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ORTHOPEDICS AND REHABILITATION DEVICES ADVISORY PANEL MEETING

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P R O C E E D I N G S (8:20 a.m.)

Agenda Item: Call to Order, Opening Remarks, Conflict of Interest Statements

MR. DEMIAN: Good morning everyone. We are ready to begin this meeting of the Orthopedics and Rehabilitation Device Advisory Panel. My name is Hany Demian. I'm the executive secretary of this panel, and a scientific reviewer in the Orthopedic Devices Branch.

I would like to remind everyone that you are requested to sign in on the table attendance sheets which are available at the tables by the door. You may also pick up an agenda and information about today's meeting, including on how to find out about future meeting dates through the advisory panel phone line, and how to obtain meeting minutes or transcripts.

I will now read two statements that are required to be read into the record, and these are the deputization of temporary voting members, and the conflict of interest statement .

Appointment to temporary voting status. Pursuant to the authority granted under the Medical Device Advisory Committee Charter dated October 27, 1990, as amended April 20, 1995, I appoint the following people as voting members of the Orthopedic and Rehabilitation Devices Panel for the duration of the panel meeting on April 28, 1998: Drs .

Richard Coutts; Yadin David; Jeremy Gilbert, Joseph Hale; Stephen Li; Kinley Larntz; Michael Urban.

For the record, these people are special government employees, and they are either a consultant to this panel or a consultant or voting member of another panel under the Medical Device Advisory Committee. They have undergone the customary conflict of interest review. They have reviewed the material to be considered at this meeting.

Now 1'11 read the conflict of interest statement. 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 any impropriety. To determine if any conflict existed, the agency reviewed the submitted agenda and all financial interest reports by the committee participants.

The conflict of interest statute prohibits special government employees from participating in matters that could affect their or their employers' financial interest, however, the agency has determined that the participation of certain members and consultants, the need for whose services outweigh the potential conflict of interest involved is in the best interest of the government.

Waivers have been grants for: Drs. Barbara Boyan; Harry Skinner; Cato Laurencin; Stephen Li; Kinley Larntz; and Jeremy Gilbert because of their interest in firms which

could potentially be affected by the panel's decisions. The waivers will permit them to participate in all matters before the panel during today's session. Copies of these waivers may be obtained from the agency's Freedom of Information Office, Room 12A-15 of the Parklawn Building.

We would also like to note for the record that the agency took into consideration other matters regarding: Drs . Barbara Boyan; Cato Laurencin; Stephen Li; Edward Cheng; and Richard Coutts. Each reported involvement with firms at issue, but on other matters unrelated to the meeting's agenda. The agency has determined therefore, that they may participate fully in today's deliberations.

In the event that the discussion involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participant should excuse him or herself from such involvement, and the exclusion will be noted for the record. With respect to all other participants, we ask that in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose product they may wish to comment upon.

Before turning this meeting over to Dr. Boyan, I would like to introduce our distinguished panel members who are generously giving their time to help the FDA in matters being discussed today, and other FDA staff seated at this

table . We'll just go around the room, and everybody will introduce themselves and give their affiliation.

[Introductions were made.]

DR. BOYAN: Good morning. I'm Dr. Barbara Boyan, the chairperson for the meeting. Today the panel will be making recommendations to the Food and Drug Administration on a reclassification petition for bone cement, and one guidance document for bone growth stimulator. I would like to note for the record that the voting members present constitute a quorum as required by 21CFR part 14.

Agenda Item: Open Public Session

We will now proceed with the open public hearing of this meeting. I would ask at this time that all persons addressing the panel come forward and speak clearly into the microphone as the transcriptionist is dependent on this as a means of providing an accurate record.

We are requesting that all persons making statements during the open public hearing of the meeting disclose whether they have financial interests in any medical device company. Before making your presentation to the panel, in addition to stating your name and affiliation, please state the nature of your financial interest, if any.

This open public hearing is going to be limited to bone cement. We have set aside time in the program -- coaching from the executive secretary. This one can be any

topic . This is a general open public hearing. If there is anybody in the audience that would like to make a statement to the panel for any purpose, come forward now.

Seeing no one in the audience, I would like to ask Mr. Demian to enter into the record some testimony that arrived by mail.

MR. DEMIAN: Thank you, Dr. Boyan.

This letter was received from Chris Wilson, and it's in regards to advanced biosurfaces cartilage replacement knee restoration procedure. It reads :

"Mr. Demian, after reading in The St . Paul Pioneer Press about cartilage replacement procedure developed by Advanced Bioservices, my mother and I found their phone number, address, dug out her knee x-rays, and drove 90 miles to see if she could get into a clinical trial."

"We have yet to hear from Dr. Jeffrey Felt (?) . My mother is a healthy 78 year old, and has no cartilage in either knee. She is now taking prescribed pain killers which cause her nauseousness. She does not want to have a knee replacement surgery, because she has friends who are not doing well after the operations -- problems with the prosthesis, complications, infections, rejections, and years of agony. "

"In the last two years she has changed from an active bird watcher and golfer to a sedentary life, which I

fear will lead to other health problems. I understand that the European trials have shown promising results, and while we appreciate the need for caution on your part, people in mother's position are in a hard spot. They face massive invasive surgery with no out other than a wheelchair if the artificial joint does not take."

"If new procedures hold promise of a much greater, gentler routine, with a quick recovery, and which may give her a superior joint. In the end, if this procedure fails to hold up, she still is a candidate for the invasive procedure, and really isn't any worse off."

"We hope that you can see fit to give an approval for a large clinical trial. Assuming you find the same sort of positive results as seen in Europe, that you move to make the procedure available as quick as possible. Each day is precious, and the possibility of living them pain-free and active after what appears to be an almost outpatient level treatment is tantalizing. I know that you have to be careful, but three years seems like a long time right now, and I'm hoping that the process can be speeded up somehow. "

" Just hoping that you can help someone I love to walk without pain, thank you for your time, Chris Wilson. "

Dr. Boyan.

DR. BOYAN: Thank you, Mr. Demian.

Now since there are no other requests to speak in

the open public hearing, we will now proceed to the open committee discussion. I would like to introduce Mr. Jim Dillard, deputy director of the Division of General and Restorative Devices to provide an update since the last panel meeting, and general introduction to the concept of a reclassification petition.

Mr. Dillard.

MR. DEMIAN: Let me just clarify. Mark Melkerson, the branch chief for the Orthopedic Devices Branch will give the update from the last panel meeting, and then Jim Dillard will come in and talk about the reclassification.

Agenda Item: Open Session - FDA Update From Last Panel Meeting

MR. MELKERSON: Good morning. I'm sorry for the delays here.

As Dr. Boyan stated, I'm here to give you a quick update. This is from the January 1998 panel meeting. At that panel meeting there were four petitions submitted by OSMA proposing reclassification of both pre-amendments and post-amendments devices, and also discussed a classification of an unclassified pre-amendments device.

The pre-amendments reclassification petitions covered constrained cemented elbows, non-constrained shoulders, semi-constrained shoulders and patella-femoral, semi-constrained, all for cemented use. These devices are

currently being worked into a mass reclassification effort.

The post-amendment portion of these devices, non-constrained shoulder, semi-constrained shoulder are going to be combined as per the panel's recommendations. The others are being worked on again as Federal Register notices.

The unclassified premos(?) device, calcium sulfate is currently undergoing preparation as a Federal Register notice. These Federal Register notices are being slightly delayed by the Federal Register notices needed for the FDA-MA regulations that are currently being written and conceived.

Thank you very much.

MR. DILLARD: Good morning. I wanted to formally say thank you to the panel members, and that we appreciate greatly that you have given your time to come and help us out, not only with reclassification of bone cement, but with a guidance document, the bone growth stimulator guidance document, and formally welcome you to our beautiful building here at 9200 Corporate Boulevard.

I'm not sure that we've had a panel meeting here for the Orthopedics Panel, but it may be the first of many in our efforts to help curtail costs. Since we are having many panel meetings, especially in the orthopedics area, we may be doing a little bit more of this. So hopefully this meets with your satisfaction, but any feedback would be

welcomed.

What I'd like to do just real quickly this morning, and then I would also like to introduce the topic of guidance documents this afternoon is talk a little bit about classification. I know you have heard about this in your training, and certainly you dealt with it at the last panel meeting.

But just to refresh everybody's memory, we do have three classes of devices. We have Class I, which are devices where general controls are adequate to provide reasonable assurance of safety and effectiveness of a device. Class II devices are ones in which Class I controls or general controls alone are not sufficient, but for which special controls can be developed to control for the risks associated with the product area.

In Class III, which tends to be the more higher risk kinds of products, Class I and Class II types of controls are insufficient alone to be able to control for the risks of the product. So you can't place the device either in Class I or Class II. So a pre-market approval or a product development protocol is necessary.

Also just to let you know, there is a new part of the statute in FDA-MD termed evaluation of automatic Class III designation. It's Section 207, which actually gives us a new tool for classification also. It is not on this slide

it is so new, but what it allows is for certain low risk devices that are based in Class III, based on a finding of not substantially equivalent because there is no predicate device or pre-amendment device on the market to compare it to.

We do have a new classification process that we can go through for those low risk products, to potentially classify them or reclassify them in Class I or Class II. That also is a classification process that we have contemplated taking some products to various advisory committees . At some point in time you may be involved with that classification process also.

Also to refresh your memory, the type of reclassification that we are talking about today, bone cement, is a pre-amendments device that was formerly regulated by our Bureau of Drugs, or Center for Drug Evaluation and Research as a drug product prior to May 28, 1976. So we term those transitional devices.

Transitional devices based on the 1976 Medical Device amendments put forth that all transitional devices were Class III devices automatically, needed and a PMA or a PDP to go market. The reclassification petition before you today contemplates the down classification of those transitional devices.

What we are really asking you to do today is to

look at the reclassification petition, and based on those criteria that we have for classification and reclassification, give us a recommendation as to whether or not you support the petition or not.

Again, based on classification, what Congress contemplated was the FDA with public input to place the lowest regulatory class to provide reasonable assurance for safety and effectiveness for the product types. As with some of the reclassification efforts, some types of petitions and some types of product areas, we do need to seek advisory committee input.

Transitional devices are one of those product areas where in Section 513, we need to bring this to you for a recommendation. So that’s what we are here for today. We also allow for opportunity for public comment through a proposed rule, and gaining comments from the public and going to final classification as appropriate.

So with that, Dr. Boyan, I think I'll turn it back to you, and you can start the formal part of the meeting.

Thank you.

DR. BOYAN: Thank you. We will now begin the discussion of the reclassification petition for bone cement. We will begin with the petitioner’s presentation, followed by the FDA presentation. We will then have another open public session specifically related to bone cement.

We will then have a general panel discussion of this topic, followed by panel discussion aimed at answering FDA's questions, while going through the reclassification worksheet and then supplemental worksheet. That is, we will discuss the FDA's questions as we fill out the worksheet. We will finish by voting upon our recommendations.

I would like to remind the public observers at this meeting while this portion of the meeting is open to their observation, public attendees may not participate except at the specific request of the panel.

The petitioner for this presentation is OSMA, and the FDA presentation will be made by Hany Demian as the lead reviewer, Orlee Panitch as the medical officer, and Chang Lao as the statistician.

So I would now like to call OSMA up to the podium and ask them to begin their presentation. Remember, everybody needs to identify themselves by name, by affiliation, state whether they have monetary interests in any device company, and every time they speak, say their name one more time.

Agenda Item: Open Session - Reclassification of Bone Cement, Petitioner Presentation

DR. SMITH: My name is Dan Smith. I'm with Biomet . I believe I have a financial interest in this petition.

You have two of my handouts; first of all, my slides. You will see that several of those, in the interest of time, have been removed from my presentation, and the other handout is what I call the skinny petition. It's the heart of the petition, with all of the reference material stripped out of it. When I refer to your handout, that's the handout that I'm talking about.

Mr. Dillard kind of scooped me on the background of the regulatory history of PMMA bone cement, so I'm going to skip over those slides and get into the device description. PMMA bone cement is composed of a powder and a liquid component. The powder component is typically about 89 percent polymer, 10 percent radiopacificer, and 1 percent initiator. The liquid component is typically 98 percent monomer, 2 percent accelerator, and 100 ppm stabilizer.

The proposed indications for PMMA bone cement as a Class II device are fixation of prostheses to living bone in orthopedic musculoskeletal surgery for all of these reasons; any of these reasons.

The proposed contraindications are active or incompletely treated infection or allergy to any of the cement components.

The current definition of PMMA bone cement as a Class III device is a device that is intended to be implemented that is made from methylmethacrylate,

polymethylmethacrylate, esters of methacrylic acid or copolymers containing polymethylmethacrylate and polystyrene.

I have underscored esters of methacrylic acid there, and I think it's noteworthy that every bone cement approved for use in the U.S. or in wide use around the world employs the same ester of methacrylic acid, and is methylmethacrylate. Other esters have been evaluated and have some potential benefits, but no other ester of methacrylic acid has been shown to be safe and effective in wide use.

The proposed definition for PMMA bone cement is a Class II device. It is device intended to be implemented that is comprised of a liquid component consisting primarily of methylmethacrylate, and a powder component composed primarily of polymethylmethacrylate and/or copolymers of methylmethacrylate and styrene or methyl acrylate.

So in addition to some rewording of this definition, the primary changes are that the monomary component the cement has been limited to methylmethacrylate. Copolymers of methylmethacrylate and methylacrylate as in Palaces are recognized as viable constituents of a Class II bone cement.

I should also point out that boneloc, a cement that has employed unique liquid and powder compositions has

been associated with lower or substandard clinical results, would not conform to this definition because of its unique formulation.

About one year ago when the writing of this petition was initiated a literature review was performed to find recently published peer reviewed reports dealing with cemented arthroplasty in large patient populations. Of the several thousand papers that were located or identified dealing with the clinical results with cements, and using those criteria, those papers were cut down to seven primary references on cemented hips, four primary references on cemented knees, and one primary reference on shoulders.

You will find summaries of all of these primary references on pages 14-19 of your handout.

In addition to those summaries, we have with us today authors from three of those papers who will be presenting after the end of my overview of the petition. Dr. Daniel Berry will present the Mayo Clinic experience. Dr. Richard Johnston will report his results from the Iowa Methodist Medical Center. Then Dr. Henry Malchau will report results from the Swedish National Hip Arthroplasty Register.

Sources for the listed complications are package inserts for approved cements, review of the scientific literature, and medical device reports. You will find

descriptions for each of the identified complications on pages 20-30 of your handout. The only complication that I will discuss in any detail during my presentation is going to be bone cement implantation syndrome.

I'll note that my shorthand here as we go through the complications -- an exclamation point implies that based on the literature, there is an established correlation between that complication and cement use; a question mark implies that there is little or no literature-based support for a correlation.

Bone cement implantation syndrome is a term that has been used to describe a particular set of signs or symptoms as we see here, that may occur during or shortly after cement implantation. The generally accepted mechanism for BCIS is diffuse microembolization of the lungs as a consequence of intramedullary contents being forced into the vascular system during cement delivery, cement pressurization, and prosthesis insertion.

We see here the other identified complications.

The complication incidence is generally not well reported in the literature, however, on page 31 of your handout you will find the literature base complication incidence that was available in the literature.

Let's look for just a moment at medical device reports for PMMA bone cement. Medical device reporting was

established in December 1984, and it might be assumed that since that time approximately 3 million cemented arthroplasties have been performed.

On that background we see that 214 reports consistent with bone cement implantation syndrome-type complications have been reported. Other commonly reported problems are associated with mixing and handling problems with the cement and packaging.

Based on that 3 million procedure assumption, you can see that the reported -- and I stress the reported -- rate of BCIS, reported death rate MDRs is quite low.

Let's look now at the special controls that have been identified to control these identified risks to health. Again, I'm going to move over these pretty quickly. Now on pages 37-39 you will find a complete list of the special controls identified for the identified risks to health.

1'11 just briefly say, as I scan through these slides, that typical controls would include: a 510(k) requirement for substantial equivalents; proper labeling, packaging, and insert; package insert information; conformance to established standards and GMPs; and the FDA prerogative to require clinical data if substantial equivalents to an approved cement is in doubt.

Pre-clinical testing. The foundation of pre-clinical testing can be found in the ASTM and 1S0 standards

for PMMA bone cement. Additional pre-clinical testing is listed on pages 41 and 42 of your handout. That listed testing is just about identical to the draft FDA guidance document for pre-clinical testing of bone cement.

The recommended properties for characterization include: physical and chemical properties; mechanical properties; variation on the copolymer composition for adequate level that is deemed significant, or if any new additive is employed, biocompatability testing is appropriate. The table summarizing the physical and mechanical data for several approved PMMA bone cements appears in the petition and in your handout on pages 47-5o.

To summarize, we believe the petition presents data establishing the safety and effectiveness of PMMA bone cement . We believe that clinical results, which you'll hear about in just a moment, are impressive. We believe the risks to health are well documented. We believe that regulatory controls have been identified which will eliminate or minimize the identified risks to health. Therefore, it is proposed that PMMA bone cement as defined in the petition be regulated as a Class II device.

Thank you. We'll now hear from Dr. Berry.

DR. BERRY: Good morning. My name is Daniel Berry. I'm an orthopedic surgeon at the Mayo Clinic. I have a subspecialty interest in hip and knee arthroplasty.

I have no financial interests relative to this discussion to disclose.

I have been asked to speak on the results of long-term use of cemented total hip arthroplasty for the first portion of my talk, and then briefly discuss the bone cement implantation syndrome results from our clinic secondarily.

1’11 start out by pointing out that our group, as well as other groups have previously published information at 20 years demonstrating that total cemented hip arthroplasty provides good clinical results in the majority of patients.

A slide on your demonstrates the number of patients in a series of 333 hips that were followed for 20 years at our institution over 1, 5, 10, 15, and 20 years graphed against the relative amount of pain that the patients expressed. You can see that the pain relief even at 20 years in surviving patients was over 90 percent of the patient population.

The majority of patients maintained relatively good functional status as a dramatic improvement from their pre-surgery status. By 20 years some patients had diminishment of their ambulatory status primarily we believe related to age factors, as the average age of this patient population was 85 by the time 20 years had elapsed.

When one looks at a global score relative to their

hip function, the majority of patients maintained excellent pain relief and functional status even over 20 years. Again, most of the drop off at 20 years we believe was related to age-related features.

That was by way of introduction. I would now to present to you information gleaned at 25 years from survivorship of 2,oOO cemented total hip arthroplasties. You'll recognize that since the introduction of total hip arthroplasty much has been learned about the factors that contribute to success and failure of the procedure, but in the past limited sample sizes and follow-up periods to some extent have limited the rigorous analysis of demographic factors that govern the long-term complication rates and rate of component failure.

The purpose of this study was to analyze effects of patient demographic factors and diagnosis on the survivorship of acetabular or femoral components, and on the most common complications of hip arthroplasty. To do this study we looked at 2,000 consecutive primary total hip replacements . They were all done at our institution between 1969-71. They were all done using bone cement of simplex type, and the cement was implanted using so-called first generation cement techniques.

The mean age of the patients at time of surgery was almost 64 years. Of the range demonstrated, there was

an equal number of female and male patients approximately. This slide on your right shows the age distribution of patients at the time of surgery.

All of our patients are followed prospectively after joint implementation. These are the follow-up intervals . The last follow-up was by interview and exam of 309, a letter questionnaire of over 1,000, and a phone questionnaire of 649.

Our survivorship method used the Kaplan-Myer technique. Our endpoints were reoperation, revision for any reason, and revision for aseptic loosening. Please note that this study is a survivorship analysis with reoperations and revisions as an endpoint, not a radiographic analysis.

By the time of the completion of the study almost three-quarters of the patients had died; 567 of the patients with hips were living. Ninety-five percent of our patients were followed for at least 25 years, and 98 percent were followed for at least 20 years, giving us a relatively high follow-up rate.

Now importantly in this study we do not believe that we lost many patients that had a revision between the time of their last follow-up appointment and the time of their death, because the mean length of follow-up between our last clinical follow-up and death was only 0.6 years, and more than two years had elapsed between the time of

their last follow-up and death in only 51 patients. The primary reason for this is that we always contact patients yearly. If the patient died with the prosthesis intact, we generally speaking, heard from family members that that was the case.

In this group of 2,000 patients there were 296 reoperations over the first 25 years; 242 of those were revision surgeries for any reason, the balance being made up of hardware removal, cases usually trochanteric wires, and of those 151 of the hips were revised for a specific diagnostic of aseptic loosening of the arthroplasty.

This is a breakdown of acetabular revisions and femoral revisions; aseptic loosening the most common reason for acetabular revision, the second most common being instability problems. On the femoral side, aseptic loosening again was the most common reason; the second most common reason being prosthetic femoral component fracture, primarily we believe related to the type of metal used at the time of surgery, as well as implantation technique in which many times the components were scratched.

This is the information you will be interested in. This the 25 year survivorship data. The survivorship free of any sort of reoperation in these cemented hip replacements was over 75 percent at 25 years. The revision for any reason was slightly over 80 percent, and revision of

aseptic loosening of this cemented on either the acetabular or the femoral side, 86 percent survivorship at 25 years.

These are the survivorship curves, the top curve being the revision for aseptic loosening curve, the bottom curve being the reoperation curve for any reason. You will note that the curves are roughly one year of time, and that the survivorship does not drop off dramatically with time.

We looked at the effects of various demographic factors and the likelihood of failure of these cemented implants. Males had a statistically poorer survivorship than females, both on the acetabular, as well as the femoral component sides.

We looked at the effect of patient age, and found that there was a poorer survivorship for each decade earlier in life that the total hip arthroplasty was performed. So if one looks at the survivorship curves, these are patients in their eighties at the time of surgery, their seventies, sixties, fifties, forties, and less than 40.

Demonstrated graphically in this bar graph, you can see that for patients less than 40, the survivorship was around 68 percent; for patients greater than 80 it was 100 percent; the steepest part of the curve for patients in their fifties and sixties.

Diagnosis also played a role in the likelihood of survivorship. Patients with low activity, such as patients

with rheumatoid arthritis and polyarticular disease have a higher rate of survivorship statistically. Patient who develop metal dysplasia of the hip a lower rate of survivorship of both the acetabular components, even when adjusted by multi-variate analysis for age. We believe that is probably related to abnormalities in the bony structure on acetabular or femoral sides of development dysplasia patients.

When one looks at the acetabular or femoral implants separately, the 25 year survivorship for the two implants was almost identical; in our series, 89.6 and 89.7 percent respectively. But it is important to note that the shape of the curves was not the same. The acetabular curve shown in yellow tended to accelerate with respect to failure with time, while the femoral curve tended to plateau with time .

Similarly, the acetabular failure rate was higher than the femoral rate in younger rates, whereas the converse was almost always true in the older patients. Note that in the younger patients the acetabular survivorship was poorer than femoral survivorship.

The goal of this study was to try to provide rigorous quantitation of the demographic factors that governed the long-term survivorship of total hip arthroplasty, and to provide for you, the information on

long-term survivorship of this particular cemented implant system.

We hope that in addition to establishing a benchmark for the likelihood of failure over 25 years, this also defines patient populations and risk, it quantitates the risk of failure of cemented total hip arthroplasty at 25 years .

The endpoint chosen was revision. We chose that because it's the most definitive and least ambiguous method of defining failure. We believe that the clinical and radiographic results, though not presented, are important and complementary to the survivorship data, but impractical to report for a study group of this size.

Finally, we hope this provides a baseline to which newer technologies might be compared in the future, and defines populations that have the best results with cemented hip arthroplasty, and those that might most benefit from other technology.

So I'll conclude there with respect to the 25 year survivorship data and the long-term survivorship data of hip arthroplasty, and now move onto a very brief discussion of the so-called cement implantation syndrome. This work was done by one of my partners and colleagues, not myself, but he has asked me to present it on his behalf.

As you heard previously, fat embolization is

recognized to be one of the elements that makes up the so-called cement implantation syndrome. It is recognized that fat and marrow elements and air are released during bone manipulation, and it occurs not only with arthroplasty, but has also been recognized to occur with fractures, open introduction, internal fixations, and both hip and knee replacements.

Its effects include pulmonary effects, cardiovascular effect, necrologic effects, and systemic effects. The clinical presentation can manifest many forms. It can be with no sequelae. It can provide transient hypotension or arrhythmia. It has been associated with sudden death, post-operative pulmonary insufficiency, and necrologic deficits, presumably by paradoxical embolization in certain patients.

The study that I will present to you briefly covers the years 1969-88. During that time, 21,000+ hip arthroplasties were done at our institution. Importantly, the breakdown in terms of the diagnosis leading to hip arthroplasty was fracture in about 1,600 of those patients, and other, primarily osteoarthritis or other degenerative conditions or inflammatory conditions of the hip in slightly over 20,000 patients.

During that time there were 19 interoperative deaths at our institution. Of those 19 interoperative

deaths, the mean age was 82.6 years. They were predominantly females, and there was known cardiovascular disease in 18 of the 19 patients in whom the process occurred.

