

the fight against HIV/AIDS in the Republic of Namibia.

The GRN assisted by the CDC Global AIDS Program conducted a mid-term evaluation of the performance of the national HIV/AIDS program activities in 2003. The results led the GRN to fund the MoHSS to expand efforts to address HIV/AIDS, including PMTCT and ART programs. However, funding for these vital services remains limited. Therefore, MoHSS is the only available organization approved by the GRN to implement PMTCT and comprehensive HIV/AIDS care in the public sector health facilities.

The specific services which the CDC-GAP/MOHSS project will deliver are directly associated with the CDC prevention and care strategies implemented under the Global AIDS Program in the Republic of Namibia and integrated into the MoHSS project. [INSERT JUSTIFICATION STATEMENT FOR SINGLE ELIGIBILITY. IF THE AWARD IS LEGISLATIVELY MANDATED, PLEASE CITE LEGISLATION.]

C. Funding

Approximately \$5,000,000 is available in FY 2004 to fund this award. It is expected that the award will begin on or before May 1, 2004, and will be made for a 12-month budget period within a project period of up to 3 years. Funding estimates may change.

D. Where to Obtain Additional Information

For general comments or questions about this announcement, contact: Technical Information Management, CDC Procurement and Grants Office, 2920 Brandywine Road, Atlanta, GA 30341-4146, Telephone: 770-488-2700.

For technical questions about this program, contact: Dr. Tom Kenyon, Global AIDS Program, c/o U.S. Embassy Windhoek, 2540 Windhoek Place, Washington, DC 20521, Telephone: 264 61 203 2271, Fax number: 264 61 226 959, E-mail: Tkenyon@cdc.gov.

For budget assistance, contact: Shirley Wynn, Grants Management Specialist, CDC Procurement and Grants Office, 2920 Brandywine Road, Atlanta, GA 30341, Telephone: 770-488-1515, E-mail: zbx6@cdc.gov

Dated May 3, 2004

William P. Nichols,

Acting Director, Procurement and Grants Office, Centers for Disease Control and Prevention

[FR Doc. 04-10532 Filed 5-7-04, 8:45 am]

BILLING CODE 4163-18-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Anti-Infective Drugs Advisory Committee Meeting; Cancellation

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is canceling the meeting of the Anti-Infective Drugs Advisory Committee scheduled for May 10, 2004. This meeting was announced in the **Federal Register** of April 19, 2004 (69 FR 20940).

FOR FURTHER INFORMATION CONTACT: Tara P. Turner, Center for Drug Evaluation and Research (HFD-21), Food and Drug Administration, 5600 Fishers Lane (for express delivery, 5630 Fishers Lane, rm. 1093), Rockville, MD 20857, 301-827-7001, fax: 301-827-6776, or e-mail: TurnerT@cder.fda.gov, or FDA Advisory Committee Information Line, 1-800-741-8138 (301-443-0572 in the Washington, DC area), code 3014512530.

Dated: April 4, 2004.

Peter J. Pitts,

Associate Commissioner for External Relations.

[FR Doc. 04-10499 Filed 5-7-04; 8:45 am]

BILLING CODE 4160-01-S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Food Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

Name of Committees: Food Advisory Committee, Dietary Supplements Subcommittee of the Food Advisory Committee and Contaminants and Natural Toxicants Subcommittee of the Food Advisory Committee. The Food Advisory Committee and its Dietary Supplements subcommittee will meet for the first portion of the meeting; the Food Advisory Committee and its Contaminants and Natural Toxicants subcommittee will meet for the second portion of the meeting.

General Function of the Committees:

To provide advice and recommendations to the agency on FDA's regulatory issues.

Date and Time: This meeting will have two parts. The first portion of the meeting will be the Food Advisory Committee and its Dietary Supplements Subcommittee and will be held on June 7, 2004, from 8 a.m. until 5 p.m.; and on June 8, 2004, from 8 a.m. until 1:45 p.m.

The second portion of the meeting will be the Food Advisory Committee and its Contaminants and Natural Toxicants Subcommittee and will be held on June 8, 2004, from 2 p.m. until 6 p.m.

Location: Bethesda Marriott, Grand Ballroom, 5150 Pooks Hill Rd., Bethesda, MD.

Contact Person: Linda L. Reed, Center for Food Safety and Applied Nutrition (HFS-006), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD, 301-436-2397, or FDA Advisory Committee Information Line, 1-800-741-8138 (301-443-0572 in the Washington, DC area), code 3014510564. Please call the Information Line for up-to-date information on this meeting.

Agenda: FDA has received health claim petitions concerning the following topics: (1) Glucosamine and chondroitin sulfate and osteoarthritis, and (2) crystalline glucosamine sulfate and osteoarthritis. The purpose of the portion of the meeting of the Food Advisory Committee and its Dietary Supplements Subcommittee is to gather information and to receive advice and recommendations relating to the etiology of osteoarthritis, its modifiable risk factors, and the relevance of scientific studies cited in the petitions to substantiating the substance-disease relationship.

