

FOOD AND DRUG ADMINISTRATION

**Radiological Devices
Panel Meeting**

August 18, 1997

Proceedings By:

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PROCEEDINGS

(9:30 a.m.)

Agenda Item: Call to order and the Chair's Introduction

DR. HALBERG: I would like to call this meeting of the Radiological Devices Panel Meeting to order, and I would like to request that everyone in attendance sign in at the door, there are attendance sheets just outside the door.

I would also like to note for the record that the voting members present constitute a quorum as required by 21 CFR Part 14. At this time I would like the panel members to introduce themselves, stating their specialty, title, institution, and whether or not they are a voting member.

My name is Francine Halberg, I have the privilege of serving as Chair of this panel. I am a radiation oncologist who specializes in breast cancer. I am at the Marin Cancer Institute in San Rafael, California, and Associate Clinical Professor at the University of California, San Francisco, and perhaps we can just go around clockwise. Mr. Monahan?

MR. MONAHAN: I am Jack Monahan. I am a reviewer here in ODE and the Executive Secretary for the panel.

MR. TURNER: I am Charles Turner, I am an Associate Professor of Engineering and Orthopedic Surgery at Indiana University. My expertise is in biomedical engineering and acoustics, and I am a consultant on the panel.

MS. WHELAN: Good morning, my name is Patricia Whelan and I am a clinical social worker at St. Vincent's Hospital, Manhattan, working primarily with people

with AIDS and I am here as the consumer representative.

DR. DESTOUET: Good morning. I am Judy Destouet, I am Chief of Mammography with Advanced Radiology in Baltimore, Maryland, and I am voting member of the panel.

MR. SMATHERS: I am Jim Smathers, Professor of Radiation Oncology, Radiation Oncology Physics at U.C.L.A. and I am a voting member of the panel.

DR. GRIEM: I am Melvin Griem, Emeritus Professor, University of Chicago, broad-based in radiology and a voting member.

STERNICK: Ed Sternick, Vice President of Clinical Affairs at NOMOS Corporation. I am the industry representative on the panel and nonvoting.

MS. YIN: Lillian Yin, Director of Division of Reproductive, Abdominal, Ear, Nose and Throat and Radiological Devices.

DR. HACKNEY: I am David Hackney, I am a Professor of Radiology at the University of Pennsylvania. I am a neuroradiologist and a voting member.

MR. MELTON: My name is Joe Melton, I am Eisenberg Professor of Epidemiology at Mayo Clinic with an interest in osteoporosis, and I am a consultant to the panel.

DR. HALBERG: Thank you. I would like to note for the record that one of our regular panel members, Dr. Naomi Alazraki, cannot be here due to other commitments. Mr. Monahan, would you like to make some remarks?

FDA Introductory Remarks

MR. MONAHAN: Yes. Let me first request that members of the panel speak into the microphones. Some people in the back are having difficulty hearing, and it will also aid for the transcription of the meeting. I would like to read a statement concerning appointments to temporary voting status granted by Dr. Bruce Burlington(?), Director of the Center for Devices and Radiological Health.

Pursuant to the authority granted under the Medical Device Advisory Committee Charter, dated October 27, 1990, and as amended April 20, 1995, Dr. Charles Turner and Dr. Lee Joseph Melton have been appointed as voting members of the Radiological Devices Panel for the August 18, 1997 panel meeting.

For the record, these individuals are special government employees and consultants to this panel, under the Medical Devices Advisory Committee. They have undergone customary conflict of interest review, and they have reviewed the material to be considered at this meeting. The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of an impropriety.

To determine if any conflict existed, the agency reviewed the submitted agenda, and all financial interests reported by the committee participants. The conflict of interest statutes prohibits special government employees from participating in matters that could affect their, or their employer's financial interests, however the agency has determined that participation of certain members and consultants, the need for whose services outweighs the potential conflict of interest involved, is in the best interests of the

government.

A full waiver has been granted to Dr. David Hackney for his financial interest in a firm at issue that may potentially be affected by the committee's deliberations. A copy of this waiver may be obtained from the agency's Freedom of Information Office, Room 12A-15 of the Park Lawn Building.

We would also like to note for the record, that the agency took into consideration matters regarding Dr. Lee Melton. Dr. Melton reported a financial interest in a firm at issue, but in a matter not related to topics to be discussed by the panel. The agency has determined, therefore, that Dr. Melton may participate fully in today's deliberations.

In the event that the discussions involve any other products or firms, not already on the agenda, for which an FDA participant has a financial interest, the participants should exclude themselves for such involvement, and their exclusions will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

If anyone has anything to discuss concerning these matters, please advise me now and we can leave the room to discuss them. Okay, let's move on, then.

FDA also has a conflict of interest policy regarding persons making public statements at advisory panel meetings. Dr. Halberg will ask all persons making

statements, either during the open public meeting or during open committee discussion portions of the meeting, to state their name, their professional affiliation, and disclose whether they have any financial interest in any medical device company.

I want to give you the parts of the definition of financial interest in a sponsor company. They include, first, compensation for time and services of clinical investigators, their assistants and staff in conducting the study, and appearing at the panel meeting on behalf of the applicant.

Second, a direct stake in the product under review, such as an inventor of the product, a patent holder, or owner of shares of stock.

Third, owner or part owner of the company. No statement of course is required from employees of the company. The FDA seeks communication with industry and the clinical community in a number of different ways.

First, FDA welcomes and encourages pre-meetings with sponsors prior to all IDE and PMA submissions. This affords the sponsor an opportunity to discuss issues that could impact the review process.

Second, the FDA communicates through the use of guidance documents. Towards this end, FDA develops two types of guidance documents for manufacturers to follow when submitting a premarket application. One type is simply a summary of the information that has historically been requested on devices that are well-understood, in order to determine substantial equivalence.

The second type of guidance document is one that develops as we learn

about new technology. FDA welcomes and encourages the panel and industry to provide comments concerning our guidance documents.

Finally, I would like to remind you that the next meeting of the Radiological Devices Panel is scheduled for November 17. Please mark this on your calendars. With respect to future meetings, a list of tentative dates for meetings in 1998 are February 23, May 11, August 17, and November 16. You may wish to pencil these dates on your calendars, but please recognize that the 1998 dates are very tentative at this time.

With respect to matters previously before this committee, I would like to review what happened following the last panel meeting. At that panel meeting, there were two applications before the panel, both dealing with ultrasound contrast agents. The first application was an amendment to an approved PMA and concerned using the contrast agent for determining fallopian tube patency. That application was approved and approval was granted for that new intended use.

The second application was for a new ultrasound contrast agent called FS069. At the time of the meeting a Citizen's Petition had been filed with the agency that sought clarification on the jurisdiction on all ultrasound contrast agents. Subsequent to the meeting, a court injunction was placed on the agency until a determination could be made by FDA as to the jurisdiction of those agents. Some agents were being reviewed in the Center for Drug Evaluation and Research, and some were being reviewed here in CDRH.

The agency has determined that all future ultrasound contrast agents, and the ones previously brought before this committee, would be reviewed by CDER. Those applications have been transferred to CDER, and in the future, all ultrasound contrast agents will be reviewed in that part of the agency.

At this time, I would like to turn the meeting back over to Dr. Halberg.

Agenda Item: Open Public Hearing

DR. HALBERG: Thank you. We will now proceed with the open public hearing session of this meeting. At this time, public attendees are given an opportunity to address the panel to present data or views relevant to the panel's activities.

Dr. Richard Mazess, President of Lunar Corporation, has requested time to address the panel. If there are any other individuals who wish to address the panel, could you please raise your hand and identify yourself? If not, I would like to proceed with Dr. Mazess.

MR. MAZESS: Thank you. We will ask you to turn the slide projector on, if you will. My name Dick Mazess. I am a Professor Emeritus of Medical Physics at the University of Wisconsin. I have been involved with bone densitometry for 35 years and developed the first commercial bone densitometers. In the last 17 years, I have founded the Lunar Corporation, I am President of Lunar Corporation. I guess you could say I do have a conflict of interest.

What I wanted to do was present some views about densitometry in general and about ultrasound densitometry in particular. I think it is an important

technology that is coming along. The manufacturers and industrial analysts generally believe that there will be 20,000 to 30,000 ultrasound densitometers in the United States that -- or perhaps even more -- that the average case load would be about 1,000 patients per year, meaning that somewhere between 20 and 30 million determinations are going to be done annually in the United States, and that makes this a very important decision area with regard to medical practice and medical cost-effectiveness over the next decades.

Now, what are the clinical indications for bone densitometry? The FDA has usually established something called substantial equivalence in the 510K(?) process, but I think the concept is fairly clear, that there should be a very high correlation between technologies, in order to say that they are equivalent, and the correlation coefficient typically is above 0.95.

An example of this of course the inter-correlation of bone densitometry devices, x-ray bone densitometry devices from different manufacturers. These correlate at about 0.98. I would suppose in the x-ray area, digital radiographs perhaps with film radiographs might correlate in terms of anatomical structures at that kind of high level.

Below that level, I think there is a real question that one has to deal with: what are the clinical indications? You cannot simply say that a device is equivalent and therefore will be used in exactly the same way, but the real question is, what will the clinical uses be? And I think the PMA guidelines specifically say, documentation of the clinical use.

The clinical uses of bone densitometry or for fracture risk assessment, use

in patients with clinical risk factors -- people taking corticosteroids, or whatever the clinical risk factor may be. And secondly, a different type of risk assessment is screening in subjects without any clinical risk factors, they may have other factors like low body weight, but they are otherwise asymptomatic.

So far as I know, there has been no documented study using any kind of technology, x-ray or ultrasound, showing that screening densitometry is justified. So, really, fracture risk assessment should be considered in light of use in patients with clinical risk factors, not in the general population.

A secondary, really of clinical use is monitoring bone changes, and there are two types of bone changes that one is interested in in the bone area. One is just monitoring the losses occurring with age, and secondly -- or with demineralizing conditions like corticosteroids or excess thyroid hormone. And then, monitoring therapy effects to see how a patient responds. Those are the kinds of clinical indications, and I will deal with going through this very rapidly.

Substantial equivalence to BMD. A high correlation with x-ray BMD would be a good indication that a device is equivalent and could be used equivalently. The available studies in vitro do show that ultrasound variables are very highly correlated with Bone Mineral Density, measured by physically or by x-ray. So, in vitro, and I think Dr. Genant will show this, his group has done a very nice study of this.

Both the speed of sound or velocity, and the attenuation, correlate highly, about 0.98, with the bone density. So, there is no question but that in the range of human

densities -- and that differs for porcine and bovine bone -- but within the range of human densities and porosity, there is a very good correlation, indeed.

Now, that correlation decreases when one goes to measure even in cadavers -- and this is a study done by D.D. Hans, where he measured ultrasound on the ordinate, and then they have BMD measured by x-ray absorptiometry, and there is a good correlation here, but a drop to 0.94. And this was just due to the presence of overlying soft tissue.

If we look at the kinds of results obtained in vivo, the correlations typically range from about 0.7 to 0.9. These are studies done with our Achilles Ultrasound Densitometer, and the correlation here, in 778 subjects, is about 0.86, fairly good correlation. But again, it is not to 0.95. The correlations of the UBA 575(?), which is the predecessor to the Sahara device, again, are fairly good. This is a correlation of 0.8 between BUA, broad-band attenuation, and BMD, measured in vivo. So, I think the correlations are not as good as one would see in vitro, but there are relatively high correlations on the range of 0.7 to 0.9.

Now, we have to recognize the correlation of 0.8 means that only 65% of the variance in BMD is accounted for, and 35% is due to extraneous factors, and those extraneous factors so far as I can determine are things like skin thickness, temperature of the heel, coupling of the gel, or coupling of water. A number of other factors that really are simply extraneous factors that affect the measurement.

Now, given that the correlations are not above .95, I think it is incumbent

to actually examine what the clinical indications are, and the question becomes, how good are these technologies, or ultrasound, for fracture risk assessment, and I will address it particularly for patients with clinical risk factors.

A consensus group developed a position paper on this recently. This is Klaus(?) Gluer(?) and a group of about 35 or so experts in the area. I believe Dr. Genant was the co-chair on this group, and developed some specific comments on quantitative ultrasound. With regard to fracture risk prediction, this is what that group had to say; basically, that the two water bath-based systems have been shown to predict the risk of osteoporotic factor. So there is fairly good agreement in the clinical community on that.

Clinical use of ultrasound depends upon adequate, normative databases; that is, you have to have good reference data if you are going to make fracture risk assessment, and the FDA is very clear on this in their guidelines, certainly, for the 510Ks(?), that one must have randomized representative reference populations. This has been a problem at some times in the past.

The group also said, prior to recommending any other QUS device for fracture risk assessment, prospective validation is important. Now, I do not believe that that is really necessary, but I do think that a retrospective study is necessary to show that a device really can discriminate normal and abnormal.

This is a study that was recently published by Greenspan with various ultrasound devices, one can see correlations of 0.83 to 0.91 with BMD, but there is a great deal of difference in the sensitivity, in this case, measured by a Z-score, comparing

fracture subjects to unfractured. And the Z-score range is about -0.6 for the BMD itself, and ranges 0.4 to 0.67 for the ultrasound devices. So, simply correlating to BMD is not a necessary indication of identical or similar diagnostic sensitivity.

With regard to the need for reference population, particularly a randomized population, we have examined that point recently by collecting data on a randomized population, that is the open circles. And then we also compared it to a self-selected population; that is, simply going out and selecting volunteers who would come in and get measured, and this is with an ultrasound device.

You can see there is really little bias in the young normal, or young adult portion of that group, but as one moves out to the elderly, you tend to preferentially self-select healthier individuals among the elderly. So, I think there may be a problem in a reference population, if it is not fully randomized, particularly in the elderly.

With regard to monitoring bone changes, I will talk about this a bit and tell you what the consensus group said. Basically, the consensus group said that there is little information about long term precision in vivo, and there is relatively few studies of changes over time, both with aging and with response to therapy. And they said that some of the variables needed to be expressed, not just as percentages, but as standardized coefficients of variation, because speed of sound has a very low precision error. That is a problem.

Let me show you the kinds of response that one can see in ultrasound of the heel. This is the response with estrogen, an increase of about 5% over three years.

Very similar to the kinds of changes one sees with measurement of femur BMD, for example. One sees the same kind of response, about a 4% increase, with lensranaide(?) treatment over two years. And of course, there is a loss in the control group. So it is very much like bone density in that regard.

The precision of measurement, as an example of -- can be very peculiar. Look at the second row here, the SOS -- Speed of Sound -- precision with the Achilles is .3%, and you would think, that is really wonderful, but it is not; it is due to basically the value being a very large value, and a .3% precision in Speed of Sound is different than a .3% precision for BMD, and one really has to standardize these precision errors, as was done in the last column of this table.

Notice also that the precision error can be quite different in the osteoporotic group than in the young adult group. This is again in a study by Greenspan that just was published this month. For BMD, measured with the various devices that we have available to us today, and the variety of sites, we usually see that the precision error increases in an osteoporotic population. That is, the absolute precision error is relatively constant, but because bone density goes down, the relative precision error goes up.

That appears to be the case, also, with some ultrasound devices, but not with all. With some, it is relatively constant. I think it is very important that the precision error for any type of technique that we have be expressed and be given in the labeling. My personal believe is that a precision error of 2%, similar to that of BMD, is requisite if a device is to be used the same way that a bone densitometer is used. But in any event,

regardless of what the criterion is, I think that decision in an osteoporotic population needs to be specified to the end user.

This is a study of precision in osteoporotics with the Achilles, the Cuba device, the Sahara device and the QDR(?) 4500 x-ray densitometry study by Richard Estelle's(?) group from the U.K. that will be presented at the ASBMR. And one can see a wide difference in the precision error of the different devices. So, I think that these precision errors for some of the devices are much higher than would be, I think, reasonably accepted in clinical practice. And certainly, they should be specified at the very minimum to the end user.

With regard to the conclusions, I do not know what correlation is sufficient to make ultrasound densitometry useful or equivalent to bone densitometry. Certainly, if the standard error of estimate in predicting the T-score is one, and the 95% confidence limits are two, that is not very encouraging. I do not know what precision error is really necessary. I would say 2% or 3% is necessary, but whatever it is, it should be specified.

I say the same thing, regardless, the ultrasound variable, the labeling should include specific comments with regard to these areas. One, that the ultrasound variable, whatever it is, correlates highly -- that should be above 0.95, or 0.85 to 0.94, or moderately, or poorly, whatever the characterization is, give the correlation.

The second thing, there should be some indication of whether the measurement variable relates to fracture risk or not, because after all, this is going to be used to determine whether 20 million women go on to therapy or not. So, it is a very

important thing. And then one needs to know, for both monitoring purposes and for diagnostic purposes, what the uncertainty of that measurement is. Thank you. I think I beat the hour.

Open Committee Discussions

Agenda Item: Charge to the Panel

DR. HALBERG: You did, indeed, thank you. Are there any other comments on the public? If not, we will now proceed with the main task for today, which is consideration of PMA P970017, submitted by Hologic, Incorporated for their Sahara Bone Sonometer, intended to estimate Bone Mineral Density. I would now like -- is Dr. Stein going to be the first presenter? Okay, let me introduce Dr. Jay Stein, who is the Chief Technical Officer at Hologic.

Hologic Inc. Presentation of P970017

Agenda Item: Introduction

MR. STEIN: Good morning. My name is Jay Stein and I am Chief Technical Officer and a Co-founder of Hologic. As you know, today we are here to discuss Hologic's PMA submission for the Sahara Clinical Bone Sonometer. However, before proceeding with my prepared presentation this morning, I would like to address briefly the comments made during the opening public session by Dick Mazess, if that would be alright.

DR. HALBERG: Absolutely.

MR. STEIN: Dick, who spoke during the public session, is the President

of Lunar Corporation, which is, I would have to say, Hologic's favorite commercial competitor, in x-ray bone densitometry. Lunar currently markets an x-ray device to measure bone density in the heel, and the ultrasound device being presented to the panel today is expected to compete very directly and very heavily with that Lunar device.

The issues -- the main issues raised by Dick related to bone density correlation and fracture risk will be treated fully later this morning by Drs. Genant and Barren who are attending this meeting. And whereas many of Dick's points were accurate and well-presented, at this time I would like to comment that Hologic does not agree with Dick on some of the issues that he raised.

For example, in particular, we do not agree with his narrow view and definition of clinical equivalents using correlation. For example, during our prepared demonstration, we will demonstrate, for the Sahara device, the correlation between ultrasound and x-ray satisfies all of the requirements for clinical significance, and that the use of an arbitrary correlation coefficient, such as .9, is not the appropriate question in a clinical environment.

Well, with that said, I would like to proceed now to my prepared remarks. I would like to just for a minute, briefly review our company's history as a manufacturer of bone densitometry systems. We were the first company to introduce dual energy x-ray absorptiometry, or DXA devices, for bone densitometry in 1987, and we are quite proud that the DXA technique has now become the standard in the field.

We introduced the first fan beam DXA system in 1991, and our current

flagship product, called the QDR 4500, is a high speed, high resolution system, which is very CT-scan-like in that it uses similar detector arrays and a fan beam geometry. We currently have an install base of over 4,000 DXA systems worldwide, and we are currently installing equipment at a rate of more than 1,000 units per year.

This is a photograph of the most advanced densitometer we manufacture, the QDR 4500, and there are approximately 1,800 of these units installed, worldwide.