Fully 84 percent of the patients that had a sudden interoperative death were associated with a femoral neck or intertrochanter fracture being treated with arthroplasty; very few with just osteoarthritis or rheumatoid arthritis.

The sudden death occurred during cementing of a component in all cases; on the acetabular side in 2 of 19; on the femoral side in 17 of 19. The great majority of these patients were either Class III or Class IV patients according to the American Society of Anesthesiologists, and the great majority of them also had associated medical problems, many of them several.

These are the data which you will be interested, the overall rate of sudden death during hip arthroplasty at our institution was 0.09 percent; non-fracture diagnoses accounted for very few of these, 0.015 percent, but fracture-related diagnoses had a significantly higher risk, 67-fold higher, with a rate of 1.0 percent.

When one looks at the cemented versus uncemented question, in non-fracture diagnoses the rate of this occurrence with cemented prostheses was 0.2 percent; non-fracture related diagnoses in uncemented implants was 0

percent. So we do believe that this process is associated to some extent with cementation, although not exclusively.

Femoral neck fractured accounted for a considerably higher rate of problems when cemented than uncemented as you see on the slide at your left.

So to summarize, the process appears to rare in elective total hip arthroplasty. It is most common in cement arthroplasty for fracture problems. It probably is caused at least in part by embolization of debris found in air that occurs during all hip arthroplasties. The physiologic consequences are usually minimal, but cardiovascular collapse is possible in a group at risk.

The group at risk appear to be elderly with previous cardiovascular disease documentation; fracture cases and tumor cases; patients with an intact primary canal with no venting possible; and specifically, patients undergoing a cemented long stem implant.

We do not have proof, but we believe at the present time, as I believe does the rest of the orthopedic community that prevention of some of these cases is possible with specific techniques at the time of surgery, including lavage of the femoral canal, selective vent holes in the femur, minimizing pressurization of the cement column in certain patients, and avoiding cemented long stem in specific high risk patients. In patients who have shown

hemodynamic instability during surgery, proper hydration or if necessary, changing interoperative plans.

Thank you for the opportunity to address the panel .

DR. SMITH: Next up will be Dr. Johnston, presenting his results from the Iowa Methodist Medical Center.

DR. JOHNSTON: Hi. I'm Dick Johnston. I've been in private practice in Des Moines, Iowa. I'm also a clinical professor of orthopedic surgery at the University of Iowa. This is opposed to the previous and subsequent presentation, is a single surgeon series, my own personal results.

I'm going to talk about effectiveness of the total hip replacement. I'm going to talk some about the complications of hip replacement, and then talk about durability of hip replacement.

This sort of sums up my experience. I've done about 5,oOO hips.

DR. BOYAN: One moment please. Could you just state for the record if you have a financial interest in any device company?

DR. JOHNSTON: Not related to cement, I do not.

This sums up my experience from 1970-96, when I quit doing surgery. I used Simplex-P this entire time. I

was finger packed from 1970-76. From 1976 on it was with a plug and retrograde filling of the femoral canal with a gun. I used the cement in a highly viscous state throughout.

In 1983, I began to centrifuge the cement, and then that has been true the rest of the way. This was Charnley prosthesis up to here; Iowa prostheses through the rest of the way.

We have done a number of studies here. As a matter of fact, these have been reported in the literature except this little gap right in here. This number one here is the Schulte paper that you have in your packet. The paper that I'm going to present to you later on today on durability is this one, number six down here in the under 50 group.

These are my results of this group of patients that is in the Schulte paper, only this is two years post-operatively, 326 hips. You see better than 96 percent have moderate to severe pain pre-op, better than 90 percent have none or minimal pain post-operatively; 100 percent are improved.

Activity level, almost 90 percent have light or minimal activity pre-operatively, and 81 percent have heavy or average activity post-operatively; 78 percent improve; 21 percent the same; 1 percent worse.

Ability to perform job or other desired activity,

91 percent made significant concessions pre-operatively; 91 percent made no or occasional concessions post-operatively; 91 percent improved.

This is a report from Borne(?) and Rorbach(?), 1993, using health status instruments that were not invented, or at least I hadn't heard of them in 1973. This is a sickness impact profile. A general health status measure, time trade off in six minute walk, also general health status measures are improved by about two standard deviations of the pre-operative standard deviation. The Walmach(?) is a hip-knee arthritis measure, functions improved by three standard deviations. The Mactar(?) is a personalized health status measure, and it improved by five standard deviations, as is the Harris.

Just to give you an idea, to improve a population one standard deviation pre- and post-treatment is very good results. Here are three standard deviations, and this is as much as five standard deviations. It's practically an entirely different population. These are some of the best results of any medical treatment available.

It's also some of the most cost effective. Here, with not considering the cost of disease, Borne and Rorbach found the cost per quality was $8,000 for the first three years . Carried on out to 20 years, it would be even less than that, although because of the age that these people

were when they were operated on, very few returned to work.

These are my deaths. They were more in the older folks than in the younger folks. Here is the average age of death. It's about 75. The average age of the whole group was 65. The average age of the revisions was 81. There is a bimodal distribution of age in the revisions, a young group and an old group, but this was old even for the old group .

There is another slide on deaths that I got out of place I guess. We'll go to dislocations and come back to death.

Dislocations -- 1 had a lot of dislocations. That was low on my priority list of thing to prevent. It varied from 4 to 22 a year. That is scattered through the years; there was no pattern at all.

Nerve injury, I had four of them scattered through the years. Arterial injury, I had one. It was a revision. It's reported as a case, reported in the Journal of Bone and Joint Surgery. I pulled the femoral artery apart with the enema, and then we had to go in post-operatively and resect it and sew it back together.

Non-fatal pulmonary emboli are about 2 percent. I don't have hard data on this, plus, it's not a very hard endpoint.

I had no episodes of hypotension. As opposed to

what Dan just told you, I did practically no acute fractures in this group. I didn't not do total hips for acute fractures except in a very rare instance; so probably no more than a dozen through the years.

Bleeding was not a problem. Urinary problems went to routine in dwelling catheter.

Here is the other death slide I was looking for. You see I did about 200 of these operations a year from 1970-96, and our deaths diminished here in more recent years as the internists got better at treating heart disease primarily, and also the medicine that they give to reduce the problems with GI bleeding. The death rate here at one month was 0.4 percent, and it wasn't much higher in revisions . Again, pulmonary embolism is shown here; six of them due to pulmonary embolism.

Then infection -- the first few years at 4 percent was in a standard operating room, permeable gown and drapes; 1974-80 in a clean air room with impermeable gowns and drapes; 1980-89 with hoods, body exhaust system, and prophylactic antibiotics for the first time, down to 1 in 1,200. Then beginning in 1989, the hospital went to a packed system, as opposed to a flat system here, and then we were into the cut corners behavior, and the infection rate went back up nearly 1.0 percent.

So that is the effectiveness and the

complications, and now we'll talk about durability. This is a paper that we gave at the recent orthopedic meeting in New Orleans. A Charnley prosthesis, polished stem, all patients under age 50, and all with a minimum 20 year follow-up. This is a highly stressed group of patients.

The purpose was to evaluate the durability in the young patient. All these were performed by me between 1970-76, Charnley prostheses with hand packing cement. The cement technique was graded this way. The clinical results and the radiographic results were recorded in the standard manner. Males and females were about equal. Forty-two was the average age. You see the bulk of them are in the fifth decade.

This is the diagnosis, a lot of congenital hip problems, osteoarthritis. This is remote infection, the residual of infection.

So had we 69 patients and 93 hips, 72 hips living, we lost none of them. Here is the radiographic follow-up, an average of 23 years. Revision, 19 percent for acetabular loosening, and 5 percent for femoral loosening. Then a radiographic 15 percent for a total; 34 percent on the acetabular side failure, and 13 percent on the femoral side. So in this younger age group where they are stressed more, we do see a difference in acetabular and femoral results.

Clinical results are good at 20 years. This is

our worst case of osteolysis, which is not part of this discussion anyway. Here is the survival curves for revision for acetabular loosening, and revision for femoral loosening.

Here is a typical result pre-operatively. Here is post-operatively. Here is 20 years post-operatively; no change. So the Charnley total hip arthroplasty performed well in this young patient population. Acetabular results were less durable than the femoral results, but even with hand packing cement techniques, the femoral construct, the cemented Charnley total hip performed well long-term in this active population. Only 5 percent total, and 6 percent of living cases were revised for femoral loosening, and an additional 7 percent were radiographically loose.

Thank you.

DR. SMITH: Now we will hear from Dr. Malchau on the results from the Swedish register.

DR. MALCHAU: Good morning. My name is Henrik Malchau. I'm an orthopedic surgeon at the Solgren's(?) Hospital in Goteborg, Sweden. My main interest in the orthopedic field is total hip replacement. I have a lot of interest in bone cement, but not economically.

I will present the results from the Swedish register. The register was initiated in the late seventies by the Swedish Orthopedic Association. Our department in

Sweden doing total joints was offered to be part of this registry, and everybody has actually joined the register ever since that.

The purpose of this register is to inform whatever parties are interested in information from this specific treatment. As I told you, all departments are participating in this study on a voluntary basis.

The aim of the study is to describe the epidemiology of total hip replacement in Sweden; to make a risk factor identification for primary recent surgery; to improve the surgical technique by recent fact time analysis; to have benchmarking comparing different regions in Sweden; and overall to make an assurance of total hip replacement in Sweden.

The logistics consist of three different databases of the primary total hip since 1992, with the patient I.D. ; one of the recent total hip reported as copies of the medical record; and one of the surgical technique reported annually per unit.

The information in the register consists of 148,359 primary hips, of which 93 percent are cemented, 3,3 percent uncemented, 3.1 percent hybrids with uncements cups and cemented stems. Altogether we have 11,198 revision total hips.

This is the development since 1979 for the

cemented implants, 138,000. As you can see, of those 7.2 percent have come to revision. That is a true revision rate, not the survival or anything else. Looking in the same sense, in the hybrid implants we have 4,564, 3.4 percent revision. The follow-up is shorter.

Looking at the uncemented, close to 5,000 total hips in this time span, of which 12.5 percent has been revised; certainly a much higher rate for the uncemented.

The failure endpoint definition in the register is exchange or removal of one of those components, and that is depicted now in the survival analysis. We are only looking at the group of 9,634 hips with first time revisions. The rest are treated in a separate way. Results on percentage today was shown as a scientific exhibit at the recent meeting in New Orleans. I think you have got a copy of this handout. It is not in the literature reference list.

The reason for revision, the main problem as we heard from the Mayo Clinic is acetabular loosening, 72.3 percent. Over the years, primary deep infection constitutes 7.2 percent; fracture of the bone, 4.7 percent; dislocation including technical error, 7 percent; and a variety of less frequent reasons for revision.

The overall result percent in the Kaplan-Myer technique here is subdivided in two times. Prior to 1979-86 is the early cementing technique, or old cementing

technique; 1987-96 which you could say is the second and current rate for cementing technique. Here is the number included in these, and you have the 95 percent confidence interval .

For the cemented we can see a clear improvement. For the uncemented there is no difference between the two observation cohorts. For the hybrid there is no difference either where the few have been used in the first time.

Looking then at the cumulative frequency of revision with deep infection all implants, everything done in Sweden, 79 come along for this curve, and the nine year follow-up you have an overall frequency of 0.8 percent, with a steady improvement down to in the order of 0.3 percent that is the result of obtained with infections and the current prophylaxis.

Looking at the cemented implant, the cumulative frequency of revision, all the different cement brands used in Sweden, all the different implants. The 1979 comes along here, the 10 year result, 10 percent revised. We see a steady improvement over the years down to 1991, with a now six year follow-up, and around a 1 percent revision acetabular loosening in patients operated on due to osteoarthritis .

Doing the same kind of statistics on the uncemented implants, we can't still show any improvement.

There might be what we call a certain ratio of uncemented implants out there giving better results, but we can still not see it in the register.

Looking at the survival, looking at patient characteristics, we had with the old technique superior results for females compared to males as we heard from the Mayo Clinic. The modern technique seems to take out that difference, and we can obtain now the white curve here, almost identical results for males and females.

Looking at then the surgical technique, which is very important for the good, long-term result. We do Poson(?) models looking at the different techniques you can use in order to get a good indentation of your bone cement into the bone. That includes: brush lavage, distal block, a proximal sealant femur and pressurization, vacuum mixing, gross reduction of the cement. We have a number of multi-variables which includes the type of cement, and I will come to that.

In the Poson models are included 137,000 primary hips with 7,477 revisions, and more than 860,000 observation years. These are the types of cements used in Sweden listed here: the Palaces, antimycin(?), the green, and the yellow here, Palaces constitutes over the last few years 90 percent of the market. Sulfex(?) has disappeared. CMWU is not used that much in Sweden, neither is Simplex.

Cement application implies today a retrograde filling in the femur, and 50 percent of hand application or series application in the acetabulum.

The brush for cleaning the bone prior to cementation is used in 90 percent of the clinics now, positive lavage in virtually all cases since 1995.

The distal femoral block was used, and used by everybody since 1987 and onwards, but the proximal femoral seal pressurizing the cement is not that commonly used; only two-thirds are used in that.

This comes back to what is the early death risk. We have death register in Sweden, and we have been running the cohort operated on between 1990-94, approximately 60,000 hips, and see how many of these patients have died, and when have they died actually. We are doing a time dependent Poson model estimating the death risk with the index operation of early 1990. The age of the index operation is 65 years. These are not included in any of our previous presentations . This is new data actually presented for the purpose of today,

The death incidence in different diagnosed groups: osteoarthritis women is the blue one; a controlled population age matched from the general register; osteoarthritis men. You can see those two groups have lower death risk than the controls. Rheumatoid patients have a

higher death risk when operated on for total hips.

Then focusing on the first 30 days, now look at the hip fracture first. A patient admitted to a hospital for a hip fracture and operated on with everything else and a total hip, we observe for the men a death rate a number 17,000 deaths, which we would expect to be 5,4oo. A clear increased ratio, meaning that these patients have a much higher risk for dying than a controlled population.

If those look at those operated on for the primary total hip, we do find the same, but not as pronounced as the whole hip fracture group. This problem most probably reflects that the patients are fragile, are old, have cardiovascular disease in high frequency. We don’t find any specific difference between men and women. Women actually may be at higher risk even than the men.

Looking at the mortality within the first 30 days after total hip replacement here in the patients group operated on due to osteoarthritis, 56,000 patients, we can see there is no concentration of early death, implying a high risk with the cementation procedure. The trend for this curve is although, a higher risk in the early post-operative stages.

And we have to conclude the death risk discussion. Here we can see that overall the patients we operate on due to osteoarthritis with the primary total hip have a lower

risk than a controlled age and gender-matched control population.

All right going back to the cementation or cementing technique, the reduction is most probably due to good marketing used by everybody since 1994, because if you look at the risk factor analysis of the patients operated on due to osteoarthritis revised to acetabular loosening, we do find a significantly increased risk in the patients in which that has been used. I'll come back to that in a moment.

The positive lavage, the proximal femoral sealant, the distal femoral prop all seems to decrease the risk for loosening.

This is a time dependent Poson model looking at vacuum versus manual mixing, and after four years post-operatively there is an increased risk which is probably due to technical mishandling of the vacuum mixing systems. It could be a too early stem insertion in a too low viscous cement . After four years we still see a beneficial effect of vacuum mixing, and we need longer follow-up to really justify the use of this.

Looking at the different cement types, having in mind that all the cements are doing good, but there are differences in between the different cement brands, with Palaces, Palaces antimycin, Simplex in one group, CMW with a slight worse result. The Sulfex cement is risk rated 1 in

this .

So in conclusion, acetabular loosening constitutes the main problem. The most serious complications declined three-fold over the past two decades. That cementing technique improvement was implemented in Sweden we believe is partly a result of the register. We found that the revision in this time span is only 7.2 percent for the primary cemented implant, which in our opinion sets the standard for this surgical procedure.

So our concluding statement would be that there is no scientific documentation in this register, in the Norwegian register or whatever showing superior results of uncemented fixation compared to cemented; at best equal results are presented.

Then having in mind that the costs for an uncemented are substantially higher, although there is different pricing between the different countries.

Thank you.

DR. BOYAN: Thank you very much. Is the FDA ready to present?

Agenda Item: Reclassification of Bone Cement, FDA Presentation

MR. DEMIAN: Good morning, ladies and gentlemen, Madame Chair, distinguished panel, members of the audience. I am Hany Demian, a scientific reviewer with the Orthopedic

Devices Branch. The device type under consideration is polymethylmethacrylate cement.

I would like to thank Lonnie Witham(?) and Dan Smith of OSMA, and the orthopedic surgeons Drs. Malchau, Johnston, and Berry for their presentations.

The FDA review team consisted of myself as lead reviewer, Dr. Orlee Panitch as the medical officer, and Dr. Chang Lao as the statistician. Today, our presentation will be brief.

I will discuss the proposed CFR classification, the proposed indications for use, the proposed device description, and we'll go into the summary of supporting information, the device pre-market application history, the medical device reports, the risks to health, the special controls. Then Dr. Panitch will present the bone cement implantation syndrome, followed by Dr. Lao's presentation of statistical considerations. Then 1'11 come back on and briefly summarize the panel questions.

Currently PMMA bone cement is classified under CFR 888.3270 as a transitional Class III device previously regulated as drug. PMMA bone cement is made from methylmethacrylate, polymethylmethacrylate, esters of methacrylic acid, or copolymers containing polymethylmethacrylate and polystyrene. The device is intended for arthroplastic procedures of the hip, knee, and

other joints for the fixation of polymer or metal prosthetic implants to living bone.

The proposed reclassification definition only includes bone cements comprised of a liquid component consisting primarily of methylmethacrylate, and a powder component composed of polymethylmethacrylate and/or copolymers of methylmethacrylate and styrene or methylacrylate . This has the same intended use.

I'm just going to flash up these proposed indications for use. These are the same ones that the petitioner presented. I won't read them again.

The petitioner has proposed the following device description. PMMA bone cements would be defined as self-caring two component system, including a liquid and powder component . The liquid component would be composed of methylmethacrylate as the monomer, and then you would have an accelerator and a stabilizer. Typically, the accelerator would be dimethyl P-toluidine. The stabilizer would be typically hydroquinone.

For the powder component you would have one or two polymers, and that would PMMA, MMA-styrene copolymer, MMA-MA copolymer. The radiopacificer is typically barium sulfate or zirconium dioxide. These are found at 10-15 percent weight ratios. Then initiator is typically benzoyl peroxide, found I-2 percent.

The petitioner has provided 10 articles supporting the pre-clinical issues, and 14 articles supporting the clinical use for bone cements. For pre-clinical issues the petitioner has identified comprehensive chemical and physical analysis, as well as mechanical test methods used to characterize these bone cements.

For the 14 clinical articles, 8 were on the hip, 4 were on the knee, 1 was on the shoulder, and 1 was on several joint arthroplasties. The limitations of these large device registries include comprehensive data limited to hip and knee joints, and different cementing techniques used in the U.S. versus Europe.

Later in the presentation Dr. Chang Lao will discuss the statistical considerations regarding these articles. Overall, the clinical success appears to be impacted by the anatomical site, the viscosity of the bone cement, and the age of the patient.

In total there have been 11 pre-market approval applications for PMMA cement, and 12 investigational device exemptions . Currently, there are five companies marketing the device in the United States.

Since 1985, the FDA has received 368 medical device reports for bone cement. The following is a breakdown based on the key words. There were 11 emboli; 174 reactions; 176 malfunctions; 4 infections; 1 contact

dermatitis; and 2 fliers.

Next I will present the breakdown for the reactions and for the malfunctions. For the reactions, 95 percent of them were associated with death; 32 percent were associated with cardiac arrest; 10 percent were associated with myocardia; 34 percent were associated with a drop in blood pressure; and 42 percent were associated a hypotensive episode.

For the malfunctions 63 percent were associated with the set time; 23 percent were associated with the packaging of the material; 4 percent were associated with the cement fracture; 2 percent were associated with non-adherence of the methylmethacrylate to the surrounding bone or the implant; 9 percent were associated with an inconsistent mixture.

The limitations of the MDRs include: events going unreported; incomplete reporting; and not knowing the denominator for the number of devices implanted.

Based on the literature and the medical device reports, the following risks to health were identified by the sponsor: bone cement implantation syndrome -- and Dr. Panitch will go into this later on; cement burns due to the exothermic polymerization in vivo; intrapelvic collection of the cement and heterotopic bone; foreign body reaction; changes in liver function; handling problems; loosening or

migration of the device; infection; user reaction; ignition of the monomer. I have listed other, if there are any other risks to health not covered that you may identify.

In considering reclassification from Class III to Class II the petitioner has identified the following special controls to minimize the risk to health. These include: FDA guidance document; standards such as ASTM and ISO; device labeling; design controls; and others. I have listed others, again, if you can identify any others.

Now Dr. Panitch will discuss bone cement implantation syndrome, and the potential mechanisms associated with it.

DR. PANITCH: Good morning. I would just like to highlight some of the points with bone cement implantation syndrome, and highlight the controversy that exists regarding the mechanism that causes this syndrome.

The constellation of symptoms are shown here, as presented by the sponsor. It is important to note that this is most commonly seen in elderly women who have sustained hip fractures and undergone total hip replacement. Many of these are elderly women who are coincidentally, or maybe not so, undergoing spinal anesthesia. If you look directly at this population, you will see the incidence has been reported up to 1 percent.

This is as reported by the sponsor, the commonly

reported mechanism. I would like to point out that the embolization can be comprised of thrombus, fat and/or air.

I would like to give a couple of MDR examples to highlight the controversy. I think this one is fairly clear cut, and as pointed out by Hany, that there is a limitation in the MDR information. In this report we're fortunate to have transesophageal echocardiagraphy during surgery. In this surgery there was demonstration of several large thrombi entering and then exiting the site of the heart, clearly at the same time of hemodynamic instability.

This is similarly and 87 year old who is also undergoing hip prosthesis. An autopsy on this patient who also had a similar unstable episode, and subsequently coded, she was found to not have any evidence or air or fat in the lungs.

Finally, the third example here is again an elderly female with a hip fracture. In this patient we are fortunate to have the ABGs that occurred during the code, and 30 minutes into the code we could see that there really is relatively no hypoxia with a PO_2 of 347. This is suggestive that perhaps there is another mechanism at stake.

There are three reported mechanisms that I have included here. This one is from 1979, and I think here we highlight that perhaps the embolization causes a release of serotonin, histamine and other mediators of anaphylaxis.

This has subsequently been tested, and histamines have been demonstrated to be released. Treatment prior to surgery with antihistamines, however, has not been proven to be effective.

This is from 1987, again another anaphylactic reaction reported where peripheral vasodilatation was observed. This was felt to be because of absorbed methylmethacrylate, and the complement cascade felt to be elicited from it.

Finally, the last mechanism, and this **was** just reported in ORS where the methylmethacrylate monomer was infused in dogs. In this model there was an increased capillary permeability that led to pulmonary edema. It was felt that this perhaps was contributing to the instability.

This concludes the controversy. At this point I would like to introduce Dr. Chang Lao to do the statistical interpretation.

DR. LAO: Good morning. I'm Chang Lao, Division of Biostatistics with FDA. Good morning, Madame Chairman, panel members, and audience. Today I'm going to present a statistical interpretation for this petition.

The first part is the limitations of the 14 articles presented, and then a discussion of the statistical methods. The discussion of limitations consists to two points, the inability to validate the statistical results,

and no working data and no survivor analysis.

Then I'll talk about the assumption of the statistics which is the assumption of the survivor analysis with the Cox model. Next 1'11 talk about the statistical approach to the Kaplan-Myer clinical outcome table versus the Greenwood(?) formula calculated at a 95 percent confidence interval of true survival. Then 1'11 talk about the Cox model. Then there will be time for panel questions.

The 14 papers submitted. This is a summary of one of the 14 papers. I considered this paper with the most detailed results, a 1995 paper from the Norwegian registry data by Prof. Havelin. Table 1 is an overall summary for Prof . Havelin's particular paper. As you can see, the high viscosity is the three different cement brands, and low viscosity CMW compared with boneloc for the other two years.

All high viscosity have a 5.5 years data, and the boneloc has only 2 years data. The number of divisions and the number of risk at the 5.5 years as you can see from this summary is 3,788 in total number of the sample size at the beginning of the 47 Division III. The risk is about 47o risk at 5.5 years.

As you can see, the sample size decreased quite a lot from 3,788 to 470. I think the reason is maybe the patients didn't have the opportunity to finish the study at the time the paper was published, or the patients dropped

out from the study we consider the loss to follow-up or even death.

There is no working data of course for the 14 papers, because they are published papers; many without detailed survivor or Division III analysis. Three papers have the survivor analysis tables. The remaining 11 papers have the Kaplan-Myer graph only or a partial table article.

The assumptions for the statistical survivor analysis assumes the statistical procedure to enter time to event in the article. Neither the device treatment know the risk to patient change during the study period. Since it is incomplete, loss to follow-up independent of survival due to device rate drop out.

