advertisement. I'm the project officer for this very large contract, the Osteoarthritis Initiative. The goals of the Osteoarthritis Initiative are to create a research resource to aid in the identification and evaluation of biomarkers as candidates for surrogate endpoints for OA.

The mechanism we chose for this--and this was done through collaborations. Dr. Witter, as he told you, was the introductory speaker for our first session; Dr. Felson, Dr. Abramson, Dr. Altman, many people have been involved in this process over the years--was to develop a prospective natural history cohort of individuals with early OA and with risk factors. So this is here the definition of what we've been talking about today. How do you define when the disease starts? And this is what we're hoping to try to capture in the Osteoarthritis Initiative, the early phases of osteoarthritis development.

This will be a natural history cohort study, no treatments, and these individuals will be followed for five years. We're going to be

collecting clinical information, a WOMAC assessment, functional assessment, physical exam, dietary supplements, treatments that these individuals might be using. We will have an extensive database of MR and X-ray images and biospecimens as well.

This is a public-private partnership that is funded through government and private partners, and you can see from this slide that we have many NIH Institutes involved in this, as well as three pharmaceutical partners who have chosen to work with us to move forward the area of biomarkers for OA.

The particular individual academic centers involved in this study, the clinical centers are the Ohio State University under the direction of Dr. Rebecca Jackson; University of Maryland under the direction of Marc Hochberg; University of Pittsburgh under the direction of Kent Kwoh; and the Memorial Hospital of Rhode Island under the direction of Dr. Charles Eaton. All of these are coordinated under the University of California-San

Francisco center run by Dr. Michael Nevitt.

The research resources from the OAI should, we hope, stimulate basic research on biomarkers, facilitate drug development through the identification of biomarkers of disease onset, identification of biomarkers for disease progression, which we've heard today may be quite different, and elucidation of the basic disease processes and risk factors.

The long-term results from the OAI may include a more thorough understanding of OA and its manifestations in at-risk populations; positive interactive relationships between the parties involved, that is, companies, academia, and the government; and more efficient and safe assessments in clinical trials.

And I'll also mention at this point that there is also a very large similar study being carried out under the leadership of Dr. David Felson, the Multicenter Osteoarthritis Trial, the MOST study, that will generate similar data.

So although we don't have it now, we're

very hopeful that within three to five years there will be a very rich database, and one of the things I didn't mention is that this resource will be public and will be available to investigators throughout the world for their own investigations and hypothesis testing and data mining.

I thank you for your attention.

DR. MILLER: Thank you, Dr. Lester.

Any questions or comments for Dr. Lester?

[No response.]

DR. MILLER: If not, thank you.

Our next speaker is Dr. Robert Arnot, network news correspondent, who will explain mechanical and chemical changes in joints that evolve from initial joint tissue insults or injuries to full-blown osteoarthritis. You have 15 minutes, Dr. Arnot.

DR. ARNOT: Good afternoon. I am a physician. I am a journalist. I have reported for the last 20 years for three different networks on osteoarthritis as well as a variety of other diseases, spent the last year and a half in Board

of Governors with the 1st Marine Expeditionary Force and various components of the U.S. Army, and I am glad to be back here in Bethesda, Maryland.

Also, my only financial stake in this is that I am the author of a book called "Wear and Tear Arthritis," and I have a very personal stake in this book. I wrote it because I was diagnosed with severe osteoarthritis in my right hip. I have osteoarthritis of both of my knees. And I was on 12 to 16 Advil on a regular basis. I was unable to really bend over to play with my then-six-year-old, unable to play tennis or ski or do any of the things that I wanted to. And I really embarked on a course to see what I could do in terms of preventing any further deterioration in my own condition.

Now, we have heard a lot of evidence here this morning and this afternoon, and it does kind of tend to pile on. We in the news media and as physicians tend to look at one clinical study, one watershed event, that more than any other really changes clinical practice. I know many of you know

this study from Lancet, but I just want to very briefly review it because this is the study that physicians that I routinely run into at Stanford, at Harvard, at Johns Hopkins, across the country, use as their basis for treating their own patients with osteoarthritis and for trying to prevent those who may be at risk of osteoarthritis.

Now, as you know, there were 212 patients with knee osteoarthritis who were randomly assigned 15 mg of oral glucosamine, or placebo, once daily for three years. There were weight-bearing X-rays that were done, anthro(?)-posterior radiographs of each knee in full extension, taken at enrollment and then one and three years later, also looked at symptoms.

Now, what we know if we look here is this: 106 patients on placebo had progressive joint space narrowing with a mean joint space loss after three years of 0.31 millimeters. But look at what happened in those who were treated. In those 106 patients, there was a loss of 0.06 millimeters. That's basically statistically insignificant; in

other words, they had little real loss.

When you look at their WOMAC score, the symptoms worsened slightly in the patients on placebo, and there seemed to be improvement in those who had glucosamine.

So, again, this is the study that we reported on the "Today Show" with Katie Couric. It's a study that we used on "Dateline NBC," really is that sort of watershed event.