The purpose of the portion of the meeting of the Food Advisory Committee and its Contaminants and Natural Toxicants Subcommittee is to discuss data needs pertaining to the evaluation of furan, a chemical formed during thermal treatments of food. Elsewhere in this issue of the **Federal Register**, FDA is publishing a notice that requests the submission of data and information pertaining to the occurrence of furan in food, its mechanism of formation as well as its mechanism of toxicity.

Procedure: Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Written submissions may be made to the contact person by May 24, 2004.

For the portion of the meeting of the Food Advisory Committee and its Dietary Supplements Subcommittee, oral presentations from the public will be scheduled between approximately 3:30 p.m. and 5 p.m. on June 7, 2004.

For the portion of the meeting of the Food Advisory Committee and its Contaminants and Natural Toxicants subcommittee, oral presentations from the public will be scheduled between approximately 4 p.m. and 5 p.m. on June 8, 2004.

Time allotted for each presentation may be limited. Those desiring to make formal oral presentations should notify the contact person before May 24, 2004, and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, the specific portion of the meeting at which they wish to present, and an indication of the approximate time requested to make their presentation.

Persons attending FDA's advisory committee meetings are advised that the agency is not responsible for providing access to electrical outlets.

FDA welcomes the attendance of the public at its advisory committee meetings and will make every effort to accommodate persons with physical disabilities or special needs. If you require special accommodations due to a disability, please contact Linda Reed at least 7 days in advance of the meeting.

Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C. app. 2).

Dated: April 29, 2004.

Jeffrey Shuren,

Assistant Commissioner for Policy

[FR Doc. 04-10589 Filed 5-7-04; 8:45 am]

BILLING CODE 4160-01-S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2004N-0205]

Furan in Food, Thermal Treatment; Request for Data and Information

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; request for data and information.

SUMMARY: The Food and Drug Administration (FDA) is requesting the submission of data and information on furan, a heat treatment related byproduct that has been detected in

certain thermally treated foods. FDA is seeking data on the occurrence of furan in food, on sources of exposure to furan other than food, on mechanisms of formation of furan in food, and on the toxicology of furan, including mechanisms of toxicity. FDA will evaluate the available data and will develop an action plan that will outline FDA's goals and planned activities on the issue of furan in food. Elsewhere in this issue of the **Federal Register**, FDA is announcing a meeting of the agency's Food Advisory Committee (FAC) on June 7 to 8, 2004.

DATES: Submit data, information, and general comments by July 9, 2004. Data and information received by June 1, 2004, may be shared with the FAC before or at that meeting.

ADDRESSES: Submit written comments, data, and information to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments, data, and information to <http://www.fda.gov/dockets/ecomments>.

FOR FURTHER INFORMATION CONTACT: Lauren Posnick, Center for Food Safety and Applied Nutrition (HFS-306), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20741, 301-436-1639.

SUPPLEMENTARY INFORMATION:

I. Background

A. General

During investigations relating to review of a petition for certain uses of irradiation in food, FDA scientists identified the substance furan in a number of foods that undergo heat treatment, such as canned and jarred foods. Furan is a colorless, volatile liquid used in some segments of the manufacturing industry. The presence of furan is a potential concern because, based on animal tests, furan is listed in the Department of Health and Human Services Report on Carcinogens (Ref. 20) and is considered possibly carcinogenic to humans by the International Agency for Research on Cancer (IARC).

FDA has developed a gas chromatography/mass spectrometry (GC/MS) method that is capable of detecting and quantitating low levels of furan in food (Ref. 1). Although furan had previously been reported in foods, FDA has recently applied this method to a wider variety of food samples than previously reported in the literature. FDA has analyzed approximately 120 food samples for furan (including replicates of the same brand/product) and found furan levels ranging from

nondetectable (within the limits of detection of the method) to approximately 100 parts per billion (ppb). Jarred baby foods and canned infant formulas are among the foods in which FDA has found measurable furan. FDA has recently posted these furan data on the agency's Web site at <http://www.cfsan.fda.gov/~lrd/pestadd.html#furan>, along with a description of its GC/MS method to provide other researchers the opportunity to review and use the method.

FDA is requesting data on the occurrence of furan in food, on sources of exposure to furan other than food, on mechanisms of formation of furan in food, and on the toxicology of furan, including mechanisms of toxicity. This notice summarizes information currently available to FDA about the occurrence of furan in food, consumer exposure to furan, the mechanisms of furan formation in food, and the toxicology of furan, including the mechanism of toxicity. This notice also identifies the areas in which additional data would be helpful to FDA in learning more about furan and evaluating the risk, if any, posed by the presence of furan in food. These areas are outlined in more detail in section II of this document.

Finally, FDA will evaluate the available data and will develop an action plan that will outline FDA's goals and planned activities on the issue of furan in food. Possible elements of the action plan include an expanded survey of furan levels in food; studies to address mechanisms of furan formation in food; possible strategies to reduce furan levels (if a risk assessment indicates this is necessary); and toxicology studies to address such issues as mechanisms of furan toxicity and dose-response. Elsewhere in this issue of the **Federal Register**, FDA is announcing plans to seek, from its Food Advisory Committee at a meeting scheduled for June 7 to 8, 2004, advice about what data are needed to assess fully the risk to consumers, if any, posed by furan.