The survivor analysis with Kaplan-Myer for the other group or Klinger life table for group data. The cusp proportion has a digression model in short identifies important risk factors like cement type, gender, age, or occupation, demographical risks to the revision. Then to estimate risk ratio of the revision between the comparison and the reference cement groups.

The assumption here assumes the risk ratio is the proportion between the present reference group independent of time, not changing over time. The statistical approach is Kaplan-Myer, which is probably limited estimate is appropriate for any group relatively large or small data.

It can be grouped if required. The clinical option was approved for the group data, the large data.

Now I want to talk a little bit about Peters form of the Kaplan-Myer, the extent of either, and the 95 percent confidence interval for this. Choose some other probability.

The difference between Peter's method and the Gluer(?) formula, the Gluer formula is in wider use by most publications . The difference here is the number of subjects at risk at a space or time point should be reasonably large with observed revision(?) if possible. The purpose is to have the larger estimate and the 95 percent confidence interval must use some other probability.

If the number of subjects is small, with no observed event, we will recommend the Peter's method. The Peter's method is British method from 1977. Prof . Peter is at Oxford and he was considered one of the well known statisticians in clinical literature.

Another standard formula is the Gluer formula. The Gluer method is insensitive to the small number of subjects' risk without observing revision with a standard error and unchanged 95 percent confidence interval of true survival, regardless of the small number of subjects, the risk at the later medically important follow-up times.

The Cox Proportional-Hazards Model is statistical

assumption change, the risk at which does not change over time. One of the graphical checks is a plot mass log survivor at time against time. The two comparison groups should be parallel or near the parallel, not having a crossover.

Other than that, there are many, many graphical or advanced statistical variables. What happens if an assumption was not made? Then are the risk ratio and risk factor would be potentially biased or misleading.

Conclusions -- none of the 14 published papers validated the Cox model assumption.

Here is a summary of Prof. Havelin's 1995 paper. This figure compares different cement type for the different component, femoral versus acetabular. As you can see on the left side of the graph, boneloc is only at two years follow-Up . The other has 5.5 years follow-up. The CMW-3, which is a low viscosity is 94.1 percent. The 95 percent confidence interval, as you can see is not overlapping with the HV, high viscosity. The boneloc is 95.5. No confidence interval was given.

So if the boneloc at 2 years was compared with all other groups at 2 year, then it would be highly significant with a P of less than 0.001. On the right side similar findings are also true. Boneloc was 98.8 percent at 2 years, much lower than the other two groups.

This chart compares different cement brands, CMW-1H -- H means high viscosity -- and CMW-3 low viscosity. As you can see here it is CMW-3 the 94.1 percent at 5.5 years, which is significantly lower than the other except for boneloc. Boneloc of course at 2 years is much lower than the other comparison groups.

The previous slides was for the femoral. This is for the acetabular. We don't see too much difference here about the comparison groups.

This one is to summarize the Cox Proportional model to estimate risk ratio, to compare the risk among different groups. I used the HV on the left side, the high viscosity reference group. The boneloc has about 8.7 times higher risk of revision than the high viscosity. CMW-3 has 2.4 times higher than the reference group in the femoral.

In the acetabular you can see almost a similar pattern there. But in the CMW-3 it is 0.05. It is even smaller than the HV. But boneloc shows the same picture here .

This is the last table. I don't go into detail here. This is a slide that is modified from the previous table. This is a hypothetical example here called the hypothetical clinical life table comparison of a lower 95 percent confidence limit. The cumulative survivor probability by Greenwood formula or Peter's method.

If you assume at year 1, 2, 3 you have 100 heaps(?) get into the study, and a low loss of 10 heaps lost to follow-up during that interval and no withdrawn patients, a number of risk, so it would 95. It's one of the things is subject half of the ten, because that's the way a life table is calculated.

So assume the number of revision is 10. Then the probability of revision is 10 divided by 95, or 0.105. Then you go through the calculations. Please see the last two columns. The Greenwood formula and the Peter's method are pretty close to each other. The survival probability at the end of three years of 0.895. It's the lower 95 percent confidence interval; close between Greenwood and Peter.

The next interval, the patients get into the next interval, 80 patients, because you have 100 patients at the beginning, 10 lost, 10 revisions, so 20 is out, so 80. Continue this process until the last interval. You have a very small number of patients get in the last interval, only 10 patients. If you have 5 lost, the number of risk at 5. You observe no event. So the last 2 lower 95 percent confidence interval between Greenwood and Peter are quite different.

The Greenwood formula is by most of the publications is 57 percent, but the Peter's correct method is only 37 percent, which is adjusted for the limited sample

size at the last interval, and adjusted for the number of non-observed revisions due to the small number of patients at risk in the particular interval. The formula is at the bottom of the chart. The reference is given.

MR. DEMIAN: Thank you, Dr. Chang Lao.

Now I'm going to summarize the panel questions which the agency is seeking recommendation for this reclassification petition. I'm not going to read the questions, I'm just going to summarize them. The first one deals with a classification. You are going to see this on Question 4 of the supplement data sheet when you are filling out the reclassification worksheet.

The second one deals with the viscosity of the bone cement and issues surrounding this. This is Question 5 on the supplemental data sheet.

The next one deals with the cementing technique, and it is Question 5 on the supplemental data sheet.

The next one deals with the technical problems associated with bone cement. Basically we're asking have all the risks to health for bone cement been adequately assessed.

The next one deals with the intended use in hips, knees, and other joints, and this is Question 4 on the supplemental data sheet.

This question deals with the special controls.

Have all the special controls been adequately identified to control the risks to health? That is Question 7 on the main data sheet.

This one is specifically for the pre-clinical special controls, and this is just a laundry list of these pre-clinical test methods that can be used. You're going to find this is Question 7 on the main data sheet.

The last one is, when is it appropriate to use clinical data as a special control?

We request that you discuss the presented panel questions when you are completing out the reclassification worksheets . Thank you.

I will turn this meeting back over to our chairperson, Dr. Boyan.

DR. BOYAN: Thank you, Mr. Demian.

Before we have presentations from our panel reviewers what I would like to do is declare a five minute break.

[Brief recess.]

Agenda Item: Open Public Session (Bone Cement)

DR. BOYAN: [Administrative remarks.]

Now I would like to return us back to the actual order of business. We have had the petitioner presentation. We've had the FDA presentation. We will proceed with the open public hearing session of this meeting. I would ask at

this time that all persons that want to address the panel specifically related to bone cement come forward and speak clearly into the microphone, as the transcriptionist is dependent upon this means of providing an accurate record of this meeting.

Again, we're requesting as before that all persons making statements during this open public hearing disclose whether they have financial interests in any medical device company. Before making your presentation to the panel, in addition to stating your name and affiliation, please state the nature of your financial interest, if any.

I realize that you all say you have no financial interest as they relate to bone cement, but you have a financial interest in one of these companies that is unrelated to bone cement, and bone cement is only one small part of the business.

Seeing none, I am going to ask Mr. Demian to summarize a letter received by him from Helmedica(?) .

MR. DEMIAN: Thank you, Dr. Boyan.

This letter is dated April 15, 1998. It was written by John Decheroff(?) , director of regulatory affairs and public policy. In this letter he basically comments on the classification of bone cement that is proposed. In the petition these comments that are in this letter were also submitted in the petition, and they were in regards to the

restrictive nature of the classification that was proposed. It did not include esters of methyl acrylic acid. He goes on to say in the letter that this may restrict future bone cement compositions from coming to market through the 510(k) process.

I think that covers it Dr. Boyan.

DR. BOYAN: Thank you. Now we will move on to general panel discussion. The first presenter will be Dr. Harry Skinner, who will review the critical aspects of the reclassification petition.

DR. SKINNER: Thank you, Dr. Boyan. I think that virtually everything has already been said about bone cement . I think that we orthopedic surgeons are very familiar with this. Some of us have used it for more than 20 years. We understand its handling characteristics. We understand its clinical characteristics, and from the data provided prior to the meeting and at this meeting, we know what it’s clinical history is over long periods of use.

I don’t have any particular problems with a reclassification of this from Class III to Class II. I would make certain suggestions regarding it, however, if possible. One of these would be that the indications be expanded to include long bone tumor reconstruction. I think the other indications are appropriate.

I think the additions that are suggested to the

package insert are appropriate. But I think that the package insert is a problem in that when the bone cement is opened, the package insert is always thrown away. I would suggest rather than just including changes in the package insert, that a brochure be prepared that the orthopedic surgeon could have access to prior to the actual use of the material, since when he is using bone cement it is almost always when he is scrubbed. It is awfully hard to read those package inserts with those gloves on.

Now in addition to that I think that many of us have grown up with the history of bone cement, and understand its handling characteristics and the problems that can happen when the room is warm or when the patient is warm or when bone cement is warm. I think that the brochure I'm talking about that I would recommend be to provide some of that information that so proper handling techniques could be taught to people who are unfamiliar with it, who have a shorter history in orthopedic surgery.

I think that all of the general and special controls that have been mentioned are appropriate and would be suitable for applying the safe use of bone cement as a Class II device.

DR. BOYAN: Thank you very much. I would like to now turn over to Dr. Jeremy Gilbert, who will present a pre-clinical review.

DR. GILBERT: Well, I too would concur with Dr. Skinner's comments on the long history of bone cement and its successful use. I think we saw from the clinical data that its survivorship and success is really the standard I think for total joint replacement.

In terms of the pre-clinical review, one of the things that came out to me in this discussion was the issue of the difference between low viscosity and high viscosity cements. There are some physical reasons why there are differences in the viscosity of the cement. Things like monomer to polymer ratio, polymer molecular weight, things of that sort, even particle shape and size can influence the viscosities .

I think if we are going to make a distinction between low and high viscosity those distinctions ought to be made at a more physical, material characterization level than simply just the viscosity. So I would suggest that molecular weight/poly-dispersity be one of the things that is included in information on the bone cement.

I suppose in thinking this over one of the things I was concerned about was what defined PMMA bone cement. As we heard the letter from Helmedica, they are concerned about what are the appropriate monomers and polymers to be added or included in a bone cement. I guess my feeling is that we have a lot of data on a few compositions, and it is those

compositions that I feel most comfortable reclassifying. If we go to other chemistries, I get less comfortable with that. So I guess I would argue against the Helmedica letter.

In terms of mechanical properties -- well, let me back up for a second. Along the lines of compositions, I also believe it is important to have in the insert or somewhere, a complete description of the cement that would include the amounts of initiator and accelerator, the amounts of radiopacifier, and as I indicated, molecular weight of the polymer. I think those are important for understanding the behavior of these cements.

If I go the issue of mechanical property, I think it would be reasonably well accepted that it is fatigue of bone cement that is probably the most critical mechanical property to be concerned with. There have been different approaches to measurement of fatigue, so-called stress controlled and strain controlled fatigue testing. I think that issue needs to be carefully looked at. I suppose my preference would be for more of a load control test as being appropriate.

Also, viscoelastic properties were mentioned. Creep is another concern in these long-term processes, and I think that needs to be thought about as well.

Two other comments. We saw this morning a little

bit of a discussion about BCIS, bone cement implantation syndrome. One question that comes to my mind, and perhaps somebody in the audience or around the table might be able to tell me, have there been any studies that have looked at things like differences in the cementing technique on the incidence of BCIS, namely, pressurization techniques? If you pressurize the femoral canal during insertion or during delivery, will that change the incidence of BCIS? So I think that's a thought that I had listening today.

The other thing I didn't really hear discussed was the issue of particle debris generation from bone cement. Dr. Boyan is shaking her head. What was initially called cement disease I suppose, and after it happened in cementless it was cementless disease. I still wonder about the contribution of bone cement to that disease process.

That ends my comments.

DR. BOYAN: Thank you very much. We have reached a critical juncture where the actual arrival the worksheet is important. Where is the worksheet?

We are going to go around the table now, and I'd like to start with Dr. Urban, if I could, and ask you to specifically address issues related to the bone cement implantation syndrome. Then go on to Dr. David, and ask Dr. David to then be the next speaker. We will go through and ask our industry representative if he will add any comments.

We'll go around this way, and then finish up with you Dr. Hale.

So Dr. Urban, would you like to begin the general discussion?

DR. URBAN: Well, to begin with, my experience and that of my colleagues in the literature is that there are always physiological consequences of cementing femoral prostheses. The question always is whether there are clinically significant consequences. Usually there are not I think, because of the patient population, or the situation the patient is being observed in.

Hence, the sicker patients, elderly patients, in cases where using a long stem prosthesis where there has been a pathological disease, where there has been a fracture, where there is, as was pointed out, regional anesthesia -- regional anesthesia can cause a decrease in semi-vascular resistance.

And if the clinician taking care of the patient hasn't done enough to insure that there is adequate hydration, adequate cardiac index at the time of insertion of even a primary hip that is cement, the release of substances, possibly methylmethacrylate monomer itself, and probably possibly other intramedullary contents can cause enough physiological changes to result in hypotension, arrhythmias and cardiac arrest. I think that these are real

consequences of putting in a cemented prosthesis.

I think that the question was asked whether things can be done to limit that, and I think that there are things that can be done to limit it in situations where there are higher risks, in situations where there are fractures, particularly peri-prosthetic fractures. I think to leave areas of the bone open, and I think lots of orthopedic surgeons do that, so that there is actually leakage of the cement during the insertion of the prosthesis decreases the amount of pressurization of the canal.

In some cases not to put a restrictor in will decrease the amount of pressurization; to make sure there is adequate lavage of the femur prior to insertion. These have been studied not only in humans, but in animal models, and discussed at length in many, many orthopedic and other related meetings.

What worries me somewhat about a general classification for bone cement, which was also pointed out, is there are differences in the physical properties **via** the chemical properties of cement . Some of the cement, because of its nature of being more or less viscous, can be more infiltrated. If it is more infiltrated, is it more likely to cause the release of intramedullary debris?

It seems to me that there is a body of evidence that is available to look at for that. The Swedish

registry, which looked at the differences in cement with regard to the longevity of the prosthesis should have the capability of looking at the differences of cement with different properties, to see whether there was a different in peri-operative complications.

So in a reclassification to Class II it would worry me if the chemical composition of those agents that were allowed was too broad so that numerous cements were allowed on the market which had possible chemical compositions which could cause deleterious physiological effects was allowed without extensive clinical evaluation.

The other feature which I'm curious about is the mixing of the cement, because there has been discussion briefly at this meeting this morning, but also extensively in the literature about whether centrification, vacuum mixing, hand mixing is better.

Whether there is less porosity of the cement at the end, which affects its longevity. Whether is more of the monomer, which is actually polymerized in one form of mixing as another, and hence the possibility for lower physiological consequences at the time of cement. I'm not so sure that has been adequately addressed either.

DR. BOYAN: Thank you. Dr. David.

DR. DAVID: I have very little to add to what has been said so far. Based on the information presented this

morning there are three points I would like to make. One is relating to the technique, and I think those were addressed by my colleagues already. I would just like to emphasize that that should be part of the labeling.

Those relating to patient selection criteria. Cement versus cementless, and resembling therefore outcome of perhaps younger patients in cementless application, and therefore the results we see in the studies.

The last point may be somewhat minor, but it caught my attention that there are cases reported in the MDR that the monomer ignition took place in the operating room. I would be concerned that the appropriate controls would be in place to remove that, because of the catastrophic effect that can take place.

DR. BOYAN: Thank you. Dr. Silkaitis.

DR. SILKAITIS: Yes, I have just two comments, one pertaining to the down classification. The second is in regards to education.

In regards to the down classification process, I view this more or less like making a generic product. We have the fact that the ingredients are defined, the risks are known so that it can be communicated through labeling, that as long as the performance characteristics of the biomechanical testing is defined, then making bone cement consistently then is defined.

So in essence, you don't have to repeat a clinical trial every time you make the same product. It's just from a different company. So that's my comment in regards to the down classification product, that we're just basically genericizing the bone cement with this specific ingredient list.

In regards to education, education is certainly key. The way that surgeons are educated on that is through training courses and through the package insert; primarily through the package insert. I agree with Dr. Skinner that we need to find a better way. One of the things that I would certainly recommend is also that the societies, the orthopedic societies, the neurosurgeons' societies also take an active role in communicating that surgeons ask for the package insert before the product.

It is certainly available, because a lot of times at annual meetings we will pass out information, only to see it in wastebaskets later on. The package insert is freely given out. It is requested from the salesperson, so that the surgeon would have the opportunity and luxury in his office to review in more detail.

One of the questions, is that enough or should there be additional information on the package insert to satisfy some of the things that you had. Certainly if we make another brochure –- and I'm not sure what the mechanism

would be to give it to them -- that's where I would ask the societies to encourage their surgeons to ask for the information from the companies, and the companies will certainly provide that.

That's it.

DR. BOYAN: Thank you. Dr. Altman.

DR. ALTMAN: Thank you. There is obviously a need for the bone cement. There are apparently some risks involved. I don't know of anything in medicine or dentistry that doesn't have some risk, so I guess the issue is acceptable risk. I think the risk here is acceptable.

I agree with Dr. Skinner. I think the more we can educate the physician, the better off the patient is going to be, so I'm all in favor of a reclassification with these conditions .

DR. BOYAN: Dr. Aboulafia.

DR. ABOULAFIA: 1'11 keep my comments brief too, because I think most things have been addressed. I agree with the recommendations that technique for proper use of the cement be added to the package insert; things that may reduce the incidence of BCIS. We don't know for sure that lavage does, but I think there is a general consensus. While you don't have to say they must do it, you can say it has been recommended by some that this may decrease the incidence of BCIS.

The other thing I think Dr. Skinner already addressed was the indications be expanded to include reconstruction of large skeletal defects resulting from tumor. We use it all the time now. Benign or malignant, I wouldn't say either one. I would just say from tumor, and I wouldn't limit it to long bones, because we do also use it in flat bones.

Then the only one was with contraindications, it says currently as it is proposed that bone cement is contraindicated in the presence of active or incompletely treated infections. I understand what they are talking about is you don't put that total hip in when there is ongoing infection, but when we do take out a hip for infection, most orthopedists or many orthopedists use it an off label fashion, and use methylmethacrylate with antibiotics .

So it almost makes it sound even worse than what we are already doing, and I would say that is common, if not a routine practice. So if they wanted to put something about contraindication in the face of infection, it might be better to say contraindicated in the presence of active infection where revision total hip arthroplasty is contraindicated. In other words, you aren't putting in a cemented revision total hip without a bone infection, but you can put an antibiotic cement spacer in the knee or

beads, et cetera.

DR. BOYAN: Dr. Laurencin. Can I ask you, Dr. Aboulafia, can you repeat that phrase one more time?

DR. ABOULAFIA: PMMA bone cement is contraindicated in cases where revision total hip arthroplasty is contraindicated due to active or incompletely treated infection.

DR. LAURENCIN: I find the proposed down classification quite satisfactory with the additions set by Dr. Skinner for use in treatment of tumors, and also in conjunction with antibiotics for treatment of infection.

DR. BOYAN: Dr. Cheng.

DR. CHENG: I just expand indications as Dr. Skinner said for both primary and malignant bone tumor.

Then with regards to the infection issue, we do use it off label for antibiotic beads, in the construction of them quite a bit. There are one stage reconstructions being done using antibiotic impregnated cement a la Dr. Clyde Duncan's(?) technique. So I think the phrase proposed by Dr. Aboulafia probably needs to be modified, basically indicating that non-antibiotic impregnants should not be placed in an active infection.

I would propose that another condition be added. If the use of antibiotics in cement is to be given as an indication, as it is already being done routinely with the

other cements now, then perhaps it might be useful for the surgeon to have some elution characteristics of antibiotics. You can't do all of the heat stable antibiotics, but tobramycin being the most widely used. One could at least study that and cite what the elution characteristics are.

DR. BOYAN: In the package insert?

DR. CHENG: Well, I think the same as the other pre-clinical mechanical testing. I think since surgeons are going to use it for antibiotics, they ought to know what the elution characteristics are.

DR. BOYAN: Dr. Coutts.

DR. COUTTS: Just about everything I was going to say has been already been said. I think we have to work on the language for this infection use, and I think the issue of adding antibiotics to cement touches on a non-approved use of the cement. Even though it is commonly used in clinical practice, it is an off label use. So I think we are going to have to struggle with the language on that one a bit. I agree that to categorically say that cement should not be used in the face of infection would fly in the face of common clinical practice today.

I thought the language was a little deficient in terms of dealing with the bone cement disease. It just says that appropriate action should be taken to prevent it. I think what some of those actions are, as Dr. Urban pointed

out , should be included in the package insert, such as making sure that the patient is properly hydrated, and that the cardiac function is as good as it can be, as well as issues that the surgeon can undertake to try to prevent it such as the lavage, and decrease in the pressurization if there is a high risk or concern.

I would agree that we should add the indication of tumor reconstruction.

DR. BOYAN: Thank you. Dr. Li.

DR. LI: Thank you. First, I would like to thank the sponsors, the physicians, and the FDA for providing an excellent overview and review of the area of bone cement and total joint replacements.

I am in complete agreement that the currently available cement in the U.S. has provided excellent clinical performance over the years, and I have no problem with their performance whatsoever.

So my comments are actually from a different viewpoint than the previous speakers, as perhaps the panel's only polymer chemist. My profession is in fact to modify the properties of polymers for total joint replacements. Let me say with absolute certainty that my issues are not with currently available cement, and how possible down classification would impact the submission of future bone cement .

So let me tell you also with complete certainty as a polymer chemist, I can construct a polymer with the exact definition of the proposed classification, and it would in fact be the world's worst bone cement. So I think it shows a little naivety in terms of polymer fabrication that simply describing the specific monomer, and saying primarily composed of a particular monomer is anywhere near sufficient in describing the cement that would absolutely be safe for clinical use.

So the other issue is off label use. The physicians have mentioned one, which is the addition of antibiotics. There are other procedures that are also off label . Physicians turn out to be a very clever and inventive bunch, and labeling of techniques for instance for heating the monomer prior to insertion of the hip stem, or heating the powder itself, or heating the hip stem itself while inserting the femoral stem into the femoral canal to decrease the curing time, so the set time is faster to reduce surgical time has become a very common practice, but a very off label -- obviously -- use of this material.

So do these off label procedures impact future cements? I think kind of fortunately the clinical experiment of using these on patients has said that with the currently available cements, all these techniques do not seem to adversely affect the clinical performance, however,

these off label uses may in fact affect future bone cements in a different way.

In the sponsor's application they said that there was an existing list of properties that one could look at, that Dr. Gilbert mentioned; things like molecular weight and compressive strength. They had a comment in there that although these were measured, there is in fact connection with these properties with clinical performance.

Now on a general scale, that's true, but let me point out to you that in fact from the presentations this morning we have one cement, Palaces, that at least in one study seems to be a little bit better than the rest, and one cement, boneloc, which seems be severely worse than the rest .

Now even given the fact that boneloc has a very different chemistry, you should note that the physical properties may have been predictive. For instance, boneloc had the lowest four point bend strength, the lowest fracture toughness, and the lowest stress controlled fatigue. So it's a little pejorative to say that physical properties are completely unpredictive of performance.

On the other side, Palaces, which in some studies has appeared to have some advantage, keep in mind as Dr. Gilbert pointed out, that Palaces has a very different molecular weight distribution than the other four bone

cements, and it also has the highest fracture toughness value .

So it's not exactly clear that we measure these properties for no good reason, other than to characterize the cement. At least with the clinical experience, there is in fact a good example, Palaces, and a bad example, boneloc, that in fact have different physical properties.

Dr. Boyan I'm sure is going to cover the biological responses, so 1'11 leave that alone, and assume that you are going to cover that when we get there.

So let me finish up by saying that I think that if regardless of the classification for bone cement, I think the characterization of the material and the specific set of a mechanical test regime is absolutely required regardless of the classification. The sponsors make a couple of indications that fatigue and fracture testing is not particularly standardized. This is in fact true, but on the other hand there are in fact a limited number of accepted fatigue and fracture toughness tests that I would strongly recommend, if not almost demand, that these specific tests be indicated in however bone cement ends up to be classified.

So the phrase "appropriate testing must be" from my materials standpoint is almost no requirement whatsoever, because ahead of time we would not for instance be able to

predict that a molecular weight distribution for instance would give you good or bad performance.

So there is a little lack of understanding from the basic science standpoint between the actual polymer structure and clinical performance. So in the absence of this direct connection, I think a specific test regime should be laid out, and should not be left to the applicant for the submission of a new bone cement.

DR. BOYAN: Thank you, Dr. Li. Dr. Larntz.

DR. LARNTZ: Just a few comments related to statistics. Dr. Lao made a number of points that are very important . Because the historical data we have is from papers for which the data themselves are not available, it is very difficult to validate whether all the assumptions are correct and appropriate for the data. That is almost always true, so I think that's important to notice.