Now, I think in looking at the problems before the panel today, the biggest one seems to have to do with this idea: Is this a suitable biomarker or isn't it? When you look at the loss of cartilage, I would put to you this is as good a biomarker as cholesterol or as good a biomarker as bone density.

I will just read to you--the FDA seems to have already decided this issue on its website, and it says that, "The FDA in its tentative conclusion states that biomarkers are parameters from which the presence or risk of disease can be inferred rather than being a measure of the disease itself.

In conducting a health claim review, the FDA does not rely on a change in the biomarker as a measurement of the effective dietary factor in a disease unless there is evidence that altering the parameter can affect the risk of developing that disease or health-related condition."

Now, this is the case for serum cholesterol in that high levels are generally accepted as a predictor of risk for coronary heart disease. I would argue it would be pretty hard to dispute that the losing of cartilage, that the lesser amount of cartilage puts you at higher risk of a bad event.

Now, for those of you in the FDA who look at drug trials, you look at coronary heart disease, and what you would say is you are not really looking--you have no markers of disease except bad events. Does someone have a heart attack? Do they die? Do they have to have angioplasty? Do they have to have bypass surgery? And it's very much the same thing with osteoarthritis. You have bad events. The bad event can be bone on bone,

osteoarthritis with severe pain and disability, and the need for a procedure, and, of course, that procedure would be joint replacement. So I would argue strongly here that this is a very powerful biomarker.

The second problem area has to do with what's the point at which a patient is actually diagnosed with osteoarthritis. Take, again, coronary heart disease. You can have somebody absolutely packed and loaded, look at their coronary arteries, look at the (?) thickening here. They can have all kinds of unstable plaques and up and down their left anterior descendant, and yet they are not diagnosed with coronary artery disease. Why? They have no symptoms.

So I think when you look at the burden of the disease there and the ability with coronary artery disease to say that you have prevention if you have fewer events, you're allowed to do, I would gesture, or certainly claim with osteoarthritis.

Now, here's the key point: I know that

the FDA has been very concerned that in this Lancet study, it would say, well, gee, they already have disease. The fact is, well, what do you mean they have disease? The key thing is that X-ray changes precede the clinical diagnosis and precede the onset of symptoms in most people. Take those over 60. In those over 60, about one-third of patients have symptoms, yet the vast majority or almost all already have changes on their X-ray. That means that the majority of patients are not formally diagnosed with osteoarthritis.

The great difficulty has been that right now today there are millions and millions of Americans who are chewing away at their articular cartilage and yet they are not diagnosed with osteoarthritis.

Now, the third difficulty seems to be the diagnosis of osteoarthritis. What I did in my book was to look at sort of three different phases. Phase one was what I call wear and tear, pure mechanical destruction of cartilage. In England, they actually divide the disease into two phases.

They have osteoarthrosis, which is going to be the mechanical grinding away of cartilage, and then you have osteoarthritis, where you actually have chemical changes that further degrade the cartilage, such as the increase in metalloproteinases.

As many of you have indicated, and my colleague from the NIH, there really isn't any marker to sort of say you have made that transition from the chewing away of cartilage to the point that you actually have osteoarthritis.

So when you look at what is prevention here, I would argue that if you are preventing events such as the replacement of joints, if you are preventing events such as the bone-on-bone sort of end-stage disease here, you are, in fact, preventing disease. And if you take myself, I went from taking those 16 Advils a day to taking none. I do take the glucosamine and chondroitin sulfate on a daily basis here. I have this as a regular program of yoga and joint strengthening. I was told four years ago that I would have to have a

joint replacement. I have not had that joint replacement I was supposed to have had. I am now completely pain free, back to playing tennis, back to downhill ski racing, and after, feel terrific.

So just to summarize these points here, the diagnosis itself, most people go undiagnosed; therefore, I guess you could say they don't have disease. And yet if you were to take an X-ray, you would see that there already are changes there. Those changes are probably mechanical. They probably don't already have any of the biochemical changes of osteoarthritis. And if you can at that point basically intercede and decrease the amount of cartilage that they have lost, you are going to be preventing events. Just like in coronary artery disease you are preventing a heart attack or you are preventing the procedure having to be performed, such as PTCA, here you are preventing these critical events.

Now, the other part of this in terms of evidence-based medicine is, well, what about the risk/benefit? I say to physician friends of mine

and they will say to me, I give this to somebody in terms of trying to prevent osteoarthritis or someone who actually has osteoarthritis. What's the downside here? The downside is that they, by being given these supplements or these nutrients here, don't end up having a fatal bleed. And they may not end up with further destruction of their cartilage.

So in terms of risk/benefit here, let's look at a study by Rush Presbyterian in which 53 subjects with symptomatic, radiographic evidence of wear and tear arthritis of the knee were studied. They took acetaminophen to relieve their pain. When the gait was analyzed, those with decreased knee pain tended to decrease the load on the degenerated portion of their knee. Loading the worn and torn cartilage with forces high enough to do further damage.