B. Occurrence of Furan in Foods

Furan is the parent compound of a class of derivative compounds collectively known as "furans." These compounds are found in a wide assortment of foods and may contribute to food's sensory characteristics (Ref. 2). The nonderivatized furan (i.e., furan) has been identified previously in a small number of heat-treated foods, including coffee, canned meat, baked bread, cooked chicken, sodium caseinate, filberts (hazelnuts), soy

FOOD ADVISORY COMMITTEE and DIETARY SUPPLEMENTS SUBCOMMITTEE

**GLUCOSAMINE AND CHONDROITIN SULFATE
AND OSTEOARTHRITIS**

June 7-8, 2004

Tentative Agenda¹

June 7, 2004 - Monday

- 8:00 Welcome and Member Introduction
Dr. Sanford A. Miller
Chairman, Food Advisory Committee (FAC)
- 8:20 Conflict of Interest Statement
Linda Reed
Acting Executive Secretary, FAC
- 8:30 Opening Remarks
Dr. Robert E. Brackett
Director, Center for Food Safety and Applied Nutrition (CFSAN)
- 8:35 Background and Questions to Committee
Dr. Barbara O. Schneeman
Director, Office of Nutritional Products, Labeling, and Dietary Supplements,
(ONPLDS)/CFSAN
- 8:45 Questions and Clarification
- 8:50 Overview of Legal Framework
Louisa Nickerson, Office of General Counsel/FDA
- 9:05 Questions and Clarification
- 9:10 Overview of Petitions: FDA's Review Process and Issues
Dr. Craig Rowlands, Biologist, FDA/ONPLDS/CFSAN
- 9:40 Questions and Clarification
- 10:05 Break
- 10:20 Petitioner: Weider Nutrition International, Inc
Dr. Luke R. Bucci, Vice President of Research, Weider Nutrition Group
- 11:05 Questions and Clarifications

¹ The times indicated on this tentative agenda are approximations. Breaks will also be called as deemed appropriate by the Chairman.

11:20 Petitioner: Rotta Pharmaceutical, Inc
Dr. Roy D. Altman, Professor of Medicine and Rheumatology, University of Miami
and University of California-Los Angeles

Dr. Lucio C. Rovati, Executive Medical Director, Rotta Research Laboratory

12:05 Questions and Clarifications

12:20 Lunch

1:35 Current State of the Science on Etiology of OA and Modifiable Risk Factors for OA
Dr. Lee Simon, Harvard University

2:20 Questions and Clarifications

2:25 The Role of Animal and in vitro Models in OA Risk Reduction
Dr. James Witter, Center for Drug Evaluation and Research/FDA

2:55 Questions and Clarification

3:10 Break

3:25 Public Comment

4:50 Questions and Clarification

5:00 Adjourn

June 8, 2004 - Tuesday

8:00 Call to Order, Review of Charge and Questions
Committee Chair

8:15 Review of Issues
Dr. Craig Rowlands, FDA/ONPLDS/CFSAN

8:35 Questions and Clarifications

8:40 Committee Discussion

10:00 Break

10:15 Committee Discussion (Continued)

11:30 Lunch

12:30 Concluding Deliberations, Recommendations, Response to Charges and Vote

1:30 Concluding Comments
Committee Chair

1:45 Meeting Adjourns

**FOOD ADVISORY COMMITTEE and
DIETARY SUPPLEMENTS SUBCOMMITTEE
JUNE 7-8, 2004**

**GLUCOSAMINE AND CHONDROITIN SULFATE
AND OSTEOARTHRITIS**

FULL FOOD ADVISORY COMMITTEE

Douglas L. Archer, Ph.D.
Professor
University of Florida
Food Science & Human Nutrition Department
359 FSHN Building, Newell Drive
P.O. Box 110370
Gainesville, FL 32611-0370

Patrick S. Callery, Ph. D.
Assistant Dean for Research and Graduate Programs
West Virginia University
1 Medical Center Drive, HSN Building, Room 2028
Morgantown, WV 26506-9530

Annette Dickinson, Ph.D.
President
Council for Responsible Nutrition
1828 L Street, NW
Suite 900
Washington, DC 20036-5114

Goulda A. Downer, Ph.D.
President/CEO
Metroplex Health and Nutrition Services
6323 Georgia Avenue, NW
Washington, DC 20011-1117

Johanna Dwyer, D.Sc, RD
Senior Nutrition Scientist
Office of Dietary Supplements, NIH
6100 Executive Boulevard MSC 7517
Bethesda MD 20892

Ms. Jean M. Halloran
Director, Consumer Policy Institute/Consumers Union
101 Truman Avenue
Yonkers, NY 10703

Norman I. Krinsky, Ph.D.
Emeritus Professor
Department of Biochemistry
Tufts University School of Medicine
136 Harrison Ave.
Boston, MA 02111-1837

Daryl B. Lund, Ph.D.
Executive Director, North Central Regional Association and Professor of Food Science
University of Wisconsin-Madison
1450 Linden Drive
Madison, WI 53706

