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FOOD ADVISORY COMMITTEE AND DIETARY

SUPPLEMENTS SUBCOMMITTEE

THE ROLE OF GLUCOSOSAMINE AND CHONDROITIN SULFATE IN OSTEOARTHRITIS

AND

FURAN CONTAMINANTS IN FOODS

Tuesday, June 8, 2004

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C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. MILLER: Good morning. We are going to begin the second day of the meetings of the Food Advisory Committee. This morning and the first part of this afternoon will be spent with the committee deliberating the information that we have received so far and try to develop a consensus response to the three questions that were presented to us by the FDA for us to respond to.

Before we begin our work for today, there is a couple of issues I need to make and Linda also has some administrative things that need to be brought to your attention.

First, two of the members of the committee, Dr. David Felson and Dr. Annette Dickinson will not be with us today. They were unable to stay for the two days of the meeting, and I think we will miss them. But, for the record, they won't be with us.

Secondly, it is really important that we stick to the time frame as closely as possible. We

have another subject to discuss, the Food Advisory Committee has another subject to discuss, and that is the contamination of foods with furans, and we have to be out of this room, I have been informed, by 6 o'clock at the very latest, otherwise, we will find ourselves in the middle of a wedding, that that is not going to help our deliberations to any great extent.

So, we will do that. At 1:45, this section of the meeting will adjourn and the temporary voting members and the members of the Supplements Subcommittee that have joined us will be excused, with our thanks, of course, and we will continue on with the furan part of the meeting with a new group of temporary voting members, and so on, and so forth.

Linda.

MS. REED: Good morning, everyone. I just have a couple of administrative announcements, information I want to give you. If anyone needs transportation back to their respective airports, please see Sharon Barcelos [ph], who is sitting out

front at the registration desk, and she will get that arranged for you.

Also, just as a reminder, I believe checkout is at noon for anybody who needs to check out. Also, if you would like to have your briefing materials Fed Ex'd back to your business or residence, we have Fed Ex boxes and labels outside also where Sharon is sitting, if anybody wants to take advantage of doing that versus carrying it back with them, so please see Sharon for those details.

Thank you.

DR. MILLER: Dr. Craig Rowlands from the FDA will again present the questions to us. He is also available, if anybody has any questions they need for clarification, or information that they might need in order to come to some decision on these questions, please address them to Craig.

I have asked them to put the questions up on the screen and leave them up there, so that they will be in front of us during our discussions today.

Craig.

Review of Issues

DR. ROWLANDS: Good morning. I am going to read the questions as I read them yesterday, which is I am going to combine Questions 1, the A and B, and then Questions 2, the A and B, and then Question 3, I will read as written.

Question 1 is: Is 1(a), joint degeneration, and Question 1(b), cartilage deterioration, a state of health leading to disease, which is a modifiable risk factor surrogate endpoint for OA risk reduction?

Then, we would like to know what are the strengths and limitations of the scientific evidence on this issue.

Question 2 is: If we assume that for 2(a), joint degeneration, and for Question 2(b), cartilage deteriorating, 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, that is, individuals without osteoarthritis, from consumption of the dietary substance?

Question 3 is: If human data are absent, can the results from animal and in vitro models of OA demonstrate risk reduction of OA in humans?

3(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?

3(b) If limited human data are available, what data should be based on human studies and what data could be based on animal and in vitro studies to determine whether the overall data are useful in assessing a reduced risk of OA in humans?

If there is any clarification needed or anything on those questions, you can ask me or actually you could ask any of the FDA staff for any clarifications if you like.

DR. MILLER: Any comments? Dr. Cush.

DR. CUSH: Well, actually, I would like to provide a clarification, I think to Question 1(a). I would like joint degeneration to be considered separately from cartilage deterioration.

Joint degeneration, I think would basically be an analogous definition of osteoarthritis. I don't believe that it is a state that leads to, I mean it is a net result that is osteoarthritis. It is a poor choice of words, and should not be any kind of labeling, and should be rejected outright.

I think to move on to cartilage deterioration, which is sort of the target of the initial damage of the disorder, something that we measure. Joint degeneration is too global, too vague, but it nonetheless does imply the net result of osteoarthritis.

So, that term I believe is faulty and should be eliminated.

DR. ROWLANDS: Okay. Of course, the questions are written separately as 1(a) and then

1(b).

Committee Discussion

DR. MILLER: Any comments or response to that? Yes.

DR. BLONZ: Edward Blonz. Now, the question I would pose to that is, does the joint degeneration process begin and then lead to osteoporosis, or as soon as joint degeneration has begun, you are already there? Osteoarthritis, forgive me.

DR. CUSH: Again, this goes back to yesterday's definition of the transition from healthy to disease state, which is an impossibility to define I think in this instance, and I don't believe that joint degeneration implies a lesser, more minor, or protein state of the net result, which is osteoarthritis.

I think it embodies what we see in osteoarthritis, which is again the whole joint being affected by more primordial events that begin with cartilage pathology.

DR. MILLER: It seems to me, as I said

yesterday, it seems to me that there is a fundamental issue that somehow or other we need to comment on, and that is the question on which much of the discussion is based, and that is, there is at some point when osteoarthritis or any of the pre-quals [ph] of osteoarthritis that we are discussing to see whether they have any ultimate impact does or does not exist.

I mean, to exaggerate, if you listen to the conversation about the continuum, and you can argue the continuum begins at conception and ends at death, and those kind of continuums are not unknown in biology, and it just seems to me that we need to address that question, if the basic issue that the FDA is trying to deal with is going to be responded to.

Yes, David.

DR. ABRAMSON: I think, Dr. Miller, that is the nub that we are struggling with, and I think one of the issues that is important to review from yesterday's discussion is that our clinical ability to detect osteoarthritis is very crude at the

earliest stages and particularly the imaging technology is very crude, and we rely on that.

So, histologically, we all would be able to sit around a table with a pathologist and differentiate normal cartilage from early degenerative changes of cartilage, and that is how, in fact, when you do studies of OA, you define it pathologically, not by imaging.

Imaging is useful for clinical trials, as Dr. Simon said, and also for clinical care of patients, but the disease, as is atherosclerosis present for years perhaps before the patient is symptomatic, but a pathologist can see atherosclerosis and a pathologist can see osteoarthritis, and that doesn't happen necessarily when you are 15 or 17, it happens in the later decades.

The other related dilemma is the disease osteoarthritis pathologically can be detected early with fibrillations and fissuring, but then in only some people does it advance at a rate that they get it at age 55 or 75, or perhaps 100, but there is a

continuum where I think we would call this cartilage abnormality osteoarthritis.

So, I think the limitations of our diagnostic tools are part of the problem here, but the disease can be detected if one looks carefully enough at many of these earlier points.

DR. MILLER: Well, it is impossible--I will just lay this on the table--to say that you can't distinguish a period in which osteoarthritis or the phenomenon that lead to full-blown osteoarthritis can't be determined.

DR. LANE: I think that that is true. I mean what Dr. Abramson says is we neither have the imaging techniques, nor do we have a measurement in the blood or serum that you could at which point say this, like cholesterol, we don't have a cholesterol, we don't have a level of a marker of bone or cartilage turnover that we could say this person is at so high a risk of getting OA that we should do something about it.

We neither have an imaging tool nor a serum marker in this continuum, and until the

person comes to medical care with pain in their joint, it is unclear. Even if they have a x-ray and it's abnormal, it is unclear they are going to get a clinical disease.

As Dr. Felson said yesterday, only 30 percent of people who have significant radiographic changes ever have clinical painful disease.

DR. MILLER: I understand that. What I am just trying to say is that if that be the case, and there is a consensus that that is the case, then, that is what we ought to say. That is all I am trying to say.

DR. LANE: Okay.

DR. MILLER: Dr. Cush.

DR. CUSH: I would like to reiterate a point that was brought up by David Felson yesterday, and that was in spite of what appears to be a struggle as to what we know and what we don't know, no rheumatologist has difficulty making a diagnosis of osteoarthritis. It is a very certain disease, it is easy to diagnose.

What we are talking about here, in this

continuum that may begin with genetic factors, and then biochemical factors, then immunologic events, then physiochemical events, and then sometime shortly thereafter, symptoms might ensue, and then are followed by damage and the functional consequences of disease.

All along the way, imaging, depending on how good or sensitive it is or is not, or a biomarker, how sensitive it is, it may be present or it may be absent, but they don't factor as much into this as the symptoms do, so it is when symptoms begin that we recognize this constellation of findings and we make this diagnosis.

What is not known is what is pre-OA, we don't have a diagnosis of pre-osteoarthritis. In fact, we don't have great risk factors. We know risk factors, we know there are some genetic risk factors, which is for a minority of individuals.

We know that obesity and we know that certain lifestyles or occupations are risk factors for osteoarthritis, and those are modifiable, but by the way, none of those subsets have these

nutritional supplements been applied to and shown to have protective benefit.

So, you know, we are being asked to address whether or not some intervention might be applied to a healthy population to protect us against the disease.

