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FOOD ADVISORY COMMITTEE AND DIETARY

SUPPLEMENTS SUBCOMMITTEE

THE ROLE OF GLUCOSOSAMINE AND CHONDROITIN SULFATE IN OSTEOARTHRITIS

Monday, June 7, 2004

8:03 a.m.

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Harihara M. Mehendale, Ph.D.
Steven Zeisel, M.D., Ph.D.

Temporary Voting Members

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.

Also Present:

Jeanne Latham, Executive Secretary, Dietary Supplements Subcommittee

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

DR. MILLER: Good morning. I want to take this opportunity of welcoming you to this meeting of the Food Advisory Committee. Today and tomorrow the committee is going to deal with two topics, one dealing with the role of glucosamine and chondroitin sulfate in osteoarthritis, and the other having to do with furan contaminants in foods.

For that reason, in order to expand the expertise of the committee, we've invited some temporary members to join the committee, several dealing with the glucosamine and chondroitin sulfate issue and several having to do with the issues concerned with furans.

As always, we have much too full a schedule, and as always, I'm going to insist that we stick to our time. We have to give everybody an opportunity to speak and speak for the time limits that they've been assigned, and we also have to provide enough time for us to discuss the issues to the extent that the committee needs and feels that

discussion is needed. Towards that end, as you make your presentations and you have exceeded your time, I'll let you know. And I'm not sure exactly what I'll do if you continue to talk, but--

[Laughter.]

DR. MILLER: The very least would be to turn off your microphone and ask questions concerning the meaning of your data.

To begin the meeting, I'd like to introduce--or have them introduce themselves, the members of the committee. This morning we will deal with the glucosamine and chondroitin sulfate issues, and tomorrow we'll deal with furans.

I'll begin by introducing myself. My name is Sandy Miller. I'm a senior research associate at the Center for Food Nutrition Policy at Virginia Tech University.

DR. RUSSELL: I'm Robert Russell. I'm director of the USDA Human Nutrition Research Center on Aging at Tufts.

DR. DICKINSON: Annette Dickinson, president of the Council for Responsible Nutrition.

DR. ARCHER: I'm Doug Archer, professor, Food Science and Human Nutrition at the University of Florida.

DR. CALLERY: Patrick Callery, pharmaceutical chemist, from West Virginia University.

DR. DOWNER: Goulda Downer, president and CEO, Metroplex Health and Nutrition Services, Washington, D.C.

DR. McBRIDE: Margaret McBride, child neurologist at Akron Children's Hospital.

DR. BLONZ: Edward Blonz, nutritional biochemist, from Kensington, California.

DR. ABRAMSON: Steve Abramson, Director of Rheumatology at NYU and the Hospital for Joint Diseases and Dean for Clinical Research at NYU.

DR. FELSON: David Felson, rheumatologist, from Boston University.

DR. ESPINOZA: Luis Espinoza, Chief of Rheumatology, LSU, New Orleans.

DR. KALE: Scott Kale. I'm a rheumatologist at Rush Presbyterian and St. Luke's

in Chicago.

DR. LANE: Nancy Lane, rheumatologist, University of California-San Francisco.

DR. ZEISEL: Steve Zeisel. I'm professor and Chair of the Department of Nutrition at the University of North Carolina at Chapel Hill.

DR. MEHENDALE: Hari Mehendale, professor of toxicology at the University of Louisiana at Monroe.

DR. HARRIS: I'm Ed Harris, professor of biochemistry and nutrition, Texas A&M University.

DR. NELSON: Mark Nelson, Vice President for Scientific and Regulatory Policy, Grocery Manufacturers of America.

DR. WASLIEN: Carol Waslien, Chair and professor, Nutritional Epidemiology, University of Hawaii.

DR. LUND: Daryl Lund, University of Wisconsin-Madison, Food Science, and Executive Directors of the North Central Regional Association.

DR. DWYER: Johanna Dwyer, professor at

Tufts University, and Director of the Frances Stern Nutrition Center and New England Medical Center, and I'm spending the year in Washington.

DR. KRINSKY: Norman Krinsky, emeritus professor of biochemistry, Tufts University School of Medicine.

MS. LATHAM: Jeanne Latham, Food and Drug Administration, Executive Secretary of the Dietary Supplements Subcommittee.

MS. REED: Linda Reed, Acting Executive Secretary of the Food Advisory Committee.

DR. MILLER: Next we have certain administrative things that we need to go through, and Linda Reed, who is the Acting Executive Secretary of the Food Advisory Committee, will present those rules of the road and issues concerning conflict of interest.

MS. REED: Good morning, everyone. As you've heard, I'm Linda Reed, the Acting Executive Secretary of the Food Advisory Committee. I was asked to take a few minutes to refresh everyone's memory about a few rules of the road, if you will,

in terms of Advisory Committee operations.

It is my understanding that all of the committee members have been provided a copy of a Committee Member Guide to FDA Advisory Committees. There is a copy of the Member Guide at the registration desk for anyone who may be interested in looking through it. The Committee Member Guide is in need of updating, but, by and large, it does provide good operational review.

FDA relies on Advisory Committees to provide the best possible scientific advice available to assist us in making complex decisions. Our goal is to do that in as open and transparent a manner as possible. Part of that openness carries with it a request that the members try to avoid even the appearance that issues are being decided or conclusions are being reached outside of the meeting.

We understand that issues raised during the meeting may well lead to conversation over breaks and during a meal. In fact, we hope the discussions are thought-provoking.

We have had instances where members have come back from a break and said, "You know, we were talking over the break, and we would like to request that the FDA provide us with some additional information so we can better understand thus and such." That is perfectly acceptable.

What we don't want is to have a situation where, after the break, the members come back and say, "We were talking over the break and decided that an answer to a question is..." From our perspective, that would be particularly troublesome because neither the agency nor the public would have had the benefit of listening to the entire discussion, the question raised, and the responses.

In fact, FDA has adopted a policy that only the matters can be reached by a show of hands, procedure matters, for example--I read all that wrong. Excuse me.

In fact, FDA has adopted a policy that the only matters that can be decided by a show of hands are procedure matters, for example, break times. All other votes and comments must be placed on the

record, attributed to the member making that statement. The policy goes even further. If a member has to leave the meeting early, the member waives that right to vote. You may wonder why the person may lose their right to vote, but the answer is fairly simple. FDA believes that all parts of the meeting and discussions are important. Consequently, voting on issues without having the benefit of the discussion would be premature.

The issue of openness is larger than what transpires during the course of the meeting. I would like to call your attention to the section in the Member Guide titled "Member Interaction Before, During, and After a Meeting." In essence, this section underscores the fact that all communications with the members should be routed through the committee's Executive Secretary. That would be myself. No one, not even FDA staff, with the exception of the Executive Secretary, should be contacting the members about upcoming meetings, topics, et cetera. This same guidance applies to consultations between members prior to a meeting.

If a member receives an inappropriate contact, the member should feel free to notify myself and/or refer the person making the contact to me. Our goal in having all contacts routed there the Exec. Sec. is to minimize any situations that could be misinterpreted.

Appearance issues are always difficult, because, as is true of many things, appearances can be deceiving. We ask that our members, guest speakers, liaisons, and everyone attending the meeting be mindful of how an interaction between a member--and anyone, for that matter--might be perceived.

Please let me be clear. It is not my intention to question anyone's integrity or motives. But I'm very sensitive to the issue because I have--and I imagine you all have, too--seen highly respected individuals become an object of negative attention based on a misperception. And I certainly wouldn't want anyone in this room to become such a target.

I'm confident that everyone here today is

sensitive to these issues and can appreciate that my comments are intended as a gentle reminder.

Lastly, as you settle in, please take this opportunity to silent any cell phones or other devices that ring, beep, or play show tunes. And I appreciate your attention for that statement.

Now I'd like to read the conflict of interest statement into the record.

DR. MILLER: Just to be certain that there are no mistakes, does anybody need any clarification?

[No response.]

DR. MILLER: If not, why don't we go on.

MS. REED: Okay. As Dr. Miller mentioned, we have the pleasure of having two of our subcommittees and several members of our sister center Advisory Committee serving throughout the meeting, and we thank you for being here.

And with that, I would like to read the conflict of interest statement into the meeting record. And as with the rules of the road, this is a rather long one, so please bear with me.

The authority to appoint temporary voting members to the Food Advisory Committee is granted to the Center Director. Relying on that authority, Dr. Robert Brackett, Director, Center for Food Safety and Applied Nutrition, has signed letters appointing Dr. Luis Espinoza, Dr. Scott Kale, and Dr. Nancy Lane as temporary voting members of the Food Advisory Committee of the June 7-8, 2004, committee meeting. These members will serve on the committee for the first portion of the meeting, the subject of which is osteoarthritis.

The authority to grant permission to borrow special government employees currently serving on the Advisory Committee in a sister center, in this case the Center for Drug Evaluation and Research, is granted to the Associate Commissioner for External Relations, Mr. Peter Pitts. Relying on that authority, Mr. Pitts has signed a memorandum granting permission to Dr. Steven Abramson, Dr. John Cush, and Dr. David Felson to serve as temporary voting members on June 7-8, 2004, for the first portion of this meeting.

They will represent the Arthritis Drugs Advisory Committee.