Margaret C. McBride, M.D.
Chief, Division of Neurology
Children's Hospital Medical Center of Akron, Ohio
One Perkins Square
Akron, OH 44308-1062

Sanford A. Miller, Ph.D.
Adjunct Professor and Senior Fellow
Virginia Polytechnic and State University
5450 Whitley Park Terrace, #704
Bethesda, MD 20814

Mark F. Nelson, Ph. D
Vice President, Scientific and Regulatory Policy
Grocery Manufacturers of America
2401 Pennsylvania Ave., NW
Washington, DC 20037

Robert M. Russell, MD
Director
Jean Mayer USDA Human Nutrition Research Center
On Aging
Tufts University
711 Washington Street
Boston, MA 02111

Brandon Scholz
President & Chief Executive Officer
Wisconsin Grocers Association, Inc
One South Pinkney Street, Suite 504
Madison, Wisconsin 53703

Carolyn I. Waslien, Ph. D., R. D.
Professor, Nutritional Epidemiology
John Burns School of Medicine University of Hawaii
1960 East West Road
Honolulu, HI 96822

Dietary Supplements Subcommittee Members

Edward Blonz, Ph.D.
Consultant
139 Purdue Avenue
Kensington, CA 94708-1032

Edward D. Harris, Ph.D.
Department of Biochemistry and Biophysics
Texas A&M University
College Station, Texas 77843-2128

Michael McGuffin
President, American Herbal Products Association
8484 Georgia Ave., #370
Silver Spring, MD 20910

Harihara M. Mehendale, Ph.D.
The University of Louisiana at Monroe
Professor and Kitty DeGree Endowed Chair in Toxicology
Department of Toxicology
College of Pharmacy
700 University Avenue
Sugar Hall #306
Monroe, LA 71292-0495

Steven Zeisel, M.D. Ph.D.
Assoc. Dean for Research, School of Public Health
Professor & Chairman, School of Health & School of Medicine
Univ. of North Carolina at Chapel Hill
CB # 7400 Rm 2213 McGavran Greenberg Hall
Chapel Hill, NC 27599-7400

Temporary Voting Members

Steven Abramson, M.D.
Professor of Medicine and Pathology
NYU Medical Center
Hospital for Joint Diseases
Department of Rheumatology and Medicine
301 East 17th Street
New York, NY 10003

John J. Cush, M.D.
Chief, Rheumatology and Clinical Immunology
Presbyterian Hospital of Dallas
Arthritis Consultation Center
8200 Walnut Hill Lane
Dallas, TX 75231

Luis Espinoza, M.D.
Chief, Section of Rheumatology
Louisiana State University
Medical Center
1542 Tulane Avenue
New Orleans, LA 70112

David Felson, MD, M.P.H.
Chief, Boston University Clinical Epidemiology Research Training Unit
Boston University School of Medicine
715 Albany Street
Boston, MA 02118

Scott A. Kale, M.D., J.D., M.S.
30 S. Michigan Avenue, Suite 500
Chicago, IL 60603

Nancy E. Lane, M.D.
Associate Professor In Residence of Medicine and Rheumatology
San Francisco General Hospital
1001 Potero Avenue
Building 30, Rm 3300
San Francisco, CA 94110



**FOOD ADVISORY COMMITTEE
and
DIETARY SUPPLEMENTS SUBCOMMITTEE**

**GLUCOSAMINE AND CHONDROITIN SULFATE
AND OSTEOARTHRITIS**

June 7-8, 2004

**BETHESDA MARRIOTT
Grand Ballroom
5150 Pooks Hill Road
Bethesda, MD**

FOOD ADVISORY COMMITTEE and DIETARY SUPPLEMENTS SUBCOMMITTEE

**GLUCOSAMINE AND CHONDROITIN SULFATE
AND OSTEOARTHRITIS**

June 7-8, 2004

Briefing Materials - Table of Contents

Tab 1 – List of Attendees

Tab 2 – Meeting Agenda

Tab 3 – Petition Summaries

Tab 4 – FDA's Tentative Conclusions

Tab 5 – Questions for Food Advisory Committee

Tab 6 – Appendix

Subtab 6 a -- Review Articles

- i.** Brandt, K.D. Animal models of osteoarthritis. *Biorheology*. 2002; 39(1-2):221-235.
- ii.** Felson, D.T., Lawrence, R.C., Dieppe, P.A., Hirsch, R., Helmick, C.G., Jordan, J.M., Kington, R.S., Lane, N.E., Nevitt, M.C., Zhang, Y., Sowers, M., McAlindon, T., Spector, T.D., Poole, A.R., Yanovski, S.Z., Ateshian, G., Sharma, L., Buckwalter, J.A., Brandt, K.D. and Fries, J.F. Osteoarthritis: new insights. Part 1: the disease and its risk factors. *Ann Intern Med*. 2000a; 133(8):635-646.
- iii.** Felson, D.T., Lawrence, R.C., Hochberg, M.C., McAlindon, T., Dieppe, P.A., Minor, M.A., Blair, S.N., Berman, B.M., Fries, J.F., Weinberger, M., Lorig, K.R., Jacobs, J.J. and Goldberg, V. Osteoarthritis: new insights. Part 2: treatment approaches. *Ann Intern Med*. 2000b; 133(9):726-737.