Again, I have a problem with connecting the dots. We saw some good research and good results applied to people with disease, but applying them to the general population who may or may not have this is, I think a gigantic leap of faith that is going to be difficult to make.

DR. MILLER: Dr. Zeisel.

DR. ZEISEL: I would like to suggest that we approach this bit by bit, and not jump to the treatment of OA or prevention of OA at this moment, but rather the question before us is, is cartilage degeneration a predecessor of OA in the individuals who develop OA.

Now, that doesn't mean that everybody who has cartilage degeneration is going to go on to develop OA, but in the individuals who develop OA,

is cartilage degeneration a predecessor, and from what I have heard, I would argue that it is, that people who go on to develop OA start with cartilage degeneration.

Again, we might parse that very finely, but, in general, you have some cartilage degeneration that gets worse and worse until some point when you develop frank symptomatology that is picked up.

So, if we can agree on that, we can agree on a Question 1(b) that it's a deterioration of state of health leading to a disease. Now, it doesn't always lead to the disease, but it is clear that sometimes it does.

Is that a reasonable statement?

DR. LANE: Well, I have a little trouble with it, because you are saying that the cartilage degeneration is starting out leading to something, and I think, as was brought up yesterday, the joint is a structure, and what leads to the painful disease OA is cartilage and bone changes.

So, I ask Dr. Abramson should we separate

out the cartilage, I am not so sure.

DR. ABRAMSON: Well, I guess the semantic issue here is I would argue that cartilage degeneration is the earliest phase of osteoarthritis, therefore, it is not a normal state.

DR. ZEISEL: Well, again, I think that we cannot come to any resolution here as a committee if we--you know, it's like arguing when birth starts. We can get down and keep going back and back.

I think that our problem here is that we all realize that realistically, there is a stage at which cartilage falls slightly behind in its repair versus synthesis rate, and that that is a minuscule change that is only detectable by the finest cell biology, but eventually, it goes on and it can't be the disease at the first mistake. Otherwise, then, there is nothing you could ever prevent, because you have the disease the first time the first cartilage cell doesn't make the right amount of cartilage.

So, I think realistically, it is hard to accept that you define the disease as when the first cartilage cell doesn't make the right amount of cartilage.

DR. ABRAMSON: That does become a theological discussion, but the point that I would make is how do we define cartilage degeneration even for this discussion, and I would suggest that although we talked about OA as being an inevitably disease-related disease, in point of fact, it is not--when you are 75 years old, maybe only 30 percent of people have it.

I can tell you in our laboratory, we rely on getting normal tissue age matched before we do studies by the pathologist, and you can find lots of people who come to surgery for fractures or other reason who have absolutely normal cartilage at age 70, that you then have to say, okay, I am going to do my study, and that is a normal person age 70, and this is a person who has osteoarthritis.

So, the notion that it is a normal process

with time, I think, you know, it depends at what point in time, and it is not necessarily therefore everyone is going to get OA and at the earliest sign. So, you can have normal cartilage, and I would suggest that the degenerative changes that the pathologist can see is osteoarthritis.

DR. ZEISEL: But we have also heard, I believe, that you can have abnormal cartilage, and not have osteoarthritis, that, by definition, there are some people going around with abnormal cartilage and they do not have osteoarthritis by the clinician's recognition of that disease.

So, having abnormal cartilage cannot be the sine qua non of having osteoarthritis. What I am trying to say is that it can precede it, and therefore, there must be people who will develop osteoarthritis who have the start of cartilage degeneration, and the question at hand is, is that a marker that is worthwhile following as something that you could intervene in. I mean I think that is what Question 1(b) is.

DR. MILLER: Well, couldn't that be a rate

function? In other words, a rate of degeneration that could take place, and if you don't live long enough for it to express itself, so to speak.

I mean the problem, let me see if I can focus this discussion a little bit, a little more, the problem that the FDA faces is being able to determine whether or not the results you are looking at is mitigation of existing disease or is it risk reduction--I have to be careful what words I use--whether it is a risk reduction function.

That is the problem that they face, and there are many ways to deal with this. One is to get a consensus for an arbitrary distinction at what point one process begins and the other ends, recognizing that you are trying to deal with a point on a continuum.

I am not sure we could do that here, but if there is some agreement, we can recognize that.

DR. LANE: I think, Dr. Miller, that is a very important point, because research that Dr. Felson and our group do has shown us surprisingly that the risk factors for getting the disease at

this point, with the research done, are different than what causes it to get worse.

So, armed with that data and the literature for both hip and knee OA, we may have to make a bit of a distinction even though theoretically, we think the continuum should, we really don't have the data to support that today.

DR. MILLER: Basically, you have got to draw that bright line somewhere.

DR. LANE: That's right, we have to put a dotted line, that is exactly right.

DR. MILLER: Recognizing that there is a big variation.

DR. LANE: That's right.

DR. MILLER: We have a number of people that have been trying to get some questions in here, and to be fair, I have got to give them a chance.

Dr. Espinoza.

DR. ESPINOZA: I don't have any problems with the question posed by FDA regarding joint deterioration and cartilage degeneration.

Cartilage degeneration might be the hallmark of the disease that we call osteoarthritis, but osteoarthritis is much more than that.

I definitely feel that joint deterioration should be considered at least a relevant question for us to discuss here.

DR. MILLER: Dr. Nelson.

DR. NELSON: Following up on the questions about the continuum, we are interested in risk factors for this particular discussion, correct?

DR. MILLER: Right.

DR. NELSON: As I understood it, there could be 75-year-olds that have no anatomical changes, and clearly they have no risk of developing osteoarthritis, but then there are others that do, in fact, have these changes, but have no symptomatology, so they have risk factors, but it hasn't led to the problem.

As I understood it, the disease was, as I think Dr. Zeisel allude to it, the disease is really considered a disease once the patient presents symptoms.

In that situation, would not, in fact, cartilage deterioration be a risk factor that may or may not be modifiable, but before the disease appears?

DR. ABRAMSON: The difficulty for me here is that we define osteoarthritis as when the symptoms begin at one level, but we can all look at an x-ray and say this asymptomatic patient has osteoarthritis of the knee or back, so there is three levels by which we make this diagnosis.

We make a clinical diagnosis, we make a radiographic diagnosis, and we make a histological diagnosis, and depending on which part of the elephant you are looking at, the elephant still has osteoarthritis, the disease of tissue degeneration.

So, I think the analogy to other diseases then becomes important, and it depends what the FDA wants to call the onset of the disease. If it limits itself to symptoms, that is one way of looking at it, but is hypertension a disease if the person doesn't have a stroke until it had 20 years of hypertension, is a plaque in the coronary artery

atherosclerosis if the patient hasn't had angina.

So, I would suggest that the disease is a set of pathogenic events in tissue and tissue injury that we don't have either the imaging technology or the patient may be asymptomatic up to a point, but eventually that patient who has that disease will most commonly get some kind of symptom.

The symptoms of osteoarthritis don't come from where a lot of the pathogenic changes are happening because there is no nerves there, but eventually, the organ fails, eventually symptoms will occur, so I think this is a definitional problem. I think the disease can be all of those different things, and this discussion I think has to decide which of those things we want to call osteoarthritis.

DR. MILLER: Dr. Kale.

DR. KALE: It seems clear that the degeneration of cartilage is necessary, but not sufficient to create the syndrome of osteoarthritis, but if we are forced to acknowledge

that every human being will develop this condition of cartilage degeneration, but may or may not develop the syndrome of osteoarthritis, then, we have embraced a very large definition, which is fine.

I feel uncomfortable holding the petitioners responsible for changing that or clarifying the universe for us when we can't do it ourselves.

The notion that you could prevent the syndrome from developing by using a product like chondroitin sulfate or glucosamine, with the possibility of reducing a universe of patients from having the symptoms, and given again that we are all going to develop some evidence of cartilage degeneration, seems like a very worthy idea, and the fact that we can't define a modifiable risk factor for our satisfaction seems an unfair burden to place on the petitioners.

My basic point is that in a certain sense, walnuts are to LDL as chondroitin sulfate or glucosamine is to reduction of cartilage

degeneration, and in that sense, the modifiable risk factor would be, for the purpose of this hearing, would be modifying the risk factor of degenerating cartilage.

You could reduce the degeneration of cartilage and, in some patients, some fortunate few or some fortunate many, they would not go ahead and develop osteoarthritis and perhaps the rest would.

That is no better than we can say for Lipitor or any other drug or any other drug as we are trying to treat diseases relevant to, say, cardiovascular disease.

DR. MILLER: Dr. Cush.

DR. CUSH: I think that it is clear we can't make any 100 percent certain statements about relatedness and/or discrete time variables where events, pathologic or otherwise, lead to actual disease.

I think what we can say is, you know, use the term "reasonable certainty," and I think that is much more operationally important here.

I would use the analogy that is a

catastrophic motor vehicle accident or skiing accident a risk factor for developing osteoarthritis? Yes, it is. I mean such an individual is more likely than not to have his or her cartilage damaged to the point that it will lead to a secondary osteoarthritic joint.