Mr. Pitts in the same memorandum also granted permission for Dr. P. Joan Chesney to serve as a temporary voting member for the second portion of the meeting concerning furan on June 8, 2004. Dr. Chesney will represent the Pediatrics Advisory Subcommittee of the Anti-Infective Drug Advisory Committee.

With that said, we have a total of seven temporary voting members who will participate in one of these two parts of this meeting.

Because of the breadth of topics to be discussed at this meeting, all of the members and temporary voting members have been screened for any and all financial interests associated with the regulated industry. Based on this review, FDA has determined, in accordance with 18 U.S.C., Section 208(b)(3), to grant general matters waivers to Dr. Steven Abramson, Dr. Marian Allen, Dr. Douglas Archer, Dr. Edward Blonz, Dr. John Cush, Dr. Johanna Dwyer, Dr. Luis Espinoza, Dr. David Felson,

Dr. George Gray, Dr. Edward Harris, Dr. Scott Kale, Dr. Norman Krinsky, Dr. Nancy Lane, Dr. Harihara Mehendale, Dr. Margaret McBride, Dr. Sanford Miller, Dr. Robert Russell, Dr. Carolyn Waslien, and Dr. Steven Zeisel.

The granting of these waivers permits individuals to participate fully in the matters before this committee. Copies of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

In an effort to enhance consistency within the FDA, the agency has recently adopted a policy whereby all public commenters will be asked to report any personal financial interests that could be affected by the committee's deliberations. A copy of the policy was provided to all individuals who registered to make comments at this meeting. Additional copies of the policy may be obtained from the registration desk.

Similarly, we have asked our guest speakers to complete a financial interest and

professional relationship certification for guests and guest speakers to identify any potential conflicts of interest. Dr. Luke Bucci, Dr. Lucio Rovati, Dr. Roy Altman, and Dr. Lee Simon will speak at the first portion of the meeting. Dr. Bucci has declared that he has a financial interest in the Weider Nutrition Group. Dr. Lucio Rovati has declared he has a financial interest in the Rotta Research Laboratorium in Monza, Italy. Dr. Roy Altman has declared he has a financial relationship with Rotta Pharm. And Dr. Lee Simon has indicated that he has no financial relationships with dietary supplements or the pharmaceutical industries.

Dr. Don Forsythe and Dr. Glenda Moser will be guest speakers at the second portion of the meeting. Both have indicated they have no financial interests in the food industry.

I have one final administrative announcement. We have received two written submissions from Nutramax Laboratories, Incorporated. The submissions have been provided to our members, and

copies are available at the registration desk for those attending the meeting.

Almost done. Lunch will be provided today and tomorrow for our members and guest speakers. We hope this will avoid some of the time crunches we have experienced in the past and facilitate returning to the meeting in a timely fashion, as this meeting is a very full one.

I want to thank you again for your attention as I read the statement and welcome all of you again. Thank you very much for being here.

DR. MILLER: Thank you, Linda.

As many of you know, there was a change in leadership at CFSAN since the beginning of the year. Dr. Robert Brackett was named Director of the Center when Joe Levitt left. At our last meeting, Dr. Brackett had an opportunity of being introduced to the FAC. However, at that time he had not been--he had been named, but he hadn't assumed the position of Center Director. He's with us today, and he's going to make some opening remarks.

Bob?

DR. BRACKETT: Well, thank you, Dr. Miller, and good morning to all of you. It is a distinct pleasure for me to be able to provide some very brief opening remarks and to welcome you to this Food Advisory Committee.

As was mentioned, you have a very, very full schedule, and so I am going to keep my comments brief. But I did want to offer the fact that this is something that I support very highly, the Food Advisory Committee meeting. I think that it enables FDA to enhance the expertise that we have available to us; it allows for a breadth of different views on some important scientific issues. And the two that we've got today and tomorrow--that is, chondroitin sulfate and glucosamine and then, tomorrow, furan--are two that have been in front of us a lot in the last year. So, you know, I myself am going to find the results of the discussions quite interesting.

I had originally intended to stay both days all day because I did want to hear some of the

scientific discussions, but I have found out that my schedule has changed since I returned from Europe last week, and so I will only be able to stay a little bit today, and unless things change tomorrow, I will not be able to be here tomorrow. But I wish that I could.

One of the things I do want to say is in supporting the Food Advisory Committee, the fact that you have scientific discussion in an open, transparent manner, I find that it's enhancing to our experts to be able to hear what outside scientists say. But as a former member of this committee before I came to FDA, I also found that participating from the outside in this also helped sort of give a little more depth and breadth to the scientific expertise for those that come here.

As mentioned, we're having some extra experts coming from our Center for Drugs as special government employees, and that is always enriching to the discussion as well.

I hope that things can move along on time and that you will have the opportunity to give all

of the opinions that you have and all the discussion that is required from this meeting. It's something that, again, as I say, I am looking forward to very much, and I really do want to again wish you here--but I don't want to belabor the point because I do know that you have a lot going. And, again, thank you for coming. Thank you for participating. I know this does take a lot of time out of your professional schedules as well.

So good morning and welcome.

DR. MILLER: Thank you, Bob.

Let us turn now to the basic issues of why we're here. Our first speaker from the FDA will present the background and the questions the committee is being asked to consider. I would like to emphasize how important it is that we listen to this very carefully because if we don't stick to the topics and we allow ourselves to drift and not focus on what we're here for, we're not going to be able to come to any conclusions by the time this meeting has been completed. So please listen to this very carefully.

Thank you.

DR. TARANTINO: In order to listen to it, I'll have to lower the microphone dramatically. But I have done so.

Good morning, everybody, Dr. Miller and members of the committee. I am Laura Tarantino. I am not Barbara Schneeman. Dr. Schneeman, many of you may know, is the newly appointed Director of the Office of Nutritional Products, Labeling, and Dietary Supplements. Unfortunately, she couldn't be here today, so on her behalf, it is my great privilege and pleasure to welcome you. And as Bob Brackett did, once again, thank you for taking time from what I know is a very busy schedule to come here and to allow us to benefit from your expert knowledge.

My job, as Sandy mentioned, is to outline the task that we're asking you to focus on over the next day and a half during the part one of this two-part meeting, and perhaps to review and amplify on and actually maybe translate a little bit the questions that we're asking you to consider.

As you're aware from the background materials that you got, the agency is evaluating health claim petitions that concern glucosamine and chondroitin sulfate and osteoarthritis. In a few minutes, Louisa Nickerson of FDA is going to give you some brief background concerning health claims to give you context and an idea of the framework in which we are operating. But I want to emphasize that the questions that are in front of you actually are--and the questions that we're asking you to consider are not about health claims per se.

Furthermore, as you'll have noted from your background material and the information, the questions are also not about glucosamine and chondroitin sulfate specifically. Rather, what we are asking you and what we're asking your help about is in assessing the science needed to demonstrate reduction in risk of osteoarthritis in healthy people. Health claims have to do with the relationship between a substance and a disease and reduction of risk of a disease in healthy people.

What we put in the Federal Register notice

about this meeting is actually pretty much on point. In part, it reads, "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 that substantiate the substance/disease relationship."

Okay. Let's see. This is this, and this advances? Yes, it does. Thank you.

The first question--and as I say, I am going to try to translate a little bit because they look pretty long and involved on your piece of paper, but this is identical to what you have in your background. It is revised spatially to simplify it a little bit, but same words.

The first question really then is about modifiable risk factors. That is, are joint degeneration or cartilage deterioration a valid risk factor for osteoarthritis that can be modified, and can be modified in this case by diet, a dietary substance, leading to a reduction in risk of osteoarthritis in healthy people? That's really

what we're asking about.

We recognize that there really isn't complete knowledge, as you well know, about the etiology and development of osteoarthritis. But in this case, as is true with the other questions, and, really, as is true generally in the way we do business, the information that's available today is what we're going to have to use to make essentially a binary decision. We recognize that our conclusion could change as information changes, but what we really need to ask you is your views on which way does the needle point on this and the other questions with the information we have in front of us today.

The second question really gets to the relevance of studies and information on patients with osteoarthritis, to the questions we need to answer. The petitions cite many intervention studies in patients with osteoarthritis, and this question really is asking about the relevance of that data, and the data and information that could show that a substance treats osteoarthritis or may,

for example, slow joint degeneration or cartilage deterioration in osteoarthritis patients. What is the relevance of that information? Can that information be validly extrapolated to the question in front of us, which is reduction of risk in healthy population?

And the third question, (a) and (b), has to do with the utility and relevance of *in vitro* models and of animal models. Some of the data before us are from animal or *in vitro* models of osteoarthritis. So this question is really asking what's the relevance and utility of these models for assessing disease risk reduction in humans and what sort of data would we really need to be able to base--that we could use these particular studies for, what kinds of information.

And later this morning, Dr. Rowlands is going to talk about all of these in much more detail. Furthermore, he's going to present a survey of our review of the issues raised by these questions and going to present the tentative conclusions from our analysis thus far. After

that, the petitioners will present their analyses and their rationale for their conclusions. And, finally, you're going to hear from some additional experts who will try to review the state of the science on the issues raised and the questions we've put before you.

We're certainly very interested in hearing from this committee your reaction to our and the petitioners' analyses and your responses to each of the questions based on the information available today. Again, what we're really looking for is, based on everything you know, what you've seen in the background packages, and what's there, which way, again, does the needle point on each of these questions.