Subtab 6 b – Petitions

- i.** Weider Nutrition International, Inc. (petitioner A)
- ii.** Rotta Pharmaceutical, Inc. (petitioner B)

Glucosamine and Chondroitin Sulfate and Osteoarthritis Food Advisory Committee: Petition Summaries

Two health claim petitions were submitted to FDA. One petition was submitted on behalf of Weider Nutrition International, Inc. (petitioner A) and the other was submitted on behalf of Rotta Pharmaceutical, Inc. (petitioner B). The claims concerned the relationships between the consumption of: (1) glucosamine and/or chondroitin sulfate and reduction in the risk of: osteoarthritis; joint degeneration; and cartilage deterioration (petitioner A), and; (2) crystalline glucosamine sulfate and a reduced risk of osteoarthritis (petitioner B). The following is a brief synopsis of the scientific data provided in the petitions, and the conclusions reached by the petitioners. This synopsis is of the petitions alone and does not include any FDA conclusions. The petitions can be found in the appendix of the briefing book.

I. Synopsis of Petitions (Note: Letters “A” and “B” preceding reference numbers correspond to the citations from petitioner A (Weider Nutrition International, Inc.) and petitioner B (Rotta Pharmaceutical, Inc.), respectively.)

A. Substance

Glucosamine is a glycoprotein derived from marine exoskeletons or produced synthetically. It is sold as the sulfate sodium chloride (sulfate) salt, hydrochloride (HCL) salt and N-acetyl-glucosamine. It is an endogenous substance that is required for the synthesis of glycoproteins, glycolipids, and glycosaminoglycans (also known as mucopolysaccharides). These carbohydrate-containing compounds are found in tendons, ligaments, cartilage, synovial fluid, mucous membranes, structures in the eye, blood vessels, and heart valves.

Chondroitin sulfate belongs to a class of very large molecules called glucosaminoglycans (GAGs), which are made up of glucuronic acid and galactosamine. Chondroitin is manufactured from natural sources, such as shark and bovine cartilage. Pure chondroitin is a relatively large molecule, weighing about 16,900 daltons. The species or tissue of origin, and the extraction method used, can affect the size of the molecule.

B. In vitro mechanistic data

Studies in human and animal primary cell cultures, established cell culture models, and tissue/organ cultures have reported various biochemical effects following exposure to glucosamine sulfate, glucosamine hydrochloride (HCl), and chondroitin sulfate. Preliminary research suggests that glucosamine affects cytokine-mediated pathways regulating inflammation and cartilage degradation and immune responses. Glucosamine seems to inhibit interleukin 1-beta (IL-1 β), thereby reducing inflammation and cartilage degradation (A113/B8, A132, A133, A134, A135, A136, A137, A138/B10, A139). Glucosamine reportedly stimulated proteoglycan synthesis, which may also be through inhibition of IL-1 β (A14, A113B8, A132, A133, A138/B10, A140/B9, A142, A143, A144, A148, A149). In addition, glucosamine reportedly possesses immunomodulatory activity (A150, A151) and has been reported to be a substrate for and stimulate new chondroitin sulfate synthesis (A113/B8, A147).

Chondroitin sulfate has been reported to stimulate production of proteoglycans (A142, A153, A155, A156, A157) and prevent cartilage degradation (A153, A159, A165, A166, A172), possibly via inhibition of IL-1 β (A153, A158). Reports also suggest a role for chondroitin sulfate

Glucosamine and Chondroitin Sulfate and Osteoarthritis Food Advisory Committee: Petition Summaries

in prevention of inflammation (A137, A160, A161) and immunomodulation (A131, A165, A166, A167, A168, A169, A170).

C. Animal models of OA

Dietary glucosamine sulfate has been reported to reduce kaolin- and adjuvant-induced tibio-tarsal arthritis in rats (A141) and glucosamine-HCL, with and without chondroitin sulfate, was reported to reduce cartilage degradation in a rabbit model of OA (A219). Consumption of glucosamine-HCl has been reported to enhance the rate of new articular cartilage proteoglycan synthesis in mice (A144). Diets supplemented with chondroitin sulfates have been reported to prevent articular cartilage degradation induced by chymopapain in rabbits (A162), Freund's adjuvant in mice (A163) and in a rabbit surgical instability model of OA (A219).

D. Human clinical studies

1. Mitigation of Symptoms

Relief of OA symptoms has been reported in OA patients taking glucosamine hydrochloride, glucosamine sulfate, chondroitin sulfate, and combination products of glucosamine plus chondroitin sulfate. The majority of the studies are on glucosamine sulfate relieving the symptoms of knee OA. Studies lasting from a few weeks to three years have reported that oral glucosamine sulfate/hydrochloride, chondroitin sulfate and their combination products can significantly improve symptoms of pain and functionality indices in patients with osteoarthritis (A111/B36, A173, A176/B25, A178/B32, A179/B26, A180/B16, A181/B15, A182/B31, A185/B34, A186/B29, A192, A193, A196, A197, A205, A206, A207, A208, A211, A212, A213, A218, A220/B48, A221/B47, A227, A228/B28, B27). Relief of OA symptoms by glucosamine and chondroitin sulfate has been compared with the non-steroidal anti-inflammatory drugs (NSAIDs) ibuprofen (A184/BB33, A185/B34, A186/B29, A187/B46), diclofenac sulfate (A208) and naproxen (A215).