Similarly, although that is much more of a macroscopic insult, here, we are talking about microscopic insults, hence, I would say that cartilage degeneration or deterioration is also a risk factor for the development of osteoarthritis, and a statement using sort of a reasonably certain terminology.

I think most of us, I wasn't happy with it, but I think that we know that, in fact, that that is not a good thing, and there is a reasonable risk for development of osteoarthritis.

DR. MILLER: Dr. Dwyer.

DR. DWYER: I think where I am confused is, is it a risk factor or is it a sign that the disease is already present. To me, it seems like it is a sign, from what some of you experts say, it

is a sign that the disease is already there. So, it is not a risk factor, it is a sign of the disease, which is different, at least in my head it is different.

DR. CUSH: For the person who gets the disease, yes, it is, but as we have said, there are people who have cartilage abnormalities who will never have symptoms.

DR. DWYER: But that doesn't bother me because all of these diseases are multifactorial, so there are a lot of people who have a whole bunch of different characteristics, but they don't get the disease.

DR. CUSH: I don't understand. I mean you are going to discard those people who have, and not consider them, is that what you are saying, people who have cartilage abnormalities, because again, if we are going to accept that they are not important, then, we may be overtreating or subjecting a large segment of the population to products that they may not need. I think we have to consider them.

DR. MILLER: Dr. Zeisel.

DR. ZEISEL: Let's retreat to some ground that has already been covered, I believe, by the FDA. Individuals, treatments that can lower cholesterol are allowed to say that they are beneficial in the prevention of atherosclerosis and cardiovascular disease.

We all know that everybody 17 years and up has atherosclerosis already to some extent, that none of them, if taken apart by a pathologist, won't show atherosclerosis, and yet we don't say they have the disease, and we are willing to say that in even a 30-year-old or 40-year-old or 50-year-old, lowering cholesterol is reducing a risk factor for cardiovascular disease even though they have it by any definition, that we all have some cardiovascular disease right now.

So, I think drawing on that analogy, saying that reducing cartilage degeneration is a reduction in risk for developing osteoarthritis seems to be a fair parallel, and just as everybody with high cholesterol doesn't go on to develop an MI or need a bypass, everybody who has abnormal

cartilage doesn't go on to need a knee replacement or whatever.

So, I think we have a fair analogy to a situation that is already in place, and that if we start from there, we can move on to ask some of the more difficult questions about whether changes in evidence of this risk factor have anything to do--in diseased patients have anything to do with changes in patients who you would not have clinically said had the disease osteoarthritis.

DR. MILLER: Dr. Blonz.

DR. BLONZ: So, we keep coming back to the same point. Are we dealing with, as soon as it's here, you have got the disease, or is it a process which can be thought of as a risk factor that basically puts you in queue to the point that all we are doing is waiting for you to report the symptoms and then get the radiographic confirmation, and then you are officially labeled, and the disease is put on your chart?

So, we are dealing with terminology and subjectivity, not having the objective factors like

we might have with coronary artery disease where we can measure this biomarker of cholesterol in the bloodstream.

So, we are actually dealing with the second half of the question, the strength and weaknesses before we deal with the first half of the question.

So, I will pose it, of course, to the experts in the field. If we had a measure of joint deterioration prior to the reporting of symptomatology by the patient, if we had this marker, would this be something, if we could modify it, we could reduce the risk?

DR. MILLER: Isn't that one of the reasons the NIH study is being one?

DR. LANE: Yes.

DR. MILLER: Now, again, just throwing an idea on the table, it is perfectly possible for us to say that if the data was available, it is almost an arbitrary distinction, because we can't get away from the concept of a continuum, and if this is going to be useful, then, we may just have to say

that.

Dr. Lane.

DR. LANE: I would like to comment on that, two points. One is I think there is a continuum that keep being jumped to, and I am concerned about it. One is we know that if you have heart disease and your cholesterol is high, and you take the statin and you lower the cholesterol, and the disease slows down its progression, and that data led us then to looking at lowering cholesterol in people who didn't have clinical disease, and then found that, gee, it did prevent the onset of the clinical disease.

But even though we know cardiovascular disease is a continuum, we have strong evidence to support now that lowering your cholesterol prevents an event of the clinical disease, and I feel strongly that we need to show that all we know, I know so far with the medications on the table, if you have disease, they do something, but we don't have anything on the preventive side, and your point is well taken that until we know what those

markers or surrogates are to tell us disease is coming, we are just jumping into an unknown area.

That is why I am a little concerned about making parallels.

DR. ZEISEL: There are lots of people with high cholesterol that don't get heart disease, there are lots of people with low cholesterol that go on and have MIs, it is just as uncertain, but somehow people have said they are willing to say that there is enough of a relationship that they are willing to use this imperfect biomarker, and I think cartilage degeneration is that similar thing.

There are some things that don't exactly fit, that don't always follow, but, in general, you feel that a person is at higher risk if you come in and their cartilage is degenerating, of coming down with a clinical syndrome, and I think the same thing is true with cholesterol.

Many people have very low cholesterol and go on to have heart attacks. They have heart attacks for other reasons than cholesterol, and that may be true with OA.

DR. MILLER: Dr. Waslien.

DR. WASLIEN: I think we need to look at the history of the development of these two indicators to call an analogy with cardiovascular disease when it took us 20, 30 years to do the clinical lipid trials to prove that indeed lowering cholesterol would have an effect.

I think we are at the stage of saying maybe reduction in cartilage will have an effect, but we don't have data to prove it. So, to jump to the conclusion of saying, well, we will use this as a marker when we don't have the kind of many years, I mean the cholesterol history is 40, 50 years old, of knowing that people had elevated cholesterols, but not knowing if it made any difference.

So, I think we are in that stage of saying yes, people have degenerated cartilage, but will changing that degeneration have any effect on osteoarthritis, I think those trials are needed before we can say anything.

DR. MILLER: Well, it is possible for us to say that there is a relationship, we don't

understand it yet, and that once we get the data, it can be used, and to indicate we don't have the data yet. I mean there are a lot of possibilities.

The DRI Committee at the Institute of Medicine ran into this with the relationship between saturated fat and cholesterol. The American Heart Association published a chart that showed the relationship between saturated fat in the diet and cholesterol, serum cholesterol, went to zero, in other words, you had some increase in cholesterol even at very low levels of saturated fat intake.

They came to the conclusion that they had to make an arbitrary distinction, is it possible not to have saturated fat in the diet.

Dr. Cush.

DR. CUSH: I would like to first caution everybody to stop talking about diseases which you know too much about, meaning like, you know, hyperlipidemia and stroke, because we have great models and, as was stated, many years of history, and we don't know that the analogy to

osteoarthritis is going to be as clear.

It seems logical, but it may, in fact, not be, and osteoarthritis may not be one disease, but may be several. I mean, for instance, in lupus, a disease that we know a lot about, that we see a lot of it, but all of those patients have some degree of renal damage that one would pick up on biopsy, but yet there is only a small proportion of them with certain types of damage that will go to develop renal failure and outcomes there.

Again, we have to be careful about extrapolation from other human models, and even animal models, that there is a gigantic leap of faith which makes us all the more uncertain.

I think that cartilage and cartilage deterioration could be a surrogate marker for the disease, but the problem is that that is not something that is measure in daily routine practice. We don't measure that, we don't examine that, I don't image that. As we heard, there are lots of problems with quantifying and assessing cartilage damage even in well constructed trials.

But I think we have to move on, because I think we have said this over and over that as Dr. Blonz said, if you have cartilage deterioration, you are in queue. It is a risk factor for the development of disease. I think that that is something that has been said over and over. I don't know there is much disagreement with that at this point.

So, I mean I think that question has been answered and we can move on.

DR. MILLER: Dr. Russell.

DR. RUSSELL: This is a question for the rheumatologists. Is there some point along the continuum of joint deterioration where it becomes really much more likely that a person will develop osteoarthritis?

I mean I realize you can have significant deterioration without developing the clinical syndrome, but is there some point along the continuum to say, well, this person is really likely to?

DR. CUSH: No. You are asking for more

certainty that has already been expressed, so no.

DR. LANE: Not only no, but what is surprising is if you take all the data we have, an x-ray, and everything else, and the people that you think should have it don't, and the people that have sometimes a more normal x-ray, when they go to surgery, et cetera, do.

DR. RUSSELL: Thank you.

DR. MILLER: Dr. McBride.

DR. McBRIDE: I have a little trouble with the analogy with the cholesterol, because, as a neurologist, if you have a stroke, it's a big deal, and it is not the same kind of a continuum as osteoarthritis.

We are a little bit bogged own here with semantics, but if you look at the FDA definition of a modifiable risk factor, which is what we are being asked, it is a measurement of a variable related to a disease that may serve as an indicator or predictor of that disease.

If we all agree that by the time you have pain and dysfunction that you have the disease, it

is hard not to call cartilage deterioration a risk factor. Certainly, it would not be ignored in any kind of early studies looking at prevention. I mean there is a whole other question of whether or not modifying it during the disease means that you can modify the risk. We have to take that up.