Our purpose here today is to discuss our PMA application that we have submitted for the Sahara Clinical Bone Sonometer, a term meaning an ultrasound densitometer. This is a small portable radiation-free system which estimates Bone Mineral Density of the heel using ultrasound, and is shown in the photograph on the slide.

Now, heel BMD using x-ray has been used for many years to assess skeletal status in the evaluation of patients at risk for osteoporosis and other conditions that result in reduced bone density. But, because the Sahara uses ultrasound, we are seeking clearance through the PMA process, rather than through the more routine 510K process, that has been applied to conventional x-ray bone densitometers. However, we believe that the information and data that we will review today demonstrates the safety and effectiveness of the Sahara System, in performing very largely the same kind of measurement as that performed by conventional heel x-ray systems.

As a very quick background and overview of our submission, I wanted to start with the fact that osteoporosis is a growing health problem in the United States and around the world, with approximately now 23 million women currently suspected of

having the disease, so it is a very important health problem, particularly a women's health problem.

The disease is characterized by reduced bone mass and increased risk of fractures. Until recently, few treatments were available, but now there are a number of effective treatments including estrogen, biphosphonates(?) and calcitonin, available for physicians to treat those at highest risk, and additional treatments are being tested clinically and are expected to be available in the next few years.

X-ray technology has been used for many years to assess skeletal status, and it has been demonstrated in many studies that BMD is a strong risk factor for osteoporosis and can be used effectively by physicians to help determine which patients should be considered to be candidates for treatment.

The availability of the new treatments has, as a result, increased the need for wider access to BMD measurement. As an interesting but possibly important note, it is pretty well established now that BMD is more predictive for osteoporotic fractures than blood pressure is for predicting stroke, or cholesterol is for predicting myocardial infarction.

Blood pressure and cholesterol are measurements used in conjunction with other risk factors in evaluating individuals at risk for stroke and myocardial infarction. In a very similar way, BMD is one of a number of risk factors used in evaluating patients at risk for osteoporosis.

Of the many anatomical sites at which BMD can be assessed, 20 years of

experience has produced a large body of knowledge indicating that the heel, which is nearly entirely comprised of spongio-trabecular bone is an excellent and sensitive site to measure. The data that will be presented today -- and this is one of our major themes -- will demonstrate that the agreement between Sahara and x-ray-based estimates of heel BMD, is as strong as the agreement between any pair of accepted x-ray-based methods when assessing the same bone.

Furthermore, Sahara is safer, at least in the sense that it uses no ionizing radiation, it is easy to use, less expensive, and more portable than current methods of assessing skeletal status, and we believe it will allow many at-risk individuals who have not previously had access to bone densitometry, to be evaluated and to be considered for treatment. This wider availability is particularly important in view of the most recent NHANES III epidemiological survey that has estimated that 70% of women with osteoporosis are currently undiagnosed.

So much for the introductory march, I would like to just show you the outline of today's presentation. My introduction will be followed very shortly by an overview of the field of bone densitometry presented by Dr. Harry Genant, Professor of Radiology at UCSF, and then the Sahara device itself, and the clinical studies, which are the basis of this application, will be presented by Dr. Eric Von Stetten, Principal Scientist at Hologic, and I will finish with a few concluding remarks.

Also in your audience today, representing Hologic, are David Ellenbogen, Co-founder and Chief Executive Officer, and Steve Nakashige, President and Chief

Operating Officer. In addition, Dr. Peter Steiger and Richard Follard(?) of Hologic are here to participate when necessary, and Drs. Barren and Lavin(?) are here to provide clinical and statistical expertise. Dr. Waznitch(?)'s name is shown on the slide; he experienced slight delays on his long journey from Hawaii, and unfortunately will not be joining us today.

We have asked one of the leading researchers in the field, Dr. Harry Genant, to speak here today. Dr. Genant is a pioneer in the field of bone densitometry, well-known for his development of QCT, or Quantitative Computer Tomography. He is the Director of the Osteoporosis and Arthritis Research Center at UCSF, a leading research center in the world, which currently includes over 50 M.D.s and Ph.Ds performing research in osteoporosis, and whose group is recognized as an independent center for the evaluation of bone densitometry technology. His group has evaluated almost every technology and commercial instrument introduced for skeletal assessment.

Dr. Genant has authored or co-authored over 250 publications on bone densitometry and osteoporosis, and he is present today at our invitation, is being compensated for his time and travel. So, at this time, I am quite pleased to turn the microphone over to Dr. Genant. Thank you.

DR. HALBERG: Thank you.

Agenda Item: Overview - Bone Mineral Densitometry

DR. GENANT: Thank you very much, Jay. Members of the panel, ladies and gentlemen. It is a privilege for me to be invited to participate here today, and I have

been invited to provide an overview on the subject of bone densitometry, the methods, and clinical applications. This overview will provide a basis for the material that will be presented subsequent to this presentation.

Now, as an investigator and researcher in the field of osteoporosis over the past 25 years, I have had research support from most of the major manufacturers of bone densitometry equipment, some of whom are listed here, as well as many of the pharmaceutical companies that are active in the field of osteoporosis treatment development. I also have served as a consultant for many of the equipment manufacturers, again, as well for some of the pharmaceutical companies.

As we have been hearing, and as I am sure we all understand, osteoporosis is a problem of considerable magnitude from a public health standpoint and from a general medical standpoint. It has been estimated that perhaps 16% of U.S. white women have osteoporosis, and that the lifetime risk for fracture for a U.S. white woman may be on the order of 18%. And I might point out that women sustaining a hip fracture, close to 20 to 25% will die as a consequence of this hip fracture in the ensuing year, and an additional 20 to 25% may be in convalescence indefinitely, so that is certainly a staggering figure.

Equally staggering is the cost of osteoporotic fractures, estimated to be at 14 billion -- not 14 million -- per year, truly a substantial figure. Further, with the gradual aging of our population, it has been predicted that the incidence and prevalence of hip fracture will increase, perhaps threefold, by the year 2040. So, we are talking about a very substantial problem that, if effective intervention and treatment is not initiated, will

continue to expand.

The fact is that effective treatments are now available, as Dr. Stein had indicated, and I am sure many of you are aware. And because of the availability now of increasingly effective drugs, bone densitometry addresses the important need of diagnosing and identifying those individuals at greatest risk for osteoporosis and as candidates for treatment or prevention.

Now, how may that be done? Well, quantitative bone mineral analyses constitute a variety of techniques that have evolved over the past perhaps 30 to 35 years, and the major ones are listed here. I will explain these just briefly, because we will be focusing in particular on the x-ray-based systems and quantitative ultrasound.

Radiographic absorptiometry is one of the earliest techniques introduced. This technique has focused on assessment of the hands, particularly the phalanges and the metacarpals, and continues to be used today. Single photon absorptiometry was a method introduced perhaps 20, 25 years ago, and has been largely replaced in the last several years by single x-ray absorptiometry, both of these techniques focusing on the peripheral appendicular skeleton, particularly measuring the radius and the calcaneus.

Dual photon absorptiometry was introduced as a means to measure the central skeleton, particularly the spine and the hip, and in the past seven to ten years, has been largely replaced by dual x-ray absorptiometry.

Quantitative computer tomography has also received attention, since the 1970s, as a technique that in particular can measure both the trabecular, and in some

cases, cortical bone, at the spine and then more recently, in the peripheral appendicular skeleton, the radius.

Quantitative ultrasound techniques have been investigated for the past 20 to 25 years but only in the last several years have these been brought into the clinical realm, principally, in Europe and in Asia, where they are fairly widely utilized. Magnetic resonance, to date, is an investigative tool.

Here one can see the relative use of these various techniques plotted against time since about 1980 through about 1995. One can see that the earlier techniques of SPA and DPA, for example, have largely now been replaced by some of the newer techniques. Quantitative Computer Tomography continues to be used because there are many CT-scanners available, but one can see that DXA, after its introduction, has rapidly become the most widely utilized technique.

In relatively recent years, the peripheral measurement techniques have also seen a resurgence, with peripheral quantitative CT, with ultrasound techniques, and single x-ray absorptiometry. And with the ultrasound techniques now, as I indicated, fairly widely utilized in Europe and in Asia, where they have been approved for clinical application.

Now, in understanding the various bone densitometry techniques, we must look at the manner in which the skeleton is constituted. It has been estimated that the skeleton is made up of about 80% compact, or cortical bone, and a smaller percentage, perhaps 20%, of trabecular, or cancellus bone. But since much of this cellular activity

occurs on the surface of bone, that is bone resorption, bone formation, and the surface to volume ratio is much higher on trabecular bone than on cortical bone, the bone turnover rate, the intrinsic bone turnover rate, has been estimated to be up to eight times greater at sites rich in trabecular or cancellus bone, and it is for that reason that there has been considerable attention focused on some of the measurement techniques that can, in fact, quantify, spongy bone.

The anatomical sites that have been addressed or have been assessed by bone densitometry are listed here. The spine, of course, a site rich in trabecular bone, is known to be responsive to changes with age, to disease, and to therapeutic interventions. The hip, of course an important site because of the impact of hip fractures, in terms of medical morbidity, mortality, and cost. The heel has also been a frequently measured site, in part because it is rich in trabecular bone, perhaps about 95% trabecular bone, and it is also a weight-bearing bone, and this may have some importance with regard to its ability to predict the most important fractures, a hip fracture.

The radius has also been a site of measurement, in part because of the occurrence of callus(?) fractures at the distal wrist, and also because it is readily accessible, although it does contain mostly a cortical bone at the sites where it is generally measured. The tibia, the phalanges, the patellar, have also been addressed but have not been as widely explored.

Now, first I would like to review some of the inter-site correlations, and I think some of this discussion will address some of the points that Dr. Mazess had raised in

his opening comments.

I would like to review, first, a very large study that is being coordinated in San Francisco, and that is a study of osteoporotic fractures that has examined close to 10,000 women over a period of many years, utilizing a variety of bone density techniques. This is the study that Dr. Steve Cummings is the Principal Investigator on.

We have conducted a study of a subset of these patients, about 5500 patients, constituting the basis for the data shown here. And that is, we have looked at the pair-wise correlation between x-ray-based bone density measurements at the various anatomic sites, and the correlations across these sites are shown here. Note that these three sites, the trochanter, neck and worge(?) would all be hip sites, measured by DXA, the spine also measured by DXA, and then we have the radius, both distal and proximal, measured by SXA and the calcaneus, also measured by SXA and x-ray-based technique.

You will notice that within a given anatomic site, that the correlations here are only on the order of about .75 up to a maximum of .9, and that does not necessarily invalidate the measurement of worge, triangle, or the measurement of the neck relative to the trochanter, it simply is what one will expect due to anatomic variations.

Now, importantly in the context of our meeting here today, we will look at this column for the calcaneus, because you will see that the correlations here, which range on the order of about .5 to .6, are very similar to the correlations that one finds for the spine when correlated with the other sites, or for the proximal or distal radius. These correlations then, on the order of about .5 to .6, up to .7, but the calcaneus being very

representative. And so this is the level of correlation that individuals in the field have come to expect amongst anatomic sites and even within anatomic sites.

Now, shown in a somewhat different form are the same data on this particular slide, where we have the total hip, trochanter, neck, worge, the radius, calcaneus, and spine, and in the lower left-hand, the numeric correlations that I have just reviewed, and then over on your right, we have scattergrams, or cloud representation of the 5500 patients, each little dot representing a patient, and one can appreciate the strength of the correlation and the dispersion from the regression line, from these scatterplots.

One can look at the calcaneus, for example here, and see that the strength of the correlation and the scatter is at least as good as one sees by measuring the spine, the very traditional site of measurement, or by measuring the radius, very similar correlations at the calcaneus. And of course, not quite as strong as the correlations that one achieves within a given anatomic site.

Now, how does this translate, these correlations, how do these correlations translate to the percent agreement that you might see, again in the same population, if you classify women based upon the relatively widely utilized criteria of a T-score, that is, the number of standard deviations below young normals, a T-score of 2.5, -2.5, here based upon the manufacturer's normative data for young, healthy women with an average age of about 30.

What one can see here is that the percent agreement that one will see in this

classification is on the order of 60 to 70%. If we look at the calcaneus, for example, here, we can see the level of agreement here is just as strong as the level of agreement for the spine, for the radius, and you will see that even within the femoral neck measurements, or rather the proximal femur measurements, for example, that the worge triangle does not have as strong agreement as the neck or the trochanter, or the total hip. But, I think that this is a very important point, that this is a fact of life and clinicians and researchers in particular have recognized that this is the level of agreement that one will see and that we deal with, in applying these bone density techniques.

Now, this slide simply shows the same information in a more graphical depiction. Here, the percent agreement is shown in the vertical axis, for the various pairwise comparisons of these techniques. And one can see that, by and large, we have got percent agreements that are somewhat on the order of 60 to 80% amongst most of the techniques, with the possible exception of the worge triangle, which has a somewhat lower percent agreement.

What about, then, the clinical utility of Bone Mineral Density assessment? I think that there are some very compelling reasons in support of the density value. First of all, I think it is now widely recognized and generally accepted that BMD is itself the strongest, and the most quantifiable, risk factor for osteoporosis. Further, and very importantly, and some of the members of the panel have done work on this subject, BMD is a surrogate for bone strength, and that in fact, it predicts fracture risk.

Also of importance from the standpoint of perhaps considerations with

regard to the PMA, is that BMD measurements form the basis for the operational definition of osteoporosis. This is in part based upon the WHO criteria.

Finally, a number now of large scale prospective studies -- this includes the Hawaii Group, Philip Ross and Richard Waznitch, the Soft Group, based on San Francisco, the Epidose Study, which is a very large European study, all of these prospective studies have demonstrated a strong and a somewhat similar predictive power of measurements about BMD at the spine, hip, and heel, for hip fractures, or other forms of osteoporotic fractures.

Let's talk a little bit further about BMD and fracture risk assessment. I think a very important concept that we must keep in mind is the concept of a gradient of risk, and a number of people have supported this concept, and I think it is generally fairly widely accepted, and that is, that if one looks at various anatomic sites -- here, the radius, proximal and distal -- here, the calcaneus and the lumbar spine -- one can see that, if we divide bone mass measurements into quartiles, that as we have a decreasing of the bone density, at any of these anatomic sites, there is an exponential increase in the fracture risk, here represented as fracture incident rate.

These are data from Philip Ross in the very large prospective Hawaii Study. And one can also appreciate that measurements of BMD at the calcaneus are at least as strong as measurements at the other anatomic sites in providing this gradient of risk and fracture risk prediction.

So, referring now specifically to heel measurements, clearly, the utility of x-

ray-based BMD at the calcaneus has been well-established now in at least three or four very large prospective studies. The heel, furthermore as a peripheral, and as a readily-accessible site, is well-suited for ultrasound measurements, and that in part is why manufacturers and researchers, relatively early on, turned to the calcaneus as a site to apply quantitative ultrasound.

We will talk further about quantitative ultrasound. Now, a substantial amount of the work on quantitative ultrasound has focused, as I indicated, on measurements at the calcaneus, where one uses a transducer to transmit and receive the signal, and based either upon water bath systems, or more recently, upon the dry systems where gel is used for coupling.

With this type of a device, one derives two principle fundamental parameters, one relates to the Speed of Sound or the ultrasound transmission velocity, through the calcaneus, and the second relates to the attenuation, as a function of frequency, within the calcaneus. And furthermore, some of the investigators and some manufacturers, Lunar for example, with the Achilles System, have promoted the combination of the attenuation and the Speed of Sound for a parameter referred to as stiffness, although not stiffness in the true bio-mechanical sense -- and I will address that further -- but combining the information from both to give an additional parameter, as also is being proposed in the PMA submitted for today's review.

Now, further in support of this concept of the close correspondence between BMD and quantitative ultrasound, are these images from the work of Pascal

Logiet(?) in Paris, who has done some very seminal work in the area of ultrasound, where we show on the bottom an image of the calcaneus, represented in a gray scale, as are the other images in gray scale, the one on the bottom being derived as an x-ray-based, bone density image -- this happens to be quantitative CT, or a CT image -- and the two above are both ultrasound-based gray scale images, the first one representing BUA, the second representing Speed of Sound.

I think it is quite apparent to the eye that what is represented with the x-ray-based system is very similarly displayed with regard to this gray scale representation, by both BUA and Speed of Sound. So, this, in a visual sense, shows fairly dramatically the relatively close correspondence between these parameters.

Now, further in support of this concept, again from the work of Pascal Logiet, and also recently, published as well as presented at a number of international scientific meetings, are the data that he derived from specimens of the calcaneus, where he looked at the relationship between quantitative ultrasound and BMD.

What one can see is, if we look at BUA versus BMD here, at the calcaneus, here, velocity versus BMD, that these are very strong correlations, with r -values of about .87, and about .94, in the case of velocity. And so, what this indicates is that there is a very close correspondence, particularly when some of the error sources are reduced, from both the BMD measurement and the ultrasound measurement, then the correlations are quite strong.

I think equally important, is the fact that if you look at the velocity and

BUA, this correlation is extremely strong, on the order of about .95. Now, what that means is that these two measures are in fact giving very, very similar information, but perhaps this is also supportive of the rationale of combining the two measures to give a more robust measurement, such as stiffness, or the QUI parameter of the Sahara System.

Another point that one can derive from this is that while these correlations are strong, on the order of about .9, they are not perfect, and that may mean that, in addition to the ultrasound measurement of BMD, or reflecting BMD, that there are other factors, aside from the error sources, and those other factors may be its ability to assess structural elements, and of course this is possibly an added benefit with the ultrasound benefit, but clearly, substantially, there is a very strong relationship to BMD.

Now, further in support of the concept that QUS parameters are reflecting very closely what happens with regard to x-ray-based BMD, are the data shown on this slide. In yellow, we have the reference data, based upon, on the order of 2,000 patients, and you will see more of this a little bit later in the presentations, but this represents a Sahara reference range, as a function of age, for women.

In red, one can see a plot here of the x-ray-based reference data from the Dove Osteoanalyzer, measuring also the calcaneus. So, now at the calcaneus by ultrasound and by BMD, we see a very similar age relationship. We also see a very similar population variation. So, this also is fairly compelling in terms of the similarity of the information by both of these methods.

Now, perhaps even more importantly, is the comparability of the

ultrasound measurement, compared with the x-ray-based BMD, with regard to fracture risk prediction, and shown here are data from the study of osteoporotic fractures -- again, the study that Steve Cummings is Principal Investigator on -- representing data collected in close to 10,000 women over a period of five to seven years.

We have data for BUA of the calcaneus, and BMD of the calcaneus, and if we look across here for predicting hip fractures, vertebral fractures, or all fractures, we see that at the calcaneus, BUA and BMD are giving virtually identical fracture risk prediction at these sites.

You will also notice, that if you contrast that with BMD at the spine, and BMD at the hip, that there is also very close comparability to even these central anatomic sites, with regard to prospectively obtained fracture data, with the possible exception here at hip fracture, where direct measurement at the hip may provide some relative advantage, compared to any of the other non-hip measurements. But in general, the point is, that the ultrasound parameters are giving fracture risk prediction very comparable to the x-ray-based BMD measures.