2. Joint Degeneration and Cartilage Deterioration

Radiographic evidence suggests that glucosamine sulfate and chondroitin sulfate may slow joint degeneration in patients with osteoarthritis. OA patients taking glucosamine sulfate for up to three years had significantly less knee joint degeneration, less joint space narrowing, and significant symptom improvement when compared with placebo (A180/B16, A181/B15). Progression of knee joint space narrowing was reportedly prevented in OA patients taking chondroitin sulfate for one to three years when compared with placebo (A194, A207) or baseline (A193, A205, A206).

Compared with placebo, consumption of chondroitin sulfate for three years did not prevent development of OA in finger joints that were non-affected at the start of the study, but a significant decrease in the number of patients with new "erosive" OA finger joints was reportedly observed (A198). In a separate two year study, chondroitin sulfate plus naproxen did not prevent development of OA in finger joints that were non-affected at the start of the study, but compared with naproxen alone, a significant decrease in the number of joints with new erosions was reportedly observed (A215).

Investigators have reported biochemical evidence from OA patients that chondroitin sulfate may protect against cartilage and bone degradation. Compared with placebo, one year treatment of

Glucosamine and Chondroitin Sulfate and Osteoarthritis Food Advisory Committee: Petition Summaries

OA patients with chondroitin sulfate was reported to decrease markers of bone metabolism (serum osteocalcin, urine pyridinoline/deoxypyridinoline) and cartilage metabolism (serum keratin sulfate, cartilage oligomeric matrix protein¹ (COMP)) (A193, A205). Compared with pre-treatment levels, short term treatment (5-10 days) with chondroitin sulfate elevated synovial fluid proteoglycan and hyaluronic acid levels and decreased collagenolytic activity, phospholipase A2 and N-acetylglucosaminidase (A119/B49, A131).

II. Petitioners' Conclusions (see Appendix for copies of the petitions)

A. Petitioner A (Weider Nutrition International, Inc.)

The following conclusions are found on page 23 of petitioner's Exhibit 1 (scientific summary) submitted by petitioner A.

1. Maintaining the structural and functional integrity of the proteoglycan component of the extracellular matrix of articular cartilage is required for preservation of healthy joint architecture and biomechanics.
2. Imbalanced metabolism favoring catabolism within the extracellular matrix of articular cartilage produces degenerative changes in the proteoglycan composition of the matrix.
3. Compromise of the structural and functional integrity of the proteoglycan component of the extracellular matrix of articular cartilage results in net loss of articular cartilage tissue, inferior biomechanical competence and structural deformation of joint architecture.
4. Net degradation of the extracellular matrix of articular cartilage, accompanied by the production of spontaneous repair matrix with abnormal proteoglycan composition, results in asymptomatic subclinical osteoarthritic change.
5. The progression of degenerative asymptomatic osteoarthritic change to osteoarthritis is not inevitable.
6. The progression of degenerative osteoarthritic change is required in order for abnormalities in articular cartilage composition and structure to progress to osteoarthritis.
7. Osteoarthritic change in the absence of joint pain represents a modifiable risk factor for later development of osteoarthritis.
8. Dietary supplementation with D-glucosamine, glucosamine-HCL, glucosamine sulfate or chondroitin sulfate contributes to the preservation of articular cartilage, inhibits the initiation of osteoarthritic change in articular cartilage and inhibits the progression of osteoarthritic change to symptomatic osteoarthritis.
9. Dietary supplementation with D-glucosamine, glucosamine-HCL, glucosamine sulfate or chondroitin sulfate is an effective modifier of osteoarthritic change and reduces the risk for osteoarthritis.

B. Petitioner B (Rotta Pharmaceutical, Inc.).

The following conclusions are found on pages 5 and 45 of the petition.

“The scientific evidence in this Petition convincingly establishes 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. Given the physiological mechanism of action of crystalline glucosamine sulfate and other factors, there also are sufficient data

¹ Not clearly identified as serum or urine COMP levels.

**Glucosamine and Chondroitin Sulfate and Osteoarthritis Food Advisory Committee:
Petition Summaries**

demonstrating the ability of crystalline glucosamine sulfate to be effective in reducing the risk of developing osteoarthritis.” (page 5)

“The preventative effects of crystalline glucosamine sulfate in this patient population with “mild osteoarthritis,” a patient population very similar to the “healthy population,” combined with the well-known mechanism of action for crystalline glucosamine sulfate support the ability of crystalline glucosamine sulfate to be effective in preventing the onset of osteoarthritis.” (page 45)

Food Advisory Committee: FDA's Tentative Conclusions

I. Introduction

FDA relies primarily on human studies that are primary reports of data collection when attempting to establish a diet-disease relationship and has consistently identified two endpoints with which to identify disease risk reduction for purposes of health claims evaluations: a) reduction in incidence of the disease, and; b) beneficial changes in modifiable risk factors/surrogate endpoints for the disease.¹