DR. MILLER: Dr. Krinsky.

DR. KRINSKY: I agree with Dr. McBride, with her comments, but the thing that concerns me about the cholesterol/cardiovascular disease analogy is that I don't see where we have a cholesterol, and lacking a cholesterol, the analogy fails, so that unless there is an appropriate biomarker for determining the moment or, at some time, the extent of your cartilage deterioration, how does one evaluate this short of having a patient wait a week, a month, a year before they report pain. I don't see whether you can evaluate that.

DR. MILLER: Well, just a matter of clarification, it would seem to me that there is no reference to a time scale here, in other words, how

long after you have identified joint degeneration do you have to develop full-blown osteoarthritis for that to be a reasonable relationship. I don't see that. All you have to do is be able to ultimately show that there is some relationship no matter how slow the rate may be.

Dr. Harris.

DR. HARRIS: I would like to return to Dr. Miller's point regarding the possibility that we may be diagnosing something that is not related to arthritis or may not have the same outcome.

In preparing for this meeting, I did do some reviewing of the literature that basically the question of could there be other factors involved, and one thing that struck me very unusually was a condition called Wilson's disease in which there is actually an accumulation of copper in the joints that leads to swelling, and so forth.

I was hoping to find papers that would suggest that Wilson's disease is indeed a very good predictor or people who suffer that disease are going to be perhaps coming down early with

arthritis. I could not find that evidence, but it does indicate that there could be other mitigating factors here other than just one case we are dealing with two different diseases and mixing the two of them together may be the wrong thing to look at.

DR. CUSH: Wilson's disease is just like a car accident or whatever provokes the cartilage insult. The deposition of copper in the cartilage, it is the first event that leads to its deterioration. It is the same as other deposition diseases or other forms of secondary osteoarthritis.

DR. HARRIS: Yes, I think that was the point I was trying to make, that there could be other factors. Perhaps this is addressing the question of the etiology, but it is also addressing the question of a misdiagnosis.

DR. MILLER: Dr. Kale.

DR. KALE: Yes, I am one of the proponents of the LDL/osteoarthritis analogy, and I still think that it holds, and I think it holds to a

reasonable degree of medical certainty, because the final common pathway, again necessary but not sufficient, in the development of osteoarthritis has to be some degeneration of cartilage whether the degeneration is primary or secondary as in the case hemochromatosis or Wilson's disease or trauma or infection or rheumatoid disease, whatever it happens to be.

if there is a reasonable likelihood that a product, call it glucosamine or chondroitin sulfate, can preserve the cartilage and reduce its likelihood to a reasonable degree from degenerating and becoming a sufficient, unfortunately, as well as necessary, cause of the syndrome of osteoarthritis, if you can prevent that, then, it strikes me it has the same status, without meaning to demean it, as walnuts. It is a modifiable risk.

You modify the risk of osteoarthritis by providing a dietary product that seems to work beneficially on cartilage to preserve it. In that sense, once again, I would retreat back to the analogy as being reasonable. Walnuts is to LDL as

chondroitin or glucosamine is to cartilage.

DR. CUSH: That latter point, I mean you now have ventured into the proof of intervention having an effect on the biomarker and outcome.

DR. KALE: What I am trying to do is say that there is a modifiable risk factor, and that is cartilage, probably, and I agree with what you said earlier, that if you can make a reasonable assumption, I think this is still reasonable, based on clinical data, I mean obviously we haven't got the sort of data you have for--there is not a generation of data as there is for cholesterol. So, the best one can do under the circumstances.

The other point I would make, by the way, it seems to me, because I am old enough to remember this, that coumadin and linoxin, these are drugs that were never tested, we simply believe they worked in the patient populations for whom we used them, and we continue to do so, and that is a reasonable presumption, and it seems to be a reasonable presumption.

I am making a similar reasonable

presumption about this particular product.

DR. MILLER: Well, we have to be careful using drug examples. The standard for evaluating drugs is different than the standard for evaluating foods.

DR. KALE: Okay. Vitamin D to rickets.

DR. MILLER: All right. I will buy that.

Dr. McBride.

DR. McBRIDE: I was just going to, in answer, say that we are not trying to say that this is the only risk factor, but it is a risk factor. The question is, is it a risk factor. We are not even asked to say is it modifiable, that is a whole other question, but we are being asked is it a risk factor.

It seems like to me it would be hard to say that it is not.

DR. MILLER: Dr. Archer.

DR. ARCHER: I just need some clarification on a point. I thought I heard Dr. Cush say that in the diagnosis, he didn't diagnose it radiologically, in which case, I am now talking

about deterioration of cartilage.

If that is the case, are we talking about joint space reduction, which is kind of one step back, so we are looking at a predictor of another predictor? So, I am getting a bit confused as to what it is we are actually talking about here.

If cartilage deterioration is something that you really don't know about until the patient presents with symptoms in most cases, is that a predictor, or is it a reasonable predictor?

DR. MILLER: Dr. Abramson.

DR. ABRAMSON: I guess that comes back to our fundamental discussion, is Alzheimer's disease a disease before a person is overtly demented, or is it a pathological event that happens over time, the signal for which symptomatologywise, we see towards the end stage of that process.

Again, I think, and we have different views, I think the LDL may not be a good analogy because it is truly a surrogate marker of a process that leads to damaged tissue, and one of the reasons that there is discrepancies as to whether

lowering or not is helpful, is it may be not even a true marker of the disease, but a surrogate for something else that a statin is doing, for example, whereas, fibrillated cartilage arguably is the earliest phase of the disease that we call osteoarthritis, like the first plaque in the brain of someone who is going to get Alzheimer's disease.

I would be certainly willing to say it is a necessary event along the pathway that ultimately leads to clinical symptoms, but kind of the medieval discussion we are having now is, is this the disease or is it a marker of the disease. Perhaps that has some legal ramifications with regard to the charge to the committee because I would argue that it is not normal joint, it's the first event in a very protracted process, and that process where we are struggling in the field is to figure out, even if we jump beyond the histology and we jump to the imaging and biomarkers, trying to predict who is going to get the disease, knowing the earliest markers, has led to a lot of surprises. Things that we think are going to

predict bad outcome tend not necessarily to be the case.

So, I think, you know, just to come back, I think it is how we define earliest phase of disease versus a marker of that disease when we are in the tissue itself that we are kind of having a debate over.

DR. MILLER: Dr. Dwyer.

DR. DWYER: I just wanted to make sure I had understood what particularly the rheumatologists had said.

Are you saying that cartilage deterioration and joint degeneration are risk factors of disease, the first step in a protracted process that may or may not be modifiable? In other words, is the argument really over whether there is modification, everybody agrees that there is a risk factor?

DR. ABRAMSON: I guess what I am saying is that the earliest phase of a disease--the disease has a set of histological changes that a pathologist will differentiate, hemochromatosis,

you know, OA from RA, from earliest phases of these diseases, you can determine by pathological criteria.

Just having that earliest phase of fibrillation or fissuring, which is what they early see, the deterioration, it doesn't predict that that patient is going to develop clinical symptoms, and people follow different courses. Understanding why some people follow different courses, I think is the challenge in this particular field, but the disease arguably starts with these earliest classical changes of osteoarthritis.

DR. DWYER: So, it goes back that it is necessary, but not sufficient.

DR. MILLER: Dr. Blonz.

DR. BLONZ: So, I am looking at the semantics of the Question No. 1. If this were worded is a degenerated joint a state of health, that is very different than joint degeneration.

Similarly, is a deteriorated cartilage, then it is a fait accompli, so we know there is a homeostasis going on within the joint milieu where

you end up getting synthesis and degradation hopefully in balance, but as soon as that turns into a negative where you have more degeneration than resynthesis, you have the process of degeneration or deterioration in the joint and in the cartilage.

When this progresses to the point where you have a change that could be identified histologically or symptomatically, then, you would end up getting this diagnosis.

So, if we can look at the process and then take the step forward, is this a process that once it begins, once you have got that negative going on, can this be modified prior to the diagnosis of osteoarthritis, then, we may be able to step forward and to answering 1(a) and 1(b).

DR. MILLER: Dr. McBride.

DR. McBRIDE: I again just keep coming back to the issue, the semantics of the earliest joint degeneration or cartilage deterioration, whether or not that is a disease, I don't think we are going to be able to answer, but the question is

can you imagine that if you have 100 people with--and you name the measurement, however it can be measured--that show cartilage degeneration and 100 who do not, is it too big a leap in faith to say that the 100 who have it are at higher risk for osteoarthritis? That is what a risk factor is.

DR. MILLER: Dr. Nelson.

DR. NELSON: A question for the rheumatologists. Is an individual with clear anatomic signs of deterioration and change, but expresses no pain or says he or she has no pain, is that person in a healthy state?

DR. CUSH: Go ahead.

DR. ABRAMSON: Well, yes, they can certainly be in a healthy, functional, non-disease--that is a difficult issue. That depends on how you define health. That is why I would argue that joint degeneration is not normal age matched, in other words, you may have the disease, but not have symptoms of the disease. It is not a normal state for your cartilage.

