

# 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.<sup>1</sup>

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.”<sup>1</sup>

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

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<sup>1</sup> 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>).

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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 predisposition<sup>2</sup>. Serious joint injury can lead to OA; however, OA usually results from a combination of systemic<sup>3</sup> 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 OA<sup>4</sup>.

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.<sup>5</sup> 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.

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<sup>2</sup> 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>)

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

<sup>4</sup> 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.

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

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### 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.<sup>6</sup> 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 Intakes<sup>7</sup>, Dietary Guidelines for Americans<sup>8</sup>). 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.

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

<sup>7</sup> Institute of Medicine, National Academy of Sciences

<sup>8</sup> U.S. Department of Agriculture and U.S. Department of Health and Human Services