Before I close, I want to make just one brief aside. Some of you may have seen a notice published in the Federal Register last Thursday. That notice is regarding a consumer study that the agency was proposing to carry out related to testing consumer reactions to various types of claim language involving glucosamine and

chondroitin sulfate. In the event any of you became aware of it, I just want to make very clear that the notice and the studies described in that notice are in no way relevant to today's proceeding. The study that was discussed is directed at consumer perceptions, and consumer perceptions is an area that the agency is very interested in in terms of the whole claims area, but it does not involve the scientific questions that are before you today. The notice, in fact, was published in error and contains some misstatements and will be corrected. But the timing was unfortunate because there was a possibility that it would get confused with what we are bringing before the Advisory Committee. But it is quite a different issue entirely.

So I think I'm going to repeat what Bob Brackett said. We very much look forward to today's and tomorrow's discussions on this subject. I'm sure they'll be very helpful to us, as has been true of other Advisory Committee meetings, in reaching a solid and well-justified and well-

documented decision on these petitions. Advisory Committees in the past have helped us enormously in making sure that our decisions benefit from objective, public discussion and examination of issues from all sides.

I expect your deliberations will be lively, will help us greatly. Again, welcome and thank you for your attention.

DR. MILLER: Thank you.

Before we go on, Dr. John Cush joined us. Would you introduce yourself for the record?

DR. CUSH: Jack Cush. I'm a rheumatologist from Presbyterian Hospital, Dallas. And I'm on the Arthritis Advisory Board.

DR. MILLER: Thank you.

Laura, why don't you wait a minute and see if there are any questions. Any questions for clarification? This is very important that we all understand what we're supposed to be doing here and what we're supposed to be working on. So if you have any questions, Laura will be here, of course, throughout the meeting and if questions come up--

DR. TARANTINO: We will probably come back to this a couple times, too, but yes.

DR. FELSON: "Healthy people" is a hard one to deal with. So if this were to be taken or if something were to be taken for people who already have disease to prevent worsening of disease, does that fit the criterion?

DR. TARANTINO: I guess if you could differentiate that from treating the disease--it's not an easy distinction to make. I'd be interested to hear the discussion.

DR. ZEISEL: May I ask, just to clarify, because that is the crux, I think, of today's discussion. There can be a stage in which cartilage degeneration or other symptoms occur in which osteoarthritis is not yet diagnosed, and that would be a healthy person preventing progression to the point where the disease is diagnosable? Is that the idea?

DR. TARANTINO: Yes, if there is someone who--well, either the general population without symptoms, it's that population, can you show that

it would inhibit progression to disease?

DR. ABRAMSON: This can go on a long time, but if a person has atherosclerosis--

DR. TARANTINO: Yes, I was going to say, I suspect--

DR. MILLER: Excuse me. Please identify yourself for the record.

DR. ABRAMSON: Steve Abramson. This is a very subjective kind of debate, and I would only have paused at this moment because the analogy of someone having asymptomatic osteoarthritis is not dissimilar from having asymptomatic coronary heart disease, perhaps. And if a person has coronary heart disease and is asymptomatic, are they a healthy person or not a healthy person? I think these are the kinds of things that we have to--not make osteoarthritis a disease that's necessarily different from other common diseases that we take care of.

DR. TARANTINO: I would agree.

DR. MILLER: Okay. Thank you, Laura.

Next is Louisa Nickerson from the Office

of General Counsel to give us an overview of the legal framework for this.

MS. NICKERSON: Good morning. My name is Louisa Nickerson. I'm a lawyer for the FDA, and I'm here to try to give you a little bit of legal context for what you're being asked to do.

I am not going to even attempt to explain the entire regulatory system for health claims because, for one thing, we'd be here all day; and, second, because it's not necessary. As Dr. Tarantino has emphasized, you're here to address scientific issues.

Nonetheless, we thought it would be helpful to tell you just a little bit about how FDA regulates health claims and about how FDA defines certain terms that you may have come across in the background materials that were provided to you.

Being a lawyer, I'm going to start with a disclaimer. I want to emphasize again that your role is to advise us on scientific issues, and so the information that I'm going to provide is for background only. You should not--we're not asking

you to resolve any regulatory issues or to draw any legal conclusions because that's the agency's role, and for us to ask you to do that would not be an appropriate use of the committee.

I want to say a little bit about regulatory categories. There are some products that are drugs; there are some products that are dietary supplements. Again, I'm not going to try to go into the ramifications of the full definitions of those terms. But I do want to point out first that there is some overlap between those categories: for products intended to affect the structure or function of the body and also for products that are intended to reduce the risk of disease.

The other point that I wanted to make is that if a product is intended to treat, mitigate, or cure disease, there is no overlap. That kind of product is regulated as a drug. And that's true even if it's labeled as a dietary supplement and even if it otherwise qualifies as a dietary supplement.

So let me give you a couple of examples in the context of osteoarthritis. The claims for relief of the signs and symptoms of osteoarthritis and effective arthritis pain relief, those are both treatment claims that make the product a drug. In fact, as many of you probably know, those are actual claims that are made for osteoarthritis drugs on the market.

I also want to talk a little bit about the definition of "health claim," which I think Dr. Tarantino has already mentioned. Our definition of "health claim" is not the same as the ordinary English meaning of that term. I think when a lot of people hear "health claim," they think it means just any claim about health, and in some contexts, it certainly does mean that. But FDA defines that term in a very specific and narrower way. Our definition of "health claim" is "any claim made on the label or in the labeling of food, including a dietary supplement, that expressly or by implications...characterizes the relationship of any substance to a disease or health-related

condition." And if you're wondering the difference between label and labeling, they do mean different things. The label is the immediate product label; whereas, labeling is a broader term that also includes other promotional material that accompanies the product, such as brochures, leaflets, catalogues, that sort of thing. But it does not include advertising.

To give you a couple of examples of health claims that FDA has authorized by regulation, there is a claim for foods containing soy protein: "25 grams of soy protein a day, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease. A serving of [name of food] supplies __ grams of soy protein." That's a type of claim about a beneficial substance in food.

There are also claims that relate to limiting the amount of substances that may be harmful, that may increase the risk of disease if eaten in excess. So, for example, for low-sodium foods, there's a health claim: "Diets low in sodium may reduce the risk of high blood pressure,

a disease associated with many factors."

So since health claims are about the effect of a food substance on a disease or a health-related condition, it's important to understand how FDA defines those terms. They are defined by regulation: "Disease or health-related condition" means "damage to an organ, part, structure, or system of the body such that it does not function properly...or a state of health leading to such dysfunctioning..." except that nutrient deficiency diseases, such a scurvy and pellagra, are not included in the definition for regulatory purposes.

So a couple brief examples. Diabetes would be considered a disease. Insulin resistance would be considered a health-related condition, that is, a state of health leading to disease.

It's also important to note that the scope of health claims is limited. Health claims are about reducing the risk of a disease or health-related condition. They're not about treating, mitigating, or curing diseases. That is the

position that FDA took in responding to a health claim petition for saw palmetto and relieving the symptoms of benign prostatic hypertrophy a couple years ago, and that position was upheld by a federal appellate court at the beginning of this year in the case of Whitaker v. Thompson.

So applying that concept, an example of a claim that would not be a health claim--and this is actually the claim that was proposed for saw palmetto--"Consumption of 320 mg daily of saw palmetto extract may improve urine flow, reduce nocturia and reduce voiding urgency association with mild benign prostatic hyperplasia." And that is not a health claim because it's about treating or mitigating BPH by relieving its symptoms.

That's all that I wanted to cover today. As I mentioned, I was not intending to provide a comprehensive view of the regulatory framework, but just touch on a few relevant terms and issues.

Are there any questions? Yes?

DR. HARRIS: Ed Harris. I would like you to clarify just why a nutrient deficiency, which we

know can lead to quite a bit of abnormal metabolism, why is that not considered in your context a health claim--or disease state?

MS. NICKERSON: Because--it's not that we don't consider it a disease scientifically. It's that obviously Vitamin C is good for preventing scurvy. We didn't want people to have to go through the health claim regulatory process of coming to us with their data when it was obvious that, you know, Vitamin C would work for that use and other nutrients would solve other--would cure other nutrient deficiency diseases.

Yes?

DR. DWYER: If this example is not a health claim, is it a drug claim?

MS. NICKERSON: Yes. That would be a drug claim.

Yes?

DR. BLONZ: Edward Blonz. The concept of functioning properly, is this an age-specific dynamic definition?

MS. NICKERSON: That's a scientific

question, so I'm not going to try to address that. Craig, is that something that you can address later?

DR. ROWLANDS: [Inaudible, off microphone.]

MS. NICKERSON: Anyone else?

DR. MILLER: Dr. Cush?

DR. CUSH: This is Jack Cush. Would this be a health claim if it were to stop at "improving urine flow and reduce nocturia" and didn't go into association with BPH? Again, it would be being--use the health claim because it improves symptoms without necessarily trying to comment on relatedness to disease?

MS. NICKERSON: Well, I don't think it matters if the disease is mentioned, as long as you have characterizing symptoms of the disease. So one can recognize from what conditions described are that, okay, we're talking about the typical symptom complex of BPH, which is what those are.

DR. CUSH: Right.

MS. NICKERSON: Then it doesn't make a

difference if they use the words BPH or not. It's just the difference between an implied claim and an express claim.