Now, whether you are a normal person, to

the extent that most of us may have some OA and like to think ourselves as normal healthy individuals, I mean is another kind of discussion.

DR. CUSH: So, to answer your question, in Dr. Abramson's lab, he can have a age matched individual who has no symptoms, but may have some joint degeneration or may have none at all.

But you can also have someone who has joint degeneration, whatever that may be, and no symptoms, and that person can have what we call a neuropathic joint or Charcot joint due to syphilis. Obviously, that is not a good state of health.

I strongly dislike the term joint degeneration because of the vagueness of it and the multitude of inputs that may lead to it, you know, land mine gout, rheumatoid arthritis, syphilis, whatever, all lead to joint degeneration. I would not want the FDA to be joined to that term for these proceedings, but that is my impression. I would ask the chairman to address these points maybe directly at each of the rheumatologists, and then see if we can move on or not.

DR. ESPINOZA: Just to confuse you some more, you know, we made the diagnosis routinely of osteoarthritis in individuals, they are totally asymptomatic now. That is routinely.

DR. MILLER: Dr. Cush, would you argue that cartilage deterioration has the same problem?

DR. CUSH: No, because as Dr. Abramson pointed out, cartilage deterioration is the pathognomonic finding, maybe the earliest finding that sets off the cascade that leads to osteoarthritis. I think it has a specificity attached to it that is appropriate to these proceedings.

DR. MILLER: So, for Question 1, would you agree--I will just lay this on the table--that there is a consensus that joint degeneration is not a state of health leading to the disease, modifiable risk factors, and cartilage deterioration is?

DR. CUSH: That is how I would characterize it. As I stated earlier, I think that if one has evidence of cartilage deterioration, as

Dr. Blonz said, you are in queue and you are at risk although it is not certain that you will get there, at least you are at risk.

It appears that it may be modifiable, yes.

DR. MILLER: I am just probing the depths of your belief.

Ms. Halloran.

MS. HALLORAN: It sounds like--so we do have consensus that joint degeneration is not a state of health, et cetera, and that cartilage deterioration is, and we can perhaps go on to what are the strengths and limitations of the evidence.

We, I think have consensus that cartilage is necessary, but not sufficient, that there may be other factors, precipitating factors that lead to disease, which are as yet unidentified and that the entire population actually falls over a certain age, falls into the people, the group at risk, so that identifying this risk pool, there may be limitations on its usefulness. At least that is what I would say.

DR. MILLER: Dr. Lane.

DR. LANE: I just wanted to clarify something for the record. I actually think, you know, I agree with cartilage deterioration, that is probably the best we can do, but we have to be very careful because you would think that we would have clear evidence that slow cartilage degeneration would modify the disease and both, for the most part, in clinical trials and otherwise, we don't have that, but I believe that I have faith in that, but that is what it is, it's faith because our multiple examples came up yesterday, and will continue to, that by slowing it, we haven't changed things.

DR. MILLER: Dr. Mehendale.

DR. MEHENDALE: I wanted to reinforce the same concept that Dr. Lane just said, and that is the implication of disease if we accept that cartilage deterioration is pathognomonic. What I heard was to about a third of the patients.

We could also say it is not pathognomonic for two-thirds of the people. So, we are still trying to protect the one third where it could be

pathognomonic. The other side of this is we make an assumption that there is something we could overcome by supplementing with these substances in the third where it is pathognomonic. I think the concept that Dr. Lane just said. I just wanted to reinforce.

DR. MILLER: Dr. Abramson/

DR. ABRAMSON: We are making some progress, but I would like Dr. Rowlands now, because we are not coming down to the language, I am not fully sure I understand.

How do we define, what is meant by cartilage deterioration and what is the distinction between that and cartilage degeneration?

DR. ROWLANDS: These were specifically worded by the petitioners. That is how we chose these terms. FDA did not come up with these terms, but they have been used in the literature, and this is the language that they wanted in the claims, so that is why they were actually worded this way.

DR. ABRAMSON: I hate to beat a dead horse here, but I don't understand--maybe Dr. Cush who

did make a differentiation--I am not sure that I understand if we agree to one and not the other, what is the distinction that we are being asked to make by the petitioner.

DR. ROWLANDS: These are specifically written as separate questions, so that if you can agree to one and not the other, that is fine. You don't have to link them together. They are written specifically to be separate, so that you can actually conceptually deal with them separately if you wish, that's fine.

DR. CUSH: I would respond by saying that it was written, in 1(a), the more pedestrian sort of terminology that, you know, something may be good for joint health and protecting its joint degeneration, and whatever, and that is again a very lay person's view of what is obviously a much more complex issue, as I indicated with may analogies and why I wouldn't want that.

I think that nonetheless, the lay public has some knowledge of cartilage as being involved here, and that may be the target of therapies and

interventions, so to use that also.

I think it would obviously be much more advantageous to any product out in the public domain to have the more generally accepted, more widely recognized terminology albeit misleading.

DR. MILLER: Does that clarify the situation for you as much as it is going to?

Dr. Blonz.

DR. BLONZ: Let me pose the question then. If you have cartilage deterioration, do you not also have degeneration of the joint?

DR. CUSH: Yes, and the converse, no.

So, my statements go to is it a modifiable risk factor or surrogate endpoint of OA risk reduction.

What we learned yesterday and what we know from the literature is that weight reduction is a modifiable risk factor for osteoarthritis, certain occupational adjustments are modifiable risk factors. What wasn't stated, but probably is true from other lines of evidence, is that control of inflammation would be a modifiable risk factor for

OA progression.

What we don't know is changes in this parameter as modifiable risk factor for OA reduction.

DR. MILLER: Dr. Lane.

DR. LANE: I want to just make a point for the record. A modifiable risk factor is actually one that you have tested and the evidence is strong, evidence meaning a randomized controlled trial or a couple population studies.

Weight loss has never--there is one epidemiologic study in OA from Framingham that shows that people who lost 12 pounds over five years had less knee pain. There has never been a randomized controlled trial showing that weight reduction change joint degeneration, i.e., cartilage narrowing or pain.

So, we use modified risk factor, that would assume that there is some very strong evidence behind it. We all believe that weight loss is going to help, but it has never been shown, so careful, careful.

DR. MILLER: I think if you read the question, there is a way of dealing with that. There is really two questions that are being asked. One, are they modifiable risk factors, and, two, what is the evidence to support it.

I think it is perfectly possible to say that yes, it's a modifiable risk factor, but the evidence isn't strong or whatever.

DR. LANE: I agree.

DR. MILLER: Dr. Zeisel.

DR. ZEISEL: Why don't we just try to move forward and say that we have some consensus that cartilage deterioration is a modifiable risk factor, but the evidence for it is not particular strong.

DR. MILLER: We are coming to that. I just want to make sure that everybody feels that they have had a chance to express their views.

Dr. McBride.

DR. McBRIDE: It sounds like part of the difficulty we are having is with the word "modifiable." Actually, in the definition of risk

factor or at least in the first part of that definition, that word "modifiable" doesn't appear.

I am sure we are probably not allowed to change the question, but if we put the word "potentially," would that help?

DR. LANE: I would say yes because, you see, where we are at here is pathologically, and I don't even know if Steve and I know the answer to this, if you have a little bit of cartilage narrowing, that may mean already that your cartilage is going, and even though you might lose 50 pounds, your cartilage is still going to go.

So, it is potential.

DR. MILLER: I think one point that would be worthwhile re-emphasizing again is that this, like most biological processes, are multifactorial, there are a number of factors that are certainly going to affect the outcome.

From what I understand, and naively listening to the discussion over the last two days, that there isn't enough data to be able to really define what these multiple factors, how they

interact, et cetera.

I think as far as being able to say potentially, we could say whatever we want. We don't have to modify the questions. We just have to say yes, cartilage deterioration is a state of health leading to disease or is a potential modifiable risk factor, so we can just lay that out any way we see fit.

Dr. Zeisel.

DR. ZEISEL: So, the argument is not that it's modifiable, we clearly saw evidence that you can modify cartilage deterioration, make it go up or down, what the argument is, is whether that modification has anything to do with delay of the onset of OA.

DR. MILLER: Right.

DR. ZEISEL: So, it is a modifiable risk factor, and the strength of evidence that it modifies OA is weak, but there is no question that you could modify cartilage because we have seen that you can have more or less. It may not be perfect cartilage, but that is for an argument. It

certainly is a modifiable factor just like taking cholesterol down or up can be done, or taking atheromas up or down can occur.

So, I think it has to be a modifiable risk factor, it just may not modify the risk for osteoarthritis, which is a different question, which is where the scientific evidence comes in.

DR. MILLER: Right.

Dr. McBride.

DR. McBRIDE: Well, I don't think we heard very much evidence that it is modifiable in the pre-disease state with disease defined as symptoms.

DR. MILLER: Again, I think the issue is we can agree that cartilage deterioration is a modifiable risk factor or potentially a modifiable risk factor, modifiable potential risk factor, but we don't necessarily have to say that there is any evidence that there is anything that does that. That is a different question.