However, if we think about the papers that we did review, all of the data were from registries of some sort or another. In fact, because they are observational data as opposed to randomized comparative data any differences in assignment of treatments to either bone cements, or if you want to compare cemented and uncemented or any other item, any assignment that is done in this observational way, there could be differences that are not related to the item you think that you have here.

So differences in bone cement could in fact be associated with differences in patient selection. I do understand that there may be different treatment by age for instance . So if we see differences in outcome, they may in fact due to age, as well as to differences say in cement or procedure.

Given that, however, and given that we have incredibly large registries, which I think are wonderful, but we have to remember there are limitations to observational data, it does appear that we have seen that there are differences in bone cement with respect to outcome. It's not true that all bone cements are exactly identical with regard to outcome, at least in these observational studies.

So with respect to future bone cement, new bone cement could be different from the others. I think that is possible. Now how do we evaluate that? In actual fact, the rates of revision, particularly in older patients is very low. In younger patients it is actually higher, and statistically if you were going to study numbers of patients, you would want to do your studies in younger patients, but you would have to decide that.

But you would have to do very, very large studies, and very long-term studies to actually do any clinical studies with respect to bone cement. That seems very clear

to me, given that we have to have 100,000 patients to get significance at some level, that seems to have to do a lot of patients in a clinical study. So I'm not sure it's practical to do a clinical study, and I guess as a statistician it's sad, but I recognize that, okay?

Now beyond that, so what do we do? Well, if bone cement is really good, which is seems to be, and does its job really well, that's great. But it puts very strong importance on the pre-clinical testing of the material, and I think it is absolutely imperative that pre-clinical testing be done in a comparative way.

That in fact as Dr. Li has said, there may not be standardized procedures, but if the testing is done so that the same procedures are used in comparative ways for comparing the various bone cements that are proposed to currently used bone cements, I think that is an absolutely imperative action to be taken for submission of information about a new bone cement. So I think this pre-clinical testing done in a comparative way is critical, and should be carried out.

I don't think I have any other comments except to say if we want to see what happens to future cements, particularly ones used in the United States, it would be very difficult to do without the registries of the size that are done in Sweden and Norway, and that is an incredible

effort to undergo in our system.

And so we have to understand the risk if we put a new bone cement on the market, and it's not as good as the others, it may be very difficult to find that out for a long period of time.

Thank you.

DR. BOYAN: Thank you. Dr. Rangaswamy.

DR. RANGASWAMY: I guess the advantage of being last is everybody has brought up the same issues, and I have nothing further to add.

DR. BOYAN: Dr. Hale.

DR. HALE: Most of my concerns have also been brought up, but I do have a couple of comments I would like to make. With regards to the regulatory controls for pre-clinical testing, I too agree that those are critical particularly in terms of fatigue and creep. I'm a little bit concerned about some of the off label uses that have been mentioned, particularly in terms of antibiotics and the effect on mechanical properties.

If that is something that is happening after the product is marketed, we have very little control over what that has on the mechanical properties. Things like increasing the volume percentage of the antibiotic or the mixing techniques may greatly affect what the results of the pre-clinical mechanical-type testing are.

The other concern I have has to do with some terminology that has been presented for the labeling in terms of the BCIS and its link to overpressurization. There have been some studies that suggest specific pressure values that may be responsible for creating this condition. I guess what I would suggest that the labeling or the brochure, however we are going to go about doing this, include some more specific language about what constitutes overpressurization, so the clinician has a better sense of how much pressure is too much pressure, or at the very least specifically mentions some of the techniques that the sponsor mentioned early on for ways to minimize that pressure, like venting the canal.

DR. BOYAN: Thank you. The only comments I would add from a biological point of view are that the actual way that cells respond is not so well studied as one might think. The way that osteoblasts, any bone cells that are bone forming cells or bone maintaining cells interact with PMMA is one of the most understudied areas of orthopedic research.

A lot of effort is spent understanding how these cells interact with titanium and titanium alloys, even with stainless steel, but very little is understood about how they interact with PMMA or the particulate, and particularly the particulate.

Why that is the case is not clear to me. It may because it is well tolerated, and that the patients that have these kinds of materials placed in them, once the histology was done and it was not particularly exciting, scientists tend to stay away from the field. But as we understand more about how particles in general are affecting cells, I think that there will be some renewed interest, and that may affect how we think about the materials down the line.

I think at the present time, and with the present materials it may not be as critical to understand that right now. But I certainly think that when information becomes available, FDA should stand waiting to take it into consideration on how it handles its review of these materials over time.

So I would now like to invite the sponsor of the petition, and ask them if they would like to make any general comments in the discussion that we should take into consideration before we start on the worksheet.

Since I don't see the sponsor rushing up to the microphone, FDA, would you like to make some comments?

DR. WITTEN: Just one. While I appreciate the remarks from the panelists about adding tumor reconstruction as an indication, and also about including antibiotic mixed with bone cement, when you go through the data sheet and the

questionnaire, it should be in response to the petition, which does not include those two things at the present time.

DR. BOYAN: Thank you for that clarification. Dr. Aboulafia, your wording may get us there, don't worry. Thank you, FDA.

Well, OSMA, does anybody else in the audience have anything in particular they would like to add to the discussion? FDA, Dr. Panitch, anybody like to add -- Dr. Johnston?

DR. JOHNSTON: I would just like to make a comment about whatever the syndrome you call it, the dramatic reaction to bone cement. In your criteria for avoiding that, if you include things like overpressurization and lavage and so forth that there is skimpy for -- not conclusive evidence for -- that you are increasing the potential cost of a joint replacement, because you are going to require the surgeon to do that when he may not need to.

DR. BOYAN: Thank you. We'll take that into consideration when we get to that point. Thank you for that comment.

Yes, sir?

DR. MALCHAU: I have two comments. Looking for the risk for cementation implantation syndrome, we can actually not show any difference between men and women, looking at the hip fracture group. Or if there is any

difference, it is in favor of the men.

The second thing I would like to add is that due to the cement delivery system used in Sweden, the Palaces is used in a chilled fashion, which makes it actually a low viscosity cement. That might be part of the early failure rate when the vacuum systems are used. But besides that, we still have an outstanding, long-term result of the Palaces.

DR. BOYAN: Thank you.

DR. SMITH: I'd like to try to clarify a little bit the low viscosity, high viscosity in CMW-3. Is it Dr. Cheng Lao -- his presentation showed some comparisons between high viscosity and low viscosity cements, and I think you did a pretty good job of showing that CMW-3 is not the low viscosity cement, and it is not the definition of low viscosity cements, but just an example.

The impression that one would get from the Norwegian arthroplasty paper by Havelin is that low viscosity cements perform -- their performance is substandard to high viscosity cements. I suppose that may be true, but I think it's a little bit unwise to generalize this to the CMW-3 results to all low viscosity cements.

There was a paper by Carlson I believe in 1993 that is included in the petition where a low viscosity cement and a high viscosity cement of similar chemistries, similar strengths were compared, and the 5.5 year survival

us also. After we're to have this discussion, which we just had, we're going to have the overhead up there, which we do have . We will now go through these panel questions as they pertain to the reclassification worksheet.

As we go over these one at a time, I will ask each panel member to comment on each question. Now the way I'm going to do this is I don't want to limit this discussion, but I also don't want anybody to feel obligated to discuss that has nothing to say. So we'll define the question as best we can, and then I will try to go quickly around the room. I will always start with Steve Li and go quickly around the room, with either saying what your comments are, or saying you agree with or whatever.

The FDA is really going to use this information, so the more information we give them, the better off things will be all the way around. So if there is a way, if you feel you have to say pass, you can say pass, but please, for the sake of the FDA, if you have a substantive comment, please offer that comment. We'll see how we do with that system.

Are you going to actually read the question or am I? So basically the first question is:

1. Is the device life sustaining or life supporting?

Is there anybody here that feels that this device

is life sustaining? If there is someone who thinks that, please raise your hand and indicate yourself. Is it safe to say then we all believe that this is device is not life sustaining and life supporting? Yes. So the answer to this question is no.

We now go to item 2.

2. Is the device for a use which is of substantial importance in preventing impairment of human health?

The answer to this would be yes. Is there anybody that thinks the answer to this would be not yes? If there is a person that thinks that, please identify yourself. So the answer is yes.

Now we go to item 3.

3. Does the device present a potential and unreasonable risk of illness or injury?

We'll ask you, Dr. Skinner, to address the answer to this question for us.

DR. SKINNER: No.

DR. BOYAN: No. Is there anybody that thinks that disagrees with Dr. Skinner's position, and thinks that this device does present a potential unreasonable risk of illness?

DR. LI: I have just a question.

DR. BOYAN: Yes?

DR. LI: Does this mean the device like in any current or future form?

DR. BOYAN: The device that they have presented to us in the petition is the only one that we are considering right now.

DR. LI: So this is the currently available then bone cements?

DR. BOYAN: The one as defined in the petition as currently available bone cement. The definition of the device as defined.

DR. LI: So there could be future cements that fall underneath their proposed definition. Then I would vote yes.

DR. BOYAN: Okay then what we need to do, just to get a sense of how we are going to do this, we need to go around the table starting with you Dr. Li. You would say yes, and do you want to give us your reason why?

DR. LI: Again, I think it goes back to my earlier comments. I think in the absence of more specific certainly mechanical testing, and in my view the classification, although reasonable, provides plenty of leeway for someone who could fabricate polymers to make a material that fits the definition, yet be a lousy bone cement. If you do that incorrectly, then you can in fact end up with a very poor bone cement for clinical use.

DR. BOYAN: Dr. Larntz.

DR. LARNTZ: As the question is written, potential unreasonable risk, it is possible, yes. Just because that's potential unreasonable there, and I think Dr. Li has given good reasons for that.

DR. BOYAN: Dr. Gilbert.

DR. GILBERT: I guess I would have to vote no on this . The main reason I would do that is I believe that with the special controls that we are attempting to assert with this down classification, as well as the history that we have to compare any new cement with as it comes on to the market, that that will present a reasonable control on any unreasonable risk that may occur with a new bone cement. So I would vote no.

DR. BOYAN: Dr. Rangaswamy?

DR. RANGASWAMY: Yes and no. Yes to the product that they are giving us, and no to something new unless all the other controls are put in.

DR. BOYAN: So you are saying that if all the special controls were present, you could vote no to this question?

DR. RANGASWAMY: Right .

DR. BOYAN: So 1'11 put you in both categories. Dr. Skinner, you voted no, is that correct?

DR. SKINNER : That's correct.

DR. BOYAN: Do you want to add any comment to that?

DR. SKINNER: Yes, I agree with Dr. Li. I agree with Dr. Larntz, but the answer is no. It's not an unreasonable risk. This is a material that we are very familiar with. This is a material that has a proven track record, and there is no reason to think that the FDA is going to let a material in the future with the same composition, have mechanical properties that are going to be any different than the ones on the market at the present time .

DR. BOYAN: Before we go to you, Dr. Hale, I would to ask Mr. Dillard for a clarification.

MR. DILLARD: I just wanted to make one point. I stood up before Dr. Gilbert spoke. I think you really clarified it. 1'11 just echo that for a minute. In terms of reclassification I think one of the issues that you are facing and I realize this is a tough one, but the approach that Dr. Gilbert laid out I think is an appropriate approach.

That is to say, okay we can see the world of bone cements with the data that has been presented in this petition. I can you do a little forward thinking at this point too, to say if down classification is recommended from you as the panel, one of the things you will consider a

little further on in this are the kinds of special controls to address just those things that may or may not be unreasonable .

Don't get too hung up on the word, but let's say they are different, or it might be a magnitude change of risk associated with a different formulation or a new bone cement . What we would like to hear from you then at that point is what kind of controls might you think about in a forward thinking approach of a product that could be equivalent .

You've got to remember, if down classification is recommended here, the kind of approach we would be taking at FDA is an equivalents type of approach. So I think that both Dr. Li and Dr. Larntz, you both have issues associated with it, but I think in terms of unreasonable and the way you can separate those so you don't get hung up on this question is something that can be addressed when you get to special controls in some of the other questions in the checklist .

I hope that has clarified things a little bit for you .

DR. LI: Perhaps it's just the order of the questionnaire that is throwing me off. We never talked about what should be in the reclassification. So I looked at this as prior to agreeing on what should be in the

classification, is there a way to make a bad bone cement is how I answered the question.

DR. LARNTZ: If I may add, I clearly had pretty strong statements about the pre-clinical testing. I think it's absolutely imperative. I think if we do understand the physical properties in pre-clinical testing, it probably would take away the unreasonable risk. If we are saying we are supposed to answer this after we think everything is okay, then I --

DR. BOYAN: Actually, we're not. I think everybody is too worried about this. No matter what we answer here, because of our answer to number 2, we have to go down to item 3, where we will discuss all of these controls. Then we'll come back and we're going to vote on the motion for whether this should be classified or not classified.

So this is not the deal maker or breaker here. This is just a statement as to whether or not we think there is a risk, a potential risk. I'm just trying to get a general gist of how we are going to answer this question, and then we can go on. Right now it's an even contest for how we are answering this question, and I think with the clarification from Mr. Dillard, we might feel more secure saying no or saying yes, but we have already pushed ourselves into the full discussion by our answer to the

previous question.

Dr. Hale.

DR. HALE: Although I appreciate Dr. Li's comments, I would agree with no as well, and agree with Dr. Gilbert's reasons.

DR. BOYAN: Dr. Urban.

DR. URBAN: Yes, I think that the points raised by Dr. Li are excellent, but I would vote no with special considerations .

DR. BOYAN: Dr. David.

DR. DAVID: I feel comfortable that with the controls we have, that this is a reasonable risk.

DR. BOYAN: Dr. Aboulafia.

DR. ABOULAFIA: I think we all agree, and it's a semantic issue, so no for discussion, but procedurally we know where we are going.

DR. BOYAN: Right. Dr. Laurencin.

DR. LAURENCIN: I think it is clearly no, with the controls placed in.

DR. BOYAN: Dr. Cheng.

DR. CHENG: No, with controls.

DR. BOYAN: Dr. Coutts.

DR. COUTTS: No.

DR. BOYAN: So if we have eight that say with the controls they are comfortable. Dr. Rangaswamy?

DR. RANGASWAMY: No, with the controls.

DR. BOYAN: Okay, nine. And we have two that have made their comments, and I think their comments are being accommodated. If they are comfortable, I would like to answer this one at this point with a no.

Now we did answer yes to any of the three above questions, so we answered that yes. Now we go to item 7. Now item 7 is where this gets complicated. At this point -- we have all been here with item 7, and this is where it gets stressful . This time to focus us through item 7, we are going to start to address the panel questions specifically to help us get through this.

You can see here that we are to address certain issues . I think where we are here with the panel questions is that they are going to help us do this so that check off all these little areas correctly. The first panel question:

1. Have appropriate special controls been identified by the petition to control each risk to health?

We have already agreed that we need special controls, so the answer to the question is apparently not. Then if not, what special controls are needed?

So why don't we start down with Dr. Li, who has some really good pre-clinical controls that need to be put in, and we'll start with those.

DR. LI: So I'm not sure of the procedure here.

Am I supposed to talk about a list of what I think should be in there, or just respond with a particular suggestion of what controls should be?

DR. BOYAN: At this point do we just say yes, there should be special controls, and then we start discussing them in detail on the supplemental data sheet?

DR. WITTEN: I think you could discuss now what you think they should be, and we could fill them.

DR. BOYAN: Okay, let's go ahead and get them out on the table. Dr. Li.

DR. LI: I'm still not exactly sure. So you are looking for a specific list of what I think the pre-clinical testing should be for instance?

DR. ABOULAFIA: If there are things that you think should be added to the petitioner's special controls that they have put in place.

DR. LI: The only question I have, and maybe this is something the sponsor could answer for me, having read this a couple of times, I'm a little confused over exactly what tests you are proposing, because it seems like just about four or five pages of potential tests you could run on this . It's unclear to me if you think that anybody with a new bone cement should just pick and choose from the menu of tests, or do you think they should all be run, or what?

DR. BOYAN: Sponsor, would you respond please?

DR. SMITH: There was certainly discussion about whether we should try to specify tests that should be done. I guess in my opinion -- I believe that I speak for the other petitioners -- that specification of the tests might be better dealt with in a guidance document, as it is being dealt with, and as well as the ASTM and 1S0 forums.

The list of tests that are provided there are presented as suggested tests, either as required or as exclusive tests. I don't know if that answers your question or not.

DR. GILBERT: If I could interject for a moment. Page 41 of the handout that the panel got this morning of the fairly thick document I think lists a table of proposed physical/chemical test matrix, and Table 2, mechanical test matrix on PMMA bone cement. Perhaps we could look at that as a group.

DR. LI: That's exactly where I am. My question to them was were they proposing all, or were they proposing them as kind of a cafeteria of tests that one could pick and choose when they had an application.

DR. BOYAN: May I make a suggestion? At this point what we really want is to identify the kinds of information that we think are necessary to be known, and not put it upon the sponsor of any particular application to FDA to identify the appropriate tests that would provide that

information, because tests change over time, as the device will change over time.

DR. LI: Right . This is where my confusion was. I wasn't quite sure how to answer the question.

DR. BOYAN: I'm not sure either, but I propose my system, because to me it seems to me that we have identified certain pieces of information that we think are critical to have, and then I think it should be up to the sponsor as to whether they address those pieces of information.

DR. LARNTZ: The FDA has already established a guidance document in orthopedic bone cements, in establishing what the pre-clinical tests should be. I have been handed a guidance document that was just updated in November 1993. I would suggest that that would be the basis for the pre-clinical controls. It is a document specifically designed for orthopedic bone cement.

DR. BOYAN: Dr. Silkaitis, did you want to add anything to what just was stated?

DR. SILKAITIS: Yes, the only thing that I wanted to mention was that on page 40 they list the ASTM and the 1S0 standards, and the tests that are included in them. I'm sure that is part of the FDA guidance document also. That would be more encompassing.

DR. COUTTS: It looks to me like we have a list of boxes that we can choose. The discussion seems to be

focused around performance standards. Don't we just want to check performance standards?

DR. BOYAN: Yes, we do want to check performance standards, but we have the issue of giving more guidance to the FDA than that. On the supplemental data sheet we will spell out more what they want, but while we are at this part of the discussion, we thought it might be more convenient to go ahead and address the whole issue.

DR. LI: Maybe I can shorten this up a little bit. I just got handed the guidance document for the methylmethacrylate that is currently in place. I could have looked at it specifically for some time. Just at a quick glance, by looking over the list of tests the petitioner or sponsor has provided, the list is in fact conclusive of all the tests I would want to see. I don't really see an additional test I would want to run over certainly the combination of lists from the guidance document and the sponsor's suggestion.

So I guess my only question now -- I guess I can just decline after this -- is if this the case, then it would be left to the FDA then to decide what tests should be run when a new bone cement or a different bone cement is then applied for. Then you would handle it in accordance with whatever guidance document you have in place at that time?

DR. BOYAN: Yes. Mr. Demian has pointed out to me a couple of items that we have over here, we all have actually, which helps me sort of formulate where I think we are supposed to be. If we look at the panel question that is on the board, and we also have in our listed information the copies of the slides, there are really three panel questions all dealing with special controls.

If we just stick with the one that is up there, it actually goes back to Dr. Coutts' issue, which is that they simply want to know whether special controls identified by the petitioner to control risk to health, labeling, training, pre-clinical testing, and other, the answer is yes, but we feel there should be more. What special controls are needed? We think there are more special controls needed in each of these areas.

Then if we go to the next panel question, which is the bottom left. Here we go. Itfs up there now. If we go to these issues, these pre-clinical test methods that have been identified by the petitioner, and what you would say then Dr. Li is that those are pretty inclusive. If we then refer to the FDA guidance document of November 1993 as an indication, and then finish it off with saying or other FDA guidance documents that might be in effect.

DR. LI: If these tests are required of applications, then I am happy.

DR. BOYAN: So we are referring them to page 41 and 42 of the petition, and the FDA guidance document of November 1993.

Then the last panel question that relates to this issue is, for this device, when is it appropriate to use clinical data as a special control? I think then we have agreed in our discussion that it may be appropriate to use clinical data with a new cement. We might want to make some sort of statement like that. Is there anybody here that would like to offer that statement? No?

DR. SKINNER: Could I speak to that? I don't think that based on the comments Dr. Larntz made, that we would be able to get good clinical data on this without a very expensive study. I think that that should be left to the FDA if possible to do when they think that there is a problem or a potential problem. I think that we shouldn't mandate it.

DR. ABOULAFIA: That's true if there are only slight differences. If there are big differences like boneloc, then statistically that shows up relatively quickly. Again, I'm not talking about 100,000 patients, Irm talking about 100, 200 patients with 2 year patients.

DR. LARNTZ: One thousand patients in each group you are talking about, to find that kind of information.

DR. ABOULAFIA: No, not each group.

DR. BOYAN: Dr. Skinner's statement even would allow for us to say that should a significantly great enough difference be proposed for a bone cement, that FDA determines that it thinks it needs a clinical study, then it would be an appropriate special control to be put in place.

DR. LARNTZ: Dr. Boyan, could I make one comment with respect to the pre-clinical testing, because I think there is one more point I would like to make with respect to that . The point I would like to make is I think that standards to be set by the FDA with respect to what equivalents means, and testing should be done to prove equivalents better.

I think that's a key item here, because many tests are done with very small numbers. If you actually have statistics on them, they often don't give you very definitive information. So we have been through on this panel before, discussions on equivalents, and I think standards of equivalents should be set for the pre-clinical testing. That's all I wanted to add, is that statistical standards of equivalents should actually be done by the FDA.

DR. BOYAN: All right, here's what we've got. I'm getting training over here in FDA-ese, that's why there was some whispering over here. We do agree for special controls there should be performance standards. I have just learned that ASTM and 1S0 are not performance standards. They are

other. So we need to check other, and put the ASTM and ISO tests. You see, this is not so simple.

We have the one last thing. Just tell me yes or no, Mr. Demian. Are these essential clinical trials considered performance standards?

MR. DEMIAN: Yes.

DR. BOYAN: Okay, so we've covered it. We have checked this one. The answer to number 7 is yes. Where we stand with number 7 is pre-clinical studies as defined in the petition on page 41 and 42, and the FDA guidance document -- in effect I see more FDA instructions coming here -- that we think a clinical study would be appropriate if the difference in the material was so great that FDA felt that one was in order, but that FDA needs to set the standards for how they wish to determine equivalence, because this is the kind of study that should be done.

Did we do it?

MR. DILLARD: One quick clarification, Madame Chairman. Actually, two quick clarifications. One on the clinical data issue, it is not uncommon -- let me just take you through a real brief scenario in a 510(k) sort of program situation. It is not uncommon for a product to come in that has different specifications to the current world of products that are defined by a classification regulation.

We frequently, and it is very commonplace for us

to look at and try to make a judgment as to whether or not pre-clinical and animal kinds of testing alone would suffice for a comparative analysis. That's what we do in the 510(k) program.

Many times if we cannot determine whether or not the in vitro and animal tests will be predictive of clinical outcome, we will ask for supplemental or pivotal clinical data in a 510(k) to try to help make that determination of equivalent clinical performance. That is done every day in the 510(k) program.

So I think what is envisioned here for bone cement is if there a window or a box of specifications that we can draw around the currently existing bone cement, I think we would like comments on two things. Number one, do you think if it fits within sort of the current idea of bone cements, do you think we need clinical data for those as a special control? That might be sub-question number one.

Sub-question number two I think would be if you get outside what is known about currently available bone cements, and the pre-clinical kinds of parameters that we are talking about for special controls, do you think that clinical data would be necessary in a situation like that, or would be recommended?

I think it's not necessarily applying a special control for what is outside of the box, but more a

recommendation as to what you might see for that kind of bone cement.

The other thing is, Barbara, you made a point about performance standards, and I think there was a comment about clinical data as a performance standard. That performance standard -- and this comes up every time we have these meetings -- really pertains the Section 514 kinds of FDA performance standards that we heard about yesterday, and other can be checked for other kinds of standards like international and national consensus standards.

So unless you think we really ought to develop a mandated performance, which has to go through rulemaking, I don't think you need to check performance standard. You can list under other, which other kinds of standards you would suggest. So I hope that helps.

DR. BOYAN: So let me just say back to you what you just said. At this point, checking performance standards would confuse the issue?

MR. DILLARD: That is saying that you would recommend as a panel that we develop a mandated performance standard that is different from guidances, that is different from voluntary consensus standards, that is different from other international or national standards. So it's a much different meaning then. If you think it can be handled with those, you can check other and just list them, just as a

point of formality and the checklist.

DR. BOYAN: Okay, that's what I just did.

DR. LI: I just have a question. So suppose someone came in with a new bone cement for approval. It fit the new definition supplied by the sponsor, but had the physical properties of boneloc. Which means all the properties are exactly the same except it had a little lower four point, and a little lower fracture toughness. What would you do with that?

DR. BOYAN: Oh, are we asking them to make a comment on that?

DR. LI: The issue of performance standards -- basically I have been reading this in head to come up with a very reasonable situation, so just so long as we don't get ourselves into a boneloc kind of situation.