DR. MILLER: Dr. Krinsky?

DR. KRINSKY: Norman Krinsky. If the definition of a health claim is to reduce the risk of a disease, is that, therefore, limited to a healthy population?

MS. NICKERSON: Yes, that's our position.

DR. MILLER: Dr. Zeisel?

DR. ZEISEL: Again, help me understand. When does a condition become a disease? So prostate being slightly larger, is that a disease? Or does it have to be diagnosed as prostatic hyperplasia by a physician to become a disease?

MS. NICKERSON: Again, I really think that's a scientific and medical question that I can't address. But I will say, you know, what a healthy person is is certainly a matter of debate.

DR. MILLER: This discussion reminds me why I am always nervous when scientists get involved in regulatory activities.

[Laughter.]

DR. MILLER: I just want to remind you that the questions we're being asked have nothing to do with the regulation, or to the issue of regulation. The questions being asked is whether or not the science supports a relationship between various biomarkers, among other things, and the disease of osteoarthritis. And I think it's been too much fun trying to understand the morass of regulatory language.

All right. Thank you.

Next, Dr. Craig Rowlands from FDA will give us an overview of the petitions and say something about the review process.

DR. ROWLANDS: I can see I already have my work cut out here. I got three questions before I even got to the podium.

First, I just want to thank you, Dr. Miller, and thank you, members of the committee, for being here. I know some of you, perhaps all of you, had to do some gymnastics with your schedules to be here on such short notice, and we do

appreciate it. And what you have to say to us is very important, so we're looking forward to these discussions.

So my goal this morning is to cover some of the background you've already heard--I'll just reiterate a couple of points--and then provide you a summary of the scientific evidence that was submitted in the petitions, along with the relevant conclusions for the questions we've asked from the petitions' conclusions, provide you with our evaluation of the evidence that raised the issues which were the basis for the questions we gave you, and then I'd like to leave you with the meeting's objectives.

So the petitioners are Weider Nutrition International, Incorporated--I'll refer to them as Petitioner A--and Rotta Pharmaceutical, whom I'll refer to as Petitioner B.

Petitioner A submitted nine independent health claims based on two different substances. That would be: Glucosamine may reduce the risk of osteoarthritis, may reduce the risk of joint

degeneration, and may reduce the risk of cartilage deterioration. Also, chondroitin sulfate may reduce the risk of osteoarthritis, joint degeneration, and cartilage deterioration. And, again, the same three claims for combination products of glucosamine and chondroitin sulfate.

Rotta Pharmaceutical, Petitioner B, submitted one health claim: Crystalline glucosamine sulfate may reduce the risk of osteoarthritis.

As Louisa has already pointed out, health claims are about a substance-disease relationship. They're about risk reduction in healthy populations, not disease treatment or mitigation; those are regulated as drugs. Let me just go ahead and point out one of the questions is what is healthy, and what we look at for healthy is individuals who do not have the diagnosed disease that is the subject of the health claim. So they would be healthy if they do not have a diagnosed condition, in this case of osteoarthritis.

The substances, of course, are glucosamine

and chondroitin sulfate. Glucosamine is a glycoprotein and is an endogenous substance. It is derived from marine exoskeletons or produced synthetically for commercial markets. And it is sold as the sulfate sodium chloride, or sulfate, salt, the hydrochloride salt, and N-acetyl-glucosamine.

Chondroitin sulfate is a very different kind of substance. It's a glucosaminoglycan, which is a large molecule made of glucuronic acid and galactosamine, and it is manufactured from natural sources such as shark and bovine cartilage.

Of course, the disease is osteoarthritis, and Stedman's Medical Dictionary defines this as arthritis which is 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. That's quite a mouthful, but basically what it means is it's a disease of not just the cartilage or just the bone or just the musculature. It is a

disease of the whole joint. Dr. Lee Simon will be providing us an overview of osteoarthritis later on this afternoon, where he will talk about the etiology of the disease and some of its modifiable risk factors.

The characterized risk factors include genetic predisposition, trauma, anatomic/postural abnormalities, and obesity. However, our reading of the petitions, the literature, and our consultation with experts indicates that there are no biomarkers that are valid modifiable risk factors/surrogate endpoints for osteoarthritis. And this is one of the major goals of the National Institutes of Health's Osteoarthritis Initiative, to identify cartilage and bone metabolism endpoints, biochemical markers that could be validated as modifiable risk factors/surrogate endpoints.

The scientific evidence summarized in the petitions include *in vitro* mechanistic studies, animal studies, and human clinical studies in OA patients. Petitioner A provided a summary of all

three types of studies, whereas Petitioner B focused on the glucosamine sulfate studies in human clinical studies in osteoarthritis patients.

The *in vitro* mechanistic data were conducted in human and animal primary cell cultures, established cell culture models, and tissue/organ cultures, and these studies reported that glucosamine and chondroitin sulfate positively affected various biochemical endpoints for inflammation, cartilage degradation, and immune responses, as well as stimulated the production of proteoglycans.

The animal studies for glucosamine reported that it reduced kaolin- and adjuvant-induced tibio-tarsal arthritis in rats; glucosamine reduced cartilage degradation in rabbits; and some of these studies also gave chondroitin sulfate; and glucosamine was reported to enhance the rate of new articular cartilage proteoglycan synthesis in mice.

Chondroitin sulfate prevented articular cartilage degradation which was induced by chymopapain in rabbits, Freund's adjuvant in mice,

and surgery in rabbits.

The human clinical studies were all conducted in osteoarthritis patients, and these studies reported that glucosamine and chondroitin sulfate improved symptoms of pain and functionality using things such as Lequesne index, WOMAC's index, visual analog scales. And some of these studies directly compared these substances to the nonsteroidal anti-inflammatory drugs, for example, Ibuprofen.

These studies in OA patients also reported that there was improvement in joint degeneration and cartilage deterioration based on radiographic evidence, which were X-rays of joint space narrowing, and some of these studies also reported biochemical evidence for bone and cartilage metabolism in synovium, serum, and urine.

So the petitioners concluded from this evidence that human clinical intervention studies in OA patients support OA risk reduction in healthy populations, that is, people without osteoarthritis.

Joint degeneration and cartilage deterioration are valid modifiable risk factors/surrogate endpoints for osteoarthritis. And for Petitioner A, animal and *in vitro* models of OA are relevant to OA risk reduction in humans.

We evaluated the evidence and identified several issues which are related to the relevance of OA treatment studies to OA risk reduction in healthy populations; the validity of joint degeneration and cartilage deterioration as modifiable risk factors/surrogate endpoints for osteoarthritis; and the relevance of animal and *in vitro* models of osteoarthritis to humans.

The FDA relies upon two types of outcomes to determine disease risk reduction. The strongest evidence is a reduction in the incidence of disease. These would be intervention and observational studies in healthy people--those without OA--demonstrating that a substance reduces the incidence of osteoarthritis.

However, all of the human clinical intervention studies were conducted in OA patients.

There were no intervention or observational studies in healthy people demonstrating OA risk reduction.

FDA also relies upon studies measuring beneficial changes in valid modifiable risk factors/surrogate endpoints for disease. These would be intervention and observational studies in healthy humans demonstrating that intake of a substance produces beneficial changes in valid modifiable risk factors/surrogate endpoints for osteoarthritis.

So then what is a valid modifiable risk factor or surrogate endpoint? This is a biological entity that meets all three of the following conditions: it is associated with disease; it mediates the relationship between intake in healthy people and disease; and its expression is modified by intake of a substance in healthy people.

I've tried to represent this with a diagram at the bottom of the slide where the green box represents healthy people, the yellow box represents valid modifiable risk factors/surrogate endpoints, and the red box represents disease or

health-related condition.

Essentially, there are two relationships. Relationship 1 is between the modifiable risk factor/surrogate endpoint and the disease. And Relationship 2 is between the intervention in healthy subjects and the modifiable risk factor/surrogate endpoint.

Relationship 1 must be valid if it is to be relied upon in Relationship 2. That is, there must be evidence that the modifiable risk factor/surrogate endpoint predicts clinical outcome. Only then can intervention studies in healthy subjects rely upon the modifiable risk factor/surrogate endpoint to establish disease risk reduction.

The example given is the qualified health claim for walnuts. Because it has been established that LDL cholesterol is a valid modifiable risk factor/surrogate endpoint for coronary heart disease, intervention studies in healthy subjects that observed decreased serum LDL cholesterol were relevant for demonstrating a reduced risk for

coronary heart disease.

So then are joint degeneration and cartilage deterioration associated with osteoarthritis? I think the answer is obvious. Yes, there is clearly plenty of evidence that they're associated with osteoarthritis.

Does joint degeneration and cartilage deterioration mediate the relationship between intake of a substance in healthy people and osteoarthritis? That is, is there evidence that changes in joint degeneration or cartilage deterioration predict clinical outcome for osteoarthritis? Well, the evidence given to us in the petition and our own reviewing of the literature, we did not identify any intervention studies of any substance in healthy individuals that measured both joint degeneration or cartilage deterioration and OA incidence, precisely the type of evidence one would need if you're going to determine whether or not these are predictive of clinical outcome.

So then are joint degeneration and

cartilage deterioration modified by intake of a substance in healthy people? Again, all of the evidence provided was in OA patients.