So, can we agree that a distinction can be made between joint degeneration and cartilage deterioration in the context of this question, and

that we can argue that joint degeneration is not a modifiable risk factor, and cartilage deterioration is a modifiable risk factor?

DR. CUSH: Only in terms of OA risk reduction, because again, joint deterioration is a modifiable risk factor for a lot of different things, and this is what my career is based on. You know, I am trying to modify joint deterioration through things that we do to treat, but I treat over 100 different types of arthritis, so here today we are talking about osteoarthritis.

DR. MILLER: Okay. By the way, just to make sure everybody understands, these discussions will be reflected in the report, in the transcript of the report.

DR. CUSH: Oops.

[Laughter.]

DR. MILLER: Just trying to help you out.

I think we have discussed the strengths and limitations of the scientific evidence on this issue to some extent. Does anybody want to add any comment to that?

So, we have a consensus on Question 1? Okay.

Question 2. I have to admit that I have trouble trying to make a distinction between Question 1 and Question 2 here.

DR. CUSH: Mr. Chairman, I would like to suggest that Dr. Zeisel's sort of summary comment is probably the most accurate.

DR. MILLER: Fine.

DR. CUSH: That again, that it is a potentially modifiable risk factor, but that the association with--that it may alter OA risk reduction is questionable.

DR. MILLER: We will take your comment from the transcript, and we will take it verbatim.

DR. ROWLANDS: Take away my translation, so now you only have the question.

DR. MILLER: This again comes to the question of how to define a generally healthy population. I think we have discussed that at great length.

Do anybody else have any further comments

to make on this issue?

DR. ZEISEL: So, here, the only issue that came up yesterday is are there normal joints in patients with OA, that the study of which would give you data that has to do with deterioration in "normal" individuals, or is having OA in one joint enough to indicate that all the other joints are OA joints, because I think we all agree that studies in an OA patient do not accurately predict in their OA knee, for instance, that a treatment that might mitigate the already osteoarthritic knee's progression might have nothing to do with the incipient disease's progression earlier.

But the question is are in their otherwise not diagnosed joints, do they have OA or are they incipient OA, and therefore, you could use data in a study that used OA patients, but you could not use the OA knee, but rather the control knee.

DR. MILLER: Dr. Lane.

DR. LANE: Unfortunately, the studies that are there, and one of them was actually just NIH-funded and completed rather recently, the data,

the answer is we don't have that data, and probably that data will take another five to seven years at best to accumulate.

A very large study was done, I mentioned yesterday, where people who seemingly had a normal knee were treated with an agent that was to prevent OA, but they didn't get OA, the controls didn't get OA, so we don't have that data, unless you guys know that.

DR. MILLER: Dr. Cush.

DR. CUSH: No, I think that again we are talking about the development of OA in the contralateral meaning of the person who has an index OA, let's say, on the right side, but not on the left, and then would some intervention prevent the normal knee from developing disease, and that is the kind of research we need to look at, and that is very important research.

I think getting to this question, the language of a dietary substance treating, mitigating, or slowing joint degeneration again does sound like that used for a drug, and not for a

dietary supplement, but nonetheless, the question is, is it valid to use such research to suggest a risk of OA in the general population being reduced if that dietary substance is applied, I think only if there is research to that effect, because we learned yesterday that, you know, that the chondrocyte is different at different stage of the disease, and how it functions, and most of these trials about changing joint deterioration of cartilage deterioration thus far have been focused not on people at risk, or on normal people, but instead, have been focused on people who have the disease, well-established disease.

And to say that the cartilage would behave the same in a normal person, or a person who has risk factors, whether that be a genetic risk factor, or a traumatic risk factor, or a copper deposition risk factor is really unknown, and I think that is again a gigantic leap of faith for which I can't connect the dots.

DR. MILLER: Dr. Blonz.

DR. BLONZ: So, you if we read Question 2,

there is an assumption that that data is in hand. If we assume that research demonstrates that this has this effect, granted we don't have that data right now, but if that research existed, would show that the substances at question could produce this desired effect, would we run with it, and that is really what we are being asked to by this question.

DR. CUSH: The question states, Dr. Blonz, in OA patients, if it produced that desired effect in OA patients, would it then be reasonable to extrapolate that to a normal healthy population.

DR. MILLER: If we could define what that normal healthy population is.

DR. CUSH: All of us, for instance.

DR. MILLER: That's pushing it.

Dr. Abramson.

DR. ABRAMSON: I think just to pick up on those two points, I mean we do have data that was presented by the applicants yesterday that in real disease, in OA, there may be some slowing of progression using these compounds, but I think that is based on data and the notion of what is going on

in the diseased tissue, that, as Dr. Cush says, might not be applicable to very different circumstances in normal tissue.

I think that we have some little evidence, and Dr. Lane referred to one of the NIH studies was a study looking at doxycycline where it was looking for the development of OA in the contralateral knee, beginning with an index knee which was diseased, in patients who were likely to progress, and the unexpected outcome was that the doxycycline, which its mechanism of action is based on many of these events that we were talking about yesterday, protected the knees from progressing where those events were occurring in the signal knee, but the primary outcome was that it might also prevent progression in the high-risk, relatively normal knee on the opposite side, and it had no effect on the osteoarthritis in the contralateral knee.

If the data are correct, it tells us that interfering with processes in the disease doesn't affect normal chondrocytes from developing

osteoarthritis, and I think that is a very important study in that regard.

DR. MILLER: That is an important study.

Dr. Nelson.

DR. NELSON: Dr. Abramson basically addressed my question, which was about the contralateral knee that didn't show any anatomical indication, or even if it did show anatomical indication, would these agents slow or retard the issue.

In the study you cited, did the contralateral knee have anatomical indication, or were they clean knees, so to speak?

DR. ABRAMSON: It's a good question. With doxycycline, as I recall the study, it had either no evidence or early evidence. They were not clearly clean knees, though, but they were significantly better and sometimes had minimal signs of osteoarthritis.

DR. MILLER: Dr. Downer.

DR. DOWNER: I would like to go back. We are being asked to use the data, use it as

implications for the general healthy population, and I guess we really still do need to define what that is.

You say that it is probably all of us perhaps, and the question really is at what point or how do we actually diagnose or say this is a healthy population, is it a population of absolutely free from OA, from the signs of it, from the precursors of it, at what age or to what stage do we really define that, since the implications here are for the healthy population in fact?

DR. MILLER: Jean.

MS. HALLORAN: To respond to that point, it seems like we are talking about healthy population could refer to two kinds of healthy population, the younger one that has no signs of cartilage deterioration, or the older ones that have signs, but yet no pain or symptoms of disease, but it seems pretty clear from our experts that you can't extrapolate to either of these healthy populations from the population with disease. So, it sounds like the answer to this question is no.

DR. MILLER: Dr. Russell.

DR. RUSSELL: Going back to the question about whether a normal population would respond the same way in a disease population, there was a misstatement yesterday actually by one of the presenters on the finger joint osteoarthritis issue, because I looked at that trial last night. It was a double-blind, placebo-controlled trial using chondroitin sulfate, looking at the progression of finger joint arthritis, as well as new joints that would be involved.

When compared with the placebo controls, none of the chondroitin sulfates prevented OA from occurring in previously normal finger joints, that is, they progressed in other finger joints whether or not the person was on placebo or not.

However, the classic OA associated anatomical lesions, when they were considered, OA was less progressive in the treatment group, so there was a response, in other words, or a treatment effect in the people who had established OA, but not in formerly normal joints, there

weren't.

DR. LANE: Thank you for that clarification.

DR. MILLER: Dr. McBride.

DR. McBRIDE: I was just going to say that I think the issue of semantics of when the disease starts is less important here, partially for the reasons that you stated, but we are asked to assume, in a sense, this question creates the assumption that we are talking about pre-symptomatic joint, but that already have cartilage degeneration, and the issue is we haven't heard any evidence that that is modifiable by these substances.

DR. MILLER: Dr. Zeisel.

DR. ZEISEL: So, let's be careful. We are not being asked here to decide whether glucosamine or chondroitin sulfate has anything to do with this. We are just being asked can you design a study in patients who have osteoarthritis, that could shed light on the question about joint development in normal people.

We heard really two types of answers, Dr. Cush saying no, they are never normal, and right after that, Dr. Abramson saying, well, in the doxycycline study it didn't work, showing that normal joints or relatively normal joints don't respond the same as diseased joints, and in that case, I would interpret that as saying that you can use the contralateral knee or another joint in that person to draw some inference about what would happen in the less developed or relatively normal joint.

I think we can't have it both ways, and we don't have to get into whether anybody presented us any data that has to do with chondroitin or glucosamine in normal joints or in osteoarthritic contralateral knees. We just have to ask ourselves, for any treatment whatsoever, would we use other joints in people who have a single joint involved.

It seems to me we are hearing several answers, and we should resolve that.

DR. MILLER: That is a very important

point. We are not evaluating the petitions or any other data that suggested any one particular compound, whether it is the two that happened to be the focus of the petitions here, or any other that might come up in the future.