In my book, I took the strong stand that standard pain relievers, the NSAIDs that many patients have--and I tell my own 90-year-old mother this--that the likelihood is that they are

disguising some of their pain and that they are continuing to accelerate the damage rather than retarding the damage.

When you look at risk, acetaminophen over 4 grams a day, you do run the risk of liver toxicity, and although, of course, it is linked to alcohol intake as well, you do run the risk that you will need a liver transplant. Most physicians, including those at the BU Arthritis Center, would say that this combination, these nutrients are incredibly safe compared to any of the standard NSAIDs. As my colleague here, Dr. Theo, said, you are looking at 16,500-plus deaths a year, many of those with patients who have osteoarthritis.

Now, in the end, you would say, well, fine, if you get to make the claim that these nutrients can be used for prevention, who ends up taking them? Well, the interesting answer is those people who on a daily basis are grinding away at their cartilage, and those would be individuals who have, like myself, a high cavus foot, those who have a hypermobile foot, those who are knock-kneed

or bow-legged, who have a pistol grip hip, and anybody who has had an injury; for instance, my young niece who has an ACL injury, myself with a meniscal tear, those with injuries, those who have what I call fatal flaws; the tens of millions of Americans who are overweight, who pound as they walk around, are all doing damage to their joints.

For all of these individuals, the bottom line is that there is no preventive effort. Here you have a disease that may cause more disability than any other, that when you look at it outside of a stroke in terms of the cardiovascular disease, compared to cardiovascular disease, it's almost the same as having an MI when you have bad osteoarthritis of the hip. And yet there's absolutely nothing on a national level being done to prevent osteoarthritis, nothing in the way of yoga or strength training, nothing in physicians' offices, no agents that are currently being recommended as a way of preventing this disease. So it's a huge black hole compared to osteoporosis, coronary artery disease, cancer, and yet a disease

that basically is going to affect every single one of us.

I know a lot of my time is ending here. I know that you also don't like personal anecdotes, but I'm certainly a testament to the fact that this has worked and worked well. But I would argue strongly that, first of all, there is a real problem with the definition here of osteoarthritis, that I'm a strong believer you have a progression from wear and tear through osteoarthrosis to osteoarthritis, and at that point that you may see X-ray changes before you have actual symptoms, before a doctor is going to make a diagnosis, that you can intervene, you can intervene in a highly effective way to prevent events that are highly disabling.

Thank you very much.

DR. MILLER: Any comments or questions?

[No response.]

DR. MILLER: Thank you very much.

The next speaker is Dr. Jose Verges from Bioiberica S.A., Barcelona, Spain. You have ten

minutes.

DR. VERGES: Good afternoon. First of all, I would like to thank the Chairman and all of the panel of the FDA to give me the opportunity to speak at the meeting here in Bethesda. I am a clinical pharmacologist from Barcelona, and for me it's a great pleasure to be here at the FDA. It's a big dream for a clinical pharmacologist to have a meeting with the FDA. That means that I am very happy.

Secondly, I understand that you are very tired of speaking all day about chondroitin and glucosamine and osteoarthritis. I would like to be very precise. Also, a lot of things during the day (?) , but some of the points that I have here we speak during the meeting, no?

Chondroitin sulfate is a symptomatic slow acting drug for osteoarthritis in Europe, where it has been approved as a drug for more than ten years in several countries in Europe. Personally, I am working for chondroitin sulfate and these kind of problems more than eight years.

Some of the mechanisms of action of chondroitin sulfate, you know, this morning were very well pre-(?) . I can state that on Friday we'll be presenting to EULAR, in the European (?) in Berlin two new mechanisms of action of chondroitin sulfate that we performed in my department together with Professor du Soich in the Faculty of Medicine in Montreal in the Department of Pharmacology. And we see that chondroitin sulfate can make the addition of stromelysin, metalloproteinase 3, that is very active in terms of inflammatory diseases. And another interesting thing is that the protein NF-kappa beta, that is one protein that it's very implicated in some process, especially in chronic treatments.

If we see the clinical trials that we perform for our company, I can tell you that Bioiberica is the first producer in the world of chondroitin sulfate. All of the clinical trials that have been published in Europe is our chondroitin sulfate. That means that we know something about our product. Nine randomized,

controlled clinical trials have been conducted in Europe with our product, comparing its effect against placebo and sodium diclofenac 150 mg in more than 1,000 patients with knee and hand osteoarthritis.

The results from these clinical trials conclude that chondroitin sulfate is as effective as diclofenac and around 50 percent more effective than placebo in the reduction of symptoms of osteoarthritis. This is very well published. We published recently with Professor du Soich in the Clinical Pharmacology (?) that the effect of chondroitin sulfate should be more than 50 percent than placebo. We published that the placebo effect is more or less in knee osteoarthritis of 26 percent. That is very important when we compare with placebo to know exactly which is the efficacy of placebo in knee osteoarthritis.