Then are joint degeneration and cartilage deterioration valid modifiable risk factors/surrogate endpoints for osteoarthritis. As I said, they're clearly associated with osteoarthritis. However, we don't know whether they mediate the relationship between intake in healthy people and OA; we don't know whether their expression is modified by intake of a substance in healthy people.

So our tentative conclusion is that, no, these are not valid modifiable risk factors for osteoarthritis. We've given you questions directly asking this, and we're very interested to hear your opinions on this matter.

The last issue very quickly then is: Do animal and *in vitro* models of OA mimic human osteoarthritis? Well, we know that animals have a different physiology, *in vitro* models are conducted in an artificial environment, and when you combine

this with the fact that the etiology of OA in humans is poorly understood, it would seem to indicate that animal and *in vitro* models of OA cannot be relied upon for predicting human effects. In fact, this was demonstrated a few years ago in a study that reported that nonsteroidal anti-inflammatory drugs inhibit OA in rodents but not in humans.

The role of animal and *in vitro* models of OA risk reduction will be discussed this afternoon by Dr. Jim Witter, who is a rheumatologist with the FDA Center for Drug Evaluation and Research.

So these issues served as the basis for our questions. I'll go ahead and read them into the record. Is, for Question (1a), joint degeneration and, for Question (1b), cartilage deterioration a state of health leading to disease, that is, a modifiable risk factor/surrogate endpoint for OA risk reduction? Then we'd like to know what are the strengths and limitations of the scientific evidence on this issue. This question is essentially asking: Are joint degeneration and

cartilage deterioration valid modifiable risk factors/surrogate endpoints for osteoarthritis?

Question 2 is: If we assume that joint degeneration or 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 or cartilage deterioration in patients diagnosed with osteoarthritis, is it scientifically valid to use such research to suggest a reduced risk of OA in the general healthy population--again, these would be individuals without osteoarthritis--from consumption of the dietary substance? And this question is essentially asking: Is it scientifically valid to use human OA treatment studies to suggest a reduced risk of OA in the general healthy population?

And the final question is: If human data are absent, can the results from animal and *in vitro* models of OA demonstrate risk reduction of OA in humans? And then we have two subparts: Subpart

(a), To the extent that animal or *in vitro* models of OA may be useful, what animal models, or *in vitro* models, types of evidence, and endpoints should be used to assess risk reduction of OA in humans? And (b) is: 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?

This question is simply asking: Are the results from animal and *in vitro* models relevant for demonstrating OA risk reduction in humans?

This meeting then is about the science needed to demonstrate risk reduction. It is not about disease treatment or mitigation. This meeting is about osteoarthritis. It's not about glucosamine and chondroitin sulfate. it's a meeting about the etiology of osteoarthritis, its valid modifiable risk factors/surrogate endpoints, and the relevant models of osteoarthritis. Because it's about risk reduction in osteoarthritis, we

also feel that the recommendations of this FAC can apply to other substance-osteoarthritis relationships.

Again, I thank you for being here, and I look forward to the discussions over the next day and a half.

DR. MILLER: Thank you, Craig.

Any questions or comments? Dr. Cush?

DR. CUSH: You several times have said this is not about mitigating the disease through a substance. And in Ms. Nickerson's presentation, she stated that a dietary supplement is a product that is intended to treat, mitigate, or cure disease--oh, it's called a drug, sorry. So if it mitigates a disease, it would then be classified as a drug.

DR. ROWLANDS: That's correct.

DR. CUSH: Okay. I'm sorry.

DR. CALLERY: Pat Callery. I understand that it's not about glucosamine or chondroitin sulfate, but you do mention glucosamine as a glycoprotein, and I'm wondering what the rationale

is there, because we'll have much discussion later about salts and makeup and the difference between the particular agents or compounds. I don't think it's a glycoprotein.

DR. ROWLANDS: If I made an error, I apologize. I was simply quoting the information I was given. But that would be--we'll put on the record what exactly it is.

DR. MILLER: Any other questions?

[No response.]

DR. MILLER: All right. Thank you, Craig. Sorry. Johanna? Craig, just a minute.

DR. DWYER: Just a quick one.

DR. MILLER: Dr. Johanna Dwyer.

DR. DWYER: It's Slide 12, your diagram. The diagram that shows healthy people, valid modifiable risk factors, and you use the example of walnuts, LDL cholesterol, and coronary heart disease. And I'm focusing on the arrow from healthy people to valid modifiable risk. That does not depend, does it, on the level of HDL cholesterol? It's just that it affects that

there's a causal chain? Is that what your diagram is saying?

DR. ROWLANDS: The diagram is saying that LDL cholesterol is a valid--it's a recognized valid modifiable risk factor or surrogate endpoint for predicting coronary heart disease. And so we don't have to--when we look at the evidence for whether or not a substance will reduce your risk for disease, we don't necessarily need--because of that, we don't need necessarily incidence data in populations. We can rely upon evidence of LDL cholesterol, changes in serum LDL cholesterol, a reduction in this case. That was the point of that slide. Because we have evidence, ample evidence that LDL cholesterol is a valid modifiable risk factor and indeed does predict your risk for developing disease--and that's been established with studies where you've measured the incidence of heart disease, in the same group of people you're measuring LDL cholesterol in response to the same intervention. And so you have that kind of evidence that essentially tested whether or not it

was predictive, and, in fact, it was predictive. We have plenty of evidence.

DR. DWYER: I guess what I was after is: Does it matter what the level of LDL is? If it's outside of the 95 percentile for a population, does it matter? Or is it just the causal chain that matters?

DR. ROWLANDS: I'm not sure I understand your question, but I can tell you that we look at changes, significant changes, so statistically significant changes, decreases in LDL cholesterol, as being a beneficial effect, if that answers your question.

DR. MILLER: Dr. Russell?

DR. RUSSELL: A question going back to healthy population. I know you gave us a definition that they don't have diagnosed disease. But I'm wondering, if a population--if a large percent of a population, let's say 50 percent of the population, has some degree of a disease, not symptomatic, let's say hypertension or let's say atrophic gastritis--there's any number that we

could pick that sort of accompany aging--are these people considered healthy?

DR. ROWLANDS: So what is healthy, right? I mean, everyone is--

DR. RUSSELL: Yes, but I think it's an important question for us to grapple with, because your definition is, well, they just haven't been--they don't have diagnosed disease.

DR. ROWLANDS: Yes, I guess the way to look at it is when we are given a body of evidence and it says in the evidence that these individuals have the disease, well, then, we have to assume they have the disease. The question is to the FAC: Can you base risk reduction on that kind of evidence? And our definition in this case of disease is they have diagnosable osteoarthritis. Now, they may have other conditions. They may be unhealthy for other reasons. But the point we're trying to focus on is the disease which is the subject of the claim is the most important thing we want to focus on because that is what the claim is about.

Now, to the extent that other things may be impacting that process, the experts here can fill us in. But that's essentially our definition for health claims.

DR. MILLER: Dr. Cush?

DR. CUSH: So soy and walnuts can be given to healthy people to alter a surrogate that might help someone with a disease, and that's a good health claim. How would aspirin be classified? Because aspirin is given to healthy people and has disease benefits downstream. Presumably its surrogate would be by having an antithrombotic effect. How would aspirin be handled?

DR. ROWLANDS: Aspirin, of course, is already a drug.

DR. CUSH: Right.

DR. ROWLANDS: And so once you already have something as a drug, it cannot be a food. Health claims are about foods. But you're getting into the regulations now, so there's a technical regulatory reason why that wouldn't matter.

DR. CUSH: I was trying an example.

DR. ZEISEL: Just to help us, the question we're being asked--Steve Zeisel. The question we're being asked today, one of them, is: Can evidence in patients who already have the diagnosed disease be used to predict whether something would prevent the progression of the pre--the things that have to occur ahead of the disease being diagnosed from occurring? So joint degeneration but not to the point of diagnosable osteoarthritis, progressing to that point being prevented is--and the question you're asking is: Can we use data from people who already have the diagnosed disease to make that prediction?

DR. ROWLANDS: Yes, in a sense, that's correct. I would just also point out that risk reduction and prevention, they sound the same. They're a little bit different. We're not saying that we have to prevent it. It would lower your risk for getting it. So a little bit of a nuance there.

DR. MILLER: Dr. Krinsky?

DR. KRINSKY: Norman Krinsky. It seems to

me that you're creating a black-and-white situation, whereas there is a gray area. For example, I have prostate cancer, and I was diagnosed with the disease. But before I was diagnosed, was I, therefore, healthy and did not have prostate cancer?

DR. ROWLANDS: Based on if they gave us a paper and the evidence that was given to us said that you were looked at by a physician and you do not have prostate cancer, then we will assume you do not have prostate cancer. And I realize that is a simplistic way of looking at it, but flip it around. When you have a population that has a diagnosed disease, which is all the evidence we have here, what do you do with that?

DR. MILLER: Dr. Cush?

DR. CUSH: As a distinction between a health claim and a drug claim can be difficult in the kind of product you're talking about, is it this committee's purview to favor one over the other as opposed--or we're just here to talk about the health claim, and, for instance, there may be

not enough evidence to make the health claim, but could we discuss then the use of a product as a drug claim?

DR. ROWLANDS: This meeting is about health claims, and to the extent you believe the evidence supports risk reduction, that's what we would like to hear about.