We are just trying to give the agency some advice, so they can develop standards that could be used for any material for which such claims are going to be made. Good point.

Dr. Kale.

DR. KALE: No.

DR. MILLER: Dr. Lane.

DR. LANE: Yes. I think in the spirit of giving advice, where I feel that we have come to a stop sign or a stoplight, and we haven't gotten the green light yet, and that is, that the reason that I have a level of discomfort saying if you have OA in one knee, if the other knee is normal, follow that for the development of disease is because probably the other knee isn't normal, but that is because when I take an x-ray, it looks normal, but when I use a better technology, which the field as

you heard yesterday is starting to embrace, and that is MRI, and some fancy aspects of the MRI where you can use gadolinium and sodium, and get information about the chondrocyte metabolism and the inflammation, and how much proteoglycan there is, when we start to use those imaging modalities, we will probably be better able to say what is normal and what is a little diseased or a lot diseased, but we can't do that with x-rays.

Does that make some sense to everybody right now? So, the state of the art running a clinical trial doesn't give us the information we need to say what is normal or abnormal. Hopefully, in terms of advice to the agency, that these initiatives, that they are really driving it, using MRI to try to distinguish what is disease and what isn't disease, we will be able hopefully to do that.

That's my comment.

DR. MILLER: Is it fair to say--I am just trying to clarify this in my own mind--is it fair to say that in studies that looked at purportedly

normal tissue and diseased tissue, that the response to the test materials was different?

DR. LANE: Yes, with the caveat that using an x-ray outcome, that's right, using the x-ray outcome.

DR. MILLER: Using the tools that we have available.

DR. LANE: That's right.

DR. MILLER: Because that is a distinction because we could say, for example, and I don't know if we would get a consensus on this, that the answer to this question is no, that based on currently available data, there is no evidence to suggest that one could be used to extrapolate to the other.

DR. LANE: Yes, I agree.

DR. MILLER: I am just laying this out for everybody, because consensus means everybody.

Dr. McBride.

DR. McBRIDE: Yes, I would agree with that. I mean we are being asked is it scientifically valid to use the results of

treatment trials to suggest that you can prevent, even in some earlier stage of the illness, and no matter how you define that, and I think that is invalid.

DR. MILLER: Dr. Abramson.

DR. ABRAMSON: Just one or two points. Dr. Cush has the data on the doxycycline, and just to be more specific, the diseased knees were protected by 33 percent and progression in doxycycline, but the primary endpoint was to look at the opposite knee, which had zero or 1-plus calgrin [ph], so maybe not normal, as Nancy says, but certainly a different stage of the disease, and there was no effect.

So, at least that informs us that at different stages of the disease, a cartilage may be more or less sensitive to an intervention. Most of the studies that we have seen from the sponsor, and we all engage in, is in the more advanced disease where there IL-1 being added to the cartilage, so it more mimics the responsive side.

I just wanted to go back to Dr. Zeisel's

comment, though, because I read this as a negative answer, because it says that the data in the diseased cartilage allows us to suggest a reduced risk of OA in the generally healthy population.

It basically allows us, in my view, to ask the question in a healthy population, but not to make any statements about healthy population.

DR. MILLER: Dr. Zeisel.

DR. ZEISEL: Again, what this question to me is trying to get at is how would you design the experiment to do the experiment right. One way would be to take randomly selected people with no disease, follow them for 50 years, and ask do they develop osteoarthritis. That is an impractical experiment to do.

So, the question is, is it ever acceptable to take individuals who have a joint involved with osteoarthritis and follow their other joints, and argue that that is a surrogate for the longer study because these people are at higher risk for developing other joint disease for whatever reason, and that they have properties that are similar

enough to the general population that you could then extrapolate the data from that population to make conclusions about the general.

What I am hearing is that in a way they behave differently in their non-involved joints, that that behavior is what you, as experts, would predict for the normal population to some extent behaving differently than the actively involved inflamed joint, and that it is a reasonable surrogate, although not perfect surrogate, but in any experiment, we can't be perfect unless we are willing to wait several generations to figure this out.

Am I right that use of another knee could be designed in a study, not that it hasn't been done well by the people presenting to us today on these treatments, but that could you design a study in which you used other joints to draw data that we would then feel was reasonable to extrapolate with reasonable certainty, although not absolute certainty, and I think that is the question.

DR. MILLER: That is part of the question.

I think the other part of the question is, is there data available today that will allow extrapolation from experiments with OA patients to patients who are reportedly without OA.

DR. ZEISEL: I think that doesn't ever say anything that there is data already. It just says is it scientifically valid to design an experiment that would use that.

DR. MILLER: To use such research. I mean the question the agency faces is how to deal with claims that say that there is a risk reduction for the use of any material for OA.

DR. ZEISEL: So, I think what we can reach consensus, it is not valid to use data in the involved joint because we have said that that can be very different, and I think we can all agree with that.

So, now we are getting to the second point, is there any data from an OA patient that you could use in a study, so could you go back and re-analyze if those normal joint x-rays were available and come back to this FDA with a

presentation saying that we saw something and we met some criteria, and now--

DR. MILLER: I think you can say both. There are two separate issues.

DR. ZEISEL: Yes.

DR. MILLER: Dr. Dwyer.

DR. DWYER: So, is it the opinion of the rest of the group that very high risk people may be, in their non-involved joints, may or may not be reasonable surrogates, and we really don't know. It seems to me that it is a good bet, but we really don't know.

DR. LANE: That's right. That's the biggest issue, why we are doing the osteoarthritis initiative, because we don't yet know in those high-risk individuals exactly what is going to trigger the onset of the disease, and to say we know otherwise is really a bit unfounded at this time.

DR. MILLER: Dr. Kale.

DR. KALE: I have two questions. First of all, in the case of the doxycycline study, how long

was that study conducted for before it was determined that the--just 30 months.

And the second issue is looking back at the target tissue here, which is cartilage, I think I am embarrassingly confused about the answer to this question, which is that if you give chondroitin or glucosamine to a diseased chondrocyte, say, one involved in the process of demonstrating osteoarthritis, does it, in fact, make different endproducts than normal cartilage does when you give chondroitin sulfate or glucosamine to that cartilage.

DR. ABRAMSON: My understanding of the data is that glucosamine and chondroitin beneficially influence the cytokines, the abnormal metabolism of chondrocytes, particularly if you add IL-1, so it is very good for reasons that were well demonstrated yesterday in blocking these inflammatory processes and the metalloproteinase production.

What I heard yesterday is that since those features are not typical of normal chondrocytes,

and NF-kappa B is not activated, you know, IL-1 is not being produced, nitric oxide is not being produced, that therefore when you give glucosamine or chondroitin sulfate to a normal chondrocyte, not making those things and it works, let's say, by inhibiting NF kappa B, it has no significant effect on the normal chondrocyte with regard to these catabolic events.

Therefore, while I think the data is increasingly very interesting, that it does have beneficial effects on this inflamed catabolic chondrocyte, it is not clear to anyone I think what effect it has on a normal cartilage and whether it will prevent anything.

I think that is why when I read this statement, it says to me based on those studies of deteriorative cartilage and some interesting studies from Ajinsta and Pervelka [ph] in patients, that we can use to extrapolate what looks to be increasingly interesting evidence that the drug does work in the degenerated state, that we can then use it to say that it is going to help healthy

people, and that is the dilemma.

DR. KALE: That's my understanding, too. So, the question I had is sort of more Walt Disneyfied, which is what if the chondroitin sulfate or the glucosamine is present, because you have taken it prophylactically, in the case of somebody who would, because they are alive, ultimately develop osteoarthritis, what effect does that have on the final common pathway of IL-1, and so on, might it not modify the outcome?

DR. ABRAMSON: We don't know until the studies are done, and the tetracycline, doxycycline study is very preliminary, so one doesn't want to overstate its validity, but the tetracycline seems to work on these IL-1 mediated processes. It inhibits nitric oxide and some other things, and what Ken Brandt is beginning to think, that maybe those processes are more important in the late stage of disease, and therefore, we can't be sure that blocking those same processes in early disease will block those events in early disease that may be mediated by different growth factors that set

the thing forward. That is the dilemma.

DR. LANE: I want to reiterate that, because that is the experiment that was done. You took a relatively normal cartilage, gave it something, if it started to degenerate, you would prevent. It didn't, so that is the beginnings of--

DR. KALE: But it didn't in 30 months. The question is what is the proper geologic time frame. Thirty months can't be. I mean this a glacial disease, it may be a glacial disease.

DR. CUSH: Those people are also selected to be at higher risk because they were obese, so they had other risk factors to possibly progress.

DR. MILLER: Dr. Nelson.

DR. NELSON: Also, isn't doxycycline just one agent? I mean we aren't generalizing the issue to--

DR. LANE: No, no, we are not generalizing, but I mean, come on, this is a field without data, let's at least enjoy this data.

[Laughter.]

DR. MILLER: It is much more fun to argue

without data.