Now, further then, with a comparison of these various BMD and ultrasound techniques, I would like to review a study that we undertook in San Francisco relatively recently and which was published in the Journal of Bone and Mineral Research. In this particular very comprehensive study, we examined virtually all of the widely used, noninvasive bone mineral measurement techniques, including ultrasound, in their ability to assess age-related loss, fracture discrimination, and diagnostic classification, and I will

address only a few of these points, and I do know that some members of the panel had been exposed to some of this work.

Now, the measurements that were undertaken in this particular study included quantitative CT of the spine, dual x-ray absorptiometry, DXA, of the spine, of the hip, and of the radius. It included PQCT, that is, peripheral QCT of the radius, and radiographic absorptiometry of the phalanges and the metacarpal, and quantitative ultrasound, QUS, using two devices, the Hologic Walker Sonics System and the Lunar Achilles System. Now, all of these measurements, constituting perhaps as many as 15 measurements, were applied to the full cohort of patients, here 124 female volunteers.

These were divided into three separate groups, 47 premenopausal, healthy women, constituting Group 1; 41 post-menopausal, healthy women, constituting Group 2; and then 36 post-menopausal, osteoporotic women, defined on the basis of atraumatic vertebral fractures on lateral radiographs, this was Group 3, the three is off of there, I guess.

Now, what about, then, the discrimination amongst these three groups? Well, I will show you some results on just some of the selected BMD and ultrasound parameters. Here we have standard spinal DXA measurement of the lumbar spine, and we can see that the means and the standard error of the estimate here -- standard error of the mean, of these measurements for these three groups.

One can see that there is a statistically significant discrimination, amongst the three groups, from the young normal to the older normal, to the older osteoporotic.

And if we look at the measurements at the proximal femur, in this case the femoral neck, again by DXA, we can see somewhat similar discrimination amongst these group, perhaps a little bit less discrimination between the fracture and non-fracture, based upon the neck measurement.

Well, what about BUA in this population? Here we are looking at BUA measured by the Walker Sonics device, at the calcaneus, showing, again, a strong separation of the means of these groups, and then we have Speed of Sound measurement, using the Lunar Achilles, also showing a similar discrimination.

Now, you will also notice that there is a fair amount of overlap amongst these groups, and this is an important matter to recognize, and that we have to deal with. These BMD measurements do not provide an exact separation for presence or absence of fracture, whether this is done cross-sectionally or prospectively. When one wants to consider fracture risk, one has to factor in, not only the BMD, but other clinical parameters, and a host of other factors that will be addressed later. But nevertheless, this is what one will expect with any of these measurement techniques.

Now, what about, then, the comparison of these techniques? We will not look at all of them, we will just look at a few, to make a few of the points, because an issue that was raised early on in the open presentation was, what level of agreement is necessary for techniques to have any validity with regard to BMD? Well, here we can see two different techniques; in one case, it is the DXA of the proximal femur, the trochanteric region, contrasted with QCT of the spine, measuring the trabecular bone. These are both

relatively trabecular-rich sites, here at the hip, here at the spine, but the correlation here is in fact not .95, this correlation is on the order of .64. And this is what one generally will expect when comparing a measurement at one anatomic site to another. One can see correlations on this order, as I indicated with the earlier soft data.

Now, furthermore, let's look at this coefficient of variation, or the dispersion off the regression. This is on the order of about 24%, and when you are comparing one anatomic site to another, you may have on the order of two population standard deviations, or a T-score of two difference in predicting one site to the other. Now, this is what one could expect.

Now, another example. Here is Speed of Sound with the Lunar Achilles' system, versus spinal trabecular QCT. Here again, we have a correlation, it is a highly significant correlation, but an r-value of about .7, which is what you would expect, and again, coefficients of variation of over 20%, which represents perhaps twofold the population, reference population, standard deviation.

Now, then, looking at this even a little bit further, we need to then examine the issue of measurement by, say, two different techniques at the same anatomic site. I have already pointed out that you may have a 20 to 25% coefficient of variation, when you are going from one anatomic site to another. Now, what about measurements at the same anatomic site?

Shown here are measurements performed by two techniques at each of three sites, the forearm, the spine, and the heel. And what we can see in general is that

when you use two techniques to measure at the same anatomic site, that the correlations will in fact be a little bit stronger. Here, we have forearm, these upper two slides are from the study of this multi-modality study that I am talking about, based upon San Francisco, and down here, are data with the Sahara System on this axis, compared to DXA measurements on this axis, both at the calcaneus.

If we look at the correlations, they are fairly similar, we look at the dispersion, relatively similar, and so this is what one would come to expect; we are not seeing correlations on the order of .95, or even .9, these are correlations at the same anatomic site, PQCT to DXA.

Here we have the lateral DXA to spinal QCT; and here we have the Sahara ultrasound, to ultrasound predicted, BMD to measured BMD by DXA. Now, further plotted on here against the regression line, the other two lines represent the one standard deviation of the reference population, and if you relate this dispersion, which is the root mean square error here, to the population standard deviation, you get a ratio of close to one for each of these anatomic sites. And so that means the 95% confidence interval is about two T-scores for each of these comparisons. This is what investigators and clinicians in the field have come to recognize is simply the anatomic variation that one can see, and the variation amongst techniques.

Let's summarize a little bit about this issue of the inter-technique variation, because this is of course an important point. First of all, the different x-ray techniques, at the same anatomic site typically will vary with the scatter around the regression line, or

that is a root mean square error of about one to 1.5 population standard deviations.

Now, heel BMD estimated by both x-ray and by ultrasound, vary by about one standard deviation, so not more than, but if anything, perhaps even less than, what one can see with some x-ray techniques, and this translates then into a 95% confidence interval of about two population standard deviations, or a T-score of two. This is a fact of life, and we have to deal with this. This is true for all of the x-ray base measurements, as well as certainly the ultrasound device we are considering today.

This variation is consistent; that is, the variation we see at the heel between BMD estimated by a DXA, and in this case, the Sahara System. This variation is consistent with the variation that is observed between BMD measurements by x-ray techniques at the same anatomic site, and is clinically recognized and is acceptable.

Now, then, how does quantitative ultrasound fit into our armamentarium of BMD tools? Well, as has been indicated before, it is safer in that it does not utilize ionizing radiation and also has less in the way of regulatory constraints. It is smaller in size, portable, less expensive, and it is suitable for assessment of skeletal status, as we have pointed out.

Further, it will allow physicians to reach many patients at risk who do not currently have access to more expensive and less portable x-ray-based systems. As was earlier indicated, perhaps as many as 70 to 75% of women with osteoporosis are currently going undiagnosed.

So, I would like to summarize, then, by saying, and reiterating, what we all

know, is that osteoporosis is a common disease, and treatment requires access to reliable diagnostic approaches. Bone density is clearly the strongest and the most quantifiable of risk factors for osteoporosis, and also of importance, that the clinical utility of heel measurement by x-ray and by ultrasound approaches is indeed firmly established.

Further, the agreement that has been achieved between ultrasound measurements and x-ray-based measurements at the heel, this agreement is as strong as the agreement that is seen when you measure with other accepted x-ray methods at the same bone. Finally, that heel ultrasound is clinically useful, and clearly it expands the diagnostic capability of bone measurements.

Finally, with regard to the Sahara Clinical Bone Sonometer specifically, I would say that my review of the data that have been submitted in the PMA, as well as reference to abstracts, published abstracts, posters, presentations that I have been privileged to see and review, indicate that heel BMD estimates obtained by the Sahara System are clinically useful for assessing the skeletal status of patients.

Finally, we have used this system ourselves at our Center, and our experience confirms the usefulness of this device, and we do believe that if this device is approved, that it will have a very important and positive impact on this problem of osteoporosis and women's health issues in particular. So with that, thank you.

DR. HALBERG: Thank you.

Overview of P970017

DR. VON STETTEN: Good morning. My name is Eric Von Stetten, and

I am Principal Scientist at Hologic. In this part of the presentation, I will describe the Sahara System and how it works.

The intended use of the Sahara System Bone Sonometer is to estimate the Bone Mineral Density, (BMD in g/cm²) of the calcaneus, or heel. Sahara results are highly correlated to heel BMD results obtained by the dual energy x-ray absorptiometry, or DXA, technique.

Heel BMD results may be used by the physician, along with other factors, such as laboratory test results, radiographs and family history, in a diagnosis of osteoporosis and other conditions leading to reduced bone density.

The Sahara System is a small portable device that estimates heel BMD using the Quantitative Ultrasound Technique. In this technique, sound waves are passed through the heel, and parameters describing the transmitted sound wave are measured. These parameters are highly correlated to heel BMD, and thus the heel BMD can be estimated from these parameters.

The Sahara System consists of the measurement unit, the power cord and a foot positioning aid. Once the patient is positioned, seated in the chair, the measurement is performed in less than ten seconds. Sahara weighs 22 pounds and plugs into a standard power outlet.

The Sahara System is also available with an optional external computer. This advanced clinical option offers database capabilities for storage and retrieval of patient biographical information and measurement results. It also provides more

sophisticated reporting capabilities, such as color patient measurement reports.

Unlike traditional methods of estimating BMD, the Sahara System does not expose either the patient or the operator to ionizing radiation. Furthermore, the ultrasound power levels used by Sahara are extremely low. The power levels are so low, that in order to compare to the standard limits for imaging ultrasound systems, it is necessary to use a logarithmic axis on the bar graph shown here.

The bars correspond to the three standard measures of ultrasonic power levels, ISPTA, ISPPA, and MI, or Mechanical Index. You can see that the power levels for Sahara are five to six orders of magnitude below the ISPTA and ISPPA limits, and are a factor of 190 below the limit for MI.

The patient's foot is oriented and fixed in position within the Sahara System, using the foot positioning aid. The use of this rigid positioning aid ensures repeatability of patient positioning, which is important for obtaining highly-reproducible results.

The Sahara System is controlled by the keypad on the front of the measurement unit. When performing patient measurements, the operator uses only the On, Open Prep, and Measure buttons to operate the unit. Measurement results and messages are reported on the LCD screen, and can be printed by an internal printer by pressing the Print Feed button.

Ultrasound measurements are performed by transmitting an ultrasound pulse through the heel. The sound waves are produced by sound transducers, which are

located off to the left and to the right of this figure. The sound transducers are acoustically-coupled to soft, elastomer transducer pads, which are in turn coupled to the heel by a coupling gel. The transmitted sound waves are received by the opposite sound transducer, and quantitative parameters described in a transmitted sound pulse are computed.

The key components of the Sahara System are contained in what is referred to as the Transducer Drive Mechanism. This mechanism consists of a mechanical caliper on which the sound transducers and the transducer pads are mounted. The caliper mechanism is motorized in order to move the pads inward to come into contact with the heel, and outward to provide clearance for inserting and removing the foot. A position encoder is rigidly attached to the mechanism, allowing for precise measurement of heel width.

Prior to each patient measurement, the Sahara System performs an initialization measurement in which the pads are brought into contact with one another, and an ultrasound transmission measurement is made. The initialization measurement allows for direct comparisons between the measurement with and without the heel inserted. This method allows for accurate, self-calibrated measurements of the ultrasound parameters, and automatically removes any potential for sensitivity of patient results to variations in system temperature.

One of the two parameters measured by the Sahara System is Speed of Sound, or SOS, as shown in this figure. SOS is calculated by dividing the heel width, as

measured by the position encoder, by the time delay experienced by the sound waves due to the heel. Accuracy of Sahara SOS measurements is ensured by the initialization measurement which allows width equals zero, and time equals zero measurements without the heel. As for x-ray bone density measurements, SOS values are lower for osteoporotic bone than for younger, healthier, bone.

The second ultrasound parameter measured by Sahara is the Broad-band Ultrasonic Attenuation, or BUA parameter, which quantifies the frequency dependence of the attenuation of sound waves, in a range of 200 to 600 kilohertz. Again, as for x-ray bone density measurements, BUA values are lower for osteoporotic bone, than for younger, healthier, bone.

You may wonder why it is possible to estimate BMD using ultrasound, when it has traditionally been estimated using x-ray-absorbed geometric methods. Well, the interaction between the sound waves and the trabecular structure is quite complicated. Let me give you a schematic rationale for the sensitivity of ultrasound measurements to bone density.

In this figure, the sponge-like trabecular matrix of bone is shown, where the shaded areas are the mineralized bone, and the holes or pores are the regions filled predominantly with marrow. X-ray density is proportional to the amount of bone along the x-ray beam paths shown horizontally here.

The Speed of Sound is also related to the bone path length. This is because the SOS in bone is higher than the SOS in marrow, thus as bone is demineralized, as in

osteoporosis, shown here on the bottom, the proportion of bone along this path decreases relative to the proportion of marrow.

This is indicated by the lengths of the red and green bars. The net effect is that, as bone is demineralized, BMD decreases due to the reduced amount of bone, and the SOS also decreases, due to the smaller proportion of bone compared to marrow. The BUA parameter is also sensitive to reductions in BMD, because the attenuation of the higher frequency sound waves is sensitive to the size of the pores in the trabecular structure.

The BUA parameter is expected to decrease as the size of the pores increases, thus BUA is expected to decrease with decrease in BMD, however, it is true that in addition to being sensitive to BMD, ultrasound is also sensitive to structural and mechanical properties of bone.

The sensitivity to structural mechanical properties has been shown by a number of in vitro studies; nevertheless, our clinical data will show that in vivo heel ultrasound parameters are primarily sensitive to BMD. Because the BUA and SOS parameters are both highly correlated to heel BMD, and also because they are strongly correlated to one another, it is possible to combine the two parameters together, using a simple linear combination, to form a third parameter, which averages out some of the statistical variations present in individual parameters.

The combined parameter is referred to as QUI, or the Quantitative Ultrasound Index, a parameter that is sometimes referred to in scientific literature as

stiffness, as pointed out by Dr. Genant. The QUI stiffness parameter is also highly correlated to the x-ray heel BMD, and can be converted into units of heel BMD by simple, linear rescaling.

On the left is the printed output obtained from the internal printer of the Sahara System. This print-out is obtained by pressing the Print Feed Button on the Sahara control panel. The print-out gives the date and time of the exam, provides blanks for entering the patient's biographical information, and at the bottom, reports the estimated heel BMD in g/cm², the same units reported by standard DXA systems.

Along with the BMD, the Sahara System reports the corresponding T-score, which relates the patient's results to young adult reference values. The Sahara System includes young adult reference values for Caucasian female subjects who are at highest risk for osteoporosis, and it is possible for the user to enter locally-defined reference values for other populations.

On the right is the patient report forms supplied in tablet form with the Sahara System. It is similar to the print-out on the left, except that it also contains a part of the age-dependent reference ranges for Caucasian female subjects. Notice the physician can plot the patient's results against these reference ranges, to compare to age-matched reference ranges.

Now I would like to turn to the clinical studies. The clinical studies were performed with the following objectives. First, to directly compare estimated heel BMD results obtained by the Sahara Clinical Bone Sonometer to those obtained using

established clinically-used x-ray densitometric techniques.

Second, to assess the sensitivity of Sahara estimated BMD to clinical status, and to compare that sensitivity to that found for DXA for the same subjects.

Third, to assess the reproducibility of heel BMD results obtained by Sahara.

Fourth, to obtain reference ranges for Caucasian female subjects, as I said, who are at the highest risk for osteoporosis.

Fifth, to document the safety of the Sahara System.

The clinical study was designed to include subjects representing the entire clinical spectrum; thus, Sahara and DXA results were obtained for 247 Caucasian female subjects, from age 25 to 102. These subjects were categorized into separate groups by age, hip bone density status, and fracture status.

Study results demonstrated the safety of the Sahara System, as there were zero adverse events for the total of 2255 subjects assessed. This includes the 247 subjects from the clinical study comparing Sahara versus DXA, as well as 2208 subjects from the reference data study. Precision of estimated heel BMD results was found to be 3%, based on 1213 measurements performed on 247 subjects.

Sahara estimated heel BMD results were found to be highly linearly correlated to DXA heel BMD, with a correlation coefficient of 0.85. Of course, the QUI parameter also had the same r-value of 0.85, as it is the same quantity as the estimated BMD, except for the rescaling that converts it into BMD units. We also see that the BUA

and SOS results are highly correlated to the DXA BMD.

As Dr. Genant described earlier this morning, there are many different x-ray-based techniques presently in clinical use. In addition, there are many skeletal sites assessed by the various techniques. As Dr. Genant also showed, it is well-known that the agreement between different techniques used to assess the same skeletal site, is in general stronger than the agreement found between different skeletal sites assessed by any technique. Thus, in order to put into clinical perspective the level of agreement found between Sahara and DXA-BMD estimates at the heel, and to put this relationship to the strictest possible test, we have compared this relationship to that observed between standard, x-ray-based methods of assessing the same bone.

To perform these comparisons, data was obtained from published studies, and are in fact, as Dr. Genant mentioned, data from the multi-modality study performed at UCSF. The two comparisons we will focus on are DXA of the lateral spine, versus QCT of the spine, and DXA of the radius, or forearm, versus PQCT of the radius. Note, that the lateral DXA versus QCT comparison had the strongest relationship of any of the comparisons in Dr. Genant's study.

This plot, shown by Dr. Genant earlier, shows the key data analysis presented in our PMA submission. Each of the three plots shown here is a comparison of two different techniques of assessing BMD at the same anatomical site. The comparison on the top left is for the radius, or forearm, where DXA and PQCT results are compared. The comparison on the top right is for the spine, where lateral DXA and QCT results are

compared, and on the bottom is the comparison between Sahara and DXA results for the heel. The linear correlation coefficients for each comparison are indicated.

On each plot, the dots correspond to the individual patient results, the middle line is the regression line, and the top and bottom lines correspond to ± 1 population standard deviation away from the regression line, or ± 1 T-score. The top and bottom lines thus provide a visual scale to interpret the scatter of the data about the regression line.

A more quantitative measure of the scatter for each comparison is shown at the bottom right of each plot. This is the ratio of the standard deviation of the scatter, to the population standard deviation of that BMD measure. These quantitative ratios indicate that the scatter for all comparisons is about one population standard deviation in magnitude.

T-scores, which relate BMD results to young adult reference values, are also expressed in population standard deviation units. Thus, in clinical terms, these results indicate that if a given patient is assessed by, say QCT of the spine, and then by lateral DXA of the spine, the 95% confidence interval for the difference between the two results is ± 1.8 T-scores.

For the forearm, the 95% confidence interval is ± 2.4 T-scores, and the corresponding value for Sahara is ± 2.0 . Thus, for all the comparisons shown here, the 95% confidence interval for T-score references is about two.

The clinical study was designed to allow direct comparisons between

Sahara and DXA results for clinically distinct subject groups. This figure shows the results for the six subject groups, as indicated across the top, from young adult to elderly osteoporotic, severely osteoporotic, and extremely elderly. For each subject group, the rows of dots correspond to the individual patient results for the different parameters measured, similar to the way that Dr. Genant showed some data earlier.

The parameters included here include Sahara BUA, SOS, QUI, and finally, estimated heel BMD. The last two rows on the right are for DXA heel BMD, and DXA spine BMD. These results demonstrate that the Sahara results are sensitive to clinical status, as the results are lower for each successive group, similar to what Dr. Genant showed this morning, but more importantly, they show that the sensitivity of Sahara results is similar to both heel and spine DXA. Looking at this figure, I think it is fair to say that without the labels, it would be difficult to say which of the techniques shown above was x-ray-based, and which was ultrasound-based.