DR. MILLER: Actually, let me interrupt. The way I understood it, this meeting is not about a health claim, but is about the question of whether the science supports the relationship between osteoarthritis--I want to make that distinction because once you get into the issue of the regulation and the interpretation of the regulation, that's a morass. And I don't think we have the time to get into that discussion.

DR. ROWLANDS: That's correct. I guess I was thinking more along the lines of Question 2, which seems to be what your question is directed at, whether or not you can use what we call treatment studies to extrapolate to risk reduction. We're not interested in whether or not there is a

therapeutic benefit for treating the symptoms of a disease. That's not what our question is about.

DR. MILLER: Dr. Dickinson?

DR. DICKINSON: Annette Dickinson. It's typical, I think, for research studies on any given substance and disease prevention or treatment to be done in diseased populations because you can expect with a reasonable number of subjects to get some kind of a response.

In the case of dietary ingredients, if the intervention is with a dietary ingredient, like, for example, calcium or omega-3s, you may also be able fairly readily to get epidemiological information or observational information that indicates that high intakes of that nutrient also have a preventive effect in the healthy population.

But if you're dealing with a substance like chondroitin, for example, which might not be widely consumed in the general population unless they're supplementing it, then there will be barriers to drawing conclusions about the healthy population because it's not something they're

exposed to in meaningful amounts in the regular diet. And yet we can point to many examples, like with omega-3 and calcium, where intervention agents are also effective prevention agents. Are we allowed to take those comparisons into account, those comparative cases into account?

DR. ROWLANDS: I'm not in a position to tell you what you can and cannot take into account. If you feel it's important, then I guess that should be something you should bring into your discussion.

DR. FELSON: You didn't want this to be a discussion of glucosamine and chondroitin, so let's leave it as a discussion of osteoarthritis and whether risk factors for incident disease and progressive disease are the same. There are a number of studies--and probably Dr. Simon will review them--that suggest very strongly that the risk factors differ for incidence and progression. Bone density, for example, appears to be--increased bone density appears to be a risk factor for incident disease, and yet data suggests that it

probably--high bone density protects against progressive disease.

Vitamin D, what data there are suggest that it protects against progressive disease and has no effect on incident disease. Okay? So I think it would be beyond a scientific reasonable extrapolation to suggest that anything that treats this disease is likely to have an effect on incidence.

DR. MILLER: That was Dr. Felson.

Dr. Lane?

DR. LANE: Yes, I was just going to comment further on Dr. Felson's question. With the limited data that we now have regarding risk factors for incident and risk factors for--or variables associated with progression of disease, it's limited, but Dr. Felson brings up just about everything we know.

DR. MILLER: Any other comments?

[No response.]

DR. MILLER: We're doing quite well so far. I hate to think that my role is to watch the

clock, but I guess that's what it is.

Dr. Bucci?

DR. BUCCI: Here.

DR. MILLER: Are you prepared to make your presentation now?

DR. BUCCI: Yes, I am.

DR. MILLER: Why don't we do that and then we'll take our break after Dr. Bucci's presentation.

DR. BUCCI: Well, good morning, ladies and gentlemen, and I wish to thank the Food Advisory Committee for inviting us to make this presentation.

My role here is to do several things, and really what I'm here for is to show evidence, credible evidence, that glucosamine and chondroitin sulfate reduces the risk of osteoarthritis, joint degeneration and/or joint deterioration.

So what I'll do is--I don't think I'll spend much time reviewing the need for reducing the risk of osteoarthritis. I think that is self-evident. Also, the proposed health claims have

already been listed. What I would like to do, though, is spend a wee bit of time on reviewing the roles of glucosamine and chondroitin in reducing osteoarthritis risk. One of the ways I'll do that is by showing you what they do in normal cartilage tissue and then get into some of what I feel is credible evidence that supports these claims.

These are facts and figures taken from the Centers for Disease Control, and arthritis is the leading cause of disability in the United States. I think the numbers speak for themselves here.

What I find of great interest are the 9,500 deaths from a supposedly non-fatal disease. Now, I realize some of these figures lump rheumatoid arthritis with osteoarthritis, but medical textbooks have said that osteoarthritis has an--or if you have osteoarthritis, you have an 11-percent higher death rate than the average population. And this is from a non-fatal disease.

So obviously there is a need to reduce the risk of osteoarthritis in the general population, if for no other reason than to not have people die

needlessly.

But as you can see, there's a huge cost associated with the treatment of osteoarthritis. Its impact is enormous, and that's one of the reasons that we're all here today, is to figure out if we can reduce this enormous risk and burden to our health care.

The very bottom part of this figure shows the age ranges of incidence of osteoarthritis, and as we all are aware, this is an age-related type of condition. However, ages 18 to 44, I think people in that age group would deny that they're aged, and one out of five of them has diagnosed arthritis. Again, some of these are rheumatoid but, still, the majority is osteoarthritis since that makes up about 80 percent of the total arthritis.

The point I'm getting at here is that these people would--these are not considered aged people. It is not a completely age-related disease, and this speaks to the variety of factors.

Okay. These are the health claims that have been proposed by Weider Nutrition.

Glucosamine and chondroitin may reduce the risk of osteoarthritis, joint degeneration, and joint deterioration. I think we've seen these already so I'll proceed on in the interest of time.

What I'd like to do is give you some visual reference points so you can put what glucosamine and chondroitin do into a context and mental framework.

Uh-oh, I hit the wrong button again. This even works behind your back. Very good.

This is an artist's rendition of articular cartilage, and the point here is that this is a different tissue than others in the body, quite different, in fact. Cartilage is thought of by most people as being sort of an inert Teflon washer for your joints that cushions--makes your joint lubricated so they can slide easily and you can have adequate movement. Obviously, this is an artist's rendition, so there are a few things out of scale. But the point here is that there's no blood vessels inside of cartilage, except for some in the menisci; no nerves; no lymphatics.

These chondrocytes, which are the primary cell type in cartilage, rely on diffusion from synovial and subchondral bone blood vessels to get all their nutrients--oxygen, water, carbohydrates, protein, amino acids, glucosamine, et cetera.

This is a little more of a closeup of cartilage in a very stick-figure kind of diagram. Chondrocytes are supposed to be the only cell type in cartilage, and they manufacture this cartilage matrix, which is a combination of Type II collagen mostly, which are represented by these purple girder-like structures. And in between all the very precisely laid out collagen girders are these proteoglycans, commonly called--aggrecan is the main one. And these are composed of--what I'll show you is mostly chondroitin sulfate.

As you can see in this stick figure, these little yellow sticks running around randomly, supposedly randomly, but in between these girders represent the proteoglycans. And we'll give you a little bit better picture in a moment.

But, first of all, these proteoglycans

form around a hyaluronan backbone, HA, and hyaluronan is a glucosaminoglycan; 50 percent of it is directly derived from glucosamine. And we have these proteoglycan subunits that are attached to the hyaluronan over and over and over again, hundreds per hyaluronan. These proteoglycan subunits are relatively large molecular structures. They have a couple hundred, on the average, chondroitin sulfate chains attached to each core protein, and you have several hundred of these proteoglycan--which I've abbreviated here as PG--subunits per aggrecan or proteoglycan molecule.

Now, I think something that's extremely important for everyone here to realize and remember is that the life span of aggrecan proteoglycan in adult human cartilage is 600 to 1,000 days, two to three years. Keep that time frame in mind. I think it's important for interpretation of the results of human studies.

In other words, cartilage is a very slow tissue, and it responds to stimuli in a very slow and simple manner.

This is another artist's picture that gives you a little bit better idea of how space-filling the proteoglycans are. The chondroitin sulfates have a relatively large amount of sulfate groups that are charged and attract water, and they fill up all the space between the collagen girders that make up the shape and the structural integrity of cartilage. Various insults can physically damage and degrade the structures of cartilage, specifically the chondroitin sulfate, the collagen, as well as the hyaluronan backbone of proteoglycans. These insults are constant, ongoing, and inescapable. Free radicals are probably one of the primary insults, and any type of other risk factor eventually leads to generation of free radicals that do actually physically damage and break off small pieces of cartilage, including chondroitin sulfate, hyaluronan, and Type II collagen. Some of these pieces are actually being looked at surrogate endpoints or biomarkers for cartilage damage.

So what I'm trying to do here is give you,

again, a context or a perspective of what glucosamine and chondroitin are. I hit the wrong button again, but here we go.

One thing I didn't mention previously is that glucosamine is the major precursor for chondroitin sulfate. We'll look at that in a moment. I'd like to cover some of the human supplementation studies that have used glucosamine and chondroitin sulfate and their applicability to risk reduction of osteoarthritis and joint degeneration and deterioration.

Again, I want to reiterate the fact that cartilage turnover, normal maintenance and repair, is constant and ongoing. Your cartilage is not an inert Teflon washer. Although kind of slow and best by problems of nutrient diffusion compared to other perfuse tissues, cartilage does maintain itself all the time as we go through life. The half-life of the major structural components--aggrecan, proteoglycan, and collagen--is about one to two years. Remember the life span was two to three years. And as I've already mentioned, normal

wear and tear in healthy people--everybody, for that matter--produces these degraded fragments constantly.

Another cause is shear stress, and this is where things like trauma and injuries can enter into play. In other words, just the shear stress of overload of mechanical forces can literally break off pieces.