There is some evidence that chondroitin sulfate can stop the (?) process. We have three clinical trials in knee osteoarthritis that have evidenced stabilization of joint space width with

chondroitin sulfate treatment in comparison with placebo in the knee, and also we have two clinical trials in hand osteoarthritis, concluding that we have the possibility to stop the (?) process in fingers. This is published by the group of Verbruggen in Belgium, and it's a very interesting paper. That means that there is some evidence that chondroitin sulfate can stop the (?) process.

But it's very important to keep in mind that in Europe, chondroitin sulfate is approved as a symptomatic treatment for osteoarthritis. That means that it relieves the pain and improves the mobility of the joints. This is very important to know.

Another important issue is the safety. For physicians, it's very important because normally the people that have osteoarthritis are elderly people, and they have other pathologies. They have hypertension, (?) , and it's very important, the safety of this product.

The safety of the drug is very well documented. It's equivalent to placebo and much

higher than other anti-inflammatory drugs like diclofenac. One of the things that we proved is that chondroitin sulfate is not metabolized by enzymes from cytochrome P450. What does that mean? That means that if you give the product with other drugs, we don't have any kind of interaction with other products. That means that you can combine chondroitin sulfate with other drugs, with analgesics or hypertensive drugs, et cetera, and that is very important because there are a lot of interactions that could be a big problem for the patient and for the doctor. And that's one of the interesting things about this kind of product, they are very safe products that you can prescribe together with other drugs. This is a very interesting thing.

The pharmacosurveillance data from Europe, where no serious adverse events have been reported for more than ten years, support the safety of the product. We can say that in my department we have the pharmacosurveillance, and more or less we treat three million patients per day. That means that

it's a very important number of patients. That means that it's the best--the best clinical trial is the pharmacosurveillance, especially in Europe (?) , that is very, very serious, the pharmacosurveillance, how we can control the side events. That is a very important issue of this kind of product, glucosamine and chondroitin sulfate, the safety.

This is the recommendations of the EULAR that was published recently in Annals of Rheumatic Diseases, and you will see, for example, the level of evidence of chondroitin sulfate is 1A. It's superior, for example, to paracetamol and other anti-inflammatory drugs, for instance, and I think it's very interesting to note these data. In terms of the level of evidence, it's 1A, and its strength of recommendation is A. That is the maximum category (?) in Europe.

What are the benefits of chondroitin sulfate for patients and for doctors? I think chondroitin sulfate's clinical efficacy on symptom reduction and improvement of functional capacity,

that is clear. There is one interesting thing that the chondroitin sulfate has a carryover effect. That means that when you finish the treatment, in some patients they efficacy persists during some weeks and some months. That is very interesting for the (?) of the patient. Another very interesting issue is the pharmacoeconomics issues. We performed recently in Spain--that is my country--we performed a pharmacoeconomics study, and I will tell you that with chondroitin sulfate for 10,000 patients, we can reduce the cost of more or less $2 million for 10,000 patients (?) the reduction of analgesics, anti-inflammatories, and also the side effects for anti-inflammatory drugs. That means that from a pharmacoeconomic point of view, it's a very important issue.

There is only one chondroitin sulfate approved as a drug in several European countries, which is therefore considered as the reference product. This chondroitin sulfate is manufactured by Bioiberica and marketed in Europe by IBSA and Bioiberica, and in the United States by Nutramax

Laboratories under the trademark Cosamin.

This chondroitin sulfate is being used by the NIH study for its Glucosamine/Chondroitin Arthritis Intervention Trial. Its number is--well, this is the number. That means that we have an inspection from the NIH to our company in order to put our chondroitin sulfate in this important clinical trial that we see is there a difference between products, we will see if (?) is better or not, et cetera.

This is very important because we can make the statement that chondroitin sulfate in Europe, we have a lot of clinical data that proves that the product works, is efficacious and safe in symptomatic treatment. What happened in the United States--and you know better than me. I apologize. You know better than me that there are a lot of nutraceutical products, and this paper that now I am here speaking analyzed the contents of glucosamine and chondroitin sulfate and several U.S. drugs. And this study concluded that the amounts found were significantly different from

label claim in some products with deviations from 0 to 115 percent.

It also evidenced that characteristics such as molecular weight, flexibility of structure, sulfation, and method of manufacture may influence oral absorption. And that is very important because maybe they could have some different clinical effects and maybe could have problems for doctors that recommend those products or the patients. I think this is very important. When we speak about chondroitin sulfate, the more clinical trials published with this chondroitin sulfate, no?

In this case, we see that among all products compared, the one from Bioiberica was the highest permeability rate.

This is very important. In conclusion, in order to ensure equivalent clinical results in terms of efficacy and safety, other chondroitin sulfate products must show their bioequivalence to the reference formulation. It's very important. This is like the same in generics. You must perform an equivalence study. If not, you cannot

say that they are equivalent products. For me it's very clear as a clinical pharmacologist.

For this purpose, we propose the following method to determine the bioequivalence of two chondroitin sulfate formulations, and we propose a method that if some people are interested, they have some copies that we present, for instance, in the 47th annual meeting of the Western Pharmacology Society in Hawaii in January. And now it's near to be, you know, approved and is submitted for publication in the proceedings of the Western Pharmacology Society. And this method we can compare if one product is bioequivalent to the reference product, in this case the reference product that is in clinical trial that is our chondroitin sulfate. I would not like to explain the method, but if there are some person that is interested I can explain this interesting method.