In the course of discussions with the FDA, we have recently performed an additional analysis of the clinical data in terms of Receiver Operator Characteristic curves, or ROC curves. This analysis compared the sensitivity and specificity of Sahara and DXA of the heel, for identifying subjects with a variety of atraumatic fractures. Subject Groups 2, 3, 4 and 5 were pooled for this analysis, resulting in a set of subjects that corresponds approximately, although certainly not exactly, to a random sample of middle-aged women, the population most likely to be assessed clinically.

Area under curve values were computed for each parameter. Note that in

these types of analyses, higher area values indicate superior discriminatory ability. The area value for Sahara estimated BMD, 0.75, was slightly higher than for DXA heel BMD, 0.69, although the values are not statistically significant. Thus, this analysis shows that Sahara and DXA estimates of heel BMD have equivalent discriminatory capabilities.

As was pointed out earlier this morning, reference data is very important for densitometry equipment. Age-dependent reference ranges were obtained for Sahara in a large multi-center study. We are very proud of the fact that, to our understanding, this is the largest manufacturer-sponsored reference data ever performed for bone densitometry equipment. Results were obtained for a total of 2208 Caucasian female subjects, from age 19 to 97, giving the study high statistical power.

The subjects were recruited at nine clinical centers located across the United States, minimizing the possibility of geographical bias in the data. The data was analyzed in terms of decade-specific mean values, shown as the solid blue squares; the population standard deviation, shown by the blue bars was found to be age-independent. For comparison, the age-dependent reference data for an x-ray-based heel densitometer are shown by the red lines. The close agreement between the Sahara and x-ray-based reference data are yet another indication of the comparability of Sahara and x-ray-based estimates of heel BMD.

The following conclusions were drawn from the clinical studies. Sahara is safe. There were no adverse events or safety issues raised. Sahara is free from ionizing radiation and uses extremely low ultrasound power levels. The precision error is clinically

acceptable, as it is one-eighth of the population standard deviation.

There is a strong linear relationship between Sahara estimated BMD and heel DXA BMD, with a correlation coefficient of 0.85. The level of agreement between Sahara and DXA heel BMD estimates, is as strong as that between other pairs of accepted x-ray-based methods for assessing the same bone. Finally, the sensitivity of Sahara-estimated BMD to clinical status is similar to that of heel DXA.

Now, I would like to turn the presentation over to Dr. Stein for some concluding remarks.

Agenda Item: Conclusions

MR. STEIN: Thank you, Eric. I will now just briefly summarize, I hope, in a clear way for the panel, the basic context of our presentation this morning.

Well, osteoporosis is an acknowledged substantial and growing health problem in the United States, and there are now a number of effective treatments available to physicians for treating patients at the highest risk, and additional effective treatments are expected within the next two years. Because of this, there is a very much increasing need for more widely-acceptable diagnostic tools to assess skeletal status.

Fortunately, Bone Mineral Density meets this need, because it is a strong quantifiable risk factor for osteoporosis, and it has been proven useful in evaluating candidates for treatment. Of the BMD methods available, heel BMD using x-ray has been studied for 20 years and has demonstrated clinical utility as another method of assessing skeletal status. So, we are faced, only to answer the question, can ultrasound also be used

to estimate heel BMD in this context?

Well, these are images very similar to those shown by Dr. Genant earlier. The top two images are images made using ultrasound parameters, BUA and SOS, of the same cadaver foot as the bottom image was made using an x-ray exposure. You can see that there is substantial qualitative agreement between the ultrasound parameters and x-ray density in the heel, and the message we hope to transmit by this is that it is clearly a basic, fundamental relationship between density and the two types of technologies.

Now, it is true that ultrasound is sensitive to other and mechanical structural properties of the heel, and I think it was mentioned before that this was the reason why the correlation between these images isn't more perfect than it is, but the question that we need to answer, at least the company feels we need to answer, is whether or not the agreement is adequate, and to define adequate agreement, the answer must be given in the context of current clinical management.

This figure was also shown earlier by Drs. Genant and Von Stetten, and it indicates the level of agreement between different methods of assessing the BMD of the same bone. Two of the comparisons shown here are between accepted x-ray methods, which have been used clinically for a number of years, and the third is between an ultrasound technique and an x-ray method.

In order to make my point, I have, possibly somewhat playfully -- removed all the labels from this figure, and I believe it would be fair to suggest that if one were asked, it would be difficult to identify the difference between ultrasound and x-ray

techniques, just by looking at these unlabeled plots.

This next slide shows exactly the same information as the previous slide, with the labels corrected. Here, you can see that the heel x-ray versus ultrasound is the bottom plot, as it was in previous presentations of this slide.

The 95% confidence intervals for ultrasound versus x-ray heel is 2 T-scores and this compares to 2.4 T-scores and 1.8 T-scores for the x-ray versus x-ray comparison shown in the figure.

Investigators in the field, as Dr. Genant mentioned, accept and understand the fact that different BMD techniques may give results on a single patient that differ up to ± 2 T-scores on the same patient, and we think that that is a fair interpretation of these data, to reach the conclusion that the fact that the Sahara x-ray heel BMD results agree to within ± 2 T-scores, indicates that Sahara is clearly acceptable at the same level, inasmuch as the agreement between two x-ray-based methods is about the same amount.

Indeed, I would point out just for historical purposes, that if Sahara's performance were contained in an x-ray-based device instead of an ultrasound-based device, we generally would have chosen the more routine 510K process for presenting this product to the FDA.

Based on the data presented, we have concluded -- we hope to have persuaded the panelists to conclude -- that the agreement between Sahara and x-ray-based estimates of heel BMD, is as strong as the agreement between accepted x-ray methods, when assessing the same bone; differences up to ± 2 T-scores between techniques of

estimating BMD at the same sites are clinically acceptable, and in fact, represent everyday clinical reality, when different techniques are used. And when viewed in the context of current clinical management, the agreement between Sahara and x-ray-based heel BMD is adequate to support the claim of estimation of heel BMD.

Furthermore, compared to the current methods of assessing skeletal status, Sahara is safer in that it uses no radiation, easier to use, less expensive, and more portable. It should allow many at-risk individuals who have not previously had access to bone densitometry to be evaluated and to be considered for newly-available and effective treatments. And it will make this evaluation possible to the physician community in the BMD terms which are now widely used and understood as a criteria for examination.

We hope this presentation proves helpful in your considering our application, and having not been instructed what to do now, I suspect I need to turn the microphone over to the Chair.

DR. HALBERG: Thank you very much for those presentations. Before we go any further, why don't we take a ten minute break? I was wondering if we could ask the company to vacate that table so that the FDA presenters can use that? Thank you very much.

[Brief recess.]

DR. HALBERG: Mr. Joseph Arnaudo will be the FDA's lead reviewer for PMA, P970017, and will provide introduction of the PMA from the FDA's perspective.

FDA Presentation of P970017

Agenda Item: PMA Overview

MR. ARNAUDO: Alright, well, good morning, everybody, and Dr. Halberg and panel members, what I would like to do is, I would like to provide you with some information about the clinical bone densitometer. You have heard so much about it, I would like to give you a little more information about it.

My name is Joseph Arnaudo, as you heard. I am the prime reviewer for this PMA. I am an electrical engineer, I am with the Radiology Branch.

Let's look at the Indication again. The reason that Indication is going to be important to you, the panel, is that we are going to discuss Indication later on, and we want to look at it and kind of make sure we understand everything, all the little itsy-bitsy things it says.

The intended use of the Sahara Clinical Bone Densitometer Sonometer is to estimate the Bone Mineral Density, that is the BMD in g/cm² of the calcaneus to the heel. The Sahara BMD results are highly correlated to heel BMD results obtained by dual energy x-ray absorptiometry, DXA, technique.

Heel BMD results may be used by the physician, along with other factors, such as laboratory results, radiographs, family history, for a diagnosis of osteoporosis, or other conditions leading to reduced bone densities.

Now, some of the key aspects of the device are that, it is an ultrasound device and it estimates the Bone Mineral Density. It does this by a combination of Speed of Sound, that is SOS, and Broad-Band Ultrasound Attenuation, BUA. Patient exam time

is less than ten seconds, after the foot is inserted into the device. The device uses a through transmission mode technology, with a separate send to receive transducer about the heel. The output is just a number, as was mentioned, it is Bone Mineral Density number, a g/cm^2 , or it is a T-score value.

Now, here is a list of the FDA review team. This is a list of the preclinical reviewers of this PMA. You can see it covers engineering, physics, electrical safety, chemical and biomaterial safety, toxicology and bio-compatibility safety. Software. Electromagnetic compatibility, manufacturing, biomedical research monitoring areas. Each of these areas is looked at in depth at the PMA submission. The result was, of the nonclinical concerns that were of concern to us, they answered all of the concerns and we have no more concerns about these areas.

Labelling views were also done of this PMA, and this slide shows -- these are the label people involved in the label reviewing. We have physicians and nurses and a whole variety of people look at labeling, how the labeling looks to them, how it reads to them. The result is that the labeling is still undergoing, in fact, we are going to be talking to you today more about this labeling.

Here is a list of the clinical reviewers. The clinical data was reviewed by Dr. Sacks, and the statistical data was reviewed by Mr. Kotz.

I would now like to introduce you to Dr. William Sacks who will review for you the clinical and statistical data contained in this PMA. Dr. Sacks?

Agenda Item: Clinical Studies and Labeling Issues

DR. SACKS: Thanks, Joe. Good morning to the panel, ladies and gentlemen in the audience. You are to be forgiven if you find that a lot of what you have heard this morning leaves you a little unclear, because there was a tremendous amount of data presented, and I have sympathy for you and for clinicians out there who are expected to use the device. Unless you have spent about four or five months thinking about these things, as we have in ODE, they can be a little confounding.

I am going to try to shed light on all of the issues here in this talk. As a consequence, I will be repeating certain numbers of things that have been said already, but always trying to bring out some new aspects.

First of all, the role of bone measurement. Just as it is important to identify the most effective therapy for the individual woman, that is the agent which adequately slows her bone loss with the fewest side effects, it is important to be able to discriminate between those women for whom the benefits of medical therapy outweigh the risks; that is, those women for whom the risks of nontreatment outweigh the risks of treatment.

I want to acknowledge that there is a school of thought in the medical community that all women should be treated with hormonal replacement therapy at menopause, both to slow the rate of bone loss, and to lower the risk of heart attack, and that the increased risk of breast cancer is outweighed by the risks, certainly, of heart disease, but also of osteoporotic fractures. However, at this time at least, only a minority of endocrinologists, gynecologists, and internists adopt this approach. Of course, even if all women were to be placed on some form of bone-saving therapy at menopause, there

would still be a need for bone-measuring devices to follow the response to therapy, in order to choose the most effective agent for the individual.

Diagnostic devices to identify and follow women of relatively lower bone mass have been developed for this purpose. Because of the important role played by bone mass, the concept of osteoporosis has been the target of much debate. Even its definition has been controversial. One definition is given by the World Health Organization, it has been mentioned earlier today, and it sets a certain level of bone mass as the threshold for the definition of osteoporosis; in particular, osteoporosis is defined as a bone mass measured by some method more than 2.5 standard deviations below the mean for young, normal, Caucasian women. In current clinical usage, this is called a T-score of less than -2.5.

A woman's T-score describes her bone mass, and is defined as the number of young, normal, standard deviations above or below the young, normal mean, as defined by some reference population of young, normal, Caucasian women. Lesser degrees of bone loss with a T-score between -1 and -2.5 are referred to as osteopenia, though even this word is controversial, since many radiologists use osteopenia as a general term to include both osteoporosis and osteomalacia, or poorly mineralized bone.

Besides the definition of what level of measurement does and what does not constitute osteoporosis, the very nature of the condition is a matter of disagreement. While some define it as a disease, others point out that, like hypercholesterolemia, and hypertension, osteoporosis is merely a risk factor; the former for heart attack and stroke,

the latter for fracture. In other words, the problem is not low bone mass, the problem is fracture. If a woman with low bone mass lives a long life and never fractures, her osteoporosis was not a problem for her, other than the role that any fear of fracture may have played.

Despite the various sources of confusion, clinicians are still called upon to diagnosis, treat, and follow women with osteoporosis. Over the last few decades, a variety of devices have been developed to enable these clinicians to carry out this responsibility. Each has its own strengths and weaknesses, but when all is said and done, since measurements of bone, quantitative and/or qualitative, determine only a risk factor, and only one of several risk factors at that, clinicians who treat and follow patients need to be fairly conversant with the limitations of the measurements, and the role of the other risk factors.

Current methods of measuring quantity of bone are referred to as bone densitometry. There has been a progression, as we have seen earlier today, for methods such as RA, SPA, and DPA, to QCT and DXA, and one or two others that I have left out, just to give a sense here. These all have in common the use of ionizing radiation to measure attenuation by bone, with some using x-ray tubes as their source, and others, external radionuclides.

Ultrasound is the first modality to dispense with this feature of ionizing radiation, and I want to stress this. While no ultrasound device has been approved for this indication in the U.S. to date, it has been in clinical use abroad, as was pointed out earlier

today, as well as in experimental use in the U.S. The Sahara is the first such device to be submitted to the FDA for consideration.

Now, a word should be said about densitometry. Depending on the method, the density which is measured may be expressed as grams per unit volume, area, or length, and I give examples here of different modalities that have these characteristics -- I am not sure that the laser is showing up -- but QCT happens to give the results in g/cm^3 , that is, it is a volumetric density. DXA, that we have heard about today, gives a projected g/cm^2 , and older modalities, such as SPA, give g/cm along the radius.

These are not commensurate measurements, and correlations among them are subject to variability in the other dimensions, among other things. For example, of two women with the same volumetric density, but one with bones of larger diameter -- I am comparing A and B now -- their QCT results will be equal.

The reason for that is, that QCT measures a volumetric density and I have shown the trabecular spacing and so on to be roughly similar in the two bones, A and B, two different women, but the size is the difference here. So, they will get identical QCT results, but the one with bigger bones, that is, A, will have a higher DXA result, because it measures projected areal(?) density. It is picking up more bone on its way from left to right before it hits the detector.

Similarly, of two women with the same projectional areal density, but one with bigger bones, and I am now looking at A and C. C is a smaller bone, but has denser trabeculae, such that -- I have chosen it so that it has the same amount of projected bone

in the path as A.

Their DXA results will be equal, but the one with bigger bones will have a greater SPA result, and a smaller QCT result. You can see -- for example, the QCT I think is more important, given current usage -- that if you were to look at a volumetric density of A, it would be lower than the denser packing in C. And this gives an idea of the variability, some sources of the variability among the different methods.

Ultrasound for bone measurement, unlike ultrasound imaging, does not employ reflected waves, but rather it employs transmitted or refracted waves to measure the Speed of Sound, as we have heard earlier, through the bone, and/or dependence of attenuation of the sound beam on sound frequency, so-called Broad-Band Ultrasound Attenuation, BUA.

Some studies suggest that each of these parameters depends, not only on the gross volumetric density of the bone, which also involves its marrow and cellular contents, but also on aspects of its micro-architecture, and integrity, raising the possibility that ultrasound may detect more features of fragility than ionizing radiation methods, which measure only density.

In an attempt to minimize certain sources of variability in the population, some of the devices, including the Sahara, give a dimensionalist, arithmetic linear combination of SOS and BUA as their output. Hologic calls this the quantitative ultrasound index, QUI, and/or stiffness.

Now, we have heard a little bit about stiffness, it is in common usage in

literature, however because this linear combination is not a direct measure of the actual physical property of stiffness, which has to do with Young's modulus(?), this particular term is considered by some to be ill-advised. Stiffness. QUI is more precise, because it is vague.

The literature contains many papers describing bench-testing of ultrasound on animals or cadaveric bone, as well as in vivo correlations of SOS and BUA with each other, with the other modalities, and with fracture risk, in both retrospective and prospective studies. Let's spend a minute on this slide, because I think the crux of the issue is here.

The PMA that Hologic submitted is all in the lower right-hand corner here. It is showing a correlation between DXA and ultrasound, with particular DXA devices and a particular ultrasound device. That is one approach. One can also look at -- and we have seen data this morning -- on correlations between, say, QCT and DXA; indeed, between QCT and ultrasound, and a variety of others can be thrown in, so that you can look at inter-modality correlations.

Another way of approaching this is to show how each of them relates to fracture risk, which is after all the clinically useful end point here. While the correlations among results from the various modalities are not high, the literature shows that the various modalities, including ultrasound, have comparable ability to discriminate women with and without fractures; that is, the relationship between QCT and fracture risk, compared to the relationship between DXA and fracture risk, compared to the relationship

between ultrasound and fracture risk, are comparable in their ability to discriminate, but these papers have been done on other devices. A variety of them.

Furthermore, inter-site correlations, as we have seen this morning, within the same women, are far from perfect; that is, a woman's hip will generally have a different quantity and/or quality of bone from that of her spine and radius, or heel, at any point in time. Not only does peak bone mass vary at different sites; that is, the peak that she achieves before she starts the post-menopausal decline, but a woman's rate of bone loss will differ at the different sites; in particular, the spine tends to lose bone the most rapidly.

These differences are most likely related to differences in mechanical loading and impact at different sites in the skeleton. As a result of these only moderate correlations, different modalities may assign any particular woman a sufficiently different degree of risk, that she may be triaged differently with respect to the clinical decision, whether or not to intervene pharmacologically.

At this point in time, the most commonly used modality is DXA, not because it is the best fracture risk discriminator, but because one, it allows examination of any part of the skeleton; two, it subtracts out that part of the attenuation due to soft tissue; and three, it avoids the use of radionuclides.

Through clinical usage, it has become, so to speak, the gold standard for bone measurement, but because of the various types of density that we have seen before, and because of the less than perfect inter-modality correlations, any one of the modalities can at best be a copper standard for the rest, and this should be borne in mind during

today's discussion.

I am going to spend a couple of seconds on the issue of the biomechanics of fracture so we get a sense of what we are dealing with here, and the relative contributions of cortex and trabeculae, some of which has been mentioned earlier.

Depending on the nature of the trauma, bones may fracture different ways. Long bones, like femur or radius, more commonly suffer bending or spiral fractures, while vertebrae more commonly suffer compression fractures. In general, the cortex offers the main resistance to bending or spiral fractures, while the trabeculae share with the cortex in the resistance to compression fractures, therefore, both the cortex and the trabecular bone are important for the body as a whole, and as stated earlier, the mass of each declines with age.

However, while cortex becomes more porous and thinner with age -- just go from the top left here -- as a woman ages, several things happen. In most long bones, it continues to increase in diameter. This happens because post-menopausally, resorption occurs primarily on the endosteal, or inner surface of the cortex, while new bone is laid down primarily at the periosteal, or outer surface of the bone.

The increasing size -- even though the bone is getting thinner, the cortex is thinner, it becomes more porous, and the trabeculae become more spaced apart and thinner themselves -- that the increasing size invests the bone with a partially-compensating increase of moment of inertia against bending and spiral fractures.

Unfortunately, the femoral neck is an exception to this rule, as we see

down here at the bottom. Because it is intra-capsular, and thereby lacks a periosteum to create new bone at the outer surface, as a result, the cortex of the femoral neck thins faster than all other long bones, and it lacks a compensatorily increasing diameter, hence the popularity of the femoral neck is a site of osteoporotic fracture.

By including everything in the projected path of the x-ray, DXA and RA, or SPA and so on, measure both cortex and trabecular bone without being able to separate their contributions. In other words, DXA sweeps up everything in its path.