Cartilage does respond via the chondrocytes in the synovial lining to the molecular pieces of the most exposed macromolecular constituent. That's pretty much obvious, and these constituents being hyaluronan in synovial fluid and chondroitin sulfate in cartilage itself, since they are the space-filling macromolecules that anything that would be at a molecular level would encounter first in synovial fluid and collagen. So it kind of makes sense that these chondrocytes which are trapped in their matrix respond to pieces of the structure. In other words, the analogy, very simple analogy, would be that if you start to see bricks falling around outside your house, you know

you have a problem with the structural integrity of your house and you need to start patching up your brickwork again. It's a very simplistic analogy, but there are receptors on chondrocytes and synovial lining cells and, indeed, cells throughout the body that recognize both intact and various sizes and fragments of both hyaluronan and chondroitin sulfate.

So all these things are happening all the time, whether somebody is five years old, 50 years old, 90 years old, whether they walk with a limp or can run marathons.

Supplementation trials also have these other factors going on. Joint tissues can only maintain themselves and, thus, resist degradation, resist deterioration, and remain normal by biosynthesis of more matrix. This is a brick-and-mortar-type of idea I'm trying to get across. if the bricks and mortar start to fall apart, you have to add more brick and mortar. So the only way that joint tissues can make more matrix is to start off with glucosamine and convert that into chondroitin

and proteoglycans, and that sets the stage for collagen production on top of that. There must be a combination of collagen production and proteoglycan production to produce cartilage. It's a relatively simple tissue structurally. And biosynthesis of chondroitin is essential to the maintenance of cartilage and, thus, to the prevention of joint deterioration.

I took this quote from a textbook in 1986 called "Articular Cartilage Biochemistry," and I'll read it for the record. "The integrity of this matrix is critical for the unique biochemical properties of hyaline cartilage and depends on a maintenance of the quantity and quality of the matrix components. Such maintenance must be the result of a balance between synthetic and degradative processes within the tissue. Thus, any loss of, for example, proteoglycan from the cartilage matrix due to physiologic or pathologic processes must be balanced by *de novo* synthesis of proteoglycans by the chondrocytes."

So, in other words, if there's anything

going on with the cartilage in terms of structural damage or loss of any components, the only way to fix that is to actually make more. And the only way to make more is to use glucosamine to manufacture chondroitin, et cetera, et cetera.

Also, a review of the available literature, which is, of course, quite extensive, shows that the same biochemical signals, the same regulatory, cellular, biosynthetic, anabolic, catabolic, and metabolic mechanisms that operate in cartilage in normal health are also operating during the process of diagnosed osteoarthritis. So what I'm trying to say here is that I believe that normal cartilage is acting the same way that cartilage does in osteoarthritis to a very large extent.

Maintenance of cartilage consists of the same processes and events that occur during normal wear and tear, that also occur during normal aging, and also in persons diagnosed with osteoarthritis. In other words, all three of these situations involve use of glucosamine and chondroitin to make

more matrix.

In other words, the chondrocyte doesn't know if you've been labeled osteoarthritic or elderly or young and growing. It just does what it has to do, and that's make more matrix.

Also, I think one thing that's been alluded to extensively is surrogate markers or endpoints of progression of disease. And I think it's pretty clear from looking at textbooks over the last five decades that there is an unbroken continuum of events in cartilage from health to degenerative disease. Notice that the official definition of osteoarthritis from Stedman's Medical Dictionary really identified a very late stage, such as eburnation. That's the progression that we're trying to stop, that we're trying not to get to, is losing cartilage and getting bone on bone. That is what we are trying to reduce the risk of getting to.

So, therefore, there's no agreed-upon threshold or marker that clearly defines the onset of osteoarthritis. I think Dr. Krinsky's point

about when does diagnosis occur and when are you considered or diseased is very applicable here. In other words, if someone walks into a doctor's office and gets diagnosed with osteoarthritis that day, what were they the day before? They would have been considered healthy unless they had, of course, been looked at and determined to be osteoarthritic. So that is, I think, the question, but I think the answer is that there's really not much difference. It is a continuum. If you're going to say, well, you right there, you're osteoarthritic, and the next person that you look at and evaluate whether they're osteoarthritic or not has similar findings but no symptoms, well, is that the same thing or not? They'd be considered healthy. So there is a continuum.

There's also considerable overlap of these biochemical markers as well as the appearance of cartilage from various diagnostic imaging techniques between healthy controls and osteoarthritic subjects. I think this is well borne out in the literature. You look at the

reference ranges for some of these biomarkers in normal persons and persons with diagnosed osteoarthritis, and by normal people I mean persons that have no or very little signs of joint degeneration or damage visually by diagnostic imaging techniques, and there is considerable overlap.

In other words, I think that speaks to the fact that chondrocytes are doing the same thing in each condition. All they know how to do is make more matrix. They don't care if they're healthy; they don't care if they're hurting. So I'm arguing that the same type and extent of imbalance between matrix component synthesis and degradation is seen in both healthy and osteoarthritic subjects. If you're going to start segmenting arbitrarily, you're going to knock out a significant proportion of the population.

I'm a Ph.D., not a rheumatologist, but maybe you can help clarify this for the audience later on today, but osteoarthritis diagnosis is based on the clinical signs, subjective clinical

signs of the individual, pain and stiffness in joints, as well as X-ray evidence of structural changes in joints.

The staging is relatively arbitrary and subjective. In other words, there's no lab test you can send off to a laboratory for it and it comes back and says, yes, you have osteoarthritis. This has to be determined by physicians and by the signs and symptoms given to them subjectively by the patient as well as diagnostic imaging.

Human studies with osteoarthritic subjects have examined a portion of that continuum of joint health. They represent one window on that continuum.

Pre-diagnostic joint damage, therefore, must exist in greater incidence than diagnosed osteoarthritis. And since diagnosis is roughly about 20 percent of the population over age 50 right now, it's an enormous number. There are obviously many more people than that that perhaps would be diagnosed with osteoarthritis that are considered healthy right now--again, blurring the

distinction between disease and health.

Just looking at the situation of normal aging shows that a loss of chondroitin in cartilage and/or hyaluronan in synovial fluid occurs all the time. It happens as we age. Normal aging specifically shows decreased length or size of chondroitin and, thus, the aggrecan proteoglycans that are synthesized routinely for maintenance and upkeep. Obviously, if you live to be 80 years old, you've gone through 20 to 40 or so cycles of new cartilage or of turning over cartilage. And as those cycles keep going, the macromolecular components start to get a little bit smaller. Thus, with less chondroitin around, cartilage holds a little bit less water and actually reduces in size. I think a lot of us realize that we lose height as we age, and a lot of that is from the actual diminishing size of intervertebral disks, whether or not--it is completely unrelated to loss of bone in the spinal column, but one or two inches can be lost simply from normal aging, losing the size of cartilage because of the loss of size of

chondroitin. And that's considered normal.

So osteoarthritis obviously results from an imbalance of normal anabolic and catabolic activities in cartilage, and this is alluded to in textbooks over and over. Therefore, osteoarthritis is a deficiency of normal regulation of cartilage maintenance. And I think the data from the human studies and also from the animal and *in vitro* studies shows that both glucosamine and chondroitin sulfate help to regulate towards normal cartilage maintenance. Maintenance of the normal balance of anabolic and catabolic actions leads to a return to health and obviously reduces the risk of osteoarthritis. So a relatively simplistic concept here because cartilage is a relatively simplistic tissue. It only knows how to make more matrix.

Let's take a closer look at some of the clinical studies on glucosamine itself.

Again, much work has gone into finding that the availability of glucosamine is a key rate-limiting step for synthesis of connective tissue macromolecules. This is true not only for

cartilage but other connective tissues as well. Normally, glucosamine is manufactured from glucose, which, of course, is readily available all over our bodies. But if you supply the synthetic cells with glucosamine itself, they like it, a lot better than having to make it themselves. In other words, it bypasses several chemical enzymatic steps, and it kind of--I play Monopoly--does go directly to go--you bypass the jail and go directly to go, and straight into synthesis of GAGs or glycosamino-glycans, the major one being chondroitin sulfate.

So, in other words, glucosamine is a preferred substrate for repair, maintenance, and upkeep of cartilage, and also of hyaluronan and synovial fluid.

I've put together a list of the types of published evidence in glucosamine. There's consensus statements and review articles I've lumped as independent expert opinions. There are 14 meta-analyses that I've identified on glucosamine, all of them supportive. Large, well-designed human clinical trials are at least 80

total subjects, and several of those have been reported more than one time, but the majority of those do support some benefit for administration of glucosamine for persons with osteoarthritis.

There are smaller, well-designed human clinical trials. Again, the evidence is credible in that there is much more supportive than non-supportive. And instead of saying uncontrolled, I think I should have said unblinded human clinical trials. Many of these trials did have control groups but were open. And the animal intervention studies, giving glucosamine and then inducing arthritis, and *in vitro* studies, they are all very supportive, providing credible evidence that glucosamine has benefits for joint health. And this is kind of across the board, anything you can find. So 180 original studies, and I was very light on the animal and *in vitro* studies since I obviously, being a trained scientist, also feel that they have slightly less merit than the human clinical studies. So I didn't go crazy with those. I just listed a few of them. There's a lot more

than that out there.