DR. BOYAN: I don't think, Dr. Li, we need to address that here. I think we get another chance to tell them exactly what to do.

DR. LI: I raised it in the view of performance standards .

DR. BOYAN: In performance standards -- I think what they are trying to say to us is this. If we check off the subject performance standards, then we are saying that a whole new kind of standard needs to be developed. There are already, by your description in fact, plenty of standards

listed on page 41 and 42 for application. So we don't need to have a whole new test mode or performance standard developed. The clinical trial -- those methods exist, so we don't need to do that here.

What this is actually trying to help us do is decide whether or not we should classify this item in Class II or Class III. Once we get it classified, then our work really starts. I think where we stand right now is we have said yes to this question that there is sufficient information available in the world today to establish special controls, provide reasonable assurance of safety and effectiveness. I haven't heard anybody say that we need to have a whole, brand new event developed to accomplish this goal.

DR. SKINNER: Is this where we cover labeling? Because labeling was on one of those slides. We didn't address it, because we have discussed the pre-clinical testing.

DR. BOYAN: I think that comes up on our next sheet. We have needed restrictions coming up actually. It gives us a chance to do that there.

So let me take us through where we are right now. I think the comments here are pretty much thorough. So what we did was we said that this was not life supporting. We said that it was of substantial importance to people. We

said that it does not pose an unreasonable risk of illness or injury when the substantial controls are in place. So we did answer yes to one of those three questions. We moved down the list.

We said that there is sufficient information available in the world today to establish special controls to provide reasonable assurance of safety and effectiveness, therefore we have now classified this in Class II.

DR. CHENG: Where would we place antibiotic elution characteristics in this?

DR. BOYAN: We are not allowed to discuss that as per previous discussion, because it wasn't included in the petition. We are going to bring it up in a little bit here in another very carefully worded way.

DR. LAURENCIN: Dr. Boyan, I just wonder whether for a new cement coming onto the market, whether there should be post-market surveillance?

DR. BOYAN: A new cement coming into the market would have to go to FDA and be reviewed, and determine whether or not they think it is substantially equivalent to an existing material. If they decide it is not substantially equivalent, it will be in Class III, and then they can work that.

DR. LAURENCIN: You're saying if it was substantially equivalent and remained in Class II, whether

that material should be followed with post-market surveillance for say two to three years to insure no early failures due to the use of that cement, or to measure other outcome variables?

DR. SKINNER: Dr. Boyan, I think that the FDA has that option under any condition. I think this also addresses the question brought up by Dr. Li. I think that if someone came in with a product that was similar to the boneloc, if that was considered to be substantially the same as on the market cements, then they would probably require post-market surveillance.

DR. LAURENCIN: The question is should we be checking our box for post-market surveillance?

DR. SKINNER: But that mandates it for all of them.

DR. LAURENCIN: I'm not sure whether they should all have some level of post-market surveillance.

DR. SKINNER: One of the things you do with that is you pretty much remove the possibility of someone coming in with another bone cement.

DR. SILKAITIS: Just for clarification, we are using the term "new" bone cement. What I would like to know is where that new fits in. There is bone cement that is made with the same ingredients that have been proposed by the sponsors here, and that can be considered new bone

cement, but it really the same ingredients that are already out there. It's just made by somebody else.

Are we referring to that as new also, or are we referring to new where they made a slight modification in one of the polymers? Or are we talking about when you add polyethylene to the bone cement or some other radically new chemical is used? My understanding is that when we are talking new, we are talking about some radical new chemical being utilized as bone cement, as opposed to what's in this petition being defined as the ingredients that are listed here.

DR. ABOULAFIA: I think Dr. Li addressed that. With the definition as it currently is, he can make the single worst bone cement known to man. What we don't want to do is give permission to the single worst bone cement known to mankind. It's sort of a summary way of doing it.

DR. SILKAITIS: Could I get clarification from Dr. Li? That is, with the controls in place, using the same ingredients, if they had meet a four point bending test, would that bone cement still be the worst bone cement?

DR. LI: No, that was my whole point. My only quibble in all of this or my concern was that the approach - if this list of tests was gone through and it passed, then I would be perfectly happy. My only concern was which tests were required, and which ones weren't.

DR. BOYAN: May I clarify something? As I understand this -- and Mr. Dillard and Dr. Witten feel free to hop in if I get this wrong -- the petition is stating what the ingredients are, and within certain guidelines what the material is, the bone cement that we are reviewing. That's really the one that would have a fairly loose cover over it as to whether or not it fits the description.

If there was an altered chemistry, or some altered material that felt out of those guidelines, it would be reviewed. The sponsor may submit it as a 510(k) or a PMA. Surely they would send it in as a 510(k) and make the effort, and FDA would determine whether or not it was substantially equivalent or not. Then would be entering into the regulatory pathway at that point.

DR. SILKAITIS: Dr. Boyan, I would just like to add that that bone cement would automatically be a Class III, and I would agree with Dr. Laurencin that that would require a clinical trial. So that if it's a new bone cement

DR. GILBERT: If I could lay out in maybe just my simple metallurgist's mind how this would work. If we have a cement that fits the definition according to this proposed down classification, it would come in. The special controls would mechanical testing and other physical evaluations. You would see from that data whether it is meeting the

substantial equivalents that we need to.

If it does, then it can go through. If it doesn't, then perhaps some additional control might be necessary. I think all of that fits under the other category.

DR. BOYAN: Correct. That's the way I understand.

DR. SKINNER: I think what we have to keep in mind here is we are setting a bar for the industry and manufacturers to jump over. The FDA can raise that bar, but we are giving them the minimum bar for them to jump over. So if we make the bar too high, nobody will jump over it, and post-market surveillance could potentially do that. It could add a great deal of expense to a very inexpensive product.

DR. LAURENCIN: Just replying to that, I want to make sure I'm clear, because Mr. Silkaitis mentioned a clinical trial. I'm talking about post-market surveillance, which means monitoring what has been placed out, after it has been placed on the market, but not a clinical trial.

Again, I think that one of the things that Dr. Li said is true. There are very subtle differences in mechanical strength and other capabilities of the implant may have a great difference in terms of its clinical response. We may not make that post-market surveillance a long period of time, but I think that we would like to have

some indication if there is a problem with that cement in the short run, to be able to monitor that. I don't think that's asking for so much.

DR. BOYAN: Dr. Urban?

DR. URBAN: I have heard a couple of things, so let me just make sure I have this correct. The petition is for this specific formulation. The concerns of Dr. Li were that if there were subtle variations in that formulation, it could affect the structural composition or the longevity of the cement, and that's why he wanted performance testing.

My understanding is if they change -- if they added a new initiator or a stabilizer or a new chemical, this would no longer fit under this petition, is that right? It would be a new cement.

DR. BOYAN: That's correct.

DR. URBAN: Because it could have dire physiological consequences as well, is that correct?

DR. BOYAN: Mr. Craig?

MR. CRAIG: Yes, I just want to make a very quick point. I'm Tom Craig with Smith and Nephew Orthopedics.

Under the current requirements for any implant device, there are automatically some post-market surveillance requirements, namely MDR, that goes into effect whether it is required as a condition of approval or not.

DR. BOYAN: Dr. Laurencin has suggested post-

market surveillance. I think that we can address this by a show of hands as to whether or not we want to include it here, and then move on. So if there is a strong need for this, I think that it has been clarified to us that that is always an option of FDA to impose that. It also would be for any substantially different material as deemed by FDA, it would enter into a Class III regulatory pathway anyway, in which case that certainly would be an option.

But let's just clarify the issue and get it down on papers as to how we feel about it. So post-market surveillance -- all those who feel --

DR. LI: Just for a point of information. Is this a big deal like the performance standards with the FDA?

DR. BOYAN: Yes. We are now saying that this is the bar that needs to be crossed.

DR. LI: In the sense of going through rules and all that stuff?

DR. LAURENCIN: I don't it's a giant hoop. I think that the industry for most implants and new types of implants already goes through it. I guess we can get a commentary on it.

DR. ABOULAFIA: I think what Dr. Laurencin is trying to say is there might be a reasonable way of looking at let's say the first 300 patients for 2-3 years, not to look at every patient who has an implant over the course of

20 years.

DR. BOYAN: This would be handled under testing guidelines. So in my estimation the company would negotiate this in effect with FDA during its assessment of whether the FDA feels there needs to be a clinical study, or if they feel there needs to be a post-market surveillance. This is an option where if we check it here, it's my understanding we're saying it has to be done for every material that comes on.

Dr. Laurencin stated that's what he would like. I'm trying to get a feeling from everybody else if they agree with you in order to check this box off. Did you want to add anything?

MR. BARRIS(?) : Ken Barris from Biomet. Just to second your comment, putting in your recommendation that it requires post-market surveillance means that everyone would have to do post-market surveillance. The FDA still has the option to require a clinical trial. So I just second the comment that the MDR system of medical device reporting is in place for these products regardless of whether we talk about post-market surveillance.

It might be feasible to hear from the FDA what the specific term "post-market surveillance" means.

DR. BOYAN: I was just about to ask for that.

MR. BARRIS: Post-market surveillance has a very

specific meaning.

DR. BOYAN: Mr. Dillard, could you clarify the meaning of post-market surveillance in this context?

MR. DILLARD: Every meeting I think Dr. Boyan, for reclassification we go through this, and appropriately so. It is changing. Let me preface this a little bit by saying that FDA-MD has changed things a little bit in the post-marked surveillance world, because there is no required post-market surveillance based on FDA-MA. FDA-MA gives FDA the opportunity to look into discretionary post-market surveillance when appropriate.

We have that as a legal statutory authority to be able to do that for any device that we deem is something that we think needs post-market surveillance. We would negotiate with a company in a discretionary basis, in a discretionary way if we thought it was appropriate. So just to let you know, we have the legal statute that we have that opportunity to do that.

DR. BOYAN: I think we understand that, but let me ask Dr. Laurencin one last question before I call for a show of hands. If the device came in with the same composition as the one that is described in the petition, would you still want there to be a post-market surveillance? Would you feel it was necessary?

DR. SKINNER: Make that more specific. One that

came in that was exactly like Halmedica Simplex-P. Exactly like it; same mechanical properties, everything.

DR. LAURENCIN: Having done a Ph.D. thesis on the development of new polymers, I can tell you that the odds of synthesizing a new polymer which has the exact same properties as another polymer is about 1 in 1 million. I think even batch to batch it is even difficult. So I don't think it is really realistic. So I'm not sure what one can really comment on that.

Look, I just think that if we are looking at new materials that are going to be coming on the market, we are already moving from Class III to Class II, which is I think we're removing a large number of regulatory hurdles already. I think that obviously as tenth, eleventh, or twelfth material comes onto the market these things can maybe be lessened, but I think as new materials come onto the market, I think that a period of post-market surveillance would be reasonable. I don't think it is cumbersome. I think as Dr. Aboulafia said, maybe 200 or 300 patients in the very beginning.

DR. BOYAN: Okay, this is how we are going to handle this. There are two opinions out there. Rather than going around the table saying yes or no, yes or no, this is simply checking a box at this point. If we check this box we are obligating all applicants to the FDA to have to do a

post-market surveillance.

Now remember, we have another opportunity to handle this, and that Dr. Laurencin's comments are now on record. FDA has heard them, and they will go back and deliberate on them. This is advisory. We are advisory, we are not making laws here. We are advisory.

So what I would like now is to come to some conclusion as to whether or not we should check this box.

DR. CHENG: Dr. Boyan, I think Mr. Dillard still hasn't answered the question. I would be interested in knowing that.

MR. DILLARD: Post-market surveillance in this case would be -- I would echo what the industry has said -- as a special control, would be a requirement for every product that marched through the door, if that is a special control. And it would have to meet whatever the requirements of post-market surveillance would be.

Post-market surveillance does have again, some discretion associated with it about how much, how many, what kind of study. That is something that could be a negotiable situation. I hope that has clarified that issue.

The other point to make I think is the world according to bone cements right now is a Class III device. I only throw this out as sort of reality, which is we're on about our eleventh or twelfth PMA on bone cements. As we

approve bone cements today, under PMA we don't require post-marked surveillance, specific post-market surveillance study unless there is something that we would have seen through out the review of the PMA that would cause some heightened awareness that we would want to actually study in some sort of post-market situation.

Also in supplements, just to let you know, as we approve PMA supplements which may go from a PMMA based polymeric material to a copolymer for example, we have also cleared those with pre-clinical kind of information through a PMA supplement without clinical information, without a post-market surveillance kind of study. That's just the world of what's been happening in bone cements from a PMA Class III kinds of situation, but it again, fits the mold of what we are talking about here for the Class II or Class III classification of the product type.

DR. BOYAN: Thank you, Mr. Dillard. I'm trying to think of the fastest way to do this. The fastest way to do this is that the motion right now from Dr. Laurencin is that we check that box. Is there a second to that motion? Do I have a second?

DR. ABOULAFIA: Second.

DR. BOYAN: All those in favor of checking that box raise your hand and let me count you. Okay I have four in favor of checking the box. All those against checking

the box, raise your hand. We have eight against checking the box. The box is not going to be checked.

[Whereupon, the motion to check the box was not approved by a vote of 4 to 8.]

DR. ABOULAFIA: Does everyone fill out the sheet same, or do we put our dissenting opinions? Is it a consensus?

DR. BOYAN: You can tender your comments. You get plenty of opportunity to tender your comments. Believe me, they listen to everything everybody says.

Now we now have check testing guidelines, and we have checked other, which includes the ASTM and the ISO tests. Actually, our colleague here from the FDA knew that's what we really meant to check, was the testing guidelines.

So we have now said that there are special controls that need to be in place, but that there is sufficient information available in the world today to establish those controls. So we don't have to make any new ones. So now we have determined that for this worksheet, we have classified this in Class II.

Now we continue on to the second page.

MS. SCHULMAN: Eight, nine, and ten do not have to be filled out because we did not make a mandatory performance standard.

DR. BOYAN: Correct. Now we are at Question 11.

11. Can there otherwise be reasonable assurance of its safety and effectiveness without restrictions on its sale, distribution or use, because at any potentiality for harmful effect or the collateral measures necessary for the device's use? It needs a prescription, and we all agree it does.

Anybody that doesn't think it needs a prescription?

DR. COUTTS: I don't understand that. I have never written a prescription for bone cement.

DR. LAURENCIN: Sure you have. You've given a verbal order.

DR. ABOULAFIA: That's right.

DR. BOYAN: Dr. Coutts, don't worry. It comes up next under 11b. The answer is yes, you are going to prescribe it, and in B you are going to explain how you are going to prescribe it.

DR. ABOULAFIA: The answer is no.

DR. BOYAN: You're right. If no, go to B. Now you are going to tell how you are going to do it. Only upon the written or oral authorization of a practitioner licensed by law to administer use of the device. Any of those other people, no.

We have now completed this form.

DR. ABOULAFIA: A motion to vote on it.

DR. LAURENCIN: Second the motion.

DR. BOYAN: Wait, my instructions say that we have to vote on this worksheet.

DR. ABOULAFIA: Motion to vote on the worksheet.

DR. LAURENCIN: Second.

DR. BOYAN: To accept the worksheet.

DR. ABOULAFIA: Motion to accept the worksheet in its current working formate.

DR. LAURENCIN: Second.

DR. BOYAN: All right, I need clarification, Mr. Dillard. I know that we went through this last time. My instructions say after each worksheet and supplemental worksheet that we should vote on it. That could be read that they should be handled as a pair.

MR. DILLARD: I would, for simplicity's sake, handle them as a pair.

DR. BOYAN: We are going to handle them as a pair. Can we have the supplement sheet now? All right, our generic device is bone cement. We are the device panel. Now listen, guys, this is an implant. We do not have to write out all kinds of stuff. We can refer to the petition. We can refer to pages in the petition. We can refer to guidance documents. Any place that we don't have to write is a good thing.

4. Indications for use prescribed, recommended or suggested in the devices labeling that were considered by the advisory panel. There were some alternatives that were suggested. In the bottom panel question on page 4, does the petitioner's proposed classification based on specific liquid and powder sufficient describe the bone cement? If not, what are the types of descriptive information that should be included in the classification definition for bone cement ?

The other panel question that applies is being sought . In the petition the literature and device registries reported the use of bone cements for hip, knee, and shoulder joints. Based on this information, do the data support the use in hip, knee, and shoulder joints, other joints based on literature and device registries? For which patient populations should bone cements be indicated?

We can say indicated for use as described in the petition, and we can also add other indications that we like . I am looking for FDA have to have an exhaust failure there. Can we now add things to the petition?

MR. DILLARD: Just waiting to hear your comments before I need to clarify.

DR. BOYAN: So as I took my notes, Dr. Skinner, would yOU like to comment?

DR. SKINNER: Yes . First of all, it says hip,

knee, and shoulder joints, and we all know that this is used routinely in elbow joints. It is probably used in the spine. I don't know where it is all used. But I think that when you look for instance at the elbow joint, the distal end of the humerus is no different from the proximal end of the humerus or the proximal end of the femur. The interface between the prosthesis, the cement, and the bone is the same.

So I think that there is an analogy there that we can use to justify use in the elbow joint. So I would suggest that we add elbow joint, or even all joints to that indication.

Secondly, I would like to try to get away with adding --

DR. BOYAN: May I ask for clarification on all joints? I would like to address this to Dr. Altman. Is this appropriate for use in the TMJ?

DR. ALTMAN: Not to my knowledge.

DR. BOYAN: I think we better be careful about all joints.

DR. ABOULAFIA: How about ankle too?

DR. SKINNER: Ankle joints are being done nowadays.

DR. ABOULAFIA: With cement.

DR. SKINNER: Some people even cement little

finger joints.

DR. RANGASWAMY: [Remarks off mike.]

DR. COUTTS: Could we get clarification from the FDA? Could you say at the surgeon's discretion? I know that is a radical idea.

MR. DILLARD: You are touching on an issue right now that is very sensitive at the FDA, that we are working through which is the general to specific indication kind of issue, which is do you generally want to just say that this is -- we use bone cement here as the example -- that it is bone cement intended to be used by orthopedic surgeons for total joint replacements, or is there a need to specifically talk about the joint and/or is there a need to even get more specific and say disease states, patient populations, et cetera, et cetera.

So there is a fine line that I think you walk here, we walk here, industry walks about how specific do you need to be based on data, versus is a general kind of statement for intended use a more appropriate thing to do if there are multiple joints and multiple things that can be used. Perhaps that is an approach that you might want to consider also.

DR. COUTTS: In reality the use is at the surgeon discretion.

DR. BOYAN: And in fact in the petition it is as

well . The wording in the petition is general enough I think to cover this. It is limited, as the panel question is limited. It is indicated. The exact wording here in the petition is, as indicated for the fixation of prostheses to living bone in orthopedic musculoskeletal procedures. Then it lists a whole number of applications, and then actually in the general discussion we identified one of these missing applications . I think that's actually where we belong in this discussion.

So as it is stated in the petition, it is actually very general.

DR. SKINNER: It only covers joints though, arthroplasty.

DR. BOYAN: It doesn't only cover joints. It says indicated for the fixation of prostheses to living bone in orthopedic musculoskeletal surgical procedures.

DR. SKINNER: But an intramedullary rod is an orthosis, it's not a prosthesis.

DR. CHENG: Could I suggest a difference in wording? What about just an indication for skeletal reconstruction, and as an antibiotic delivery device? Wouldn't that just cover everything?

DR. SKINNER: I applaud your effort to get that in, but the FDA is not going to bite on that one.

DR. CHENG: Well, what about the first part.

Let's just take the first part.

DR. BOYAN: In orthopedic skeletal reconstruction; I think we have to be very careful not to generalize above the cervical spine. There are other issues related to the use of the materials in the TMJ that don't apply across the board to the rest of the body. Different physical force applies, different issues related to where it's bleeding; the proximity to the brain. So we want to not enter ourselves into that discussion.

DR. CHENG: Okay then, orthopedic skeletal reconstruction.

DR. BOYAN: I wrote that down, yes. So the alternative wording that is being proposed is that we say as indicated for use in orthopedic skeletal reconstruction.

DR. ABOULAFIA: Just on the fear that the FDA may reject it, although I would like to go with it, maybe putting in the words large bone loss resulting from tumor, which is redundant by Dr. Cheng's wording understood, but if they feel that his wording is too broad, I would still like to be able to leave it in.

DR. BOYAN: FDA would you like to comment on what we are suggesting here?

MR. DILLARD: I guess there are two issues here. I think we would appreciate it if you could clearly separate what is in the petition, because we do need to act on the

petition, and I think that's an important point here.

Then additionally, if you would have other recommendations about either indications for use, data that might be appropriate to be gathered, or other circumstances, any other kinds of recommendations, I think we would appreciate that also, but I think we do need to concentrate on the petition and try to get a sense of what you feel that petition tells us, and then add anything additional to that. If we could handle it that way, then it would be clearer to us about maybe which direction we need to go with it.

DR. BOYAN: But for clarification, we are not classifying the petition, we are classifying bone cement. So we can take the recommendations as described in the petition, as well as indications for use being orthopedic skeletal reconstruction including for bone loss resulting from tumor.

MR. DILLARD: Yes, if you would like to make those comments and recommendations, that is fine. But if can again, just clearly separate the two so that we've got a clear sense of what you think of the petition, and then anything additional or to change it I think would be helpful.

DR. BOYAN: Okay so the current wording that I have is indications for use is as described in the petition, one, and two, for orthopedic skeletal reconstruction

including for bone loss resulting from tumor. Is that addressing what has been stated?

Now on this I guess I need to say that I stated it, the way it is now written, is there someone that objects to the way that I have stated it on the panel that would like to identify themselves and make a comment?

DR. RANGASWAMY: I have a question. You could have massive infection of a long bone and lose a lot of bone, would that not also fall in? Why not just add bone tumors and infection.

DR. ABOULAFIA: Dr. Cheng's wording was broad enough that it includes everything.

DR. BOYAN: So I can eliminate including for bone loss resulting from tumor?

DR. ABOULAFIA: I prefer you didn't, but I would understand it if you did.

DR. BOYAN: 1'11 leave it, because it just makes a point . Now this is where we can attempt, without causing great grief, to put in this cleverly worded statement, if I can find it here.

DR. SKINNER: While you are finding that, can I make another suggestion?

DR. BOYAN: Yes?

DR. SKINNER: I would recommend that the contraindication in cases of infected total joint

arthroplasty be relative contraindication, and add in something to the effect that bone cement may be indicated in selected cases of infected total joint arthroplasty.

DR. COUTTS: This is still in the indications box?

DR. SKINNER: Yes .

DR. BOYAN: Bone cement may be indicated for selected cases -- could you repeat that please? Selected cases --

DR. SKINNER: Of infected joint arthroplasty.

DR. CHENG: That would be antibiotic impregnated bone cement, is that right? Or do you want to leave that out ?

DR. SKINNER: It will be when it arrives.

DR. ABOULAFIA: Maybe this is a comment for the sponsors as much as for the panel, but there elution property characteristics that happen and are well described. U. Holds(?) described that in the journal that used to be Orthopedic Review and is now the American Journal of Orthopedics . The elution properties of antibiotic cement, as well as the changes in the mechanical properties associated with it depending on how much antibiotic you put in the powder have also been well described. That is issue number one.

Issue number two is many of the times when we use the cement as an antibiotic delivery system we aren't

implanting it. It just sits in the soft tissue. So we don't care what the mechanical properties are. Literally if it stayed doughy, that would be okay. All we want to do is delivery high doses of local antibiotics. It doesn't have a mechanical purpose other than delivering the antibiotics. It is placed in the soft tissue, and it is pulled out six week later when its delivery level drops off exponentially.

So that may clarify things for the panel members, but also maybe for the sponsor. I wish that had been something that was in here.

MR. CRAIG: Just very quickly on that. As one of the sponsors, we generally try to avoid that type of thing in our labeling, because that can be taken back into the indication. That is the type of thing that in the wrong interpretation we could actually be charged with promoting that type of use, which would have us in a bad situation with FDA.

DR. ABOULAFIA: To answer that, I'm not saying necessarily to change the indication, but I didn't like the contraindication which says you should not use this in the face of infection, because we all know we routinely use it in the face of infection. That's why the wording that I proposed that Barbara was looking for was that it shouldn't be used where revision total hip arthroplasty is contraindicated.

That would speak to Dr. Cheng's statement where he said some people do do one stage revisions. I would say then well, if it's a one stage revision, then revision arthroplasty wasn't contraindicated, and you could use it.

DR. BOYAN: May I clarify something here that we need to take into consideration is that we're not looking at "antibiotic cement." So we are looking at regular cement. The regular cement would be contraindicated as originally stated by Dr. Aboulafia. I think that that might be our place, rather than trying to indicate the use of regular cement in this instance.

So I would like to hold off that comment until we get to contraindications, and deal with it in a contraindication mode.

Let's move down to identification of any risks to health presented by the device. We have got a whole series of lists of things that we need to consider. We can start off with as described in the petition. Then are there any additional risks we would like to identify that we think the petition failed to identify?