QCT, on the other hand, can discriminate cortex from trabeculae, and measure each separately, or both together. One merely needs to put a particular region of interest around either the whole bone, a portion of cortex, or just trabeculae, and you can get the results of the density in any of those areas. And that is a volumetric density.

Ultrasound also measures features of both cortex and trabeculae when it traverses a bone, as exemplified by the Sahara, but with an appropriately designed device, ultrasound can also be used to measure Speed of Sound in cortex alone by the use of refraction. This is shown in the upper diagram, and I put the lower one, the transverse ultrasound again for comparison, and I stress that the Sahara is designed to be a transverse ultrasound device.

The contributions of cortex and trabecular bone vary significantly at different body sites. In the diaphoreses or mid-shafts of long bones, the proportion is approximately 95% cortical to 5% trabecular, whereas in the calcaneus, the reverse is true, with approximately 10%, five to 10% being cortical and 85 to 90% -- I am sorry, 90 to

95% being trabecular. The spine and the hip are intermediate in these regards.

Peripheral sites are measured, not because they are more subject to fracturing, but because they are more accessible to measurement, however it is not like the drunkard who was searching for his keys a block from where he lost them because the light was better there. Peripheral sites do, after all, lose bone with age, along with those central sites, which are more important from the point of view of life-altering fractures. It remains only to see, to what extent this is true, and we have heard some of this from previous speakers.

Now, let's turn to the clinical utility. There are basically two purposes for measuring an individual woman's bone characteristics; diagnosis and follow-up. Diagnosis, to determine the need for therapy, taking into account her other risk factors, and follow-up, to assess her progress over time.

Should the need for therapy be decided based on other risk factors, such as history of past osteoporotic or low trauma fracture, then follow-up would require a baseline measurement. Based on what has been said earlier, all measurements on an individual woman should be done with the same modality, and preferably even the same device.

Every diagnostic device is judged for both its accuracy and precision. Accuracy refers to the faithfulness with which the output corresponds to the thing being measured, and precision refers to the faithfulness with which the output corresponds to itself, when measurements are repeated. That is, to the reproducibility of the output.

Accuracy is perhaps the more important for determining the need for therapy, and precision is the more important for following an individual woman. At the current stage of technological developments, screening, screening of the entire post-menopausal population is not recommended by any of the national or international osteoporosis organizations. Rather, they recommend at this stage, measuring only women at relatively higher risk, as determined from other risk factors.

Problematic, for all bone measurements, is the fact that women are subject to osteoporotic fractures at several different sites, and as stated earlier, each woman may have differing bone density at the various sites, sometimes by as much as two standard deviations, even measured by the same device.

There are some drugs in development which may prove to be site-specific, but as long as none exists, the whole woman must be treated, therefore one must logically want to identify the site with the lowest bone density in each individual, but given that bone density is only one among several risk factors, clinical practice has not always relied on measurements at the various sites, particularly since, over time, all parts of the skeleton will decline. And since there is some correlation, as a result, some modalities use peripheral sites to track the skeleton as a whole. These sites include the radius, the patellar, and the calcaneus.

The device under consideration today. As far as safety is concerned, the device is deemed of nonsignificant risk, and indeed, as we have seen, no adverse events occurred during the clinical trials. We may concentrated our efforts, therefore, on its

effectiveness for the intended use. The device under consideration today uses sound transmitted through the calcaneus to measure the SOS and BUA -- and I am going to rely on your now knowing what those mean -- from which is calculated the QUI.

QUI is then used to calculate the estimated BMD, as measured by DXA, by a linear relationship derived from regressing QUI on BMD, for the population.

As we have seen, the foot is placed into the Sahara and held in position by a leg brace to assure reproducible positioning. The transmitting and receiving transducers are placed in contact with the skin on either side of the heel, using a typical ultrasound jelly, to conduct the sound between the transducers and the skin.

This is called a dry system, as opposed to one in which the heel is placed into a water bath, shown below, a so-called wet system.

While there is additional text, I want you to concentrate on one issue, the sponsor states that the intended use of the Sahara is essentially to estimate Bone Mineral Density of the calcaneus. The clinical trials in the PMA were aimed at showing a high correlation between the Sahara output, QUI, and DXA of the heel, for each of the subjects. In other words, the gold standard for determination of BMD was taken to be DXA, as opposed, for example, to the mass of ashed bone.

The subjects were distributed among six groups of women, including young, normal, elderly normal, elderly osteopenic, elderly osteoporotic without fractures, elderly osteoporotic with fractures, and a group over 70 years of age, called extremely elderly, though I have an aunt who might take umbrage at this designation.

The trials were performed at three centers in Massachusetts, with two of them performing DXA of the heel using the Hologic QDR 1000 system, and DXA of the spine and hip, using QDR 4500, while the third center used the Hologic QDR 2000 system on all three body sites.

Each woman underwent a measurement of her heel by each device. Now, we have seen this slide before, several times, and the correlation coefficient of the relationship between the two results was determined to be $r=.85$ for the six groups combined. Let us consider the significance of this r -value. Some, including the company, would say that $.85$ is a high correlation, while others might say it is only moderate, so how can we make a relatively objective judgment on this issue?

First, the value of r is dependent in part on the range of observed values, such that the combination of all six groups, from young to extremely elderly, tends to maximize the value. Indeed, our statistician, Mr. Kotz, calculated the r -values for each of the six subgroups, and they range as low as $.7$.

However, the scatter appears to be relatively independent of the range of values chosen, as we have heard earlier, and therefore it is more meaningful to note that the scatter about the regression line between DXA and Sahara, in terms of T-score, had as we have heard, a 95% confidence interval of approximately \pm two; that is, an individual woman's T-score, using the Sahara, could differ from her T-score using DXA, by as much as two in either direction, with one out of every 20 women actually exceeding this difference. And this is to be compared with the value of T-score used to define

osteoporosis, of -2.5.

The Sahara output is expressed as BMD in g/cm^2 , and as T-score, relative to the defined reference population. Were the output to be expressed as estimated heel BMD T-score, along with the 95% confidence interval, a typical result for a woman might look like T-score -1, 95% confidence interval +1 to -3. Does the clinician receiving this report treat or not?

I want to stress one point; one cannot derive the scatter, given only the r-value; one must also know something about the range of value and the population under study, to know only that the correlation of QUI to DXA is .85, is to have no idea of the error bar in the measurement. That needs to be provided independently.

If women typically lived until 120 years of age -- and I noticed in the newspaper last week there is one woman in France who was celebrating her 122nd birthday, so maybe that is the portent of things -- she died right after she was blowing out the candles, but -- I use this merely for purposes of illustration. I am not saying whether it is desirable or not. If women typically lived until 120 years of age, the correlation of the Sahara to DXA might well be close to .95, because of the extended range of values, but the error bar in the T-scores would still be ± 2 .

Since decisions of whether or not to treat for osteoporosis are based in part on a woman's T-score, some women who would be treated based on a DXA measurement, will not be treated, based on a Sahara measurement. And vice versa. Indeed, in the population samples used in the PMA clinical trial, the proportion of women

who would receive different treatment recommendations from the two devices, all other risk factors being equal, is approximately 14% of the women shown on this. And let me just illustrate. The ultrasound T-score is the bottom and the x-ray score is along the ordinate here.

If we consider a line at -2.5, going across here, all women lying below that would be called osteoporotic by the World Health Organization definition. If on the other hand, we look at the -2.5 level for the ultrasound, the Sahara T-score, that would be separated by a vertical line, and all women to the left would have a greater than -2.5 -- or that is, more than 2.5 standard deviations below the mean, and they would be defined as osteoporotic, and therefore, if we imagine -- I am sorry we did not draw these in, but if we imagine two crossed lines here, those women who are in the upper left and lower right quadrant, are the ones who would be called osteoporotic by one and not by the other.

For example, look at some of these women down here. These are women with a T-score on the x-ray of almost -3. They would be called osteoporotic, but end up with an ultrasound result of on the order of -1 and would not be called osteoporotic.

Now, this is also true when other methods are compared with DXA, such as QCT, for which the correlation to DXA is comparable, as we have heard, to the Sahara. On this basis, the company claims that the results of the PMA are therefore clinically acceptable. It is precisely on this point, which both the panel and the FDA must decide. I will return to this point below.

Additionally, there has to date been no attempt even to guarantee that

DXA devices from different manufacturers yield the same result for the same site in the same woman at the same time. Likewise, for QTC devices of different manufacturers. Contributing to this scatter, there are several sources of variability in the population from the measurement alone.

These include thickness of the soft tissue overlying the calcaneus, that is, the width of the soft tissue between the skin and the bone on both sides. The temperature of the heel. Positioning of the heel in the device, and positioning of the transducers, relative to the calcaneus.

Temperature is a source of variation with dry systems, since they cannot equilibrate the heel to a standard temperature, however, there is literature suggesting that SOS and BUA vary in opposite directions with temperature, and therefore, the linear combination in QUI minimizes this effect by allowing these variations to partially cancel each other.

Positioning of the heel in the device is made more reproducible by the leg holder, and minimizes this source of variation, but this together with the positioning of the transducers, relative to the heel, is particularly important, since the relative amounts of bone and marrow in the pathway through the calcaneus, vary in the sagittal plane.

We have seen a couple of images shown by previous speakers that are similar to what I am trying to show schematically here, that the density here and here is much greater than in the middle and depending on what point you pick, you are going to get a vastly different amount of bone.

Some devices, including the Sahara, use a fixed distance from the back and bottom of the device for all women. Others search for and use the fixed point of lowest bone density; that is, they look for that spot in the middle there, and still others give the map over the entire posterior portion of the calcaneus, and we saw an image of that earlier.

In either case, it is relatively reproducible for each woman, but the fixed position introduces more population variation as women with different size heels put their heels into the machine. Besides the variations in the population, the device itself, as with all devices, is subject to a certain degree of imprecision.

Indeed, in addition to measuring the correlation between QUI and DXA, that is, assessing the Sahara's accuracy, a second purpose of the PMA, as we have seen, was to establish the precision, or reproducibility, of the device. For this purpose, each woman's Sahara measurement was repeated five times in a row on the same visit.

Hologic expresses the precision as the coefficient of variation -- which is typically how it is expressed, CV, which they define as the ratio -- anyone would define -- as the ratio of the standard deviation of repeated measurements on the same woman to the average value of the measurements for the entire group of subjects from young to elderly.

Their result is approximately 3%; that is, the standard deviation of repeated measurements within a short time interval in the same woman is on average, 3% of the average measurement obtained, not on the individual woman, but on the entire group of women from young to elderly. So it is some kind of an average.

Since the scatter of repeated measurements in absolute values of BMD and g/cm^2 is relatively constant from young women to elderly, but the average measurement itself declines with age, a point that has been made before, the CV for young women is lower because the denominator is greater, is lower than 3%, while that for elderly women is higher than 3%. That is, the Sahara is more precise for young women than for elderly.

To appreciate the significance of the 3% figure, it is necessary to compare it to several other figures. First, for purposes of the device's ability to diagnose osteoporosis, in order to allow treatment decisions to be made, the relevant comparison is to the standard deviation of the age-matched population -- in common terminology, the unit for the Z-score -- that can be a little confusing, and I want this slide here to be up while I make my next remarks.

Since the CV is expressed as a percentage, in order to make a comparison we need to express the standard deviation of the age-matched population as a percentage as well. Since the absolute standard deviation of the population also tends to be relatively constant over all age groups; that is, I tried to draw two semi-bell curves here, try doing this with free form on a computer -- the width of this, that is, from here to here, is a standard deviation. The width of that is roughly similar, as you slide down the scale from younger to older, and it just stays roughly the same width.

Since the absolute standard deviation tends to be constant over the age groups, this ratio, too, is smaller in young women than in older, but on average, is about 24% of the BMD measurement; that is, it is not 24% of a T-score, you cannot do that,

you have a T of average that is zero, and so you have to be comparing 24% of the absolute measurement of g/cm², where the zero is down here.

In other words, young women have a Bone Mineral Density of approximately .54, or .53, and it is 24% of that that represents the standard deviation, but that is the definition of a unit of T-score. Thus, the CV is approximately one-eighth; that is, 3% compared to 24%. This little curve is a graph of the bell curve of repeated measurements on the same woman.

It is approximately one-eighth of the age-matched standard deviation, and remains so from young women to elderly. This gives a measure of how precisely the Sahara identifies a woman's T-score. Second, the relevant comparisons in evaluating the ability of the device to follow a woman over time, are to either the average annual untreated bone loss, or to the average untreated bone loss, or to the annual bone gain, when a woman is first put on a therapeutic agent.

There is a gain in bone mass to a slight degree, maybe up as high as 5 to 10% over the first couple of years, and then it declines after that, even on therapy, but you are now declining from a higher peak, or it is a delayed decline.

Before I present these figures, I want to stress -- and I am going to say this maybe twice -- the sponsor makes no claim for the device concerning its utility for follow-up. They do express this precision of 3%, but say nothing about the issue of using the device for follow-up.

The reason we bring it up at all is that it is not unlikely that the device, if

approved, would be used for this clinical purpose, and having a rough idea of the time intervals appropriate for follow-up, will help us to assess the way the labeling should address this issue, if at all.

The annual average bone loss per year after menopause is approximately 1% of a woman's BMD, and the average annual bone gain per year, when a woman is first placed on therapy, is three to 5%, and I have just written four, just as a rough statement, with significant variation in this latter figure, depending on the agent, on the individual, and on the skeletal site measured. Therefore, with a precision of 3%, CV of 3%, and a bone loss of 1% per year, one would have to wait at least three years before natural bone loss would be expected to exceed the imprecision of the measurement.

In other words, you would have to wait at least three years before you repeated the measurement with this level of precision, before you could detect an actual change in the bone that was not attributable merely to the imprecision of the measurement. Now, these are rough, just the guidelines.

With a bone gain of 3 to 5%, one would have to wait at least on the order of one year, before the bone gain might exceed the imprecision. We will return to this issue when we present our questions for the panel's consideration this afternoon, under the heading of Other Labeling Issues.

As of this date, there is no device which is FDA-approved for estimating fracture risk, including the various radiation devices. Let me say that one more time. The FDA has approved no device, QCT, DXA, SPA, or ultrasound, for the determination or

discrimination of fracture risk. However, there is published literature showing that, while the various methods only correlate with each other moderately, and that correlation is this question on the lower level -- we saw a slide earlier that I had included QCT, but this is enough to make the point --

Various methods only correlate with each other moderately, and with comparable scatter in the T-scores, each method is, according to published literature, capable of discriminating age-matched women with and without osteoporotic fractures to a comparable degree.

Dr. Genant showed us some of those figures, and we were talking about this relationship and this relationship, and QCT indeed, also, that these relationships are comparable between various ultrasound devices that have been used in these trials, which do not, I point out, include the Sahara, and fracture risk, DXA and so on.

These comparisons show that they all have comparable ability to discriminate women with and without fracture. Therefore, DXA, QCT, and at least some ultrasound devices, all estimate fracture risk to a comparable degree. However, the current PMA does not claim to show how well the Sahara estimates fracture risks, but merely determines the correlation between this particular ultrasound device and DXA, in order to support a claim that the device can be, "used to estimate Bone Mineral Density in g/cm² of the calcaneus," by which is meant, the output of the particular DXA devices used in the clinical trial.

This is the indication for use for which we should evaluate the Sahara, and

we have already seen the degree to which it agrees with the DXA results and the size of the error bar. Just to make this point perfectly clear, the PMA does not involve -- it did not give adequate data.

Dr. Von Stetten did show -- and I will come back to that in a minute -- some preliminary data that shows the degree to which the Sahara can discriminate between women who have fractured and have not fractured, and one would use ROC analysis in these kinds of -- to give you the most information about that, but that is not what the PMA is about.

The PMA today that we are dealing with is based on a correlation between ultrasound and DXA. To show how well a device can estimate fracture risk, one would evaluate how well it discriminates between age-matched women who have and have not fractured, if the study were retrospective, and who will and will not fracture over a given number of years, if the study were prospective. Both types of studies have been done in the literature, and they both give similar results. The evaluation of such data is best performed, as I said, using ROC analysis.

Now, the PMA did include, among the six groups, as we saw before, 25 elderly osteoporotic women who had fractured -- these were in Group 5 -- and 123 age-matched women, who had not fractured. These were in Groups 2, 3, and 4. They were roughly age-matched, as Dr. Von Stetten pointed out, but this retrospective, or case-controlled data allowed the company to calculate the ROC curves, which described the discriminatory ability of both the Sahara and DXA with respect to fracture risk.

Mr. Kotz, our statistician, also performed this calculation independently, and got almost identical results, and this is our curve, that he derived. He found that the area under the Sahara ROC curve, is .75, and that under the DXA, the ROC curve is .68, as it compared to the .69 we heard earlier, basically that is the same, though he also found the difference was not statistically significant for this modest amount of data; there were only 25 women who had fractured in this data. That is not very many.

It would require a larger study to determine whether the two curves are equivalent, or whether one is superior to the other, not to mention which one. Nevertheless, this may be looked upon as suggestive for future clinical trials, to determine the relative ability of the Sahara to discriminate fracture risk.

Given all the sources of variability among the various methods and devices, even within the same site in the same woman, some discussion should be devoted to assessing the role that introduction of a new technology plays with respect to this lack of consistency, and finally, discussion should be devoted to the validity of introducing it, based only on a correlation between it and a technology which is in common clinical use, and not on a demonstration of the degree to which it estimates fracture risk.

In summary, there are six points that I want to use for summary and leave you with here. First, the claim for the device is that it gives an estimated BMD of the heel, as measured by DXA of the heel, but not that it can be used to assess fracture risk.

Second, the correlation between the Sahara and DXA of the heel is .85, but the more meaningful figure is the scattering of T-scores about the regression line, which

has a 95% confidence interval of approximately ± 2 .

Third, all inter-modality correlations have a regression scatter comparable to that between the Sahara and heel DXA.

Fourth, the claim is that the device can be used for diagnosis and treatment decisions, but not that it can be used for follow-up to assess response for treatment.

Five, the precision of the device shows an average CV of 3%, as compared with the average age-matched standard deviation of 24%.

Finally, the Sahara involves no ionizing radiation, and is safe in other respects as well. Thank you.

DR. HALBERG: Thank you. I think I will ask everybody to hold this in mind and we will break for an hour for lunch.

[Whereupon, at 12:30 p.m. a recess was taken until 1:30 p.m., that same day.]

AFTERNOON SESSION

(1:55 p.m.)

DR. HALBERG: Good afternoon. I would like to call the meeting back to order. Before we proceed with the review and discussion of P970017, Mr. Monahan will remind panel members of their responsibilities in reviewing today's premarket approval application for Sahara Bone Sonometer.

Agenda Item: Panel Discussion, Recommendation and Vote

MR. MONAHAN: Thank you, Dr. Halberg. The Medical Device Amendments to the Food, Drug and Cosmetic Act, enable FDA to obtain a recommendation from an outside expert advisory panel on medical device PMAs, which are filed with the agency.

We are asking you, the panel, to make a recommendation concerning whether this PMA should be found approvable, approvable with conditions, or not approvable. A recommendation must be supported by the data in the application, or by publicly-available information.

You may recommend that the PMA Supplement be approved with no conditions attached to the approval. You could also recommend that the PMA be found approvable, subject to specified conditions, such as, resolution of clearly identified deficiencies, cited by you or by the FDA staff.