That is all. I apologize for my English, my Catalan English, and thank you very much for your attention.

DR. MILLER: Thank you.

Any comments or questions from the committee?

DR. FELSON: I guess I would like to go back to the chondroitin EULAR recommendation, which I agree with you, I think was an important milestone. The effect sizes listed are derived from a couple of trials that just show enormous effect sizes.

DR. VERGES: Right.

DR. FELSON: One shows an effect size of three times the efficacy of a knee replacement. The effect size there, the range, mostly effect sizes for--you notice how much bigger those effect sizes are than all of the other treatments there? Mostly the effect size of knee replacement--it's actually at the bottom, but it looks like it's not been--it's covered up. It's 1 to 1.7 in the different studies. So chondroitin average effect size looks from those data like it has effect sizes that are equivalent to a knee replacement, which is pretty much as curative as we get in knee OA.

What's going on with that? I've waited

for a number of years to ask somebody from this company why effect sizes--these are not reasonable. They're not--they're on orders of magnitude, logarithmic orders of magnitude higher than effect sizes seen in any other oral preparation in osteoarthritis. They're hard for me to, frankly, believe. Why do you think that your--you know, I don't see patients of mine who have been on these things come back saying, "I don't need a knee replacement," all of them. Okay? What's going on here?

DR. VERGES: Well, this is, you know, the question. We can make the question to experts that they make the recommendations, you know? They made the recommendations in--well, according to the clinical data that is published, and they have this clinical data and they make these recommendations, no? But I cannot answer you because this is the recommendation of the experts according to the literature, and also there are some people in this committee, biostatisticians and clinical pharmacologists, that they put like this. But, you

know, for me as a clinical pharmacologist, the effects of chondroitin sulfate is very clear because I mentioned before it's 50 percent more than placebo. And this is published in a lot of clinical trials that are published in Europe.

DR. FELSON: Be careful, because that effect size is the difference between chondroitin and placebo in those studies.

DR. VERGES: I know. I know. No, no, but in terms of--in my opinion, in terms of the evidence that (?) for me is very clear in terms of clinical--and, in fact, you know, we approved in Spain the chondroitin sulfate two years ago, and the Spanish agency is the number three highest and most respected agency. And, well, it's like this, you know.

I can tell you, as a clinical pharmacologist sometimes when I make a clinical trial I ask the question if my mother would be in the clinical trial or not, no? Another issue is the mother-in-law, no? But my mother--yes, that is another issue, heh? But my mother is taking

chondroitin sulfate and is doing very well. That means that is not the level of evidence is zero. But I can tell you that, well, patients recognize very well the product works, and I think it's, you know, a very interesting product because it's a very safe product. I think if you can have a reduction of pain and (?) safe product, I think it's very important is osteoarthritis. And you know as a rheumatologist the side effects of NSAIDs and analgesics. You know, for example, the paracetamol, you know, the group from Montreal published and said when you use higher doses of paracetamol, you can have also side effects. It is not free of side effects.

We can ask this question maybe in the meeting on Friday. I will ask coming from you this question to the panel about explaining this.

DR. DWYER: Just two further questions about that, perhaps to Dr. Felson rather than to you. First of all, would you please define "effect size"? And, secondly, aren't those two conditions at very different stages along a progression of

disease?

DR. VERGES: The question is for me or the panel?

DR. DWYER: It is for somebody to define "effect size," and then to answer if those two patients who are taking the chondroitin are really the same as people who are getting--who have just had a replacement.

DR. FELSON: I'll be happy to try to address it, I guess. An effect size, the way this was done, is the change in treatment of the active treatment group minus the mean change in the placebo group divided by the standard deviation at baseline of the outcome measure for both groups. Sometimes it's for the placebo group and sometimes it's for both groups, the denominator, and I don't know which was used here.

The answer to your question is surprisingly yes, but it would bias in favor of a higher effect size for a knee replacement because people would be worse and have more room to improve, and, therefore, have higher effect sizes

at the point when they were eligible for their knee replacement. That makes this high effect size, frankly, even more hard to believe.

One of the effect sizes for one of the chondroitin trials in our meta-analysis was 4.5. That's at least three times as good as a knee replacement, if that's possible.

DR. MILLER: Any other comments or questions? If not, thank you very much.

DR. VERGES: Thank you very much.

DR. MILLER: The last speakers are Dr. Todd Henderson and Dr. Chuck Filburn from the Nutramax Laboratories. You have 15 minutes together.

DR. HENDERSON: I want to thank you for the opportunity to present this data. I also wanted to give a clarification that when we looked at presenting information, our understanding was that we were supposed to present information about the petitioners, the petitions. And, evidently, the guidelines that were set down at the beginning were slightly different, but I hope our information

is still very relevant as we are the only other manufacturer of a nutritional product here to present kind of a different perspective than the scientists that have been here thus far.