The panel questions that deal with this are now appearing on the board. Based on the reviewed literature presented by the petitioner, please discuss the different uses and what limitations we would suggest for -- oh, we're not quite there yet. Oh, yes we are. We can discuss about

viscosity. We can discuss specific indications, specific diseases. We have a place here to list the specific hazards to health.

Who is going to begin this one?

DR. GILBERT: BCIS has been already identified I believe, but I think that issues related to particles have not been identified, and I wonder if that should be included.

DR. BOYAN: It should be. I put those under specific hazards to health. I put particulate. Do yOU prefer particles or particulate?

DR. GILBERT: Interchangeable .

DR. BOYAN: Are there other indications that we should include? There are specific issues here about viscosity and about cementing techniques. Do we want to state anything in particular about that? Dr. Li.

DR. LI: It’s just a question. These are perfectly fine for the existing cements. I keep trying to ask the question when someone brings in something that’s a little different, how do you go about addressing this? In other words, I have no problems with the different cement techniques with currently existing cements, but if someone brought in a different one. I’m not sure I get at that.

DR. BOYAN: Well, one way we’re getting at it is by making the comments, because the comments will go into

the transcript, and the FDA will be very, very conscious of what we are saying.

DR. SKINNER: Dr. Boyan, I'm a little reluctant to get into different cementing techniques. That sounds like the FDA is regulating medical practice, and I really don't want Mr. Dillard regulating my practice.

DR. BOYAN: Just to give everybody a chance to give the group here a chance to regulate us, let's go around the table starting with Dr. Coutts, and we'll go backwards. Coutts and then Cheng and then Laurencin and Aboulafia, and we'll go around the other way. Are there any additional risks other than those described in the petition that we would like to identify?

DR. COUTTS: It just occurred to me that one other thing that I don't remember reading in the application is any wording about potential burning of bone; the exothermic reaction and the potential to damage bone. We should probably add that.

DR. BOYAN: Okay, exothermic. Should we say exothermic damage to tissues?

DR. COUTTS: Tissues.

DR. BOYAN: Dr. Cheng?

DR. CHENG: I have nothing to add.

DR. BOYAN: Dr. Laurencin?

DR. LAURENCIN: Nothing to add.

DR. ABOULAFIA: Nothing to add.

DR. BOYAN: Dr. Altman? No. Silkaitis?

DR. SILKAITIS: I have nothing to add.

DR. BOYAN: Dr. David? Nothing. Dr. Urban.

DR. URBAN: Nothing.

DR. BOYAN: Hale?

DR. HALE: Nothing to add.

DR. BOYAN: Skinner?

DR. SKINNER: Nothing.

DR. RANGASWAMY: Nothing.

DR. GILBERT: Nothing.

DR. BOYAN: There is one more question we need to address. Here it comes. We have got the bone cement implantation syndrome; inconsistencies in mixing and handling and setting characteristics. Those are defined in the petition though, but maybe we can say as described in the petition particularly. That addresses your issue. Bone cement implantation syndrome and technical variations. Those are in the petition.

From the literature, device registries and MDRs have all the risks to health from bone cement been adequately addressed? We thought not. We thought that it needed to include particulate, and the discussion of exothermic damage to tissue. Nobody identified anything else.

DR. LI: Just for the record as the FDA reviews the transcript, 1'11 say it again. I think small variations in cement could cause a problem that you don't see with currently existing techniques. So there may be no problem in handling and mixing of what we've got now, but that's not true universally across the board. So I just make that as a comment .

DR. BOYAN: That is a good comment Dr. Li. Here is one other thing. Specific hazards to health are the particulate, the exothermic damage to tissues. Characteristics or features of device associated with hazards. What specific things are those? Is the monomer would you say one of those, or the choice of polymers, or the choice of monomer?

DR. GILBERT: Those are proscribed by the definition.

DR. BOYAN: So there is nothing else we really need to add. That is described in the petition.

Recommended advisory panel classification and priority. We classified this in our previous sheet as a Class II, and the priority is unclear to me exactly what that means.

MR. DILLARD: I think if you gave us just sort of a high, medium, low in terms of clinical importance, scientific importance. It is a particularly crucial

question if you recommend Class III for the priority for calling for the PMAs on the product. It is not as large of an issue if we are talking about down classification. But if you would give us even a three point scale, high, medium, and low, I think we would appreciate it.

DR. BOYAN: All right, so someone make a motion that we can just all vote on.

DR. CHENG: Low.

DR. BOYAN: Low priority from Dr. Cheng. Is there anybody that would argue with Dr. Cheng?

DR. GILBERT: I guess I'm confused. Low priority means we're not really that excited about it?

DR. BOYAN: We're not hypertensive about the whole thing is the way I would say it.

DR. CHENG: I thought it was the speed with which this needed to be enacted, not the importance of this.

MR. DILLARD: I think that is one way to interpret this. It isn't particularly clear. I think what we are looking for is some sort of prioritization about yes, how quickly should we put this on the Federal Register agenda to get this down classified, I think would be a good way to look at this. Would it be a low priority, a high priority, a medium priority? How quickly should we do it? High I think here would be we ought to start on this thing tomorrow and try to get the Federal Register notice out quickly.

DR. ABOULAFIA: Motion to second low priority.

DR. LI: Can you just give us an idea of what low means like in real time?

MR. DILLARD: I think in this case if there was really a driving public health issue, that if we were to down classify something or if we were to take a regulatory action that could have large impact in a public health kind of situation, that's something that we would put kind of in the high end of the priority scale.

You specific question about does low priority basically drop off the radar screen, that is not the case. I think we want to work through these things pretty quickly, all of the classification recommendations that we're getting. Just I think in terms of trying to prioritize the regulations that are going forward in terms of public health impact, it is nice to have a little bit of discussion from the people in the community to say, high priority, it is going to have major public impact, or lower priority, not so much public health impact, but FDA -- which is what I'm hearing from you -- don't forget about this. We think it's pretty important, you still ought to do it.

DR. LARNTZ: Until you act on it, it stays in Class III?

MR. DILLARD: Correct.

DR. BOYAN: To encourage the FDA, maybe immediate

priority might better reflect the tenor of the crowd. But we have a motion on the floor on low, so we have to deal with that low motion, because it has been seconded.

DR. CHENG: I'll second a medium as well.

DR. BOYAN: Would you be comfortable with withdrawing your motion, Dr. Cheng? Can I have a new motion.

DR. COUTTS: I would make motion that we give this a medium priority.

DR. ABOULAFIA: Second.

DR. BOYAN: Those who don't want this to have a medium priority, raise your hand. We have one who doesn't. Now I've got to count those who do then. Those who are comfortable with it being medium priority, raise your hand. Okay we have 11 with the medium, and 1 with low -- 1 with not medium.

[Whereupon, the motion for medium priority by the FDA passed 11 to l.]

DR. BOYAN: Now number 7.

7. If device is an implant or is life sustaining or life supporting and has been classified into a category other than Class III, explain fully the reasons for the lower classification with supporting documentation and data. Now here we just have to say that we feel that the special controls are sufficient.

DR. LAURENCIN: I would just state see petition, all the information in the petition.

DR. BOYAN: As described in the petition. Is there anybody that does not feel that that is an adequate description to satisfy the answer to this question? If yOU think there needs to be something else added, identify yourself and tell me what that is.

Okay, we're going to go around one more time and discuss this sheet, so we can add things then. I don't want there to be no discussion here. As described in petition, special controls are adequate.

Summary of information including clinical experience or judgment upon which classification recommendation is based. As described in petition and the expert opinion of the panel.

Identification of any needed restrictions on the use of the device. Here we go, Dr. Aboulafia.

DR. ABOULAFIA: I guess to simply things, I guess I would just want where there is a contraindication, try and get rid it. So rather than trying to write in indications, I would say that it says currently PMMA bone cement is contraindicated in presence of active or incompletely treated infection. I might just say PMMA bone cement is contraindicated in presence of active or incompletely treated infection where revision -- forget that. PMMA bone

cement is contraindicated where revision total hip arthroplasty is contraindicated.

DR. COUTTS: Dr. Skinner had made a recommendation that we just change one word, which would be a relative contraindication, which I think softens the restriction, and gives the surgeon I think a little more leeway in terms of clinical judgment. Does that work, Mr. Dillard?

DR. BOYAN: Could you repeat it for me so I can hear what it was again?

DR. COUTTS: I said that the use of bone cement is relatively contraindicated in the presence of active infection.

DR. SKINNER: I added a sentence also that said bone cement may be indicated in selected cases of infected joint arthroplasty. May be indicated.

DR. BOYAN: I had that up there and then I took it out, but if you want me to leave it.

DR. SKINNER: I don't feel strongly about it. I'm throwing it out trying to help get to a consensus here.

DR. URBAN: Wouldn't it make more sense to take it -- there is a specific title here, a section here called contraindications . We can take out contraindications. Only leave in patients allergic to any of its components, and put that in the next section, which is called warnings, and say specific considerations should be given to patients who have

active infections in using bone cement for arthroplasty.

MR. CRAIG: May I make a suggestion to try to keep us from trying to explain this in court for the next 50 years? Just make it a contraindication for active infection in its packaged form, and just leave it at that.

DR. BOYAN: I know what he's trying to say.

DR. ABOULAFIA: I know what he's saying too. What we are trying to do is protect it from an off label use, and from someone saying, see, it was contraindicated. You weren't supposed to use it in the first place. Then you say, well, I used it with the antibiotics. That's different.

What he is saying is if you put in that it is contraindicated in its current form, that means without antibiotics, then you shouldn't be putting it in infected total hip. It leaves open the question for antibiotic impregnated cement. It takes it off the table.

DR. CHENG: I think if you want to look at it from a legal standpoint, I think it still does put the physicians at some risk. I'm not trying to balance the risk to the physician versus the manufacturer. But the issue really is infection. It's not arthroplasty. Antibiotic impregnated cement is used for infected fractures in some institutions. So it's not arthroplasty, it's the presence of an infection to deliver the antibiotic.

MR. CRAIG: I guess the more terrifying question is if we don't word this properly, is there going to be somebody out there that takes the plain bone cement and pops it in, in an infected situation without adding antibiotic, and saying that's okay by the labeling?

DR. BOYAN: Well, that's why I did not include Dr. Skinner's second sentence, that bone cement may be indicated for selected cases in infected total joint arthroplasty, because that then says bone cement -- he meant to say bone cement plus antibiotics may be indicated, he didn't mean that .

DR. SKINNER: We are not going to be able to put antibiotics in bone cement at this meeting.

DR. BOYAN: No, I know that.

DR. ABOULAFIA: Maybe the sponsor or the rep's suggestion is sort of a halfway reasonable compromise that says in its present form, where we as surgeons know what the spirit of that extra three words are meaning without antibiotic cement.

DR. URBAN: Why does it have to say contraindication? It seems to me still the only thing that is contraindicated at this point in time is the uses in somebody who has shown an allergy to the components. What we're really doing is saying it as a warning, its use in its present form in an active infection, and it really gives

everybody the position and the option to do what he thinks is necessary in the circumstances. It should take the manufacturer out of the risk of having it put in that kind of patient.

DR. COUTTS: It is contraindicated in the presence of infection.

DR. BOYAN: Okay, I think we have to be careful here, because we have an issue that the petition isn't asking for it, and we are not right now in a position to -- 1 think that we're making a clear statement over and over and over again that we're trying to find a way to get it done in a way that would reflect clinical practice.

The wording from the sponsor is fairly benign actually. Use of bone cement -- just go ahead and state it. It's contraindicated in its packaged form where infection may exist. Then stare at the FDA individuals in the room.

DR. ABOULAFIA: I would say where infection does exist, because every revision, it may be from infection, and we do some things in the OR that give us some idea of whether it is infected or not, but we don't get cultures back for two days. So if you say may.

DR. BOYAN: Do we also need to say some needed restrictions on the use? We should also say as described in petition, because that then brings up the issues of these various things related to the BCIS.

Now is there anything else we have identified besides what was stated in the petition, what we have just written down? Do we want to make any specific statements about the -- I don't think we want to make any statements about lavage as per Dr. Johnston's comments.

I think we have covered it pretty thoroughly actually. Let's go to Question 10. Yes?

DR. SKINNER: Dr. Boyan, one quick comment here. I don't feel terribly strongly about the concept of a brochure that I brought up. I'll make one apology to Dr. Silkaitis. I didn't mean to imply that the manufacturers tried to hide information from us or anything. He may have felt a little defensive about that.

I know that if I schedule a Halmedica total hip, I will have on my desk at some point, brochures, templates, everything. They could just as easily include a brochure on cement in that situation. Maybe this is unduly burdensome to Halmedica, because they probably have 80 or 90 percent of the market, but I think a brochure would be a useful thing to have floating around for people to read, which would include the package insert.

DR. BOYAN: We should put that somewhere here, and I'm not exactly sure where we put that. We're suggesting an additional brochure, not just the package insert.

n MR. DILLARD: Dr. Boyan, may I make a suggestion?

DR. BOYAN: Yes.

MR. DILLARD: On the original data sheet -- I can't remember exactly the number, and I don't have it in front of me, but where you talk about special controls, where you checked others in the guidelines. Labeling is a very powerful special control, and I think if there are some specific suggestions on labeling, and by labeling it sort of "written" material, so that could include supplemental brochures, physicians' manuals, et cetera, as well as patient labeling. So I'm not recommending that you put all of that in there, but that is a place where you can put it.

DR. HALE: Dr. Boyan, while we are still talking about warnings, I'd like to reiterate my comment or suggestion about overpressurization, and the clinicians can respond to this. Maybe it's not as much of a concern to them as it is to me. Using the term "overpressurize" or cautioning the surgeon not to overpressurize seems to me to be a rather vague term. How do you know how much pressure is too much pressure?

DR. BOYAN: All right, this is what I have written.

DR. SKINNER: Dr. Boyan, that is with regard to BCIS. The manufacturer, in their risk/complications table here had about 14 things they put down for BCIS. I would suggest that basically the package insert only include a

description of the BCIS mechanism, and a precaution for the surgeon and anesthesiologist to take measures anticipating potential hypotension and/or hypoxemia prior to cement application, rather than all of the things recommended in this Table 9 in the blue book under BCIS. That would remove the pressurization issue.

DR. BOYAN: Okay, repeat that for me please.

DR. SKINNER: Well, the package insert to describe the primary BCIS mechanisms, and to provide a precaution for the surgeon and the anesthesiologist to take measures anticipating potential hypotension and/or hypoxemia prior to cement application. That provides a warning. I think our anesthesiologist can speak to this, but I think virtually every anesthesiologist knows this is a problem. As long as they are adequately warned, I think that they know what to do about it.

DR. URBAN: It says here package insert precaution for attentive patient monitoring commencing with cement application. There is something written in the table here that addresses that. It says precaution for attentive patient monitoring commencing with cement application, and continuing until several minutes post-implant insertion.

DR. SKINNER: But do you want something that tells you exactly what you have to do?

DR. URBAN: No.

DR. SKINNER: No. You want something that warns you, and then you do what you think is appropriate.

DR. URBAN: Exactly. The only thing I might want here is to possibly be a little more specific about the risk populations . It says fractures. I think to say elderly with cardiovascular problems, pathological disease, long stem prosthesis. These are the ones that you see the highest incidence of BCIS.

DR. BOYAN: Okay, I think that I've got that down.

We're on Number 11, the last question here.

11. Are existing standards applicable to the device subassemblies or device materials? I think here we can say as described in the petition, particularly pages 40 and 41 or 42 and 41; 41 and 42. We had one other source. And in the FDA guidance document.

Here we go, now is there anything else that needs to be included under this category? Anybody that knows it, raise their hand. Identify yourself and tell me what it is.

DR. LI: Is this where you want to put in comments on post-market surveillance? [Remarks off mike.]

DR. BOYAN: They know to do that actually.

DR. LI: 1'11 take your word for it if you say it's coming.

DR. BOYAN: Well, it isn't coming. We just have to be sure that they remember to do it. Have we told you

enough times that you will remember?

MR. DILLARD: Yes .

MR. DEMIAN: As a point of order, can you please write your name on both sheets so we know whose sheet it is, and sign both sheets. One the first sheet it has a place for your name. On the second sheet it doesn't. So any of your comments -- we'll go back through these for each one of you. Dr. Boyan is collectively going to get a consensus for everybody as a group.

DR. BOYAN: Now I'm going to read to you what we have done. I'm going to start with the general questionnaire. We have checked that this is not a life sustaining or life supporting device, but it substantially important in preventing impairment of human health.

We say that it is not an unreasonable risk when special controls are in place. The special controls already exist, and specifically we want these special controls to include testing guidelines and other tests that might not fit under that category, particularly ASTM and 1S0 tests.

We also want under other category there to be labeling to include a brochure which describes exactly how to mix the cement and how to use it appropriately. We would like the package insert and this brochure to describe primary BCIS mechanism, and to tell the surgeon and anesthesiologist to take measures to prevent hypotension.

We have suggested this be classified as a Class II, and we recommend that it be used with the written or oral authorization of a practitioner licensed by law to administer use of the device.

On our supplemental data sheet we have indicated that this material be used as described in the petition, number one. And that it be used for orthopedic skeletal reconstruction including for use of bone loss resulting from tumor.

The risks to health that are presented by the device are as described in the petition, and we would particularly like to note BCIS, and also another risk would be technical variations in the material that could be caused by changes in mixing. Specific hazards to health that were not described in the petition include the potential of particulate causing problems, **as well** as exothermic damage to tissues causing problems.

Again, this is Class II, but we want FDA to know that we think that it has medium priority.

The device is an implant, and the reason that we have suggested lowering the classification is because we think that there was documentation and data described in the petition that would support this, and that special controls are adequate.

The summary of the information including the

clinical experience and judgment upon which the classification recommendation is being made is described in the petition, as well as in expert opinions that were presented at the panel meeting.

The needed restrictions that we would like to be sure are defined are those that were described in the petition, as well as this statement: that the use of bone cement is contraindicated in its packaged form where infection does exist. We would like for the restrictions to be more clear to the clinician concerning the populations that are at risk for BCIS. That actually might go into the package insert and the brochure.

The standards that are applicable to this device and its subassemblies or materials are as described in the petition, and particularly on page 41 and 42, and in the appropriate FDA guidance documents.

Do I have a motion to accept our worksheet?

DR. ABOULAFIA: Motion.

DR. BOYAN: Second?

DR. LAURENCIN: Second it.

DR. BOYAN: Now is there any discussion, any little changes, anything that need to be done or said? Yes, Dr. David?

DR. DAVID: I have a question. We elected to isolate BCIS in the indication. While looking at the MDR

summary, about as much as half the rate of the reports **as** BCIS are relating to package handling and operating room personnel mixing issues. What is the reason that we elect one and not the other?

DR. BOYAN: Actually we did say mixing issues. We said under identification of risk to health we did say BCIS in variations of mixing. Down under restrictions we can put the mixing there as well. Is there any objection to my adding it there? Okay.

So now are there any comments before we finally vote, to come to us from FDA? Any comments to come to us from the sponsor? This is your last chance before the vote.

Then let's vote. You have heard what we are voting on. First, we're just going to go around the table, starting with Dr. Li, vote to approve the worksheets. We're voting on the worksheets. We are only voting on the worksheets. We're not yet beyond this, only the worksheets.

Voting to accept the worksheets, starting with Dr. Li, yes or no?

DR. LI: Yes.

DR. LARNTZ: Yes.

DR. GILBERT: Yes.

DR. RANGASWAMY: Yes.

DR. SKINNER: Yes.

DR. HALE: Yes.

DR. URBAN: Yes .

DR. DAVID: Yes .

DR. ABOULAFIA: Yes.

DR. LAURENCIN: Yes.

DR. CHENG: Yes .

DR. COUTTS: Yes.

DR. BOYAN: Okay, so it's a unanimous acceptance of the worksheets as they are now presented.

[Whereupon, the worksheets were unanimously approved as presented.]

DR. BOYAN: Now we need a motion to accept the classification worksheet as filled out with a recommendation of **a Class** II for bone cement, Do I have a motion to do that?

DR. ABOULAFIA: Motion.

DR. BOYAN: Do I have a second?

DR. COUTTS: Second.

DR. BOYAN: It has been moved and seconded that bone cement be classified into Class II. Now we get to vote on this. So we are going to vote. Everybody vote, and then we'll go back around and state the reasons for the vote. Starting with Dr. Li.

DR. LI: I vote for the reclassification to Class II. I believe this is --

DR. BOYAN: Not yet. You can't speak yet; you

only vote.

DR. LARNTZ: Yes.

DR. GILBERT: Yes.

DR. RANGASWAMY: Yes.

DR. SKINNER: Yes.

DR. HALE: Yes.

DR. URBAN: Yes.

DR. DAVID: Yes.

DR. ABOULAFIA: Yes.

DR. LAURENCIN: Yes.

DR. CHENG: Yes

DR. COUTTS: Yes.

DR. BOYAN: Okay, so we have a unanimous vote to reclassify bone cement into Class II.

[Whereupon, the motion to reclassify bone cement from a Class III device to a Class II device was unanimously adopted.]

DR. BOYAN: Now I would like to ask each of the panel members to state their reasons for their vote. Dr. Li.

DR. LI: I think the proposal by the sponsor for the -- let me back up. I think the reclassification is reasonable and prudent, and will allow the development and production of perhaps improvements of bone cement, without providing unreasonable risks as long as all the testing

seems to be appropriate and the guidelines seem to be in place to secure that we won't have early disasters.

DR. LARNTZ: I support reclassification. I was particularly satisfied that the pre-clinical testing will be for testing for equivalents with currently approved bone cements.

DR. GILBERT: I voted yes for similar reasons. I also think that we do have a long history of successful use of bone cement as it is defined in this reclassification. So I have some confidence that it will continue to be successful material as long as we provide these pre-clinical controls.

DR. RANGASWAMY: I voted yes for the **very** same reasons as have just been cited.

DR. SKINNER: I voted yes for the same reasons.

DR. HALE: I voted yes also for the same reasons.

DR. URBAN: I voted yes for the same reasons.

DR. DAVID: I voted yes for the same reasons.

DR. ABOULAFIA: Nothing to add.

DR. LAURENCIN: I voted yes, but would still like to see that post-market surveillance performed.

DR. CHENG : I voted yes, but would advise the FDA to address the issue of infection and antibiotic impregnated. cement as it is being used.

DR. COUTTS: I voted yes for the reasons listed by

the others, except Dr. Laurencin and Dr. Cheng.

DR. BOYAN: So I have to tell you that we felt this was frustrating, but I have to tell you that we were way, way, way, way better at this than we have ever been in the past. Practice is making perfect.

So I would like to announce the recommendation of the panel is that bone cement be classified into Class II.

Now there are some announcements.

[Administrative remarks.]

[Whereupon, the meeting was recessed for lunch at 12:45 p.m., to reconvene at 1:30 p.m.]

A F T E R N O O N S E S S I O N 1:30 p.m.

DR. BOYAN: Okay, I am going to call the meeting to order. We are 1 minute late. We are going to call to order for the second half of our meeting.

We will now begin the discussion of bone growth stimulator guidance document. We will begin with Jim Dillard providing background information regarding the use of guidance documents, and FDA will present the panel's questions.

We will then have an industry presentation time for the industry to provide comments followed by an open public session, specifically related to bone growth stimulators.

Finally, we will have a general panel discussion of this topic followed by the panel discussion aimed at answering FDA's questions. We are going to finish by going through the panel questions.

I would like to remind public observers at this meeting that while this portion of the meeting is open to public observation, public attendees may not participate except at the specific request of the panel.

All right. I have outlined what is going to occur during the process. When FDA makes its presentation Ms. Erin Keith will be the presenter, and she has provided all of us with a copy of the slides that just came on out table top

during lunch.

Okay, I would like to ask Mr. Jim Dillard, Deputy Division Director of General Restorative Devices to give the background for the guidance document.

MR. DILLARD: Thank you, Barbara. Welcome back this afternoon, and hopefully this afternoon will go as smoothly as this morning did, and I think what I would like to do is just set down the ground rules a little bit and give a little bit of background for you this afternoon.

I just have three very quick slides. A guidance document is what you will be considering this afternoon. Just by way of background, and you will hear a little bit more from Erin, it is a revised guidance document. The last time we actually penned the original bone growth stimulator guidance was in 1988, and so what this is is a fairly significant revision of the guidance based on today's standards, and we will be soliciting your input.

so, what is guidance? We hear a lot talked about guidance. There has been a lot talked about in FDAMA. We keep coming back to FDAMA, as well as even before FDAMA was passed there was quite a bit of concern from industry that we were developing guidance without adequate input from either them or other outside organizations.

so, that being said, what is a guidance document? It is a non-binding document that generally FDA puts

together to try to give guidance to either regulated industry and/or clinical researchers in how to develop a product, how to test a product and how to get through the regulatory various processes that may be appropriate for a product type.