Examples can include resolutions of questions concerning some of the data, or changes in the draft labeling. These conditions may be changes you wish to see made prior to approval, or post-approval conditions, such as a post-market study. The

conditions should be delineated in your motion.

You may also recommend not approval, but you must make recommendations as to what is needed to make the application approvable. The Act, Section 515-B-2 through E, states that a PMA can be denied approval for any of five reasons, and I will briefly remind you of three of these reason that are applicable to your deliberations and decisions.

The three are: One, there is a lack of showing of reasonable assurance that the device is safe, under the conditions of use prescribed, recommended, or suggested in the labeling. To clarify the definition of safe, there is a reasonable assurance that a device is safe when it can be determined, based on valid scientific evidence, that the probable benefits to health from use of the device, for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh the probable risk. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury, associated with the use of the device.

The PMA may be denied approval, if there is a lack of showing of reasonable assurance that the device is effective under the conditions of use prescribed, recommended, or suggested in the labeling. A definition of effectiveness is as follows:

There is a reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use when

accompanied by adequate directions for use, and warnings against unsafe use, will provide clinically significant results.

The PMA may also be denied approval, if based on a fair evaluation of all the material facts that proposed labeling is false or misleading. If you make a nonapprovable recommendation for any of stated reasons, we request that you identify the measures that you believe are necessary, or steps which should be undertaken, to place the application in an approvable form. These may include further research.

I would also like to point out at this time, for the benefit of the panel, that information was provided this morning on studies that were not contained within the PMA, in the form of tutorials, to familiarize the panel and the audience with the use of ultrasound.

I would remind the panel that they should confine their deliberations and their recommendations to only the data supplied in the PMA. And with that, I would like to turn the meeting back over to Dr. Halberg.

DR. HALBERG: Thank you, and I would like to remind public observers of the meeting that, while this portion of the meeting is open to public observation, public attendees may not participate unless specifically requested to do so by the panel.

We were originally going to have a discussion of the draft, of the questions actually posed by the FDA. I think before we do that, I would like to ask Dr. Melton to kind of provide a larger context for us, prior to looking at those questions.

DR. MELTON: Well, I think it is obvious that we have some difficult

questions to answer that were posed to the panel, and that it would be important to do this efficiently, if we all share some basic assumptions about the condition that we are talking about.

One has to do with whether or not we are talking about a risk factor or a disease, which has been pointed out already as a source of controversy, and I think, needlessly so, because certainly, osteoporosis, or low bone density, however measured, is a risk factor for fracture, which is what we are interested in, from a societal point of view, but this is not an ethereal thing, because osteoporosis is a real entity.

If a woman has very, very low bone density, three standard deviations below the young, normal mean, there are actual physical changes in her bone that are analogous to emphysema. There are structural changes. Those structural changes have bio-mechanical consequences, and so there are functional consequences of this disease, related to reduced strength of the bone.

The confusion that we have in dealing with this, is that that functional change in the bone that is due to the structural alterations associated with osteoporosis, does not become evident until something else happens, some excessive load is applied to that bone.

If you look at this from an engineering point of view, what you find is that one element of fracture risk is the strength of the bone. Another element of fracture risk is the loads implied. And so, when we are measuring bone density, we are only measuring one piece of the equation. We are measuring the strength of the bone. We cannot expect

to have a perfect prediction of fracture risk, because we are not measuring the other aspect of fracture risk related to falling, mostly, and in fact, that is not feasible at our current state-of-the-art.

One issue that I think we have to deal with here today is, is there evidence that this technology can assess the strength of the bone? It has been shown that bone marrow density empirically is very strongly correlated with the strength of the bone, and more importantly, because there are these many other factors that you heard about this morning, the size of the bone, the actual distribution of the bone within the bone envelope; the length of the bone and all these other things, that the final test, really, is the ability of the measurement to predict fracture risk, empirically, even if we do not understand all the fundamental principles underlying that.

Another issue, then, I think we have to deal with is the sufficiency of the evidence that this technology can predict fracture risk. So, I think these are the fundamental conceptual questions that we need to deal with, the empirical questions, not the philosophical questions; is it a risk factor, is it a disease, because there is good evidence that it in fact is a disease.

DR. HALBERG: Thank you. Dr. Turner, did you wish to make any comments as we start?

MR. TURNER: Actually, if I could, I would like to make a couple of comments. I also would like to pose a couple of questions to representatives from Hologic, whoever chooses to respond.

First, I am glad that Dr. Melton has brought this discussion back to the major issue and that is, that the one quantity that we can measure in bone is some measure of bone strength, and in some ways, ultrasonic velocity and attenuation may be better measures of bone strength than Bone Mineral Density, certainly, from the physics, might suggest that. So, there are clear precedents for this technique to have efficacy. But there are issues in how the technique is applied, and that is what I would like to direct to the representative from Hologic.

The first issue is one of the different measures. As we recall, we heard three different measures, resulting from this single machine, one being the Speed of Sound, SOS, the Broad-band Ultrasonic Attenuation, BUA, and also the Quantitative Ultrasonic Index.

Now, of these three measures, only one is being presented as a clinical index to be used in screening patients from this device, that is the Quantitative Ultrasonic Index. Now, the other two measures, SOS, and BUA, have been shown with other devices in other trials to be associated and actually predictive of fracture.

My question to you is, why did you pick one measure as a primary indicator, and I believe that the description says that the other two measurements will be provided by the software, but will they be provided with appropriate T-scores, and will they be provided in a way that they could be used also for assessment?

DR. HALBERG: If you could just identify yourself, as well, for the record?

MR. VON STETTEN: Yes, I am Eric Von Stetten, Principal Scientist from Hologic. Yes, you are correct that we measure the SOS and the BUA and combine them into the QUI, which is then rescaled into BMD units. The unit reports by default the BMD -- the estimated BMD -- and its T-score, and also, if you just press the +/- key, you get the QUI and its T-score, and if you press it again, you get BUA, SOS, and you can compute those two scores, also. So, all of that information is available.

I think based on the data that we have shown and the correlations we have shown, you could probably agree that we could have equally well come up with either SOS or BUA or QUI, and said that the correlation to BMD is very high, and that the agreement is very good.

What has been done -- and Dr. Genant mentioned this -- is that people have recognized -- and in our data, it is the same case -- that the BUA and SOS are very highly correlated to one another. Since they are highly correlated to one another and to bone density, it is possible, at least conceptually, to add them together, to average out some of the individual errors in the different measurements.

Somebody mentioned temperature-dependence of the foot. If SOS goes in one direction and BUA goes in the other direction, if you add them together, then it cancels out. So there is good reason to add the two together; furthermore you do not want to report six parameters to a clinician, because one, as we have seen is complicated enough, and we do not want to make it even worse. But, for those who are familiar with BUA and SOS, such as yourself, who might want to use them, we do make them

available. So, we report the estimated BMD.

MR. TURNER: So, if a physician having read an article in the literature, wanted to make judgment based on these other parameters, those parameters would be available.

MR. VON STETTEN: Absolutely, and you can print out on the reports, and the reference data is provided, and so on.

DR. HALBERG: Do you have any other questions?

MR. TURNER: Not at the moment, no.

DR. HALBERG: Do any of the other panel members have questions before we start going through the questions that the FDA will be posing to us? If not, Mr. Monahan, do you --

MR. MONAHAN: Could I ask Dr. Phillips to assist me? If we had a portable microphone here, he would probably make me do it myself, but since he is my boss, I appreciate his help.

The intended use of the Sahara Ultrasound Device is in essence to estimate Bone Mineral Density, BMD, in g/cm² of the calcaneus. There is also a specific claim that Sahara BMD results are highly correlated to heel BMD results obtained by dual energy x-ray absorptiometry, the DXA technique, and we have added the emphasis on highly.

Correlation analysis of the data from the PMA shows an r-value equal to .845, between Sahara and DXA. Additional analysis of the paired data shows that the variability of individual T-scores has a 95% confidence interval of approximately +/- 2.

This means that some individuals would receive a treatment recommendation, based on the Sahara, which would be different from the recommendations based on DXA.

This is comparable to the variability, when the various existing methods of bone measurement, DXA, QCT, or RA, taken at different measurement sites -- for example, the hip, the spine, the radius -- are compared with one another. Despite the less than perfect inter-correlations, each method and each measurement site is found to give similar predictions of fracture risk.

Now, we are posing a series of six issues that we would like the panel to address. The first issue is, do you believe that the accuracy with which the Sahara estimates BMD, as measured by DXA, as reflected in the PMA data set, when viewed in the context of current clinical management, is adequate to support the claim, as written in the current labeling?

I will go through all six, and then we will come back, as the discussion begins. The second issue is, are there other ways to express the intended use of the device, which would improve its clarity, or more accurately, reflecting the data from the PMA?

Issue Three. Should a quantitative description of the accuracy with which the device predicts the results of DXA, be included in the Indications or Warning/Precaution sections of the labeling, as opposed to simply stating that the two are highly correlated?

Issue Four. DXA measurements of BMD have been shown to correlate

with direct measurements of bone content through comparisons with ashed bone samples, while ultrasound measurements by the Sahara have not. Should the labeling contain a reference to this issue?

Issue Five. Are there other issues with respect to the labeling, including the user's manual, which you would like to address?

The final issue for the panel's consideration, are there any issues not fully addressed in the PMA, which would require a post-marketing study?

I would indicate two things at this point, one, that other areas are certainly open for panel discussion, as the panel members see fit. Please feel free to raise any issue that you feel is appropriate.

The other thing is that Dr. Halberg has suggested that we might want to take these issues out of order, that I just presented them in, so we will defer to her in terms of the order of the issues. And I believe she wanted Number Five to go first.

DR. HALBERG: I thought it might be useful to throw open the discussion among panel members with basically the issue of, are there other things that we think should be included besides the more specific issues raised in the first three sets of questions? It may be helpful for all of us to have the set of questions that we have in our packets in front of us so we can view them all at the same time.

Let me -- having heard all of the questions that have been posed to us, are there other general issues which you would like to see raised, and then perhaps we can go back to the specific issues? Dr. Melton? Go ahead, Dr. Smathers.

MR. SMATHERS: In the manual, I would like to see more information on the standard, the quality control standard. I read through there, had to read it three times to finally find where they mentioned it. There is no indication to the user what precision of measurements they should expect when they use the QA standard. They are told to write them down for a month, but there is nothing that said what variation they should expect to see in the data.

There is a go/no go test that the computer makes, yet there is no indication of what the standard deviation on this go/no go analysis is, and I believe the user should have some better guidelines as to what to expect from the standard itself and the reproducibility that they can hope to achieve from the standard alone, without any patient variations thrown in.

DR. HALBERG: Would somebody from Hologic like to address that?

MR. VON STETTEN: Yes, in the chapter on the --

DR. HALBERG: Once again, for the transcriptionist, would you mind identifying --

MR. VON STETTEN: Eric Von Stetten, from Hologic.

DR. HALBERG: Thank you.

MR. VON STETTEN: Apologize. In the section on quality control, as you pointed out, it mentions that you perform a daily test, and that there is a go/no go as you say, decision. You get the values, and those values you are supposed to plot. The plots have limit lines on them that you manually -- I wish I had an overhead of it -- but, it

is a monthly plot, and you put on today's value, and then there is a top and bottom line, which are the same values that are used for the go/no go.

There is not a specific recommendation on the CV value that you expect to get, because one of the problems with quantitative ultrasound devices, is that any phantom has temperature-dependence in the quantitative results, so what we do is that we have done our best job to make sure that the QC phantom, which is in fact a block of an elastomer, we correct it within our algorithm for the current temperature of the machine, and we make the best correction we can, and you plot that everyday, and whether or not you get .1 or .2 or .3% CV, is not specifically relevant to the performance of the device, in that it has passed the test that it is not wildly different.

We actually are developing right now a little bit more data from some long term use of what guidelines we might recommend, and I think that we would be more than happy to recommend more specific guidelines.

DR. HALBERG: Dr. Melton.

DR. MELTON: It is not going to be possible, really, to have a device which is limited only to use in white women, so I would wonder what plans the company has for advising the users about the application of this technology in men and nonwhite women?

MR. VON STETTEN: Eric Von Stetten from Hologic. The device certainly does work in men, women, and all races. Right now, as I mentioned in my presentation, we have accumulated reference data on Caucasian female subjects because

they have a four to five times higher fracture incidence rate than males, and a two to three times higher fracture incidence rate than specifically African-American women. And you can use the device to get measurements.

Your point is well-taken that you do not have reference ranges to compare them to, which is why we designed the instrument such that it is trivial to add your own reference ranges, should they become available through published studies, or should you develop them in your own laboratory, or hospital setting.

DR. MELTON: I understand that, but I think you will have to say something in the labeling about what to do when people encounter that problem.

MR. VON STETTEN: We would be happy to listen to your suggestions on that topic.

DR. HALBERG: Dr. Destouet?

DR. DESTOUET: The manufacturer has addressed the issue of determining bone density at a single point in a woman's life. We know that if a woman is osteoporotic, intervention will then ensue with medication. There is nothing in the labeling that would indicate at what time interval a second or third reading should occur.

We have heard data presented that would indicate -- and even Dr. Genant has some data that would indicate that a second measurement should occur perhaps two or three years after the initial measurement. Does the manufacturer plan to address that issue in its labeling?

DR. GENANT: Harry Genant. That is a very important issue; that is, the

frequency within which bone mass measurements should be made, and it is also very much specific to the particular setting in which you are applying it, and also, perhaps, the medication that might be given, and so one has to keep in mind the relative precision of the instrument, the expected change that might occur, to be able to factor in the frequency during which measurements should be made.

I would say that if one looks to the densitometry, the commercially available densitometers, I believe that most do not specifically state what the timing should be, because this is an issue that is being addressed very widely within the scientific community, and I think the guidelines are being developed that will provide a basis that will include the known precision of the instrument, and expected changes, and that will vary depending upon the setting in which you are going to apply those. So, I am not certain that this really should be within the manual, or the guidelines, as they are published, as opposed to being compatible with or consistent with the broad guidelines that are being developed in the literature.

DR. HALBERG: If I can ask you to just stay there for one moment. Dr. Destouet, are you suggesting that they include in the labeling, a discussion of following patients under treatments?

DR. DESTOUET: Well, I think in the real world, that one does not take a single measurement, that these women are treated with estrogen, or they are treated with phosymes(?), or they are treated with something, and that a second measurement occurs. And -- well, not just a second. But in many cases, a yearly measurement occurs to see

how she is responding to that medication. Unless it is clear in the labeling that an annual measurement will not be precise, I could see how an internist, or a local medical doctor, may not understand that it may take longer for the Sahara to be precise.

DR. GENANT: So, I would certainly think that within the context, perhaps of guidelines, one could have a paragraph that would address the issue of how one relates and utilizes a machine, given a certain percentage of precision, or a range of precision, over what period of time would one appropriately measure to see a given magnitude of change. And that could be given in terms of broad principles, as opposed to the very specifics that would have to be tailored to each individual, and that perhaps could be helpful.

DR. HALBERG: I think that would be very helpful.

DR. DESTOUET: I think that is definitely -- I am surprised that it is not already required of other pieces of equipment out there.

DR. HALBERG: Are there other issues? I had two sort of broad issues that I also wanted to raise, before we deal with the more specific questions and, we have been touching on them, and the FDA questions actually touch on them as well, and it is really the broader issue of physician education.

Up until now, the majority of physicians performing Bone Mineral Density studies have really been physicians who have a handle on what the limitations are. A device like this is going to, perhaps, be disseminated to smaller practices in rural areas, and be in the hands of physicians who probably -- well, I won't say, probably -- who it is very

possible might not understand the limitations.

I am concerned that the labeling reflect the -- perhaps the T-score with the definition of what that means, but that some sense of limitations of the study be included as part of the labeling. That was really my first concern.

The second concern has to do with education of the patient on the physician involved in the care of women. Now on an almost -- well, at least a weekly basis and closer to a daily basis, I get people coming in, women coming in, asking to have bone densitometry studies, with absolutely no sense of what the limitations of those studies are, and I would like to raise the issue of patient education as part of the labeling as well. I do not know how other members of the panel would feel about these two issues.

DR. MELTON: Well, they are both certainly big problems, and I think the difficulty the company will have here is because the most efficient way to deal with these issues has not really been resolved, and it is a question for the whole field. If they could make a contribution to it, that would be really important, but it is a problem of the field in general, and relates to all the technologies where those same issues arise.

DR. HALBERG: Would you like to make a comment? Absolutely.

MR. VON STETTEN: There are a number of organizations such as the Society for Clinical Densitometry, the National Osteoporosis Foundation, the World Health Organization and so on, who are trying to promote education and distribute such literature and education to the field, especially as you mentioned, for the physicians who

are not yet comfortable with bone density and have not had experience with it in the past.

Hologic is very much interested in working with the FDA to figure out a way to distribute this information. In the past, we have not been able to because of regulatory concerns, because those documents make statements that we are not legally allowed to make.

We would be very interested in working with the agency and these groups to provide information, educational information and so on, and maybe because this is a PMA and there are other things that we can do here, this might be a perfect avenue to start that process moving, but we are very interested in that. Maybe Dr. Barren could just give us a couple of his insights on the clinical issues, and how that might be --

DR. HALBERG: We would welcome that.

DR. BARREN: Members of the panel, good afternoon. My name is Dr. Daniel Barren. I am a Professor of Orthopedics Medicine and Cell Biology at the University of Massachusetts. I am an endocrinologist. I mention that in the context of, I am the Director of the Osteoporosis Center at the University of Massachusetts, and perhaps unique amongst today's speakers in that I am the one who actually sees patients.

I was the Principal Investigator of the clinical study supporting the PMA. I am not financially involved in Hologic or any other manufacturer, and I am being compensated for my time and travel to be here.

I think you -- a very important issue has been raised, and that is regarding physician education, and I would just like to put it in the context that this is no better, nor

is it any worse than any other densitometer. If one accepts the DXA as either the gold or copper standard, whatever Dr. Sacks would prefer, and if I were to measure some 55 year old women, they might be osteoporotic at the spine, and others would be osteoporotic at the hip, and if I were to just take one site, I would miss some, and not make the diagnosis in others. So, everything is relative to the instrument you are looking at. This is no better or no worse.

I think a key point that was made earlier, and that an instrument such as this will have a tremendous impact, because based on the NHANES III data, 77% of the women who have osteoporosis or are at risk for osteoporosis, are currently undiagnosed. That translates into them being untreated.

I think one of the major advantages of an instrument like this is that it allows greater access to women. But, within the confines of the NOF, the ASBMR, the guidelines that are being developed by Dr. Melton and the Committee for the NOF, physician education is paramount. I do not believe that this manufacturer or any one manufacturer can do that form of physician education.

DR. HALBERG: I completely agree. I only raised that issue because I think this machine may be more widely disseminated. I do not worry about it in your hands, but as the technology gets more widely disseminated, I think it is of greater concern.

What we may wish to do is go back and address each of the issues that the FDA has raised, and perhaps, Bob, if you could put up the first issue again.

MR. MONAHAN: For those in the audience who have copies of the draft questions or issues that were distributed at the door, I would point out that we did a little bit of wordsmithing at the last moment, so the words do not agree exactly with what you have in your hand, but the intent is the same; we were simply trying to state the issues in a little bit clearer terms.