FDA also refers to modifiable risk factors/surrogate endpoints for disease as “biomarkers” and defines them 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. This is the case for serum cholesterol in that high levels are generally accepted as a predictor of risk for coronary heart disease, and there is evidence that decreasing high serum cholesterol can decrease that risk. Therefore, the evaluation of whether decreasing the intake of dietary fat reduces the risk of developing heart disease took into account many studies that assessed changes in serum cholesterol, specifically LDL-cholesterol, rather than the development of heart disease per se. For the existing authorized health claims, acceptable biomarkers are LDL-cholesterol levels for coronary heart disease, measures of bone mass for osteoporosis, and measures of blood pressure for hypertension.”¹

The human clinical studies in the petitions reported benefits from consumption of glucosamine sulfate, glucosamine hydrochloride (HCl) and/or chondroitin sulfate on indices of pain, swelling, joint tenderness, joint swelling, joint degeneration and cartilage deterioration associated with osteoarthritis (OA). FDA is focusing its review on reduced risk of OA, joint degeneration and cartilage deterioration since these are the subject of pending claims. FDA has performed an initial review of the petitions and has reached the following tentative conclusions.

II. Evaluation of the Evidence

A. Treatment Studies vs. Risk Reduction Studies

For the purposes of health claims evaluations, 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. 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

¹ Guidance for Industry: Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements, December 22, 1999 (<http://www.cfsan.fda.gov/~dms/ssaguide.html>).

Food Advisory Committee: FDA's Tentative Conclusions

glucosamine and chondroitin sulfate produce beneficial changes in valid modifiable risk factors for OA.

The clinical intervention trials cited in the petitions were all conducted in individuals suffering from OA, and all relate to treatment or mitigation of OA and its symptoms. There is no evidence provided in the petitions, nor does FDA know of any evidence available elsewhere, that demonstrates glucosamine and chondroitin sulfate reduces the risk of developing OA in a healthy population. Thus, FDA has tentatively concluded that the current evidence provided indicates that these treatment studies are not relevant to OA risk reduction in a healthy population, and that additional evidence would be needed to determine whether these treatment studies could be considered relevant.

B. Modifiable Risk Factors/Surrogate Endpoints for OA

FDA has not identified any validated and accepted modifiable risk factors/surrogate endpoints for OA. Certain risk factors for OA have been identified, including trauma, anatomic/postural abnormalities, obesity, and genetic predisposition². Serious joint injury can lead to OA; however, OA usually results from a combination of systemic³ and joint-related factors. Genetic factors have been estimated to account for about half of OA in the hands and hips and a smaller percentage of OA of the knees. Persons who are overweight have a high prevalence of OA. Biochemical markers of cartilage or bone metabolism are receiving much attention as potential risk factors/surrogate endpoints for the development of OA but, FDA has tentatively concluded that, to date, there are no validated biochemical biomarkers that can be used as risk factors/surrogate endpoints for development of OA⁴.

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, which is a major goal of the NIH sponsored Osteoarthritis Initiative.⁵ At this time, however, neither joint degeneration nor cartilage deterioration has been shown to cause OA. Thus, FDA has tentatively concluded that there are no validated and accepted modifiable risk factors/surrogate endpoints to credibly predict the risk of OA.

² U.S. Food and Drug Administration, Guidance for Industry Clinical Development Programs for Drugs, Devices, and Biological Products Intended for the Treatment of Osteoarthritis (OA) DRAFT GUIDANCE (<http://www.fda.gov/cder/guidance/2199dft.pdf>)

³ Examples of systemic factors include age, sex, ethnic characteristics, bone density, estrogen replacement therapy (in post-menopausal women), and genetics (Felson *et al*, 2000).

⁴ Felson, D.T., Lawrence, R.C., Dieppe, P.A., Hirsch, R., Helmick, C.G., Jordan, J.M., Kington, R.S., Lane, N.E., Nevitt, M.C., Zhang, Y., Sowers, M., McAlindon, T., Spector, T.D., Poole, A.R., Yanovski, S.Z., Ateshian, G., Sharma, L., Buckwalter, J.A., Brandt, K.D. and Fries, J.F. Osteoarthritis: new insights. Part 1: the disease and its risk factors. *Ann Intern Med* 2000; 133(8):635-646.

⁵ Osteoarthritis Initiative, National Institute of Arthritis and Musculoskeletal and Skin Diseases (http://www.niams.nih.gov/ne/press/2002/08_13.htm)

Food Advisory Committee: FDA's Tentative Conclusions

C. Animal studies and in vitro studies

FDA has tentatively concluded that animal studies and in vitro studies are not relevant for establishing a relationship between glucosamine/chondroitin sulfate and OA in humans. Animals have a different physiology to that in humans and in vitro models are conducted in an artificial environment. Given that the etiology of OA is poorly understood, these differences only add to the difficulty of being able to measure how well any animal or in vitro model of OA mimics the disease in humans. For example, rodent models of OA have demonstrated that non-steroidal anti-inflammatory drugs (NSAIDs) can inhibit the disease, but this effect is not repeated in humans where prostaglandins do not play the same fundamental role in pathogenesis as they do in rodents.⁶ No animal model or in vitro model of OA can measure the analgesic effects of substances on joint pain – the primary reason OA patients first seek medical attention. There are numerous other examples where differences in the physiology between species and the lack of understanding of OA pathology provides no assurance that any effect measured in animals has any relevance to the human disease or can be repeated in humans. Furthermore, animal and in vitro data are not accepted by the nutrition science community as the basis for nutrition policy (i.e., Dietary Reference Intakes⁷, Dietary Guidelines for Americans⁸). For these reasons, FDA has tentatively concluded that animal models and in vitro models are not appropriate models to establish a relationship between glucosamine and chondroitin sulfate and OA in humans.