Many times we go into preclinical, clinical and product labeling as well as postmarked activities in these guidances, but we don't always necessarily go into each one of these topic areas, but frequently we do.

Next slide?

If these look familiar, they are similar to the slides that I recently presented at Barbara's session at the Orthopedic Research Society Meeting. So, how do we use guidance? We use guidance as FDA review staff to try to train new reviewers as well as try to gain some consistency, and one of the things that we struggle with, certainly from the standpoint of all guidance is the idea about regulatory science versus basic science.

Regulatory science, we believe is founded in basic science and good scientific principles. So, hopefully, there isn't a big disconnect there, and we do try to use as much state of the art as possible that is known in both preclinical and in clinical areas.

We do adhere to and subscribe to good laboratory practices, but in some cases, especially when YOU are

talking about some of the basic science and some of the basic science work that goes into perhaps developing some of the studies that will be used, both in a regulatory way or in a marketing way, good laboratory practices is one of those things that we look at, and we hope people adhere to them, but in some of the basic science situations we know it is not always met, and that can be a thing that is negotiated with us at FDA.

We frequently try to put in pass/fail criteria. so, it gives industry as well as researchers the baseline that we are trying to work from as FDA folks, and again, very frequently we use it to help design human clinical studies which most of the time is where the guidances are the most beneficial but not only beneficial in that area.

Last slide, real quick?

How do we develop guidance? This is a process that we actually have put into place over the last couple of years . You will hear it referred to **as** good guidance practices or GGPs, and what goes into that is very open interaction between us and outside organizations, and part of that revolves around just what we are doing here today which is soliciting panel input, as well as you will hear from some speakers from industry and perhaps some outside organizations, and we think that good guidance is developed with all people on board and involved so that we can get

something that there is some reasonable consensus .

What we will do is if it is a major guidance document or a major rewrite, sort of what we consider to be a level one guidance, we will publish it in the Federal Register and will actually ask for comments, official comments and once we get comments and make revisions to a draft sort of, quote, unquote, guidance we will go forward and finalize those and make them available, and they will be what everybody works from in terms of the same page of the same guidance.

so, with that, if there are any quick questions, I am happy to answer them, but if not, as always I will be available to answer any questions that might arise during the process.

Barbara?

DR. BOYAN Are there any specific questions that the panel might like to ask Mr. Dillard?

Okay, then let us move on to the FDA presentation by Erin Keith.

MS. KEITH: Good afternoon. Can everybody hear me? Okay, good afternoon, ladies and gentlemen and distinguished members of the Orthopedic and Rehabilitation Devices Panel. I am Erin Keith, a reviewer in the Orthopedic Devices Branch. I am going to present to you some of the issues related to bone growth stimulators which

the FDA would like you to comment upon today.

The FDA has modified its August 12, 1988, draft guidance for bone growth stimulators to incorporate additional elements and revise others based on changes in technology and clinical issues.

The new draft guidance is now referred to as the Guidance Document for Industry and CDRH staff for the Preparation of Investigational Device Exemption and Premarket Approval Applications for Bone Growth Stimulators.

This document is available on the FDA web site and is currently out for public comment. I do not intend to go into great detail about what is proposed in the current version. What I would like to do is present some of the larger issues associated with the current draft guidance and bone growth stimulators in general.

However, briefly some of the major differences between the two versions of the guidance are first that the current version of the guidance contains device description items for the new bone growth stimulator technologies such as ultrasound, implantable and capacitively-coupled electrical devices.

Second, it, also contains a decrease in the length of follow-up after completion of the bone growth stimulator treatment for long bone non-unions. The proposed length of follow-up has been decreased from 2 years to 1 year, and the

current version of the guidance, also, requests more detailed information in the clinical studies section. There is a specific emphasis on non-unions in this section.

This concludes my comments on the proposed revisions of the guidance document. I would now like to move on to the specific questions and issues related to the bone growth stimulators FDA would like the Panel to discuss today.

In the original guidance the FDA recommended 2 years of follow-up for patients beyond the end of the stimulus for treatment of non-unions for long bones. Currently FDA is recommending all patients be followed for at least 1 year after completion of bone growth stimulator treatment for non-unions of long bones. FDA is seeking panel input on the following issues: Please explain whether you feel 1 year is or is not the appropriate length of follow-up after completion of stimulator treatment for non-union of long bones. Please be sure to discuss what your opinion is based on, and another related issue for this is please describe and explain your reasoning for the appropriate time frame for patient follow-up after completion of stimulator treatment for delayed unions, fresh fractures, spinal lumbar, spinal thoracic, spinal cervical indications, as well as bone conditions such as osteoarthritis, avascular necrosis and osteoporosis.

Please be sure to state the reasons for your opinion. Citations of specific published clinical studies or other references would be greatly appreciated.

For the purposes of designing bone growth stimulator clinical studies for previously failed fusions of the lumbar, thoracic and cervical spines, whether instrumented or non-instrumented, please describe clinical and radiographic indicators needed for defining previously failed fusion in patients without intervening surgically and if possible, what time points would such indicators be predictive of a failed fusion attempt. Please specify any differences for the cervical, thoracic and lumbar regions of the spine.

In addition, please describe the appropriate patient population, including whether patients with specific risk factors should undergo further analyses to determine the impact of those risk factors.

If further analysis is necessary please discuss if the risk factors require separate patient populations and/or may need to be excluded when investigating previously failed fusions or other diagnostic indications. Please specify any differences for the cervical, thoracic and lumbar regions of the spine.

In the case of long bone fracture it has been accepted that an established non-union occurs at 9 months.

Given that a patient with a non-union in the long bone is not likely to spontaneously fuse, the patient has been able to act as his or her own control. Can a parallel patient population be defined for failed spinal fusion where it is appropriate for the patient to act as his or her own control? Please discuss any differences in the cervical, thoracic and lumbar regions of the spine.

In the case of bone growth stimulators as an adjunct to standard spinal fusion procedures should the clinical study design be specific for each fusion type, indication and/or the levels of use?

For example, should the bone growth stimulator clinical study be limited to fusion type such as posterolateral and interbody fusion? Should a study be limited to specific indications such as spondylolisthesis, previously failed fusion, pseudarthrosis or something else, and should a study specifically be limited to specified levels of use involved for example by differentiating between 1 level, 1 to 2 level or 1 to 3 levels or even more levels?

Please explain the rationale behind your opinion?

Last slide?

For bone growth stimulator technologies of implantable electrical devices, capacitively-coupled electrical devices and ultrasound devices, please discuss

the important design parameters that when modified from existing designing parameters would result in the need for supporting animal and/or clinical data? For example, in the case of implantable electrical devices would design features such as the linear current density or surface area current density need clinical and/or animal data to support a change? Are there any other design features for this specific technology which should be considered?

In the case of capacitively-coupled electrical devices would changes in the design features such as voltage, current, current density or charge require clinical or animal data to support the design change? Are there other design features for this specific technology which should, also, be considered today?

In the case of ultrasound devices would modifications in design features such as frequency, pulse width or temporal maximum power require clinical or animal data to support a change? Are there any other design features for this technology as well which should be considered today.

This concludes my presentation, and the FDA would be happy to answer any questions or provide clarification on the discussion points when the Panel begins its deliberations later.

DR. BOYAN: Thank you, Ms. Keith.

The next series of presentations will be from industry. Three companies will be presenting, Orthologic, Orthofix and EBI, and would the first presenter from industry please come forward, identify who you are, what company you are with and whether you have financial interest in any device company. We understand getting a salary is a financial interest, but you may have others.

MR. MC GEE: Hi, Dr. Boyan. My name is Frank McGee . I am an employee of Orthologic, and yes, I do have financial interest in that company.

DR. BOYAN: And just as a reminder, each presentation is limited to 10 minutes.

MR. MC GEE: Okay. I would like to focus my comments on actually something that wasn't raised specifically in the FDA's presentation, but we believe a big issue in this industry and something that we would like to get some clarification on, and that is the non-union definition itself, specifically the distinction between the clinical trial definition and what has become the product labeling definition, if you will.

Next slide?

What has happened historically was there **was** a clinical trial definition which was mentioned that was primarily time based. Specifically the main parameter was that a fracture be 9 months post injury. That was

traditionally what we all did our studies on. We still believe in that definition for clinical trials, and we support it, and we think it is appropriate there.

Where the problem has begun is in clinical practice the definition of non-union is quite different than that. Certainly there is a time component that is involved, but it becomes a much more multifactorial assessment on the part of the practicing physician.

Next slide?

What has happened here is that the differences in these two definitions, the clinical trial definition and then that definition being applied in the product labeling has led to some confusion on the part of patients, surgeons and the payers, and probably the most important point there is that unfortunately due to this treatment has not been available to all true established non-union patients.

Next slide?

I would like to just go through a minute the clinical practice definition. I am sure everyone is familiar with this, but just to pull one of the many possible textbook definitions, this one happens to be from Campbells where the non-union is defined, and I won't read it for you, but I think that the first sentence is critical. It says, "The time when a given fracture should be united cannot be arbitrarily set."

Then it goes on to talk about the condition of non-union. I think the biggest point in this is that the time component is certainly not the overriding determinant of when a fracture should be considered a non–union.

Next slide?

What we find is that the clinical practice definition, the one that the surgeon is using is not primarily time based. It is multifactorial as I mentioned, and it considers many factors. All of these are obvious to everyone, the fracture type, the location, the type of initial treatment that was selected, the demographics of the patient, obviously the age, sex and then the important radiographic appearance, what is being seen on the radiographs and then obviously if there is any concomitant disease around.

The more we get to learn about this, this is really one of those things that is very difficult to define and really in our opinion falls under this idea of the practice of medicine where the physician has to evaluate all these things, time certainly being one of them but many different situations and then make some assessment of whether this is a non-healing fracture.

Next slide?

You know, I think, and everyone is familiar with this, also. This just happens to be out of a textbook. The

fundamental problem here is the various healing times that are expected or seen with various types of fractures. There is a very wide range depending on what type of fracture you are talking about, and we think you can see here from 3 weeks to 20 or 30 weeks is not uncommon depending upon the fracture type or the fracture location, and I think this is really the fundamental issue why the primary time reference doesn't hold up clinically and in fact confuses the whole situation in clinical practice.

Next slide?

so, just to summarize the determination that established non-union exists is dependent upon many pieces of clinical information. I think everyone here realizes that . Time since injury is certainly one of them but just being one of them, and although appropriate for clinical trials, the non-union definition used in the product labeling for bone growth stimulation should not be based primarily on a time reference only, and that is kind of what we think about it.

Next slide?

Those next two go together. This is the current labeling which is the indications statement for virtually all the players in the industry. This says that bone growth stimulation is for the treatment of established non-union acquired secondary to trauma, excluding vertebrae and all

flat bones where the width of the non-union defect is less than one-half the width of the bone to be treated.

A non-union is considered to be established when a minimum of 9 months has elapsed since injury, and the fracture site shows no visibly progressive signs of healing for the minimum of 9 months.

What we are supporting, and what we would like to see happen is leaving the definition intact, we are clear here that these devices for the treatment of established non-union with just removing the time reference aspect, that bottom portion in which then the proposed labeling or the new labeling would read like this. It is not an indication expansion. It is merely to take out this confusing aspect of the time reference.

I would like to just read an excerpt from Dr. Brighton which I think, Carl Brighton which I think everyone is fairly familiar with. We spoke with Dr. Brighton on this issue. He was hoping to be here today, but he was unable to be. On behalf of two companies that are in the industry he put together a statement, and I am not going to read the whole statement, but I think some of it is appropriate just to kind of cap off the position. I have been asked by representatives, and this is on behalf of Carl Brighton, University of Pennsylvania School of Medicine. I think everyone knows his background. I have been asked by

representatives of two different companies in the bone growth stimulation industry to present to you my views on the definition of non-union and on diagnosing non-union. I am happy to do so.

There was one point in the early eighties and nineties that I saw on average 150 new non-union patients per year. Thus, my experience in treating non-unions is extensive, and I have given over the years a great deal of thought to the definition of non-union and especially how to diagnose them.

Usually it takes several to many months for a fracture, excuse me, before a fracture reaches a state when no further evidence of healing on retained radiographs can occur.

However, there are times when the non-union is reached in only a few months. I have seen several non-unions that are diagnosed as little as after 3 months from the time of fresh fracture. This is to say that there was absolutely no sign of callus from day one and no changes whatsoever in the four x-ray views over a 3-month period of time.

The definition of non-union is relatively easy. The definition of non-union that I have used and which is published in JBGS, and he gives a citing of 1981, is as follows: A fracture is considered to be a non-union when all reparative process has ceased, yet bony continuity has

not been restored.

Thus, the healing and/or regenerative processes have ceased short of restoring mechanical integrity to the bone. I am not quite sure where the 9-month duration came from as a requirement for a non-union for many, if not the majority of non-unions occur prior to the 9-month period. Also, by the same criteria, I have seen many fractures that were beyond 9 months from the time of injury that were still healing by the radiographic criteria.

So, I am going to submit this to the Panel but I just would like to have that in the record, also, as Dr. Brighton's position.

Thank you, Dr. Boyan.

DR. BOYAN: Thank you.

The next speaker?

MS. BIGGERS: Dr. Boyan, may I distribute hard copies of this particular slide?

DR. BOYAN: Sure.

Don't forget to identify yourself and your affiliation, your source of money?

MS. BIGGERS: Good afternoon, Madame Chair and distinguished Panel members. My name is Mary Biggers, and I manage regulatory affairs at Orthofix in Richardson, Texas. I am an employee of Orthofix and thereby have a financial interest in the company.

As you may or may not know, Orthofix has conducted clinical trials and gained FDA approval for both fracture non-union and spinal fusion devices, the physiostim(?) and the spinalstim(?) respectively. These clinical trials as well as our ongoing product development activities are conducted under the guidance of practicing clinicians. These include Dr. Kevin Foley of the University of Tennessee and Dr. Thomas Arico of NYU.

We appreciate this opportunity to present our views on the BGS guidance document, and I want to assure FDA and the Panel that Orthofix respects FDA as an institution, and we respect its employees. However, we strongly disagree with FDA on several BGS-related issues and because of the short amount of time I have here today, I am going to speak very directly about those. So, please know that no offense is intended.

It appears to many of us in the industry that FDA has lost some of its objectivity with regard to bone growth stimulators. It appears that FDA is no longer focused on finding the least burdensome way of assessing the safety and effectiveness of the device.

We believe FDA is not considering the many years of successful BGS use that we know of, and we, also, believe that FDA may be overlooking some of their own regulations about what constitutes valid scientific evidence.

I am going to identify six issues of concern to Orthofix. Now, some of these issues appear explicitly in the BGS guidance document. Others appear in FDA's interpretation of items in the guidance document, items which we had considered to be reasonable.

First, the guidance document asserts that FDA will accept valid scientific evidence consistent with 21 CFR Part 860.7.

Now, this regulation identifies various types of human experience as valid scientific evidence. In practice, however, studies are not approved unless they are designed according to FDA's strictest interpretation. This precludes and advisory panel from ever considering other information during the PMA review process.

Secondly, the guidance document declares that BGS devices pose a significant risk because of the potential for cellular damage associated with chronic exposure. Yes, there are some interesting theoretical questions about potential cellular effects, but these questions don't necessarily make the device a significant risk in a limited clinical trial setting especially when their commercial use and off-label use has been around for close to 20 years with no serious health risks.

We assume that FDA takes this position in order to maintain approval authority over the BGS clinical studies.

Now, please understand, we do not object to FDA calling for the IDE applications and reviewing these IDE applications. We do, however, object to being limited to very specific study designs simply because of the assertion that the devices pose a significant risk.

FDA can certainly require the submission of an IDE without declaring the device to be significant risk under 21 CFR Part 812.12. If FDA wants to review the BGS IDE applications for scientific validity, it should use this particular authority rather than declare that the devices pose a significant risk.

Thirdly, to echo Mr. McGee's comments, we do feel that the traditional 9-month definition of a non-union should be removed from the labeling of approved BGS devices. Now, we, also, feel that it should be reduced for other types of clinical studies. In actual clinical use physicians typically do not wait 9 months before intervening, especially when there are approved treatments and accepted off-label treatments available. Also, a physician typically cannot wait 9 months before enrolling a patient in a clinical trial for such a study.

As was pointed our earlier a physician's determination of a non-union depends upon many factors beyond simply the time since injury. Thus, the indications statement for approved BGS devices should not state that

they are only for use after a specific time has passed. Physicians should be able to make his or her own judgment about when to apply these devices without having to be concerned about an off-label indication.

Our fourth concern regards the controls required for clinical trials. Now , we applaud FDA and are very happy that patients are able to serve as their own control in non-union studies. However, we do believe that FDA should allow a little more flexibility in the type of controls required for other study situations. Some physicians will not use a placebo control for fracture healing or spinal fusion because they feel it is unethical. Others may agree to use the control but only after informing their patients that there are approved devices or off-label alternatives.

This makes the enrollment of subjects and investigators very difficult and time consuming. Placebo-controlled studies which are typically required of us by FDA are not always needed to gather valid scientific evidence especially when a device is intended only to increase the frequency of fusion, Radiographs can be reliably used to assess union or fusion rates. Subjects cannot will their bones to grow simply because they have an expectation of success.

Therefore, it is extremely unlikely that radiographic outcome can be influenced by a placebo effect.

Also, we do have previous BGS studies that have established the absence of a placebo effect on radiographic outcome. Additionally placebo-controlled studies typically have a high rate of subject dropout and non-compliance. Obviously this is because subjects know that there is only a 50 percent chance that they are going to benefit from the device, plus these devices require daily effort and patients may not see an immediate improvement in their situation.

Therefore, we encourage FDA to consider the use of other valid controls, such as historical controls or no-treatment controls before automatically requiring a placebo-controlled study.

For the record FDA disagrees with us on this point that a placebo effect is not a consideration in a BGS study. Now, we feel that this is because FDA now insists that sponsors base the success of their device on both radiographs and clinical utility such as level of pain. Certainly yes, clinical utility or clinical outcome can be affected by a placebo effect, and that brings me to my fifth point. We believe FDA should not require that clinical utility be used as a function of the success or failure of the BGS device.

Again, radiographs are reliable for determining if a union or a fusion exists. So, the objective of this requirement is unclear to us. We don't know if FDA is

asking us to assess the merits of the operative procedure itself, sort of validating the standard of care or if FDA is seeking evidence that BGS devices actually enhance the fusion or the union, and maybe it isn't clear from GGS labeling, but these devices are not designed to enhance the outcome of the operative procedure or to reduce pain.

There are far too many variables that affect clinical utility, the extent of the original injury, the surgical technique, Workman's Comp just to name a few.

Again, BGS devices are intended only to increase the frequency of the occurrence of a union or fusion. That is why we feel FDA should not require that we base the success or failure of the device on the patient's clinical outcome.

Our final issue concerns the restrictions on the entry of subjects and unrealistic intent to treat analyses. FDA is requiring the industry to stratify patient populations and study certain subpopulations separately in order to ensure that there will be absolutely no confounding variables .

FDA would prefer that posterolateral and interbody fusions, revision and primaries, smokers and non-smokers, instrumented and non-instrumented, autograft and allograft all be evaluated separately in separate studies.

In fact, FDA has even suggested that the

particular brand of instrumentation must be standardized. Now, this either forces the sponsor into numerous redundant studies with large patient populations or ultimately results in standard off-label use of the device once it is approved and on the market and we believe this approach is unnecessary.

We recognize that covariates such as smoking or non-smoking can absolutely be responsible for success or failure, but there are well-accepted statistical covariate analyses that can be performed to determine if it is the device or the covariate that is affecting the difference in outcomes.

We believe it is reasonable to perform intent to treat analyses for effectiveness outcomes. Yet when a study is guaranteed to have a high dropout rate or a high non-compliance rate as we find with placebo-controlled studies, it becomes unreasonable.

Instead of limiting the final labeling of a BGS device to the strict population used in the trial sponsors should be allowed some amount of generalization to the population at large.

Thank you very much for your attention.

DR. BOYAN: Thank you. Next speaker?

MR. TAGGERT: Hi. My name is Mike Taggert. I am senior director of regulatory and clinical affairs for

Electrobiology, Incorporated. I do have a financial interest in Electrobiology.

I don't have slides or a very formal presentation here today, but I did want to make a couple of points. First of all, Electrobiology would like to thank the Panel for the opportunity to speak as a member of the bone growth stimulation industry this afternoon.

We are offering the following comments regarding the guidance document for industry and CDRH staff for the preparation of IDEs and PMAs for bone growth stimulation that is dated March 1998.

Premarket submissions issues are extremely important to all of us in the industry. Electrobiology, Incorporated has always tried to provide complete and quality submissions to FDA with appropriate technical, preclinical and clinical data.

However, the changing requirements and expectations regarding submissions often result in questions we cannot anticipate. As you know, this often results in delays in reviews and market clearance for both product and labeling changes which is frustrating both for FDA and for us.

So, certainly a more definitive guidance document qualifying both agency and industry expectations would be of benefit to all of us.

Some areas that we have some particular concern or interest in at EBI include the following: First, as Frank and Mary have already pointed out, the definition of a non-union is something we believe requires clarification as an important public health and, also, practice of medicine issue.

Secondly, in a previous version of this document that was, I believe, sent to HEMA for review, there was mention of consideration of a novel category for use in product labeling for patients at risk for non-unions. These would be patients such as elderly and certain other groups where treatment with bone growth stimulation may be useful prior to any demonstration of a non-union, and we would be very interested in hearing panel input on the possibility of doing a study or designing something that would allow us to look at these patients at risk.

Thirdly, we believe that the guidance document should include some guidance on addition of in vitro and preclinical in vivo data to product labeling to discuss the potential and theoretical mechanisms of action of bone growth stimulation.

As you know in the pharmaceutical industry it is a very common practice that if you look in the PDR or if you look at the package insert there are statements in there that discuss the theoretical or potential mechanisms of

action without making a claim per se but certainly allowing the physician to understand the technology and how it may be working, and we would like to see guidance on this type of labeling added to the guidance document.

Lastly, and I believe this was covered in the FDA letter to the Panel of March 31, but certainly a determination of when shorter follow-up times may be appropriate in clinical studies designed to look at bone growth stimulation as an adjunctive therapy such as in spinal fusions, we would welcome some input on how we may be able to do these with shorter follow-up times than 2 years which maybe more closely mimics what is actually going on out in clinical practice.

Once again, EBI appreciates the opportunity to discuss with the panel these issues which we believe are important not only to the health care industry but to the American public.

Thank you.

DR. BOYAN: Thank you.

Are there any other presenters from industry?

I would like to open the session up to the public now. Is there anybody from the public that would like to come forward and make a comment into the record?

Seeing none, let us go to general panel discussion, and I would like to ask our clinical reviewer,

we have two reviewers, Dr. Rangaswamy and Dr. David, and I would like to start with Dr. Rangaswamy and ask you to address these issues, please?

DR. RANGASWAMY: I did a very brief overview of what is already there, and I am not going to repeat what is in the FDA document, but I believe that the guidance document clearly defined the information that should be included in the IDE application.

The information includes the following: One is manufacturing details of the methods, facilities and controls used in the manufacture of these devices and the document expands on these issues.

The second area they cover is the device description, and this section contains a list of all the pertinent data that must be included in the application. The application must contain details of the specific characteristics of each device.

The third main item is about the preclinical data and this must be provided on these devices, and these data can be obtained either from published data of well-designed studies if available and/or animal testing.

I believe, this is my addition, this latter method is particularly important when using the device in a new situation such as the ultrasound after spinal arthrodesis.

Now, the clinical data, the guidance document

clearly states that the clinical trial should be a planned prospective study which is not a mere compilation of data from patient records.

The protocol must follow all the basic tenets of a prospective randomized study with controls, and one can define the controls later, and the data should be analyzed by the appropriate statistical method, keeping in mind that inadequate clinical data should not be hidden under a deluge of statistical information. It is very easy to get to the truth underlying these kinds of numbers.

The clinical protocol described in the document clearly defines the data to be included and the methodologies to be used in performing a clinical study. Therefore, I am not going to mention all these criteria. The list that the FDA has provided in the guidance document is complete and should be a part of any study that is to be performed.

If any of this basic data is not included the application, in my opinion, should not be considered and is incomplete . It is a waste of everyone’s time, as well as somewhat unethical to use data from inadequate, poorly designed studies using the argument that this study has been done, and we have historical data. We cannot just throw it away.

The document should include additional information

such as one, strict inclusion and exclusion criteria; two, uniform treatment protocols such as, for example, if you are treating a skateboard non-union with bone grafting and internal fixation with or without a cast such a patient should not be included in a study that is being done to determine if bone growth stimulators facilitate healing of a skateboard non-union unless you have a large number of such patients, and you are going to use them as a control against patients who haven't been operated on because then you are not testing the device; B, use of electrical stimulation after arthrodesis in the spine.

