficient data to support OA risk reduction and, if not, what data would be needed. "That is the question before us," he said.

Current State of the Science on Etiology of OA and Modifiable Risk Factors for OA
Lee Simon, M.D., Harvard Medical School, Associate Clinical Professor of Medicine

Dr. Simon explained that OA typically affects people over the age of 50 years. It is a biologic process that affects cartilage with subsequent inflammatory component. Characteristically, the major component of the clinical presentation is pain and decreased function. It is estimated to affect between 16-20 million Americans.

He discussed the joint as an organ, detailing its components. “The joint is a very complex organ,” he said, “and all the mechanistic components are extremely inter-related.”

Dr. Simon outlined known risk factors which include:

- ?? Genetics
- ?? Trauma
- ?? Overuse syndrome
- ?? Post-infectious state
- ?? Obesity.

Dr. Simon outlined the etiopathogenesis of the disease as well as OA biology. We know much more today than we knew 10 years ago, he said, but we still know less than we need to know. OA used to be called a degenerative disc disease. In fact, he said, it is an inflammatory problem. The progression of the disease includes an early cellular response in an attempt to make more collagen, then failure of the chondrocytes to maintain cartilage, and then progression of disease. We know, he said, inflammation is involved, but how important, is unknown.

Diagnosis of OA depends on symptoms, such as pain, decreased function, and crepitance or “crunching within the joint.” He outlined physical signs of OA, the identification of OA through x-ray, and the radiographic features of the knee in OA—including joint space narrowing.

Dr. Simon also discussed MRI imaging, noting that it is able to provide a 3-D image and can approximate the volume of the cartilage, may be able to identify early changes in cartilage metabolism, and can approximate early bone change. He pointed out that cartilage volume might be more indicative than joint space.

In diagnosing OA, he said biochemical markers (identified, for instance through blood or urine analysis) are not yet adequate for diagnosis or identifying patients at risk or measuring outcomes, but they may be in the future with further refinement.

Dr. Simon discussed definitions of biomarkers and surrogate markers.

In answer to the question, “What valid modifiable risk factors/surrogate endpoints are there for predicting the risk of developing osteoarthritis in humans,” Dr. Simon said that joint space narrowing is evidence of progressive OA, but may or may not be associated with the important clinical component of symptoms. Other observed x-ray changes are useful for diagnosis, but, again, are not important without symptoms. And, he reiterated, there are no valid surrogate biochemical markers at this time.

He also does not believe that joint degeneration and cartilage deterioration were generally risk factors/surrogate endpoints for OA, while they can be evidence of OA in the context of symptoms for OA. Not all patients with those conditions report pain and loss of function.

Current therapies, he said, focus on lifestyle changes (reaching ideal body weight in obese individuals, etc.) and are mostly palliative to decrease symptoms of pain. There are as yet no proven structure-modifying therapies.

The biology of OA and how to prevent it remains elusive, he said. "Whether or not we will ever be able to answer that within in my lifetime remains unclear," he added.

In the discussion following Dr. Simon's presentation, Dr. Felson noted that "we do have an operational definition of this disease," citing frequent pain in joints plus radiographic evidence. That is the threshold above which we characterize OA," he said.

The Role of Animal and *in vitro* Models in OA Risk Reduction
James Witter, M.D., Ph.D., Center for Drug Evaluation and Research (CDER)/FDA

Dr. Witter said that in February 2000, the Osteoarthritis Initiative found that there were no FDA approved therapies that alter joint structure in OA.

Dr. Witter went on to define CDER's definition of surrogate endpoint and noted that it is valid only if the effect on the surrogate leads to a clinical benefit. He said that according to CDER regulations, surrogate endpoints are candidates for drug approval, while biomarkers do not have the same regulatory implication. He also added that surrogates may be biomarkers, but not all biomarkers are surrogates.

He outlined *in vitro* considerations as well as considerations from animal models, specifically dealing with dogs and rabbits.

He concluded with a quote from Ken Brandt published in 2002: "…validation of a molecular target in human disease can be obtained only after positive results are obtained in Phase III clinical trials in humans."

In other words, said Dr. Witter, "the only way we can hit the mark, is to study the mark."