I will give you a little bit of background. We actually initiated the use of glucosamine and chondroitin sulfate combination in the United States. We're the first company to do that. Certainly our company is dedicated to quality. We're also committed to research. We've published over about 20 research papers on our products, on our brands, Cosequin in veterinary medicine--I am actually a veterinarian and was involved in a lot of those trials--and Cosamin, the human product. As Dr. Verges had pointed out, the chondroitin sulfate that's being used in the NIH study is the same chondroitin sulfate that we have in the United States.

One of the things that we did want to talk about is really how to characterize these compounds, and we feel that really being kind of in throes of this industry, there's a lot of different

quality and there's a lot of different products out there. And I guess one thing that we're concerned about is with any type of claim that may be given, if it's a broad, sweeping type of claim, many different products would take advantage of that, and I'm not sure that would necessarily be fair to the consumer. We certainly support accuracy and truth in labeling.

We would recommend that both health claims be denied, primarily due to the characterization of the materials. The work that's been done has been done on very specific materials, and there's a lot of materials out there that the consumers are going to be trying to pick up from the shelves that are not all going to be the same. And I'm not sure how you handle that question, other than perhaps looking at methods that might be able to try to get to that answer. And I'd like to introduce Dr. Chuck Filburn. Dr. Filburn is our Ph.D. biochemist, head of our research lab, and he was with the National Institute of Aging for 26 years.

DR. FILBURN: Thank you. It was very

interesting hearing your earlier discussion of what is a healthy individual, particularly in aging. Of course, you realize aging is a fatal condition. That is something we talked about a lot.

At issue here, as Todd mentioned, of all the products out there for which a health claim might be granted, what do we really know about them? And our key questions, there are two really fundamental questions here: What is actually in the bottle? And in a sense, that's what was actually used for the research for which the claims were being supported. And does it work? Again, does it work for what's in the bottle that's being offered to the consumer. And that requires both clinical research, a lot of which, as you heard from Dr. Verges, was involved with the same chondroitin sulfate that we use, but also studies on bioavailability which has been done on very few products on the market. But also in terms of characterizing what is in the bottle, there is a need to be sure what the compound is, an identity test, be accurate about how much is there, and

quality or purity, which is the flip side of identity. If there are no other, say, GAGs there, fine. But if there are other ones, then that gets to be an issue.

So let me address these concerns one after the other with regard first to the first petitioner and then the second one.

Just to reiterate what you heard before, the majority of the published clinical studies conducted on chondroitin sulfate were performed with specific, highly purified, 95-percent minimum material from Bioiberica, which we use. This specific chondroitin sulfate has been chosen for the NIH study, and it has been studied in combination with glucosamine hydrochloride for several additional clinical studies on humans, on companion animals, research animals, and was used a lot in basic research. No information has been provided by Petitioner A to support the assumption that these same results were obtained with less purified, less well characterized forms of chondroitin sulfate. The forms available to the

public differ considerably in source, sulfated disaccharides, molecular weight, purity, and often failed to meet label claims. The presumption of a similar clinical response from the various chondroitin sulfate sources currently available to the public is simply unjustified.

The same petitioner, through a letter from its attorney, stated that the evidence is extremely strong of an actual disease-reducing effect: "repair and rebuilding of the cartilage matrix." There is no claim or direct data in the petition, nor that we are aware of, that substantiates this statement.

The petitioner relies solely on what we call the CPC--cetyl pyridinium chloride--method to assay chondroitin sulfate, with no procedure to prove identity. The CPC method detects sulfated GAGs, which could be forms other than chondroitin sulfate. While the petitioners cite methods that use the CPC to detect sulfated GAGs, they do not address the issue of proof of identity, that what is being measured is actually chondroitin sulfate.

The chondroitin sulfate supplement industry as a whole suffers from a lack of uniformity and full validation of acceptable methods. Until this issue is resolved and consumers can actually rely on labeling and claims of joint support from all manufacturers, it is just inappropriate to allow a health clam on a material that in most products lacks careful characterization, especially regarding identity or purity, source, and substantiation of bioequivalence and effectiveness.

With respect to the second petitioner, it has already been drawn to your attention that it's not glucosamine sulfate that's been used for the NIH study but glucosamine hydrochloride, which is considered really the glucosamine base to be the active form of this. And I won't really spend much talking about that. That's already been discussed before.

The contention that the sulfate plays an important role in this, while present in the original petition, seems to have been understated today, and we think that is highly questionable and

will again repeat that it's glucosamine that's talked about most of the time and we think is responsible for most of the effects.

Now, we also get at the issue of assays and accuracy in determining what is in the bottle. The petitioner claims to have a validated assay that in the supplement to the petition stated that it is specific, accurate, and precise, and that is based on a potentiometric measurement. I question the claim of specificity of this assay. I have examined the attachment and found no data showing specificity for glucosamine sulfate. Many organic molecules with a primary amine group will give the same result as glucosamine when titrated as described. The petitioner claims a lack of activity from excipients as evidence of specificity. The petition also criticizes the USP method while at the same time offering it as an indicator of the exact composition of the glucosamine sulfate for which the claim is sought.