DR. HALBERG: Okay, perhaps I will reread this question and -- actually, what I might do is ask something different now, since you have been so kind as to put that up. What I might ask is that we put up the actual Indications for Use statement and I will perhaps read question one, and we all have that in front of us, and I think it might be helpful to be looking at the Indications --

MR. MONAHAN: Bob, I do not have the Indications statement. Perhaps Joseph has it.

DR. HALBERG: In the meantime, I will read Issue One. Do you believe that the accuracy with which the Sahara estimates Bone Mineral Density as measured by DXA as reflected in the PMA data set, when viewed in the context of current clinical management, is adequate to support the claims as written in the current labeling? And we will see the claims right now. Perhaps I will just read this into the record, also.

The intended use of the Sahara Clinical Bone Sonometer is to estimate Bone Mineral Density of the calcaneus. Sahara bone density results are highly correlated to heel Bone Mineral Density results obtained by the DXA technique. Heel Bone Mineral Density results may be used by the physician, along with other factors, such as laboratory

test results, radiographs and family history, in a diagnosis of osteoporosis and other conditions leading to reduced bone density.

Let me just throw this Question One open to the panel. Dr. Smathers?

MR. SMATHERS: I will play the devil's advocate. I am troubled by the word, highly. Statistics is not my strongest suit, but an r-value of .85, and highly correlated do not generally go together in my office.

DR. HALBERG: Dr. Turner?

MR. TURNER: I would just like to comment. The physics acoustics are such that there is no reason why acoustic velocity or acoustic attenuation should correlate with something like Bone Mineral Density. Ultrasound --

MR. MONAHAN: Could I ask you to speak up just a little bit?

MR. TURNER: Ultrasound, in effect, is not measuring Bone Mineral Density, it just happens to be a happenstance, a lucky coincidence that these two values are correlated, and I suppose it is a little troubling that the import of the machine is actually Bone Mineral Density, when in fact the machine does not measure that at all. Maybe the wording can be changed to reflect that it is only scaled to those numbers, just to aid in screening, and it should not be reflected as an actual measurement.

DR. MELTON: I guess I have two points. I think that is one of the keys here. Again, bio-mechanically, what we are interested in is the bone strength. It just so happens that bone density is highly correlated with bone strength, because as the structures disappear, so does the mineral. And so, the very notion of having to have a

high correlation with bone density may be superfluous, which takes me back to my question about the availability of actual in vitro data showing an actual strong correlation between ultrasound measurements and the strength of bone in a testing system.

The other issue is, how close is close? And so, when we say that the T-scores could be +/- 2 standard deviations, that just sounds enormous, and it suggests that the information that we are getting is irrelevant. But the fact is that the people are not evenly distributed across that range. Most of the people are in the middle, where there is actually a higher correlation, even though you would not know in the individual person. And the fact that only 14% of the people were differently classified by the two technologies I thought was remarkably small.

But again, when Dr. Stein presented this, he said that, you know, what we really have here is something that is substantially equivalent to existing machines, and that is the situation we are dealing with, because right now, we are building the practice guidelines for osteoporosis management, based on Bone Mineral Density of the hip, and we do not know quite what to do technically with the Bone Mineral Density of the radius, even measured with the radiologic device. And so, how these relate to patient care is just a very complex, troubling issue that we are not going to be able to resolve here today, because the field has not been able to decide how to deal with the disagreement between peripheral measurements and central measurements, for one.

I think that we are not really looking here for a number, .9, .95 or anything, because that is sort of an arbitrary, and I think, artificial straw man. What we are trying to

understand is whether the technology can usefully divide people into levels of risk.

Again, there are no straight lines here. We are talking about patient management. There is not a magical line at 2.5 standard deviations. So if a woman was 2.4 or 2.6, she is not really different. And so that is why some of the new recommendations suggest that we have to take these other risk factors into account, in addition to the bone density measurement, which helps minimize this problem slightly. That is not really an answer.

DR. HALBERG: I will get back to you for one. Dr. Hackney?

DR. HACKNEY: In terms of the wording, I think we have seen data only about predicting the results of a DXA determination of Bone Mineral Density, so how about changing the wording to say that the intended use of the clinical bone sonometer is to predict the results of DXA estimates of Bone Mineral Density, because that is what was done to provide the data that we are looking at?

Instead of saying that the results are highly correlated to heel BMD, say that they are correlated to heel BMD results obtained with DXA technique, as discussed below, and give in that below section, a more meaningful and complete description of the relationship between these measurements, Bone Mineral Density and fracture risk, as we have heard here, but make that part of the indication.

And finally, this is a comment. I am not sure it belongs in the indication, is that we have been hearing about the correlation or P-values among all the women, but obviously the interesting point is how closely these are related among the women at risk.

So, if you throw out the young women that are used in part to get the correlation and you look at women who are older, in whom you are concerned about the risk of osteoporosis, do you get equally high, or do you get lower predicted value?

DR. HALBERG: Actually, who would like to address that, I think the FDA -- Dr. Sacks?

DR. SACKS: I think, what I tried to point out this morning was, that the degree of correlation is in part determined by the range of values, and I think that is a very, very good question, because with the range narrowed from, say, not 25 years old to 85, say, but from 55 to 85, you would find that the correlation would go down, much as Mr. Kotz did each subgroup of the six subgroups, and found that they ranged a little bit, but the lowest one was actually something like .7. So you get a sense of that, that it is going to be less than .85, but we have not -- we did not separate out that set and find out exactly what it is. It will be obviously somewhere between .85 and .7, and for the whole spread, it would probably be closer to .85, but less than.

MR. VON STETTEN: I just wanted to add -- Eric Von Stetten from Hologic -- I just wanted to add, the second part of your question I think was, what is the scatter? The correlation coefficient is one thing, and Dr. Sacks did present, and I think -- correct me if I am wrong -- but Dr. Kotz showed, which was what we showed, that there is no difference in the scatter, as you go up and down the age; that is, if you take just the women that are younger, you get a lower correlation coefficient, but that scatter is still the same.

In terms of, quote, disagreements, there is still the same amount of that. It is not as if, if you just look at elderly women, suddenly you get much more scatter between, it is the same no matter what age ranges you are using, in spite of the fact that the r does change, as you pointed out.

One other quick question, in terms of the -- Question C is going to come back to this, about highly correlated, and whether it should go into the warnings and precaution. And we do agree that within the section of the labeling that talks about the clinical studies, we would be very happy to provide lots more detail, as Dr. Hackney has suggested, on the specifics of this relationship, how it was determined, and what exactly it was. So we would be comfortable with that within the clinical studies sections. We are not quite sure it is a warning or a precaution, but just --

DR. HALBERG: Now, we had a suggestion from Dr. Hackney that we change, or consider changing, in the second line, estimate Bone Mineral Density to, predict results of Bone Mineral Density. Dr. Turner, does that address the issue that you were bringing up?

MR. TURNER: I think changes in the wording in that way, yes, I think that does begin to address -- so, I think the main issues put this in appropriate context, that the measurement here is actually an ultrasonic measurement, and any risk prediction or clinical decisions are made on an ultrasonic parameter, namely, this QUI, not on Bone Mineral Density. That just is created by a scaling factor. And I believe those suggestions go a long way in addressing that issue.

DR. HALBERG: The other suggestion we had was to delete the word, highly, and then at the end of that sentence, to basically add, as discussed below, which gets to what Dr. Von Stetten was saying in terms of adding more data, with respect to clarification, and not make a value judgment about, essentially, that is a non-quantitative term, so delete the word, highly. How do people in the panel feel about that?

DR. MELTON: I think that helps finesse the issue, actually, I wonder a little bit about the selection of the wording, I presume by the company. And the fundamental problem here is, we focus, as people always do, on the limitations of any particular technology, but the real issue here is kind of a social justice issue and that is, we have poor people, and we have people in rural areas who do not have any access to this technology, and treatment decisions are being made for them, or not, on the basis of information that is much worse than this.

If this device is available to people in the field, who with any sense that it assesses bone strength, for example, like BMD does, then I think people would use it because of the advantages that have been laid out here without anybody having to get out on the end of a limb, as to what exactly is being predicted.

I do not think the users actually care much about that. And so, I would guess that that is not something that the company would care much about, that would not matter much in practice, we would all be better off not making claims that we had difficulty supporting.

DR. HALBERG: Okay, can I see a show of hands of panel members, in

support of the two changes that were mentioned?

DR. MELTON: Do you want to read them?

DR. HALBERG: I will read it.

The intended use of the Sahara Clinical Bone Sonometer is to predict results of Bone Mineral Density on the calcaneus. Sahara Bone Mineral Density results are correlated to heel Bone Mineral Density results obtained by the dual energy x-ray absorptiometry technique, as discussed below. And the rest would stay the same.

Okay. So, it would just predict results of DXA Bone Mineral Density. Can you write on that overhead, Bob? Okay. Is that good enough for everyone, what I just read? Is there anyone who disagrees with those changes? Are there any comments? If not, let's move on to the second question.

Are there other ways to express the intended use of the device which would improve its clarity or more accurately reflect the data from the PMA? To some extent, we have addressed this already in Question One. Are there any other issues? Perhaps the comment that Dr. Destouet made with respect to follow-up limitations might be included under this question. And then wording could be worked out with the FDA. Any other comments on Question Two? Dr. Melton?

DR. MELTON: I think this does raise the issue that I mentioned awhile ago, as Professor Genant pointed out, the availability ultimately of prospective data showing that the device does in fact assess fracture risk is something that should be anticipated by the manufacturers, because that will become increasingly important in the

future. And perhaps if I could, maybe they could suggest whether or not they have any plans to collect such data now.

DR. HALBERG: Would you kindly address that issue?

MR. VON STETTEN: Yes, Dr. Melton, in fact, we have already --

DR. HALBERG: Dr. Von Stetten.

MR. VON STETTEN: I am sorry, Dr. Von Stetten, I have to remember that before this is over. We have already been having some discussions with the FDA on whether or not it will be possible to use the existing fracture risk data on the Walker Sonics device, which is the precursor to the Hologic Sahara Device.

The Walker Sonics, as you know, is a water-based device, the basis of which we have designed Sahara to follow, without the water, basically, to make it more convenient. So, there is a belief that the study of osteoporotic fractures which followed almost 10,000 women over about seven years, which has been one of the larger studies that Dr. Genant talked about this morning for fracture risk, is out there and we have already started discussions on how to use that data and how it can be used potentially for a fracture risk claim for this device at a later date.

DR. MELTON: And I know for reimbursement, that is going to be very important, even if it is not a crucial issue here. And if you have prospective data on a similar device, I think some prospective data, even on this device, even for a shorter period of time, just to show it is comparable, even if it is not data of the same volume, would be really, really important and in your best interests here.

DR. HALBERG: Let me just ask Dr. Phillips to put up Question Six as well, because I believe that is partially what you are addressing. Question Six is, are there any issues not fully addressed in the PMA which would require a post-marketing study? Do we want to require at least a small post-marketing study?

DR. HACKNEY: What good would a small post-marketing study do? I could see if it is a post-marketing study that is going to try to determine fracture risk. From what we have been hearing, it is clear that would be a very large study. If we were to require it, I would assume we would require something that would give you a meaningful result. The question is, does that need to be required in order to approve this indication?

DR. HALBERG: Can we have some discussion about that?

DR. MELTON: Well, you know, despite all the confusing concepts we have heard today, the remarkable thing is the epidemiology studies all give just the same result, almost. And so, the issue is not proving that ultrasound can predict fractures, because other good studies have shown that. The issue here is only, demonstrating that this device is comparable -- produces comparable results to the other devices, and it does not require a 9,000-person study to do that. All you have to do is show comparability.

DR. HALBERG: Go ahead, please.

MR. STEIN: Jay Stein, Hologic. In that regard, as Eric mentioned, we have the intention of trying to use the study of osteoporotic fractures that used a very similar device, a Walker Sonics Device, to indeed acquire fracture risk information, and in

the course of doing that, we intend to look at the correlation between our device and the Walker Sonics Device, on a small set of patients, which we expect to be very high. And so, a post-marketing study might not be required in order to achieve the goal that the panel is discussing, which is in order to bring in fracture risk data. In fact, I am optimistic that it will not be required in order to make fracture risk data available in the very near future, but just a little bit of homework on our part.

DR. HALBERG: Thank you. So, basically, we would like -- we would perhaps like to consider asking the manufacturer to do the homework with respect to the correlation between the Walker Sonics unit and the current unit under consideration?

Okay, while we have Question Six up, are there any other issues which are not addressed in the PMA which would require a post-marketing study? If not, let's go back to -- I am not sure we actually finished Question Two, could you put that back up and just make sure that we are all comfortable that that question has been fully addressed?

If the FDA reviewers have issues contained within these questions that we are not looking at, please feel free to request time at the microphone and --

MR. MONAHAN: The only thing I can say, Bob, is they were in order when I gave them to you.

DR. HALBERG: Moving right along, I will not reread this, but just to make sure that we have -- that everyone on the panel has had a chance to look at this and feel that this question has been adequately addressed. Does anybody have anything else to add? If not, Question Three, please?

We have already discussed this in part. Should a quantitative description of the accuracy with which the device predicts the result of DXA be included in the Indications or Warnings/Precautions section of the labeling, as opposed to simply stating that the two are highly correlated?

I believe we have certainly dealt with the highly correlated language. The question is, what should we request in the Indications, Warnings, or Precautions section? Dr. Melton?

DR. MELTON: I feel quite strongly that some indication of the possibility of misclassification should be provided. I think that is in everybody's interest, the manufacturer and the practitioners, because of malpractice risk. So, it is inevitable in this system, or with any other two sets of devices, that there will be people here who were said to be not at high risk, that ultimately turn out to have fractures, when they are measured on some other device. They are shown to have osteoporosis on that device, and now everyone has a problem. And so, I do not see any reason not to provide an indication that, because of the way things are, that there is a possibility of mislabeling.

DR. HALBERG: Thank you. Dr. Barren?

DR. BARREN: Dr. Daniel Barren, University of Massachusetts. Joe, maybe it would be wise to consider, rather than the use of the word, misclassification, use words such as, inconsistency of classification, or differences in classification, because the word, misclassification, implies that one is right and the other is wrong, and we really do not have a gold standard. So, perhaps, differences.

DR. MELTON: I did not mean to be pejorative, but to indicate to the clinicians the possibility of getting different answers.

DR. HALBERG: Good. Dr. Von Stetten?

DR. VON STETTEN: Yes, Eric Von Stetten. I just wanted to add, I had mentioned before that we would be very comfortable putting that in the description of the studies and maybe some of the educational material to give a background, but I do not think that that would be appropriate, perhaps, to characterize as a Warning or a Precaution. It is information about the technique and the technology, and I think we should describe it perhaps -- or, I would suggest we might describe it in the description of the background literature and/or the device characteristics and so on.

DR. HALBERG: May I suggest that you work with the FDA on where that may best be placed?

DR. VON STETTEN: Absolutely.

MR. MONAHAN: Yes, it may be that that would be included in the clinical data section, might be an appropriate place for it.

DR. HALBERG: If there are no other comments, let's move on to Question Four. DXA measurements of Bone Mineral Density have been shown to correlate with direct measurements of bone content through comparison with ashed bone samples, while ultrasound measurements by the Sahara have not. Should the labeling contain a reference to this issue? Dr. Turner, perhaps?

MR. TURNER: I am not sure where to put it, but that I think has been my

feeling all along, is that this is not a measure of the actual bone mineral that exists there, it is a secondary measure that merely correlates with Bone Mineral Density. I am not certain where that would go, though, in the Indications.

DR. HALBERG: Dr. Melton?

DR. MELTON: Again, I understand that we can only deal with the information that we have been provided, but I would be interested in the plans of the company if they have any to provide this information that does not seem like an impossibility to get, and it is a potential marketing advantage, if nothing else, whereas if we leave it here, it is just a hole in the argument that seems to suggest a weakness, when in fact, Dr. Turner and I both agree that it is likely that it will be better. It seems, it just seems like we created a problem here where there should not be one.

MR. TURNER: I do not believe there is any reason why this technology should correlate with ashed bone samples, and it could be effective without having great correlations with ashed bone samples, as long as it is indicated, I think that would be perfectly fair, yes.

DR. HALBERG: Dr. Von Stetten?

DR. VON STETTEN: Yes, Eric Von Stetten. I think, along the lines of what Dr. Turner just said, we have just changed the Indication to saying, predicted bone density, so in fact, it is not even estimating anymore, much less measuring, so doesn't that cover this issue? I am not sure.

DR. HALBERG: Would you like to comment, Dr. Melton? Maybe you

should comment on that.

DR. MELTON: Well, again, I realize I am being maybe a little off the argument here, but my question was whether or not the company had any plans to address this issue, which will come up in other contexts. For example, the correlation of ultrasound measurements in bone strength in vitro, if not bone density. Is this a question that can be answered some time in the near future, as opposed to just leaving it as an uncertain element that sort of casts a pall over this, in my view?

DR. YIN: Dr. Yin, Lillian Yin. I am suggesting that a lot of the issues we are discussing now would be best served in the physician's education, since this is the first of a kind, of ultrasonic devices, it would be wise to do that instead of trying to stick it in the indication, wherever. A good, solid physician education. Is that okay with all of you?

DR. VON STETTEN: Eric Von Stetten again. I think we would be very comfortable with that, and to enter, however, Dr. Melton's question, there is lots of solid ultrasound in vitro data on a variety of machines, that it does in fact predict bone strength very nicely. Dr. Barren, who has done some of that work, could give you some, and review some of that right now if you would like, it is really up to you. But I think putting it in a physician's education information would be very effective.

DR. HALBERG: Great. We will request that that be done and thank you. I would like to just very briefly put up the last two questions again, since they are more general, and allow the panel to give any further input. Once again, are there other issues with respect to the labeling, including the user's manual, which you would like to see

addressed?

DR. MELTON: We were talking fracture risk again, which is what the clinician really wants. I do not think they are interested in any of the physics here, mostly, and so I understand that in the PMA, at least prospective data indicating prediction of fracture risk is not available, so I am not sure what you do here.

It is an issue that will arise, because that is the context in which clinicians are thinking about it, so I do not know what the proper thing to do here is in labeling. We were sort of making a logical leap between what the actual indication is and what the clinician is really thinking. Perhaps some of the staff could suggest how that problem is best managed.

DR. HALBERG: Dr. Yin?

DR. YIN: I would suggest that since they are doing a little bit of homework, and that homework probably will provide what we are looking for -- isn't that correct, Dr. Von Stetten?

DR. VON STETTEN: Eric Von Stetten. I was just going to suggest that the new ROC analysis might answer all of those concerns. It would give us a baseline for believing that there is some fracture discrimination capability, and that might even be without too much homework, something we could build right into the manual where it describes clinical studies. Maybe that would help.

DR. YIN: Additional little homework won't hurt.

DR. VON STETTEN: I absolutely agree.

DR. YIN: There would be some extra numbers.

DR. VON STETTEN: That would be fine, we would be happy to review.

MR. TURNER: Could you stay up there for a minute, since you brought it up, can I ask you a couple of questions about that ROC study?

DR. VON STETTEN: Certainly.

MR. TURNER: I noticed that you had 25 fracture cases --

DR. VON STETTEN: That is correct.

MR. TURNER: What type of fractures were those?

DR. VON STETTEN: If you give me one second, I can tell you exactly.