Public Comment—Oral Presenters:

Jason Theodasakis, M.D., M.S., M.P.H., FACPM, University of Arizona College of Medicine, Canyon Ranch Medical Department
Dr. Theodasakis presented his support of OA health claims for glucosamine and chondroitin sulfate. He noted that OA incidence/prevalence has been underestimated and pointed to the limitations of NSAIDs/analgesics. He also pointed out that the NSAID/analgesic safety may be overstated and the cost to society "immense." He added that OA treatments are difficult to study, but that glucosamine and chondroitin sulfate have very strong, long-term evidence for efficacy compared to other dietary supplements.

Gayle E. Lester, Ph.D, Program Director, Osteoarthritis Initiative & Diagnostic Imaging, NIH.
Dr. Lester said the goal of the Osteoarthritis Initiative is to create a research resource to aid in the identification and evaluation of biomarkers as candidates for surrogate endpoints for OA. The research is to be conducted through the development of a prospective, natural history cohort to be followed for 5 years. Materials to be collected include clinical and imaging data as well as biospecimens.

Dr. Lester also noted that the predictive value of animal models to human OA is obscure and remains to be shown.

Robert Arnot, M.D., former NBC Special Foreign Correspondent
Dr. Arnot is the author of a book titled *Wear and Tear Arthritis*. Dr. Arnot noted his belief that loss of cartilage is "as good a biomarker as cholesterol or as good a biomarker as bone density." Loss of cartilage, he said, puts you at risk of a bad event and "I would argue strongly here that this is a very powerful biomarker." The majority of OA patients, he said, are not formally diagnosed. "Americans are chewing away at their articular cartilage, and yet they are not diagnosed with osteoarthritis," he said.

Dr. Arnot also offered a personal testimonial. He noted that he had been diagnosed with OA and had been taking 12-16 Advil a day, with no relief. After taking glucosamine and chondroitin sulfate, he is pain free. If you can intercede, Dr. Arnot indicated, you can prevent events, just like you can prevent heart attacks. The use of NSAIDs, he said, only disguises pain and may accelerate damage. "There's absolutely nothing on a national level being done to prevent OA," he said, "…it is a huge black hole compared to osteoporosis, coronary heart disease, cancer..." While OA is difficult to define, "you can intervene in a highly effective way to prevent events that are highly disabling," he said.

Jose Verges, MD, MSc, Ph.D., Clinical Pharmacologist, Scientific Director, Bioiberica S.A.
Dr. Vargas presented a clinical review about chondroitin sulfate (CS) based on clinical studies and experience of the product in Europe. He summarized the clinical evidence, including the safety profile. He also noted that the chondroitin sulfate formulation produced by his company is the only one approved as a drug in several European countries. He added that it is manufactured in the U.S. by Nutramax Laboratories and being used by the NIH for its glucosamine and chondroitin sulfate arthritis intervention study. In order to ensure equivalent clinical results, he said, other chondroitin sulfate products must show their bioequivalence to the reference formulation.

Todd Henderson, DVM, Executive Vice President, Nutramax Laboratories, Inc.
Chuck Filburn, Ph.D., Director of Research & Development, Nutramax Laboratories, Inc.

Dr. Henderson and Dr. Filburn both presented recommendations to the committee that the health claim petitions be denied, noting that recent studies of the contents of glucosamine in various commercial products, particularly glucosamine sulfate, showed levels substantially less than that claimed on the labels. This situation, they said, reinforces the importance of consistent methodology and accuracy, or truth, in labeling.

Dr. Miller reiterated that the charge before the committee was not to evaluate the health claims petitions, but to provide recommendations to FDA concerning what methods are used to support these claims and to address the scientific questions provided to the committee.

Concluding Deliberations, Recommendations, Response to Charges and Vote:

The meeting was reconvened by the Chair, Dr. Miller, at 8 a.m. Dr. Rowlands reread the questions for the committee.

Question 1—Recommendation and Discussion:

a. Is joint degeneration a state of health leading to disease, i.e. a modifiable risk factor/surrogate endpoint (as discussed above) for OA risk reduction? What are the strengths and limitations of the scientific evidence on this issue?

b. Is cartilage deterioration a state of health leading to disease, i.e. a modifiable risk factor/surrogate end point for OA risk reduction? What are the strengths and limitations of the scientific evidence on this issue?