It is obvious that there is a clear need for an alternative, specific, commonly used assay

method that must be used in analyzing both petitioner's glucosamine sulfate and others on the market to ascertain what is actually present and being studied clinically.

Again, petitioner is asking for a claim for crystalline glucosamine sulfate. I think that should be clearly defined. This was discussed a little bit earlier. There are actually three ways one could get that: prepare glucosamine sulfate by a method that has a patent on it; dissolve it along with sodium chloride and crystallize it--that's called--I think is their term for crystalline glucosamine sulfate; take sodium sulfate with glucosamine hydrochloride, dissolve them, crystallize them, you can have co-crystals. One could just take the two mixed salts and mix them together. We really don't know what is going on in the industry but suspect the latter is a characteristic of most products, and yet that may dramatically affect stability. That is important in maintaining what is in the bottle because once it is ingested and dissolved in the stomach,

they're all equal. So what is the claim really on?

Again, our own studies have confirmed that recent studies of the contents of glucosamine--whether it is the hydrochloride, whether mixed with chondroitin sulfate, or glucosamine sulfate salts--in many commercial products but particularly glucosamine sulfate showed levels substantially less than that claimed on the labels. This situation reinforces the importance of consistent methodology and accuracy, or truth, in labeling.

I agree with Dr. Arnot that we need to educate the public, but I think this is a key component of that education, and I can't see how you can decide on whether to give a health claim if you don't fully appreciate how important these issues are.

Thank you.

DR. MILLER: Comments or questions?

DR. BLONZ: So, in essence, you are arguing that without good manufacturing practices in place, there should be no consideration, this should be rejected. So it's the GMPs that are the

issue, not the substance?

DR. FILBURN: The GMPs assure the substance, hopefully. The assay methods assure the substance. Even a good GMP with a bad assay method is not going to be any good. The industry and various components of the industry--the USP, the Institute for Nutraceutical Advancement and others--are working towards this end, and we are working with them. But we have been doing this for a long time, and we see a serious problem and we don't think it has been resolved.

DR. MILLER: Dr. Callery?

DR. CALLERY: We just heard, I guess an hour ago, that there was a liquid chromatography, mass spectrometry assay that was validated that would be very specific for glucosamine. If that turned out to be a validated and acceptable assay method, would you change your position?

DR. FILBURN: Well, we think we have a validated assay method that's a little different from one that's in the USP. The one that's been proposed by the Petitioner B, that would be an

excellent method. However, that involves extremely expensive instrumentation and may actually be overkill. I think that was particularly useful in doing bioequivalence studies, and I must commend them on what they did there, what they were able to show, although they used heroically high doses of glucosamine sulfate to achieve those amounts in the blood, you must appreciate. But that's what we're after, yes, used by everybody and commonly acceptable validated assays.

DR. MILLER: Dr. Felson?

DR. FELSON: In your written petition, in the first paragraph you comment on something you didn't mention in your talk: "Recent clinical studies on glucosamine sulfate that lacked industry involvement in analysis and description of data have not found the benefit previously observed in studies supported by Rotta."

Do you want to comment on that?

DR. FILBURN: That was taken word for word from a review paper that I gave heavy weight to, and I didn't want to mix the words, and I took--

this is from the McAlindon review paper which we cited in our comments. And I take it for what it says. I didn't change the wording so that it wouldn't be misinterpreted.

DR. MILLER: Dr. Russell?

[No response.]

DR. MILLER: Dr. Dickinson?

DR. DICKINSON: I just wanted to comment that the GMPs alone I don't think would resolve this issue in the absence of a quality standard, that is, GMPs are process-oriented and don't necessarily in and of themselves define a quality standard. So I think it needs to go beyond just having the GMPs in place, although we will certainly welcome having those in place.

My comment for you is that there are other examples of approved health claims, including the ones for folic acid and for calcium, where there are some criteria specified in the claim for the ingredient--in one case that it meet USP disintegration or dissolution methods, in another that it be limited to certain compounds that FDA

has concluded as GRAS. Would that kind of an approach resolve your issue?

DR. FILBURN: Not yet, because the USP monograph is still in development. We helped produce improvements both in the CPC assay and in the early old-style electrophoresis procedure to prove purity, and that hasn't been fully resolved. And as I understand, there has been emphasis or there may be an obligation--I'm not clear about this--by FDA for the food component to work with AOAC or someone who is developing their own methods. And they're not always the same. There is more than one way to do this, but each one has to be validated and we strongly believe should have a component of identity, and many of them lack that. You can get enough to show up in a CPC assay, but is it really chondroitin sulfate, or what else is there? Are you putting enough junk in to get enough chondroitin sulfate to show up? That actually is what is happening out there. That's why we're here to object to you allowing the health claim.

DR. MILLER: Dr. Kale?

DR. KALE: Not disrespectfully, if it had been your product that was now being considered for the application, would you feel the same way? Or why, perhaps a different question to ask the same kind of thing, didn't you apply for the same privilege of making the claim that's being made by the two parties?