DR. LANE: We said that here is a set of chondrocytes that were all prepped, so that when they started to make a bad enzyme, if they started to make it, you were going to inhibit it. You know, this was the perfect situation.

DR. NELSON: My other question again was to I guess the rheumatologists in this, is we have abnormal chondrocytes, we have evidence, but no symptomatology no pain, are those people still part of the general healthy population that we could use data from the contralateral knee or the contralateral hip to provide for the general healthy population whether they had--well, you would have to qualify that, I guess, whether they had some symptoms, some existence of a risk factor or not.

DR. ABRAMSON: Even if they are generally healthy and have subclinical or pre-disease, the argument could still be made that modifying end disease processes is not going to affect their progression into disease. That is the unknown,

because they are different processes that happen early on OA.

DR. LANE: And these natural history studies that are just starting up now, when we have some of that data, we will be able to comfortably begin to answer that question.

DR. MILLER: Dr. Blonz.

DR. BLONZ: So, what I am hearing is that the contralateral knee data is informative, but not sufficient to serve as a surrogate, and that seeing as we don't have information at present that can segregate those individuals in queue for imminent osteoarthritis, that to talk about the general population and applying the data we learned about, treating people with the active disease does not seem to be a connect for us at present.

DR. MILLER: I think that is a good sum.

Dr. Zeisel.

DR. ZEISEL: Again, I think it would be much more constructive for us not to get into the specific data like we have been doing. I don't agree with Steve that we are being asked to say

from this that there is an effect of chondroitin or anything.

All we are being asked here is, is it possible to design an experiment that would convince this panel that any agent can reduce the risk of osteoarthritis, and using osteoarthritic patients, and if the answer is no, then, we have to say no.

If the answer is it is informative and we would like to see that data, but it would not be sufficient to convince us, that is what we should say, but I don't think we need to get into the specifics of whether doxycycline or chondroitin or anything else made any difference, because it's immaterial. We are talking about agent X and agent Y for this type of question.

DR. MILLER: I agree, but actually, they are really two questions. One is there is no data to suggest that current available data can be used for this purpose, and that second, it simply says that it may be possible to design an experiment, but we don't know yet how to do that.

Dr. Krinsky.

DR. KRINSKY: To me, the operative terms in this question is scientifically valid, and it seems to me that what I have heard from the rheumatologists, and scientifically valid to use such research, so to me, we are not talking about the future, we are talking about the past and the present, and it would seem to me that based on what we have heard of research in the past and the present research that we do not have scientifically valid evidence for proposing that this be used for a general healthy population.

We may in the future and that would be wonderful, but we can't deal with maybes, we have to deal with science. This is why we are here, we are looking at scientifically based evidence, and not hopeful evidence.

DR. MILLER: I agree, in fact, I think there is a consensus to that fact, but what I am saying is that it may be useful to indicate that we haven't closed the door implying that there is no way of doing it.

I think that part of the problem is the lack of data in what I hear in the field.

DR. LANE: Yes, lack of data and not really having really utilized the technologies available, you know, they are in development that we could actually--

DR. MILLER: We don't have to say anything more than as I indicated, that it may be possible sometime in the future to do this, and close that door.

DR. ZEISEL: I think we have agreed that any data generated in the osteoarthritic knee itself, or joint itself, we would find difficult to accept even in the future no matter how the experiment is done as indicative of what a normal joint might do.

DR. MILLER: Right.

Jean.

MS. HALLORAN: I think we seemed to agree that the next step would be looking at what the normal joint would do under treatment, but that I at least would want to then see maybe a five-year

study of people over 50 or something like that to see how it would affect a somewhat at risk, but still asymptomatic population, that that would be data that would also be desirable.

DR. MILLER: We can get into a long discussion about what such experiments ought to contain, and I think my own feeling is that we can make some comment, but I am not sure that really that helps to answer the questions that we are being asked to deal with.

I would love to be able to get into a discussion about how to design experiments like this, particularly as a non-expert.

Well, I guess we have reached a consensus on this one, as well. Again, the nature of the discussion will be reflected in the report, and, of course, we will have a complete transcript of the discussion.

We will use certain summary statements that some of you have made in the report verbatim from the record.

It is now about 10 minutes of 10:00. I

propose we take a break now before we come back to look at Question 3. Come back in 15 minutes, please.

[Break.]

DR. MILLER: Can we reconvene.

We have discussed the first two questions. We have come to the third question, which has to do with the issue of whether animal studies can be used in place of human information in order to deal with the issue of risk reduction of OA in humans.

The first question to be addressed is to what extent animal or in vitro models of OA may be useful, what animal models or types of endpoints should be used to assess risk reduction of OA in humans.

Does anybody have any views on that subject? Johanna.

DR. DWYER: Could we hear from the rheumatologists on their views?

DR. MILLER: That is what I am waiting for, to see someone raise their hand.

DR. LANE: We were electing Dr. Abramson

who has still I think some non-human models in his laboratory.

DR. ABRAMSON: Do you want the long answer or the short answer?

DR. MILLER: Let's take something medium size and we will decide.

DR. ABRAMSON: This is a very difficult field because there is not a great consensus on what a good animal model is for OA, and usually, if you are developing drugs, you need to have a couple of different kinds.

There are genetic guinea pig models, there are anterior cruciate models that Dr. Altman referred to, and they become pieces of the puzzle as you are trying to think about intervention, you know, proof of concept, they are useful in that regard, but I think the general consensus in the community is that they provide you some information that a drug may be important in osteoarthritis, they give you some information about the pathogenesis of the disease, but the models are very divergent.

Some involve acute trauma, some injections of chemicals, and so the answer is that they are informative, but they are not predictive, and there are some drugs that may work in animals that don't work in people, at least in the rheumatoid side of the equation.

So, the answer really is that they are not applicable, they have those limitations, so it would be very hard even for more of the reasons than we talked about if you were looking at human studies that were presented, which have more interest to them in terms of prediction.

These would be very difficult, in my view, to use as predictors in humans, especially with regard to prevention.

DR. MILLER: So, the short answer is no, animal models, at least available animal models I think is the way to put it, should not be used if human data are absent.

DR. ABRAMSON: That is what I believe, yes.

DR. MILLER: Dr. Zeisel.

DR. ZEISEL: The secondary piece there, could they be used in support of human data, so that if you had human data, does it become more believable if you have supporting animal models looking at mechanism and others, so that you need fewer human studies to become convinced would be the next corollary.

DR. ABRAMSON: I believe that where the field is moving is away from animal models to test these kinds of things. I mean the Holy Grail in osteoarthritis is to find the proper imaging, the sensitive enough imaging, and the patient group that are going to progress this whole biomarker's notion.

So, increasingly, I think these questions need to get answered in the human arena. These animal models are mostly of value in drug development at this point and looking for new genes that are expressed that you can corroborate gene discovery programs, but I think everyone is biting the bullet now, both the industry and the NIH, to do imaging and biomarker studies.

DR. MILLER: I want to be sure I understand. Are you arguing that they cannot be used to support for human studies?

DR. ABRAMSON: No, I think they are a part of a body of information that are supportive, but for questions of human treatments or prevention, I think the evidence that we all need now are human studies. They help direct the animal studies, but they are not definitive enough to draw conclusions on for humans.

DR. MILLER: Dr. Harris.

DR. HARRIS: As a biochemist, I certainly would concur with the observation that we can only get limited information from animal models, and our ability to go ahead and try to extract that to humans, I think is a little risky.

On the other hand, animal models, as Dr. Abramson pointed out, are very good pointers of things to look for. Animal models and in vitro models allow us to do manipulations that we cannot otherwise do in humans. We can control the environment, we can get more insight into

individual reactions taking place, mechanistic events, and so forth, and eventually, an understanding of just how a process is taking place at the molecular level.

I would be a little bit concerned if I saw something in an animal model, and I did not see it in a human. I think that would certainly alert me to the fact that there I might be dealing with something very individualistic here, and something very unique, and the converse is also true.

If I saw it in a human and I could not reproduce it in an animal model, I would be a little bit concerned. But as far as taking the data and making definitive conclusions that this is what is taking place in a human based on what happened in a little mouse that we genetically modified, I think that is very risky to take.

DR. MILLER: Dr. Callery.

DR. CALLERY: One of the items where an animal model might be useful is dealing with an issue that I haven't heard anyone discuss, is the safety of a potential new agent and the

toxicological consequences of modifying the biochemistry is a good place to start is in animals, and I think it is useful information, but it doesn't address, that is slightly off the topic of the exact question, but there is some potential toxicology that could be unveiled by using animal models.

DR. MILLER: Dr. Dwyer.

DR. DWYER: I wondered if everybody more or less agreed with the statement in one of the articles we were given in advance of this meeting, which I enjoyed reading enormously.

It said that the utility of animal models in predicting the response to an intervention with a drug or biologic agent in humans can be established only after evidence is obtained of a positive effect of the agent in humans, which I think is what Dr. Abramson said, but I wondered if everybody else read and understood the evidence that same way.

DR. MILLER: Dr. Mehendale.

DR. MEHENDALE: I agree. It looks like we