Recommendation: The committee reached consensus on Question 1 a., agreeing that joint degeneration is NOT a modifiable risk factor/surrogate endpoint for OA.

The committee reached consensus on Question 1 b., agreeing that cartilage deterioration is a modifiable risk factor/surrogate endpoint for OA, but there is there is currently not enough data to define people that are subject to OA from those who are not

Discussion: Dr. Miller characterized the committee discussion of this question, which occurred prior to achieving consensus, as "broad and important." He pointed out that it is important how one defines the non-effected population and that we do not currently have data to define people not subject to OA.

Committee members discussed the differences between joint degeneration and cartilage deterioration and agreed to consider the two issues separately. One member raised the question of whether joint degeneration begins and leads to OA or once it is there, you have the disease. Cartilage pathology, they noted comes earlier.

Once again, they struggled with the definition of the disease and the question of when OA begins. "There is some point when OA does…or does not exist. …and we need to address that question," Dr. Miller pointed out.

Dr. Abramson responded, "That is the nub we are struggling with…our clinical ability to detect OA is very crude." The disease may be present for years before symptoms present. "The limitations of our diagnostic tools are part of the problem, but the disease can be detected if one looks carefully enough…"

In yesterday's discussion, Dr. Felson indicated that only 30 percent of the people with significant x-ray changes ever have clinical painful disease.

Dr. Lane reinforced that there is no conclusive image technology or measure in blood or urine. She reiterated Dr. Felson's point that it is unclear if people will get the disease, even if the x-ray shows problems.

Dr. Cush emphasized that in spite of what appears to be a struggle, it is not hard to diagnose OA. When a person presents with the symptoms [pain], we recognize the constellation of findings and a diagnosis is made. But we don't know what is pre-OA.

Dr. Zeisel raised the question of whether cartilage deterioration is a predecessor of OA. He said that he would argue that it is "and that at some point symptoms develop and it is diagnosed." Dr. Abramson noted that cartilage deterioration is the earliest phase of OA.

Dr. Lane noted that research from Dr. Felson and his associates indicates that the risk factors for getting the disease are different than what causes the disease to worsen.

Dr. Cush noted that we can say we have "reasonable certainty" about relatedness and time where pathologic or other events lead to disease. Cartilage deterioration, he said, is also a risk factor for OA—there is a reasonable risk for development of the disease.

Dr. Zeisel reiterated his belief that cartilage deterioration is a risk factor for OA. He noted that he feels it is a legitimate analogy to treatments that lower cholesterol. Drawing on that analogy, reducing cartilage deterioration is a reduction in risk for developing OA. That seems a fair analogy."

Dr. Lane noted that while we know some treatments can reduce the risk of heart disease. However, with OA, "we don't have anything on the preventive side…and until we know what those markers or surrogates are to tell us disease is coming, we are jumping into an unknown area," she said.

Dr. Kale said he saw a parallel between the consumption of walnuts and lowering risk of "bad" cholesterol, and a product that modifies the risk of OA. "There is a modifiable risk factor and that is cartilage," he said.

Dr. Abramson noted that LDL is a surrogate marker of a process that leads to disease. This is not the same as cartilage deterioration. Having this early phase doesn't mean it will progress and you will get the disease.

Dr. Cush pointed out that the term joint degeneration is vague and many things can lead to joint deterioration, including gout, rheumatoid arthritis, syphilis, etc. Cartilage deterioration, he said, is not the same. "Cartilage deterioration is the pathognomonic and maybe the earliest finding that sets off the cascade that leads to OA." Dr. Lane agreed that while we do not have clear evidence, cartilage deterioration is the best we can do as far as a modifiable risk factor.

Dr. Miller noted that the committee could decide that cartilage deterioration is a modifiable risk factor, but the evidence is not strong.

After discussion, committee members agreed to make a distinction between joint degeneration and cartilage deterioration, recommending that joint deterioration is not a modifiable risk factor for OA, but cartilage deterioration is.

