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**Questions for the Glucosamine & Chondroitin Sulfate (G&CS)  
and Osteoarthritis (OA) Food Advisory Committee**

**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?***

OA represents a final common pathway for some definable and mostly nondefinable risk factors: some of the definable risks that lend themselves to modification include obesity, internal derangements (eg meniscal or cruciate defects), congenital deformities (eg valgus or varus of a knee), repetitive bending, high impact.

All the above lead to joint degeneration which is the final risk factor/surrogate endpoint for OA, in that it is an indicator/predictor of this disease. In fact, while there may be no conclusive correlation between joint degeneration (joint structure changes) and clinical manifestations (symptoms) in the early stages of OA, all patients with definite OA (i.e. disability leading to the need for surgical joint replacement) have overt joint degeneration.

Long-term human studies with crystalline glucosamine sulfate have shown that changes induced by the substance on joint degeneration affect the risk of OA in that a) they limit disability by preventing symptom progression, and b) they seem to prevent recourse to surgical joint replacement.

***1) 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?*

Cartilage change is an integral part of the OA process and the most widely accepted surrogate of joint degeneration. While in humans it can be directly visualized by arthroscopy, or indirectly by ultrasound and probably with better sensitivity by MRI, plain radiography is today the better validated and universally accepted technique to study cartilage loss by assessing joint space narrowing (JSN) i.e. the change in joint space width (JSW). Assessment of JSW is valid, in that it is an accurate measure of thickness of articular cartilage as shown in cadaver studies. Furthermore, it is reliable, in that it has a good precision over repeated measurements. Finally, it is sensitive to change and different epidemiological studies have shown an average loss in the range of 0.1 mm/year in knee OA patients. For these reasons, JSN is today the accepted primary outcome measure in clinical trials of OA progression as prescribed by scientific recommendations and acknowledged by American and European regulatory guidelines (FDA: CDER, draft guidance 1999; EMEA: CPMP/EWP/784/97, 1998).

Assessment of JSW was the primary outcome measure of joint degeneration in the long-term human studies with crystalline glucosamine sulfate, that have shown an average loss with placebo in the range described above, that was prevented by administration of the substance. This effect was linked with an improvement in symptoms that lead to patient disability and, in the long run, in prevention of joint surgery.

*2) 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 patient 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 we assume that cartilage 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 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?*

In this Petition, Rotta Pharmaceuticals Inc has shown a number of evidences on how clinical research performed in patients diagnosed with knee OA, suggests a reduced risk of OA in the general healthy population from consumption of crystalline glucosamine sulfate, such as: 1) Mild to moderate characteristics of the patient population studied; 2) the similar trend observed in the contralateral joint; 3) the most evident structure-modifying effect obtained in patients with better preserved (almost normal) joint space at baseline; 4) the prevention of the clinically relevant outcomes of OA, including joint replacement; 5) the mechanism of action of the substance, involving the interaction with processes that are relevant to the pathogenesis of OA; 6) the effect in prophylactic animal models of the disease.

- 4) *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?*

It is recommended that structure modification for OA be demonstrated in two animal models. The animal models should be validated and reasonably similar to the human disease. Animal models most commonly employed are canine and lapine models. Both prophylactic and therapeutic models are recommended to simulate the human



conditions. Endpoints should include anatomic, biochemical and cellular/subcellular measurements of function.

The results in animal models should in any case be supportive of human data, as it is the case for crystalline glucosamine sulfate only.

*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?*

While we recognize there are no human studies on prevention of osteoarthritis, there are extensive data supporting the ability of crystalline glucosamine sulphate to reduce the risk of osteoarthritis in the general population.

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