DR. FILBURN: I should probably let Dr. Henderson answer that, but I think--and if I'm incorrect, say so, Todd--had we gotten it, would be it be specific to us? Would everybody be benefiting? Would the consumer be screwed? Pardon the language.

DR. KALE: That's a different product.

[Laughter.]

DR. FILBURN: No, I'm serious about that. Because of this issue of quality, what has happened is a lot of--Nutramax--I came from NIH. Evidence-based research, small company, I was totally impressed with what they had invested in research. And yet the biggest beneficiaries of that are a lot

of other companies that don't adhere to the same standards. So that's all I'm trying to do here.

DR. KALE: I understand. My question was twofold, really. One is: Do you disbelieve the data generated by the other companies, whatever they're serving up in this area?

DR. FILBURN: Some I do, some I don't. But the issue is what assay methods did they use to characterize what they studied and were they adequate for us to really know what they studied.

DR. MILLER: Dr. Harris?

DR. HARRIS: Yes, I'd like to follow up on that question. As I understand it, a source of chondroitin sulfate is shark. Is that correct?

DR. FILBURN: It can be--from our knowledge of what's on the shelves, it can be beef, different parts of beef, trachea usually; pig; or shark. The only ones that we have been involved in clinical testing on are beef trachea, highly purified.

DR. HARRIS: Okay. My concern is apparently you see no reproducibility then if one

uses a standard source of chondroitin sulfate and works from there.

DR. FILBURN: All I can comment on are some preliminary studies that we have done and constantly trying to improve our *in vitro* models to address just that question. And we do find that in some of these tests--I don't want to get into detail, but we don't get the same effects at different doses. It's just not there, and some of them have no effects at all.

DR. HARRIS: One further comment regarding your mention that there could be other factors that could be present. Is it not true that the 4 and the 6 isomer of chondroitin sulfate are the major components? And what would you then consider to be a tolerable acceptance of any other type of--

DR. FILBURN: Well, I think this is a good question. It's an issue that USP has tried to deal with in that they used--we've helped them develop an electrophoretic procedure that we were convinced couldn't be--was not better than detecting 2 percent or more of any other GAG. Beef cartilage

has a lot of keratin sulfate--some keratin sulfate. It will probably behave exactly the same in the CPC assay. You could get other--I'm not clear on--my whole point is that that assay is based on sulfated GAGs, and there's a large range of different sulfated GAGs. So you need something in addition to that, an identity test.

DR. MILLER: Dr. Zeisel?

DR. ZEISEL: Just to clarify for myself, I'm a little confused. I've heard statements that only the Bioiberica product, the Nutramax product, has clinical data of efficacy. And I heard from Rotta that only their product is the product. So could we maybe break down for the human clinical trials that report efficacy, which products are used, all of them, none of them, some of them, so that if we have to decide that one showed efficacy rather than the others, how would we figure that out?

DR. FILBURN: Well, this may help a little. Our studies have all been done on a combination of glucosamine and chondroitin sulfate,

and any that we have done have been on glucosamine alone, not clinical but biochemical, have just been done on glucosamine hydrochloride. And I really can only speak to those studies. You need to distinguish most of--Bioiberica supplies chondroitin sulfate, we use it, combine it with glucosamine hydrochloride. We do not use glucosamine sulfate. We think if they're given in equal amounts, perhaps they will have bioequivalence, but I think one needs to show that because we don't know enough about stability and we know on a label, a milligram basis, there's 63 percent of the total weight as glucosamine and glucosamine sulfate, but 83 percent in glucosamine hydrochloride. So you're not getting the same amount of glucosamine. And if that's the active base, the active form, then you're already starting off on an unequal footing.

DR. MILLER: Thank you very much. I think that leads me into making a couple of comments before we adjourn for the day.

I want to repeat again, the function of

this committee is not to evaluate the petitions that were submitted, but the results of the petitions there is to give you some idea, as many of you already well knew, of the methods that were being used in order to support the petition, and the question is: Are these valid methods? Do they predict what they supposedly claim to be predicting? And so on. So while this is a very interesting discussion, it really is not germane to the issue of the work of the committee, and I think it's very important to make that point.

Secondly, in order to clarify some of these issues, FDA prepared a statement, again, trying to redefine what the role of the committee is, and I'll just read this to clarify: The committee's task is not to evaluate whether there are sufficient data to conclude that glucosamine and/or chondroitin reduce the risk of osteoarthritis; rather, the committee should address the scientific questions that were provided to it. For the committee's information, the evidentiary standard applied to health claims is

different from and weaker than the drug standard. As I indicated this morning, FDA, not the committee, will apply that standard. I think that's important because many of you have experience with drug evaluations, and that's a different standard than used for foods. I think you have to keep that in mind.

We finished a half-hour earlier, and rather than try to start something new, I suggest we adjourn for the day, and I suggest you take another glance at the questions, which are under Tab 5 in your book.

We meet again tomorrow morning at 8 o'clock.

[Whereupon, at 4:30 p.m., the meeting was adjourned.]

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