Question 2—Recommendation and Discussion

> If we assume that 2a) joint degeneration 2b) cartilage deterioration is a modifiable risk factor/surrogate endpoint for OA risk reduction and we assume that research demonstrates that a dietary substance treats, mitigates or slows joint degeneration (cartilage deterioration) in patients diagnosed with OA, is it scientifically valid to use such research to suggest a reduced risk of OA in the general health population (i.e., individuals without OA) from consumption of the dietary substance?

Recommendation:
In terms of both joint degeneration and cartilage deterioration, the committee consensus was that the data do not support using information from OA patients to extrapolate to the healthy population. As Dr. Miller noted, "…not that you can't do it, we just can't do it now."

Discussion:
Prior to reaching consensus, committee members agreed that the data are not currently available. Dr. Cush noted that trials have been done in people with OA in one knee and not the other, but not done in healthy people. It is a "gigantic leap of faith," he said, to use such research to suggest a risk of OA in the general population.

Dr. Abramson pointed out that what works in a disease knee might not apply to a normal knee. Doxycyclene, he said, is protective in a diseased knee, but not the normal knee. At different stages of the disease, cartilage may be more responsive to intervention.

Dr. Zeisel raised the question of how to design an experiment to assess development of OA. Could you design a study in OA patients in which you used other joints and

extrapolate data to make conclusions about the general population? Are people with OA reasonable surrogates? Committee members noted that the answer to that question is unclear. Dr. Blonz pointed out that contra lateral knee data is informative, but does not mean it can apply to the general population. It may be possible to design an experiment, he said, but we don't know how to do that. "We haven't closed the door implying that there is no way of doing it," Dr. Miller said, "and part of the problem is the lack of data."

Question 3—Recommendations and Discussion

> If human data are absent, can the results from animal and *in vitro* models of OA be used to demonstrate risk reduction of OA in humans?
>
> a. To the extent that animal or *in vitro* models of OA may be useful, what animal models, types of evidence, and endpoints should be used to assess risk reduction of OA in humans?
>
> b. If limited human data are available, what data should be based on human studies and what data could be based on animal and *in vitro* studies to determine whether the overall data are useful in assessing a reduced risk of OA in humans?

Recommendation: The committee consensus was that animal studies and *in vitro* models cannot be used in place of human studies regarding risk reduction and OA in humans. They pointed out that there is value in hypotheses generation and in a better understanding of the mechanisms and interactions that might be involved. Additionally, animal studies and *in vitro* data may be useful in support of human data and in determining potential toxicological hazard, etc.

In response to Question 3 a., committee members noted that some animal models may have more applicability than others. Because of the biomechanical differences between two-legged and four-legged animals, primates are of potential interest. Ruminant animals, because of a very different absorption metabolism, is not a good model. The use of technologies, such as MRI, to monitor the course of disease could be helpful. *In vitro* models, because of the biomechanical component of the disease, are only useful for hypotheses generation.

In response to Question 3 b., committee members agreed that strong animal and *in vitro* studies can be used to augment and supplement existing human data to reach a level of certainty that is greater than human research alone.

Discussion: Discussion prior to consensus focused on the limitations of animal and *in vitro* modeling, as well as potential applications.

Animal studies, committee members noted, provide information about pathogenesis, but are very divergent. "They are informative, but not predictive," one member noted. It was also pointed out that some drugs and other substances work in animals, but not in humans.

Committee members also pointed out that *in vitro* models could be useful for looking at the death of chondrocytes, and factors that would cause it.

Animal studies cannot replace human data, especially in terms of risk reduction, Dr. Miller pointed out. It is not possible to jump from animal data to risk reduction in pre-symptomatic humans. Dr. Miller noted that a risk reduction study in humans is the first step.

The meeting adjourned on Tuesday, June 8 at 11:15 a.m.

I certify I attended the June 7-8, 2004 meeting of the Food Advisory Committee, and these summary minutes accurately reflect what transpired.

Linda Reed 8/26/04

Linda Reed Date

Sanford A. Miller 8/25/04

Sanford A. Miller, Ph.D. Date
Chair

[1] The entire meeting was open to the public. Copies of written information provided to the Committee for consideration are available from the Committee staff. The transcript of the meeting is available on the intemet at http://www.fda.govlohrms/dockets/ac/cfsanO4.html or through FDA Dockets Management Branch (HFA-305), 12420 Parklawn Drive, Rockville, Maryland 20857.