III. Summary

In summary, FDA has tentatively concluded that a relationship between glucosamine and chondroitin sulfate and a reduced risk of OA is not established. The reasons for this tentative conclusion includes the lack of relevance of animal and in vitro models of OA to human OA, the lack of valid modifiable risk factors for OA, and the lack of relevance of the OA treatment studies to OA risk reduction in the general healthy population.

⁶ Otterness, I.G., Larsen, D., and Lombardino, J.G. An analysis of piroxicam in rodent models of arthritis. *Agents Actions* 1982; 12:308-312.

⁷ Institute of Medicine, National Academy of Sciences

⁸ U.S. Department of Agriculture and U.S. Department of Health and Human Services

Food Advisory Committee: Questions - Revised

I. 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. 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 food substance 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 such that it does not function properly, except for nutrient deficiency diseases. The agency has interpreted “health-related condition” to mean a state of health leading to disease.

For 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” and defines them 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. This is the case for serum cholesterol in that high levels are generally accepted as a predictor of risk for coronary heart disease, and there is evidence that decreasing high serum cholesterol can decrease that risk. Therefore, the evaluation of whether decreasing the intake of dietary fat reduces the risk of developing heart disease took into account many studies that assessed changes in serum cholesterol, specifically LDL-cholesterol, rather than the development of heart disease per se. For the existing authorized health claims, acceptable biomarkers are LDL-cholesterol levels for coronary heart disease, measures of bone mass for osteoporosis, and measures of blood pressure for hypertension.”¹

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

¹ Guidance for Industry: Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements, December 22, 1999 (<http://www.cfsan.fda.gov/~dms/ssaguide.html>).

Food Advisory Committee: Questions - Revised

II. Questions

- 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 endpoint (as discussed above) 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 in patients diagnosed with OA, is it scientifically valid to use such research to suggest a reduced risk of OA in the general healthy 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 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 healthy 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?

Food and Drug Administration

Food Advisory Committee

June 7-8, 2004

Slides

Questions, Dr. Laura Tarantino, PhD, FDA ([HTM](#)) ([PPT](#))

Legal Framework, Louisa Nickerson, FDA ([HTM](#)) ([PPT](#))

Overview of Scientific Issues, Dr. J. Rowlands, PhD, FDA ([HTM](#)) ([PPT](#))

Glucosamine and Chondroitin Sulfate Reduce Risk of Osteoarthritis, Dr. Luke Bucci, PhD, Weider Nutrition Group ([HTM](#)) ([PPT](#))

Osteoarthritis: Etiology, Pathogenesis and Treatment Considerations, Dr. Lee Simon, MD, Harvard Medical School ([HTM](#)) ([PPT](#))

Osteoarthritis (OA): In Vitro and Animal Models, Dr. James Witter, MD, PhD, FDA ([HTM](#)) ([PPT](#))

In Support of OA Health Claims for Glucosamine & Chondroitin, Dr. Jason Theodosakis, MD, MS, MPH, FACPM, University of Arizona College of Medicine ([HTM](#)) ([PPT](#))

Chondroitin Sulfate: Clinical Review in Osteoarthritis, Dr. José Vergés, MD, MSc, PhD ([HTM](#)) ([PPT](#))

Chondroitin Sulfate - Clinical Review in Osteoarthritis, Background ([PDF](#))

Presentation by Nutramax Laboratories, Inc. ([HTM](#)) ([PPT](#))

Written Statement by Dr. Bob Arnot ([HTM](#)) ([PDF](#)) ([Word](#))

The Osteoarthritis Initiative, Gayle Lester, PhD ([PDF](#))

Crystalline Glucosamine Sulfate - Introduction, Rotta Pharmaceuticals, Inc. ([PDF](#))

Questions for the Glucosamine & Chondroitin Sulfate (G&CS) and Osteoarthritis (OA) Food Advisory Committee, Rotta Pharmaceuticals, Inc. ([PDF](#))

**Minutes of the
FOOD ADVISORY COMMITTEE and DIETARY SUPPLEMENTS
SUBCOMMITTEE¹**

**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 Osteoarthritis 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 trial 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 (EMA), 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 cyclooxygenase 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 crepitation 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 internet at <http://www.fda.gov/ohrms/dockets/ac/cfsan04.html> or through FDA Dockets Management Branch (HFA-305), 12420 Parklawn Drive, Rockville, Maryland 20857.