These are some of what I call--let's just call them biomarkers that are affected by glucosamine. The biosynthesis of hyaluronan, glycosaminoglycans, collagen. It's relatively obvious this is textbook stuff. Glucosamine is the major precursor. Also, not only being a building block, but glucosamine does have regulatory effects and has been called a biological response modifier. It does enhance gene expression of the enzymatic machinery that produces chondroitin and other glycosaminoglycans as well as collagen.

Also, glucosamine is added to collagen, and I think that's where the glycoprotein confusion might have arisen from glucosamine being called glycoprotein. Obviously, glucosamine is not a glycoprotein. It's an amino sugar. But it does get added to quite a few proteins, and especially Type II collagen. Also, glucosamine is converted into other sugars that are then glycosylating proteins throughout cartilage.

Also, glucosamine has been shown to

inhibit cartilage breakdown. There have been two large, three-year human clinical studies, and I'm sure that my compatriots from Rotta will address those. They both showed the prevention of joint space loss in knee osteoarthritis in humans.

One interesting point that I think has been overlooked in the second of these studies by Pavelka from 2002 is that when you do these types of studies, you pretty much focus on one knee that has definite signs of osteoarthritis and is causing all the symptoms. Well, what about the other knee? They actually stated that the contralateral or non-osteoarthritic knees looked better, and actually people reported that they felt better. And those weren't the knees that were diagnosed with osteoarthritis. So I propose that that's a definition of normalcy and that glucosamine in a long-term study has been documented to benefit a normal joint.

Also, there have been correlations with some of the molecular biomarkers associated with joint damage. Osteocalcium, which I didn't list on

this slide, and the chondroitin sulfate 3B3 epitope, which is one of those fragments of chondroitin that are produced from damage, have correlated with the radiological images in humans. There is one case report of an intervertebral disk actually regenerating after six months of glucosamine and chondroitin sulfate, verified by MRIs. And one of the earlier studies from Italy by Drovanti in 1980 actually looked at cartilage biopsies after the study in a couple of people given glucosamine sulfate and found that the surfaces were smooth and almost normal. But they also looked at a couple biopsies of cartilage from normal subjects to compare it to. They chose a couple of people from the placebo group that were happening to have surgery, looked at their cartilage biopsies, and they showed the typical surface fibrillation and damage associated with osteoarthritis.

So, therefore, there are indications in the literature that giving glucosamine does affect the structure of cartilage. It brings it more back

to normal.

I think the cases of joint degeneration in healthy animals that are induced to become osteoarthritic being prevented by glucosamine is relevant. It shows that glucosamine does have the ability, if it is present before any joint damage, to actually slow down, delay, and prevent the progression or incident of osteoarthritis once osteoarthritis is definitely administered. And obviously from *in vitro* studies, glucosamine can be added, and, again, that data supports glucosamine improving cartilage by inhibiting breakdown.

One interesting study by Braham in 2003, published in the British Journal of Sports Medicine, looked at people with knee pain. They said they specifically did not include people with osteoarthritis diagnosis. They just had knee pain and decreased function. After 2000 mg per day for 12 weeks, these subjects noted less pain and improved function. Most of these people were younger and had sports injuries. In fact, I think that this mirrors the continuum of joint health to

disease, that some of these people may probably have become osteoarthritic in the future. Injuries to joints are obviously a etiological cause of osteoarthritis. So, again, more evidence that glucosamine can help prevent the progression of joint damage and deterioration.

Okay. I need to move along. I will just kind of quickly go through some of the other mechanisms of glucosamine. There are anti-inflammatory effects that actually are not so immediate. They work via regulation, not direct inhibition of inflammatory events. So, in other words, glucosamine is not an aspirin, it's not an NSAID. It doesn't work like that. It works by regulating the cells to stop doing all those things, is the simplest way I can put it. And in human studies, giving glucosamine with NSAIDs has shown a synergy in the effects of the NSAIDs. Downregulation of inducible nitric oxide in joints, in cartilage; some antioxidant protective effects, perhaps by being converted into hyaluronan; and other immune modulation effects have been

demonstrated as well. Yes, these are animal and *in vitro* studies, but they speak to the mechanism of how glucosamine can accomplish the findings seen in the human studies.

Now on to chondroitin sulfate. Again, a list of the various types of published evidence shows, again, an overwhelming amount of credible evidence in favor of chondroitin supporting joint health. Eight meta-analyses, all in one form or another expressed that there were benefits derived from chondroitin sulfate administration to people with osteoarthritis or joint damage.

Again, the large, well-designed human clinical trials, of which there are a pretty good number here, were unanimous. Again, similar for glucosamine, chondroitin shows a high preponderance of beneficial evidence.

And as I mentioned for glucosamine, I was very partial in listing animal and *in vitro* studies. This is but a sampling of the many studies that are available. Chondroitin has been around for a long time, has been widely studied for

other health conditions as well. But I'm limiting these to joint health.

Let me back up one second. On the consensus statements, one of those is from the Arthritis Foundation in which they said that for both glucosamine and chondroitin, it does reduce the signs and symptoms of osteoarthritis. So for someone as conservative as the Arthritis Foundation to make that statement in their public writings and also to allow sponsorship of dietary supplements containing glucosamine and chondroitin by allowing placement of their logo on approved products I think speaks very highly that there is a consensus of medical experts somewhere that glucosamine and chondroitin do affect osteoarthritis and in a very positive manner.

One of the other consensus statement is from EULAR, the European Union League Against Rheumatism, where they list glucosamine and also chondroitin sulfate as part of the primary treatment of osteoarthritis, as part of a multi-modality approach. So, in other words, it is

considered standard therapy in certain countries.

Again, chondroitin can be--in other words, how does it work? Obviously it is a building block, and, again, it's also a regulatory building block. More chondroitin means more stimulation. And it actually works on gene expression of the enzymes involved in chondroitin sulfate and, thus, cartilage production.

A lot of work has focused on the inhibition of cartilage breakdown. One study in particular from 1986 in France looked at sports overuse injuries. It used kneecap cartilage biopsies, and after 16 weeks of 1500 mg per day of chondroitin sulfate, they noticed thicker, smoother cartilage appearance from these kneecap cartilage biopsies. So these were in people with sports overuse injuries.

This type of finding was also mirrored by glucosamine sulfate in an open-label study from Germany in the early 1980s in people around 20 years old or so that their chondropathia also improved after a few months of glucosamine.

There were at least four studies showing the prevention of new lesions in finger osteoarthritis. Okay. There it is. Two of these studies were two years in length; one of the studies was three years in length. And erosive finger osteoarthritis has a large genetic component. Causes are presumed to be genetically mediated, which means that it may be impossible to stop it. But if the progression--in other words, the progression to erosion can be prevented, then I would say that's reducing the risk of osteoarthritis. And that's been shown in these two- and three-year studies by Rovetta and VerBruggen.

Likewise, there have been at least eight studies of preventing joint space loss in knee osteoarthritis from chondroitin sulfate. These studies range from one to two years in length, and, again, with eight studies showing the same thing, the magnitude of joint space protection was about 0.3 millimeters after a one- to two-year period. In other words, the magnitude of preservation of

joint space was virtually identical to that seen by the glucosamine studies. So we are seeing that glucosamine and chondroitin both prevent the loss of joint cartilage during mild to moderate osteoarthritis. And I think another interesting point is that most of the investigators stated that the people with earlier stages and, thus, more towards normal stages appeared to have better results. Again, this speaks directly to reducing the risk of osteoarthritis and in my mind makes this more relevant to "normal" or healthy population that may have joint damage already ongoing and just being diagnosed.

Again, the biomarkers of cartilage loss were shown to correlate some of the time--not all of the time, but some of the time to the diagnostic imaging pictures. In other words, less signs of joint damage and degeneration, such as cartilage oligomeric protein, keratan sulfate, urine pyridinoline/creatinine ratios, and the deoxypyridinoline/creatine ratios. Those are markers of collagen damage and destruction. These

were reduced as the joint space loss was halted. So although I'm not going to sit here and say that glucosamine and chondroitin will rebuild cartilage, I think stopping the progression seen over a several-year period is pretty close to the same thing.

Likewise, with chondroitin, prevention of osteoarthritis in animal models being induced to have arthritis showed that it could prevent the signs of damage, degeneration, and deterioration.

There are some other interesting human studies on chondroitin sulfate. After administering 800 mg for five or ten days, the levels and the size of hyaluronan and synovial fluid were increased in subjects with knee osteoarthritis. Also, the elastase inhibitor complex levels were reduced, which means that chondroitin had a direct inhibition of degradative enzymes, as was the collagenase activity and N-acetyl-glucosaminidase activity levels. And there's at least three human studies looking at joint fluid to show direct inhibition of enzyme

activity with typical oral dosages, and that's over a short term.

Now, if you can extrapolate the effects of doing that over and over and over and over and over again for years, I think that can easily explain the cessation of loss of cartilage. If you're stopping the inhibition and improving the synthesis, what else can happen?

How much more time do I have? I want to make sure not to run over. Okay, thank you.

I also wanted to mention other biomarkers affected by chondroitin, one of which is mechano-structural or tensegrity for tension integrity. Chondroitin being a highly charged molecule and accounting for a lot of the structural integrity of cartilage itself, when it is lost, that structural integrity is lost, more mechanical forces are transmitted to chondrocytes. They do have mechano-receptors as part of what their cytoskeleton is there for. So when cartilage is lost, chondrocytes have another way to determine that. They don't need the fragments. They can just see the overall