These were a variety of atraumatic fractures. The way we recruited subjects was that they had experience in atraumatic fracture, and they -- in one of the amendments into the PMA, I tabulated what they were. Basically, there were a few hip fractures, there were some rib fractures, forearm, a couple of forearms. So it was basically a clinical spectrum of results. If you would like, I can try and find it. Does that answer your question?

MR. TURNER: That is not necessary, you answered my question.

DR. HALBERG: Getting back to the question that I had asked earlier about patient education, would it be possible to -- while that is sort of an industry-wide responsibility as opposed to a Hologic responsibility, would it be appropriate to perhaps suggest as part of the labeling that the patient be referred to the National Osteoporosis Foundation literature, or that there be some suggestion that patient education materials,

maybe not perhaps specifically from you, be provided?

DR. VON STETTEN: We will be more than happy to do that.

DR. MELTON: Actually, just for information, there is a National Clearinghouse, which is probably where they should be directed, and that is managed under contract to the NIH, by the National Osteoporosis Foundation, but it is not a proprietary thing, it is a national resource.

DR. HALBERG: Dr. Yin?

DR. YIN: Again, I would like to suggest that, since this is the first of its kind, we would like to see some patient literature on the ultrasound, and correlated to DXA, or x-ray.

DR. VON STETTEN: Certainly. We will work with the agency to finalize that.

DR. YIN: Thank you.

DR. HALBERG: And lastly, Question Six again?

DR. DESTOUET: Madame Chairman, I have a question about Number Five. It looks like an easy instrument to use and I would like to ask the manufacturer, is there a training period, is there a learning curve associated with the use of this equipment?

DR. VON STETTEN: The instrument is remarkably easier to use than most x-ray machines, because the positioning is very simple because of the foot-positioning aid. Eric Von Stetten, again. I will get it one time.

And as I pointed out in my presentation, the push-button nature of the

operation is very simple, and there really is not a whole lot of room for error.

Nonetheless, as we have done in our DXA business, we feel it is very important to educate the technician on how to do this, and we do not think you should just willy-nilly give it to the secretary and have them do an exam, that is wrong.

So, what we have done, is we have described in an operator's manual in a good level of detail, how to do that. We are also working on one of the things that we would like to -- maybe as part of the final labeling for the device, we have been working on a video that might describe how to do this that somebody could watch and it would not be reading and drudgery work. So, I hope that might answer your question.

DR. HALBERG: Dr. Yin?

DR. YIN: I have a question for Dr. Turner. You did mention QA standards and the standard deviation reproducibility. Would you like to see some of that in the user's manual, when they talk about how to use it?

MR. TURNER: I am not sure it was me who --

DR. HALBERG: Dr. Smathers.

DR. YIN: I am sorry, Dr. Smathers.

MR. SMATHERS: Sorry, I am guilty, and yes, I would. I think they should indeed indicate what they can expect to see from that standard, realizing that there will be additional variations if they tried repeated measurements on a patient then.

DR. YIN: Thank you.

DR. HALBERG: Dr. Griem?

DR. GRIEM: Yes, I would like to continue some of the discussion of the phantom. Actually, as you read the instruction manual, one places the gel on the sensors, then places the phantom in the machine, and as such, you are really measuring, not only a standard, if you can call the phantom a standard, but also the gel, the age of the gel and so forth, and it would be interesting to know whether there was any drift in the gel, any drift in the equipment over a long term period, and I think that that would also be something that might be considered under Item Six.

DR. HALBERG: Dr. Von Stetten.

DR. VON STETTEN: Eric Von Stetten. As you correctly point out, if there were issues with aging of the gel and so on and machine instability, that is exactly why you would be doing QC, and you would be doing it with gel to replicate a patient measurement, and so that is precisely why you want to do QC, and I agree with Dr. Smathers that as we develop more and more insight into what is the long term stability, we should put these things in, and we will do it in conjunction with the final labeling.

We do not -- we certainly do not know of any long term issues with gel stability and so on. You use the gel, it comes in relatively small tubes that do 10 or 20 patients, so it is not like the gel sits on your shelf for six months or a year. If you do a typical number of patients, even say, five or so a week, it is gone in two weeks. Again, I think it falls nicely in line with Dr. Smathers' comments, we will provide that kind of information and guidance.

DR. HALBERG: Thank you. Any other comments on Question Five?

Question Six? Any reason for a post-marketing study? If not, let me ask if industry or consumers have any other comments they would like to make to the panel? Or the consumer rep? Okay. How about the FDA reviewers, any questions that you would like us to address?

If there are no further items that the panel wishes to -- I am sorry.

DR. SACKS: My other half thinks it has not been covered. Alright. I think that the sharpest focus has to be on one aspect of the discussion that was the question of demonstrating its clinical utility as a predictor of fracture risk, and the approach in the PMA to just correlate it with DXA results, while the panel has suggested a couple of changes in the Indications for Use, I think that the panel needs to decide, is that adequate, or should there be a condition that the fracture risk data, or a correlation of the Sahara with the Walker Sonics, be provided as a condition for approval? I think that may focus the question a bit.

DR. HALBERG: Thank you. If there are no further items that the panel wishes to discuss, we will move to the panel's recommendations concerning the approval of PMA P970017, together with the reasons for the recommendation, as required by Section 515-C-2 of the Act.

The underlying data supporting a recommendation consists of information and data set forth in the application itself, the written summaries prepared by FDA staff, the presentations made to the panel, and the discussion held during the panel meeting, which are set forth in the transcript.

The recommendation of the panel will be approval, approval with conditions that are to be met by the applicant, or denial of approval. May I please have a motion?

DR. MELTON: I am wrestling with the last issue that was raised. I move approval, conditional on a demonstration of fracture prediction -- not the right language here -- of the sort that Dr. Sacks talked about, for example, demonstration of correlation of this device with the previous ultrasound machine. I am sure that is not elegant, but I think the committee does need to be reassured, and so does the population, that we have something in hand that is likely to actually predict fracture risk.

DR. HALBERG: Dr. Yin?

DR. YIN: I think perhaps the company is willing to do the ROC curve, and that is what is meant in graphing the fracture risk, so I think we are in good shape if they get that curve done, right?

DR. HALBERG: So, we have moved approval with the condition that the ROC data be provided. Do we wish to also include the condition that the labeling be changed? Dr. Phillips has kindly summarized the issues that we raised as a panel during our discussion this afternoon, and we touched on the fracture risk issue, we have touched -- this is the labeling issue, we would like to include -- that we would like to see the labeling changed, similar to what is projected for us here.

DR. YIN: If you would allow us, just once we get those later, this may have to change one time.

DR. HALBERG: Sure. Of course.

DR. YIN: If it is okay with you, unless you want to set up one or two committee members that we bounce it with. We would be more than glad to do that, because I think our suspense is not fair to the company, anyway, if they have fracture risk coming in. I mean, if it is okay that you give us one or two members that we can share our new Indication for Use with, and you are happy with them, we will go with that. Is that okay, anyone?

DR. HALBERG: Let me propose to the panel that we provide a subcommittee of the panel to review the revised Indications for Use, with the FDA and the company. Does anyone second that motion?

PARTICIPANT: Seconded.

DR. HALBERG: All in favor, a show of hands. Anyone opposed?

[On motion made and duly seconded, by hand vote, the motion carried.]

DR. HALBERG: The motion was unanimous. Shall we get into deciding who the subcommittee is at a later time or right now?

DR. YIN: We can anytime you want.

DR. HALBERG: Let's do that right now. Do we -- Dr. West?

DR. WEST: David West, Regulatory Consultant for Hologic. I think from my sitting in the audience, I am a little bit confused as to what exactly the motion was, and whether it is a conditional approval, or it is an approval with a commitment to work with the agency on resolution of final labeling.

I think, for the purpose of the manufacturer, they need to know whether this is an approval, or a conditional approval, and as long as I am at the podium, I might make a statement concerning the labeling requirements that might be posed on this device, relative to all other devices that are presently in clinical use.

If we look at the issue of fracture risk, one must consider all the discussion of today, and that one parameter of a patient is not a unique predictor of fracture, and just like other manufacturers of diagnostic products, they are not obligated to show the correlation of their particular device to the ultimate clinical outcome.

No cholesterol test manufacturer has to produce data that correlates the test results of their device, to myocardial infarction. And I think similarly, you cannot expect any manufacturer to do something that the clinical community as a whole must do, in developing a comprehensive model of the clinical outcomes. Thank you.

DR. HALBERG: Thank you. Dr. Sacks?

DR. SACKS: Cholesterol-measuring devices measure cholesterol, no matter what kind of devices they may be. Here, as Dr. Turner has pointed out, what is being measured is not bone density, but some other features of bone that respond -- that ultrasound responds to, and that happens to also worsen as a woman gets older. So, there is a difference between that and a cholesterol measurer.

DR. HALBERG: Thank you. Dr. Yin, first.

DR. YIN: Just to be fair to the company, they did say that they could easily correlate SOS and BUA and QUI, so therefore, I do not think we are doing justice

to the company. I think, Dr. West, what you suggest sounds reasonable, but what the company is willing to do sounds very reasonable, to us, too.

DR. MELTON: I think his concern related to the way I posed the motion, and you will have to forgive me. This is my first time here and so I am not quite positive the proper terminology to use. But I think as I understand the way the discussion has evolved here, that the actual motion is for approval?

DR. HALBERG: Approval with conditions --

DR. MELTON: Of the revised --

DR. HALBERG: Approval with conditions was what we had discussed, for clarification.

DR. YIN: No, condition with approval about this --

MR. MONAHAN: Could I, for the sake of the panel members and the audience, go over some of the possible conditions that have been mentioned this afternoon for inclusion in the conditional approval? Just so that everyone is clear on what is being done.

It was mentioned that the user's manual should contain something addressing the QA standards. Labeling should also include how one addresses the values for men and nonwhite females. There was another condition about inserting a paragraph on precision for follow-up of patients who are undergoing treatment.

Patient and physician education should be addressed, either directly or indirectly in the labeling. And Dr. Hackney proposed a new indication for use which we

have up on the board. Labeling should also include data showing that differences in classifications are possible with this device. And finally, there was a discussion about the demonstration of correlation of the Sahara results with the Walker Sonics. And someone else may have a slightly different recollection than I do. I was trying to jot down thoughts as they were being discussed, but those were the conditions that I recall. Obviously, the panel can accept or reject any of those.

DR. HALBERG: Thank you. Dr. Sternick?

MR. STERNICK: Yes, I think the company asked if there was a difference between approval with conditions and conditional approval. Is there a distinction between those two terminologies?

MR. MONAHAN: No, there are three possible options, which I went over and I will be happy to go over again, if you would like.

DR. YIN: Please, do, Jack, please, do.

MR. MONAHAN: Bob, could I ask you to put up those slides? The first option for the panel is approval, period. So there are no conditions associated with that approval. The Indications for Use statement, the labeling and everything else would be exactly as it is now, as it was submitted in the PMA.

The second option is approval with conditions. Approval with conditions means that the panel can specify those conditions which they think the company needs to make prior to marketing of their device. They can include items such as I mentioned. They could include a post-marketing study, if the panel thought that that was appropriate.

The final option for the panel is disapproval. And if the panel makes the recommendation of not approvable, or disapproval, you have to indicate why you voted in that way, and be ready to specify to the sponsor what they need to do in order to make the application approvable. There are the three options.

As I understand what has just transpired, we are really talking about approval with conditions at this point in time. If anyone needs further clarification, I will try and clarify that further.

DR. HALBERG: Dr. Von Stetten?

DR. VON STETTEN: Eric Von Stetten again. There are two things I think we do not understand, one is that there was this subpanel issue. Does that mean that the documentation that we provide for the final labeling -- I think all the issues have to do with final labeling, is that correct? There are no studies that are going to be done, just the data will be presented?

DR. HALBERG: But were you going to expand your ROC?

DR. VON STETTEN: The ROC was already submitted to the agency. What I presented today has been submitted and an amendment will be -- we will put it into the labeling, but there is no work to be done there other than to include it in the labeling.

DR. SACKS: The ROC analysis that has been submitted to the agency so far, involved the 123 and the 25 women, yes. Your P-value there was .062, and we also found that our -- by any criterion that most people use, which is it has to be less than .05, you do not have enough data to make that clinically -- I mean, statistically significant.

MR. KOTZ: We are not saying it is superior, we are saying it is equivalent to. [Inaudible -- speaker away from microphone.]

DR. YIN: One minute. Richard, if you do want to speak, please come up.

DR. SACKS: This is Richard Kotz whose name I took, not in vain, several times this morning.

MR. KOTZ: The data that has been presented for the ROC curves insofar as up here was a relatively small study. I do not think that would be nearly adequate to demonstrate equivalence. Equivalence usually implies some kind of power to the study, an ability to have some assurance that it truly is equivalent, and with the sample size that the sponsor has submitted, that it is really not going to be adequate.

When we talk about a P-value, that is a one-sided P-value, if you want to - - if we are looking at the issue of, whether they are equivalent or not, the P-value between the two devices, whether they are equal or not, is really around .13 or .12 or .13. But anyway, it is not -- it is really not enough data. I think the ROC involved with the Walker Sonics is going to provide that. I know that there are other studies done between other ultrasound devices, which have thousands of patients. And I think that would easily be very strong support for the device. And then, correlation could be shown -- I hate to use the word, correlation, but that would be --

DR. YIN: Thank you, Richard. I apologize. At this moment, you know, we really -- what we really want is to hear from the panel, and if you believe that, and you still need to make your own conclusion, that is FDA's view, but this is the time we want to

listen to the panel. And if you believe that confidence interval is okay, that is fine, too, but we need a view from the panel, not -- the FDA just merely gives you the explanation and helps you, but you have the final decision.

DR. HALBERG: Dr. Melton?

DR. MELTON: My understanding was that the company was comfortable that they could in fact provide all of this data, which would help remove any questions without the need for new studies, but maybe some new analyses that could be done in a fairly short period of time, and so that maybe there is no real conflict here between us.

DR. YIN: Thank you.

DR. HALBERG: Dr. Stein?

MR. SMATHERS: I might say, that was my understanding, as well.

MR. STEIN: Dr. Melton, as I understand the last time you made that suggestion, you suggested that if we included the correlation between the Walker Sonics unit and the Sahara unit, which would then make it possible to reference the SOS data, that would satisfy the requirement you just suggested. Is that correct?

DR. MELTON: That would reassure me.

MR. STEIN: And I believe we had, before this round of misunderstandings arose, we had agreed to do that, so we could interpret that as fulfillment of our last condition, and that is acceptable.

DR. HALBERG: That is my understanding, but before you sit down, let me just make sure all of the panel members are in agreement with that. Thank you.

MR. MONAHAN: For the record, I would indicate that the panel members nodded their heads, that they were in agreement.

[Panel acknowledged agreement with head nods.]

DR. HALBERG: Thank you.

DR. YIN: Bob, you need to go to the microphone, Bob?

DR. PHILLIPS: Just for the record, has the panel just recommended that they feel that the fracture risk study presented by the company is adequate, the 125-patient study?

DR. HALBERG: No, we have not.

DR. MELTON: No, that that study alone is not adequate, but because that was not the indication, that what we are really looking for here is, background information and support to make a more credible argument that this is clinically useful.

DR. HALBERG: In summary, if I might, the panel has -- or, there is a motion before the panel for approval of this PMA, with conditions that were read by Mr. Monahan and discussed. I am not going to reread all of those, unless requested to do so.

Can we see a show of hands for approval of that motion? The vote is unanimous. Any comments?

[The panel indicated by a show of hands that the vote is unanimous.]

MR. TURNER: Could I get one final clarification? Now, the condition we are voting on with respect to fracture prediction, has to do with the cross-correlation between this machine and Walker Sonics, is that correct?

DR. HALBERG: That is correct. I would now like to poll the voting members for the reasons for their decision. Actually, Dr. Turner, maybe I will start with you on this walk-around, go-around the table.

MR. TURNER: I tend to agree with Dr. Melton, that the end point of this type of device to the clinician is fracture, whether or not it can segregate patients on whether or not they might fracture, and the ROC analysis presented, while reassuring, was not completely convincing, and I think the further analysis that was proposed will be adequate.

The Indications concerning changing the labeling, I believe are adequate to show that this product does not actually measure Bone Mineral Density, but simply produces a correlation which can be used correctly.

DR. HALBERG: Thank you. Dr. Destouet?

DR. DESTOUET: This equipment appears to be a safe, portable device that should make accessible to many women the use of bone density measurement, and determine whether or not they need to have treatment and prevent fractures. And I think the manufacturer has shown us that with the data that they will provide, that there will be some measurement available to physicians outside and they can make such judgments.

DR. HALBERG: Thank you. Dr. Smathers?

MR. SMATHERS: Yes, it was stated by others, it is no better but no worse, and it is cheaper, more portable, and should expand the use of the technique and so I am fine.

DR. HALBERG: Thank you. Dr. Griem?

DR. GRIEM: Well, I think it appears to be a safe, effective device, without radiation exposure, that will be useful for many women in the post-menopausal years, and that, without risk, may provide additional data in the management of patients clinically.

DR. HALBERG: Thank you. Dr. Hackney?

DR. HACKNEY: I would agree it is a safe device that provides information, similar to that which is obtained with more complicated and expensive techniques, so its availability should be useful.

DR. MELTON: I think there will be continued questions about the interpretation of these data, just as there are with all other densitometers, that we probably will take years to resolve, to provide detailed guidelines for clinicians for using this technology. But the increased availability of this technology for disadvantaged people and people in rural areas to allow them to have access to the potential for treating and preventing osteoporosis, I think, makes it clear that a device like this is essential to have in the community.

DR. HALBERG: Thank you. Lastly, I would like to suggest that we do form a subcommittee just to briefly review what the labeling will be. If I may take the liberty of suggesting to the panel members to that subcommittee, Drs. Turner and Melton, is that something you both --

MR. TURNER: Yes.

DR. HALBERG: Any other panel members interested? If not, I will be on it, as well. Mr. Monahan?

MR. MONAHAN: Just for the record, I would like to go over the conditions of approval again, so that both the sponsor and the panel are very clear as to what those conditions are.

The user's manual should contain a section on the QA standard. The labeling should include how the physician is to address the values obtained for both men and nonwhite females. The labeling should also have a paragraph on the precision of the device for follow-up of patients under treatment. Patient and physician education should be addressed in the labeling, as appropriate, and this could simply recommend that the patient seek advice, or written material from another organization.

The Indication for Use is to be revised, and that will be reviewed by the subcommittee of the panel. The labeling should include data showing that differences in classification of patients are possible, given the limitations of the technology in general, ultrasound as well as the other available technologies. And the sponsor will provide a correlation of the Sahara results with other devices, such as the Walker Sonics, to give an indication of the predictive value for fracture risk. And with that, I will turn it back over to Dr. Halberg for her concluding remarks.

DR. HALBERG: I just want to say, thank you, to the members of the panel for their hard work in reviewing the material submitted by the sponsor, and for the

recommendation of the FDA concerning the Sahara Sonometer, and if there is no further business, I would like to adjourn this meeting of the Radiologic Devices Panel. Thank you all very much. Oh, Dr. Yin?

DR. YIN: All I want to do is I want to thank Dr. Halberg, for this is a very complicated issue, and this is the first of a kind, and I do want to thank the whole panel, and especially Dr. Melton and Dr. Turner for a special consultant to this panel. And I do thank the sponsor for doing a very good job presenting their data. Thank you very much, especially to our panel members.

[Whereupon, at 3:34 p.m., the meeting was concluded.]