I totally agree it is very difficult to design and ideal study on this particular issue. However, it will be critical to eliminate easily controlled variables such as, these are things that can be done, limit the number of surgeons and the centers used. You clean details of the operative technique used to perform an arthrodesis because I believe that these do make a big difference in terms of how the results will turn out; strict patient inclusion criteria in relation to diagnosis, associated medical problems such a diabetes or system disease, obesity, history of smoking and alcoholism and, also, the number of levels that are arthrodesed.

Fourth, to evaluate anterior and posterior arthrodesis separately, also, instrumented and non-

instrumented arthrodesis separately and, also, taking each of the variables individually. Otherwise you are not going to get a clean study that is going to tell you whether this works.

At this point the data that we have that I have reviewed and what has been published wasn't given here, but I have reviewed this data extensively in the past, all of it consists of very poorly designed studies. None of them is complete. Even Bert Mooney's study is terrible.

Then cervical and lumbar spine should obviously form an independent group. Now, the reason for these inclusions is that one, currently the available literature is totally inadequate on the use of stimulation after spinal arthrodesis. Two, the literature on smoking is still extremely sparse, and newer information suggests the effects of nicotine are concurrent and not cumulative, and thirdly, the operative technique must be standardized and be meticulously performed, and other bone growth factors should not be used at the same time except from say, allograft bone or autograft bone, and the groups must, also, be divided on the basis of the type of graft used.

These are some of my comments, and I think the rest of it is really well covered in the guidance document.

DR. BOYAN: Thank you, Dr. David?

DR. DAVID: I reviewed the document, find it a

good tool to increase the consistency of data submitted for review as well as comparison of data. The document as described by my colleagues has several categories that are important. Beyond the manufacturing practices the device description relating to the physical description, the use of interface, the power source, the electrical characteristics and the specific application of different technologies such as magnetic field, capacitance coupled with ultrasound, etc., are a significant influence on clinical outcome and should be well documented.

There is a section about software and firm in the document that describes the need for description of code and algorithm describing function as well as hazards. I think the issue relating to code failure as far as risk assessment needs to be strengthened.

The next section is talking about the electromagnetic comparability, and I think that issue needs to have better definition rather than just a global description of what immunity and emission control but rather more quantitative data that is required to be submitted.

Then the document is going to preclinical data, clinical data and consideration for PMA application and bibliography. What I would like to focus on in my comments is a couple of areas that I have discussed with colleagues in the field. Relating to the duration of the study for

treatment of non-unions, one year follow-up for non-union treatment by BGS seems to be sufficient. If the non-union is effectively treated by the BGS then the follow-up to confirm appropriate healing and remodeling of the fracture should not exceed weeks and possibly months but one year should be sufficient.

The FDA goal to determine adverse effect on the surrounding tissue following BGS use should not have to exceed several weeks or months since the adverse effect of such skin or soft tissue necrosis, mild stasis, etc. , should be apparently almost immediately following such a treatment.

The only effect which should not be seen with such time period would be neoplastic effects if they are assumed to exist and neoplastic effects are unlikely and could potentially take up decades to manifest.

The end point of the BGS studies usually are the fracture and non-union healing. The differentiation as far as those end points should be looking at the application of implantable versus external stimulator, not necessarily just between the technological principle of the stimulator.

In a delayed union fresh fracture of long bones, appropriate follow-up included the commendation that the fracture has truly healed by both radiographic and clinical evidence, as well as evidence that there has been no adverse effect to the surrounding soft tissue that is involved.

Once these factors are confirmed there is little reason to continue to follow these patients after the treatment by the BGS has been discontinued. In terms of use of BGS in spine, the major differentiation exists between thoracic and lumbar use. In the thoracic level the spinal cord is in proximity to the fusion site and the lumbar level the cord is absent.

In addition to the spinal BGS are usually implanted to decrease distance between BGS, electrode and the site at which the fusion is desired. The FDA must carefully examine the biological response to the stimulator housing, the methodologic response which often remains in the subcutaneous tissue even after the treatment is discontinued.

DR. BOYAN: Okay, are you through, Dr. David? Dr. David, are you meditating to read more or are you through?

DR. DAVID: No, I have one more paragraph. Study for the spinal bone growth stimulators used in adjunct to standard spinal fusion procedures should specifically consider each fusion procedure, indication level of fusion primarily because they are all factors which influence fusion rates. Comparing BGS for use with posterolateral fusion at L4-5 with BGS for use with interbody fusion at L5, S1 would be like comparing apples and oranges. Each procedure has different operative principles and fusion

rates .

Interbody fusion relies on compression while posterolateral fusion is on the tension side of the spine. Indication needs to be stratified in order to truly compare BGS to control. That is to say that the fusion for injury in a virgin back will respond differently than a fusion for a third authorized in sailback(?) . That is my comment.

DR. BOYAN: Thank you. All right. We have had comments from the FDA, comments from industry, comments from our two lead reviewers.

Now , I would like to open up the general discussion and just begin someplace we haven't begun before, Dr. Hale, let us start with you and go around the room and have you enter into the record any general comments you might have about the subject.

DR. HALE: I just have two brief comments that have to do with the preclinical effectiveness testing as listed in the guidance document and that is in terms of the biomechanical testing of the healed fracture. I would suggest to the FDA that they in looking at that data specifically look at both material and structural properties.

I mean some of the testing that I have done in the past in our lab we have noticed healed fractures or fractures that gave the appearance of being healed looking

purely at structural properties that obviously were not healed when you looked at the gross morphology of the tissue or looked at the material properties themselves.

So, I think that is an important distinction to make, and the other would be to look at the effect of any treatment on properties of adjacent native tissues, particularly if the treatment has a wide area which is being affected. This may be a minor point, but if you are going to use native bone as a comparison for the healing it would be good to know that that native bone, the adjacent bone actually has the same properties as native or normal tissue.

DR. BOYAN: Thank you. Dr. Urban, do you have any comments you would like to add?

DR. URBAN: No, I think the outline by the agency is pretty clear about clinical trials, and despite what industry has said here, I think the problem with the data so far is that it hasn't been uniform or standardized in the statistical analysis.

DR. BOYAN: Thank you. Dr. David, did you want to add anything else? No?

DR. DAVID: I just would like to call the agency's attention to some standards in the area of electromagnetic comparability that were not called in the guidance, namely, some that are involved with the association AAMI that need to be included specifically for manufacturers, as well as

for users and some guidelines that will help industry, A-S-H-E, ASHE document for managing electromagnetic comparability issues in medical environment.

DR. BOYAN: so, AAMI stands for what, American Association of --

DR. DAVID: The Association for the Advancement of Medical Instrumentation and ASHE stands for the American Society for Health Care Engineering.

DR. BOYAN: Thanks. Dr. Silkaitis?

DR. SILKAITIS: Yes, certainly in terms of clinical practice the time interval for determining non-union I agree with the comments made by the industry earlier that maybe we should take a look at that and make a recommendation to FDA to be able to remove the time course definition in there rather than dictating what a non-union is.

From a clinical study point of view certainly it should be defined so you have consistency in the protocol, but when it comes to clinical practice maybe your recommendation can be supported there.

In terms of the clinical trials I noticed here in the guidance document on Page 12 that they do talk about, and I will quote here, however, as stated previously a concurrent control group may not be necessary because a patient can be his own control.

I would like for FDA to define those situations for us. Having conducted a clinical trial with the patients who have non-unions it is very exceedingly difficult to find a standard non-union patient. They don't just get hit by a car the same way every single time, and so, we find that the patients come in various sizes, shapes and when you do a knee trial or a hip trial certainly there is more uniformity in an osteoarthritis patient, but when we get a non-union patient certainly it is a compound fracture. There are all sorts of different angles and things like that. So, the patient population is certainly a difficult one and should be taken into account, and for some reason this patient population group is maybe not as compliant as other patient populations .

So again, there is a lot of scatter in the data which is very difficult to control. I like tight studies but with the patient population that we are dealing with here and with the type of fractures that are here, the non-unions it becomes very difficult to make it a real, good study. So, I would just like to throw that out on the table for surgeons to consider.

DR. ALTMAN: The document appears under the preclinical testing to address patient safety and under clinical testing talks about IRBs. So, I think the patient's concerns are addressed here.

DR. BOYAN: Thank you.

Dr. Aboulakia?

DR. ABOULAKIA: I had a couple of comments, some of which have already been touched on. I think part of the problem that we as members of the FDA or at least for myself is that we are talking about at least in my mind two separate devices, an implantable bone growth stimulator versus a non-implantable bone growth stimulator. We are talking about something where data might be obtained one way on a particular type or group of patients in the setting of the spine that is very different than the traditional long bone fractures.

I think there is probably more, we might be able to come to some easier to agree terms or ideas of study design and indications based on whether something was implantable or not implantable.

One of the things that was brought up by industry rep was whether this posed a significant material risk or not, and I think the answer to that which is sort of the fundamental question by which all other questions follow is is it implantable or not implantable, and at least in my mind the significance of material risk from an implantable bone growth stimulator is different from one which is not implantable, and a study design that focuses on something that I believe to have substantially less risk would have

different requirements than on a device that I believe does pose potentially a significant material risk.

So, without speaking in abstracts, I would say that we have historical information on poorly controlled studies that suggest that an external non-implantable bone growth stimulator in the treatment of delayed unions, non-unions or even fresh fractures that are at risk is out there, and that data may not be the best science, but I think even some of the biggest skeptics on this sort of voodoo technique meaning we don't understand the basic science, accept the fact that there is at least some experience out there to suggest reasonably well that this is something that works and that it doesn't pose a significant risk to the health and well-being of patients.

so, I guess the standard that I would hold them to for the treatment of long bone fractures, delayed unions, non-unions or as mentioned fractures at risk would be much, much, much lower than what I would for an implantable bone growth stimulator. Maybe that is a long way of saying what many of us might be thinking.

I think l-year follow-up is sufficient. That is an easy one to make. Adverse effects for an explant or a non-implanted bone growth stimulator I think we do have historical information. Again, it is not the best science, but I think it is adequate, and this group has listened to

last month when we looked at plaster of Paris pellets there wasn't anything that resembled a scientific study, and industry rep admitted we don't have anything that even hints at a scientific study, but we do have this history from the literature, and they published literally or presented case reports, and the largest case report may have been a series of four or five patients but I think we accepted that it posed a minimal risk, and we are going to hold them to a different standard than we would an implantable device.

I agree, again, with industry, the end point is healing. They are trying to make patients get well because they cannot. They are trying to get the bone to heal, and there are patients who break and bone and never go back to work and sue their insurance carrier and sue the person who hit them and the car manufacturer and everybody else claiming pain and suffering. So, I think the end point is not function. It is simply did the bone heal or not, and that is what they are claiming. They are not claiming we can get you back to work better. It is we can get the bone to heal.

As far as controls, I don't think placebo, and I am limiting my comments to non-implantable bone growth stimulators . As far as the placebo group I don't see the point . It is treatment versus no treatment. Either the bone growth stimulator helps or it doesn't help, and I don't

see what a placebo group does for you. It is not like when you put the bone growth stimulator on that you are adding something to it, i.e. , a thermal reaction that is inherent in the sleeve of the bone growth stimulator or mobilizing the fracture.

There was some discussion about preclinical studies that require structural and mechanical evaluation of the bone. I think again based on what is not great science but science that is out there we know either the bone heals or doesn't heal and that it is a reasonably good parameter at least in humans to look at multiplaner x-rays to determine whether there is bridge in callus or not.

Now , is all callus the same, no? But once you have bridge in callus ultimately we expect that to go on to develop mature organized lamellar bone, and as Dr. Silkaitis pointed out, and I would just reiterate, no fractures are the same. You will never have a perfect study. We can use Costello and Anderson's classification, and we can talk about non-unions in the tibia in the proximal third or distal third, but it would be exceedingly difficult to have a true basic science study, and then the 9 months I think has already been addressed. I am done.

DR. BOYAN: Dr. Laurencin?

DR. LAURENCIN: I don't have many comments. I think that the draft guidance document in general is very

good and very appropriate. In terms of the comments by the different companies, I think that there is a saying that there is no royal road to learning, and I think that when we talk about treatment of non-unions the companies with their products have actually picked a very tough problem to tackle and a tough problem to get clinical answers from, first because you have to wait for a considerable period of time before you can decide that person can be studied and second, because there are confounding variables, and it is difficult to get controls, but with that said, I think that one thing that has sort of held back this segment of the industry has been the fact that a lot of information has been anecdotal.

Some shortcuts have been taken, and I think that it is still important to do well-controlled studies that answer specific questions involving these implants, and I think that if not then I think that the companies will be coming to the FDA year after year asking for or wishing to have changes made.

With that said, I think I do believe that in terms of some of the requests made that clearly if one is looking at union of a long bone fracture and one has decided that there is stable union with the bone growth stimulator removed that a l-year follow-up is probably good enough to be able to demonstrate that you have a stable fracture that

is healed.

On some of the other areas I would like to hear from the other members of the panel in terms of some of the other areas before coming to a, before I give a recommendation in those areas.

DR. BOYAN: Thanks. Dr. Cheng?

DR. CHENG: I will make my comments brief as we will be addressing some of the questions later, but in regard to the FDA, I would encourage the FDA to maintain the strict definition of science as the main problem in the previous studies has been that the design of the study or as Dr. Rangaswamy said, the data are not very interpretable because of the way it was designed.

There was a comment made that BGS devices do not pose significant risk. That is not necessarily true, especially for an implantable device which does have risks, and so if you are going to judge that device it needs to show a higher level of benefit than a non-implantable one.

The definition of a non-union, I think is variable from site to site and a strict arbitrary 9 months is a little bit false. I would agree with that assumption. However, the FDA should maintain the same definition of non-union from site to site and from study to study regardless of whom the manufacturer sponsor is.

I believe that placebo controls are necessary for

these clinical studies. Placebo can affect the outcome, the objective measurement of an outcome, and since it is impossible to blind the patient for this type of treatment; that is why you need a placebo study there, and the follow-up I think once a fracture has healed as long as the healing is well demonstrated, I don't see a need for longer follow-up than a year.

DR. COUTTS: Richard Coutts. I have just a few additional observations to make with regard to the document. Some of this is nit-picking but facts that I think were missing.

On the implantable devices I think that an additional definition that needs to be included or an explanation would be the sterilization method for the device and particularly the effects that sterilization might have on components such as if you are using gamma radiation and you have plastic components that is where you are going to have an impact on the devices.

Most of these devices tend to be taken out. So, I am not as concerned as I might be for something that would be left in forever, but you never know whether one of these devices might not be left in forever.

In the exclusion areas or rather than say that particular category I didn't think that smoking was addressed adequately in the document. This has a potentially

significant effect upon fracture healing, and I think that patients should clearly be identified and maybe substratified as to whether or not they are smokers or not, and I would make the same comments for people who are Workman's Compensation patients that that has a significant impact on their response interestingly enough.

With regard to medications I didn't think the document addressed the issue of non-steroidal anti-inflammatories adequately. Those can have an effect on fracture healing as can steroids and some metabolic drugs that are used for the treatment of inflammatory conditions.

The definition of a non-union is an extremely difficult thing. Clinically I always use 7 months rather than 9, but we could nit-pick all afternoon over whether it ought to be 7-2/3 months or something of that nature, and I don't know that we know the answer to that, and a l-year follow-up following conclusion of treatment seems perfectly adequate to me.

The issue of controls is a very important one. There is a study of bone growth stimulators on the treatment of osteonecrosis of the femoral head which had over 1000 patients treated, and it still hasn't been approved by the FDA and the major flaw of that study was that there was no control group.

Now, it doesn't necessarily have to be a placebo,

but there should be a control because you just, this modality is not 100 percent effective. It is only partially effective or a certain percentage of the patients are going to be responders, and so you have to know whether or not that percentage is greater than some other treatment or no treatment.

so, I think the argument for controls is very, very strong. It doesn't necessarily mean every study has to have controls. It would depend upon what your knowledge base is going into the particular study, but under most circumstances I have a feeling that there is going to need to be a control.

DR. BOYAN: I would like to make a few comments, and I am going to address to some extent the biology of a non-union. I would say that I think that industry has been very nice saying that they don't argue with the 9-month designation for a clinical trial for a non-union. I would argue that that is inappropriate.

For an animal study a chronic non-union or a non-union is established in a large dog by 3 months that could not be distinguished histologically from a chronic human non-union at 9 months or a year, and the preclinical data in the dog would be acceptable to FDA as preclinical establishment of the efficacy of a device. Why then would we ask the clinical trial to have to stand up to a higher

standard?

Yes?

DR. WITTEN: I was going to ask this later or clarify this later, but since it has come up, and I think a lot of your remarks relate to it, I would like to clarify it now, if that is okay?

DR. BOYAN: You may, yes.

DR. WITTEN: Okay, about this 9-month issue I just want to explain what we have been doing, and your remarks may still apply but I want to make sure you know what we have been doing.

The 9-month definition for clinical trials applies to the following, that is sponsors have wanted, this is historically sponsors have wanted to use patients as their own controls, and so the question was at what time do you know enough about the natural history of non-unions that would enable you to use the patients as their own controls with the non-union.

so, that determination previously, that recommendation has been 9 months. So, I guess it would be helpful to clarify what you are saying is that you feel that by some other time point a non-union can be sufficiently well established that patients can serve as their own controls even at that time point.

so, that is part one, but then part two of this 9

months or practice of medicine issue that has been brought up by the sponsors, really by all of them is suppose a clinical study has been performed using this 9-month definition and which has enabled the sponsor to perform a study using the patient as his or her own control, does the information from the trial translate into instead of the labeling has specified non-union as defined by 9 months, I mean I have forgotten the words that the sponsor had up there, but do we know enough from the information we have gained about 9 months to be able to generalize the label to say that if it worked for non-union as defined by **9** months then it would work for non-union as determined on a clinical basis.

so, it is really two parts to this 9-month definition.

DR. BOYAN: Actually my comments do still apply, but I like your clarification because it did make me change them slightly.

so, I would argue that in fact in an animal model we can make determinations biologically as to the effectiveness of the device in an animal that has a histologically established non-union of 3 months' duration, in fact, do make determinations to go forward into clinicals in humans on that information.

Now, in the animal you could argue that that is

perhaps a delayed union, but in my experience now which constitutes over 100 dogs of an established non-union that these dogs no matter what is done, and we have done the experiment of allowing them to wander around the vivarium up to a year and in some cases longer than a year retain the histological appearance of a chronic non-union.

If that piece of tissue was studied side by side a human non-union of long duration it would not be possible for the histologist or the pathologist to determine which came from the dog and which came from the chronic human non-union, with one exception and that is the dog non-union tissue would look prettier because it would have been surgically created by creating a large segmental defect whereas the human non-union tissue would be somewhat more convoluted and very unattractive from a histological point of view.

SO, I accept that you would say that for the patient to be his own control you want verification that that is in fact not a delayed union and is truly a chronic non-union, but you have set the bar so high for anything to work when the non-union reaches that level of being a fibrous connective tissue with all of the biological consequences of that kind of tissue being established that I would argue if something can work under those conditions it could work very effectively or at least as effectively and

perhaps more effectively and to the greater benefit of the patient if the surgeon could make the determination as to what is a medical non-union and put that device into practice.

so, now, let us talk about controls. The control issue is related to what the question being asked is, and now, I am not advocating one method over another, and I am not a surgeon. So, now, I would speak purely from a personal point of view of what is a true control. Part of what is the argument here is historical.

These materials and these devices came on the market when there **was** still a question as to whether or not there was a biological effect of any kind of stimulation, whether it be ultrasound, whether it be pulsed electrical magnetic fields, regardless of what it might be, that is when these instruments came along, and the original studies were designed to determine that it **was** not a placebo effect, that in fact, the therapy, the actual scientific reason for the therapy was in fact the causative agent, and I think that has been very important, but it is 20 years later, and there is a society that studies this kind of activity.

There are scientists that report on it. There are good biological cell biology studies that now show that in fact, these treatments do cause a biological effect.

So then the question is are we still measuring the

effect of just the modality or are we measuring the effect of the entire treatment as we would be doing in any other clinical situation which includes the fact that this patient now is going to go get treatment multiple times with a therapeutic intervention of a person that is applying hands so to speak in applying the device, much more care than they would get if they were only seeing their surgeon for a follow-up, and in fact, that might be a cause, and I would argue that for each device that FDA and the sponsor need to ask what is the question being asked.

Is the question the total treatment or is the question to determine what is the biological effect of the specific modality being tested, and once that is defined, then whether or not the placebo needs to be the control or whether or not it needs to simply be the therapeutic event that is the control, and with that I pass it on to Dr. Li.

DR. LI: I only have one comment actually and Dr. Coutts and Dr. Aboulakia mentioned it in a slightly different way. I read through the guidance document. I saw no section that pertained to the materials of construction in any manner.

Typically for any medical device it is rather spelled out what those materials are and what either ASTM or FDA guideline must be passed for that material to be implanted. So, for the implantable versions of these it

seems if not a list of acceptable materials, at least a direction for the sponsors to know how to qualify the materials or verify the materials are suitable for implantation should be provided along with the sterilization issue that Dr. Coutts mentioned.

DR. LARNTZ: This is Larntz. This issue of designing a trial is very difficult. I liked our Chair's comments on the choice of control. I think that is right on target . You have got to figure out what you are comparing it to and make the appropriate control for the comparison. That is real simple, not easy to do necessarily in practice but real simple from a statistical point of view.

There are **a** few concerns I have with respect to the philosophy of part of the document that deals with subgroups, and there is a large part of the document which talks about the possibility of many, many different subgroups having effects, and I want to be very clear that as a statistician my experience is that for the most part subgroup interactions with treatment effects don't exist as often **as we** like to think they might, and that in fact, you have got to be very careful not to design a study that will account for every possible interaction subgroup.

Those studies become impossibly large, and in fact when you get to the end of them you usually find that most of the interactions are at most marginally significant or if

so only statistically significant but not of any real practical significance.

so, I want to say that I think that that is a very difficult issue for people to think about and design because we can always think of what if, what if, what if, what if, and I tend to design the studies to say that if there are strong interaction effects of some subgroups then we should find that in the data and that should speak to itself. There are, also, a number of exploratory methods using Basian(?) methods to allow us to look at subgroups appropriately without prespecifying all of the subgroups in the world.

so, that said I think most of the effects will be in fact, main effects and things would work in general. If they work, they work across the board.

Now , what do you do if you are designing a study for a device or for something that works across the board? I heard people talk about a clean study. What is a clean study? Is a clean study done in a laboratory with white coats or is a clean study one that reflects the real world?

As a statistician I have to say that my belief is that a clean study is one that reflects the real world, and thus, patients should be selected if they are appropriate, if they might appropriately benefit from the device and that should be the eligibility criteria.

Very stringent inclusion-exclusion criteria in studies tend to have situations where a doctor came to me once and said, "You know, look at this paper. They said to do this test, that test. They met this test, that test. Boy, I sure wouldn't have time to do all those tests. How do I know the study applies to my patients?"

so, I think we should have very broad eligibility criteria and in fact, randomized study against the appropriate controls.

Now, given that I think that centers should be selected with the same thing in mind. Not all centers are pristine, clean, perfect centers. There are varieties of centers, and we should in fact design our studies to have our study take place in the variety of centers. That means that we would not expect nor would we want the demographics from our centers to all be the same.

In HIV in our study of HIV which I have done, I would want my HIV treatments to be conducted in Harlem as well as San Francisco. Believe me the demographics are quite different, and I would hope that my treatments would work in both places, and I would want to make sure I could check on that.

so, I think that if you want a device or a product that works across a broad spectrum and can be used across a broad spectrum in situations you have got to study across a

broad spectrum. That means you would have a variety of centers.

Now, that comes with some cost, and in order to then if you have such a design, then the key feature for you to look at in the design as well as in the subgroup is to look for consistency of treatment effect across centers. That is the key to pooling, not whether they have the same age distribution, not whether they have the same arrest(?) but whether the treatment effect is consistent across centers, and that is the key to pooling, and it is, also, the key to subgroup analysis, do you have consistency across the various subgroups or is there some differential, and statistical issues with respect to doing those analyses are in fact not straightforward and as simple as people would like to think.

In fact when people do pooling they often then ignore the center effect in their analysis, and that is not right. Centers do vary. Treatment effects do vary. What that means is that most studies in order to adequately allow for the variation in centers and the various across subgroups will have to have larger sample sizes than the strict who cares about the center; there is no effect of center which I actually don't believe, and so if a study is appropriately designed and allows for the various real world effects they may need to be larger, but then we will have

answers that will apply across the broad spectrum of patients and not across the pristine white-coat subgroup that we would study in a quote, pure study.

Thank you.

DR. BOYAN: Thanks .

Dr. Gilbert?

DR. GILBERT: I know very little of this area. So, I am about to tell you more than I know. I guess I am a little uncomfortable with a guidance document that looks at three very disparate technologies. I think Dr. Aboulakia, and I am sorry if I got you name wrong stated, and I agree with that very much. It is sort of like trying to lump a knee replacement, a brace, a ligament replacement in the same guidance document, sort of going after the same area but in a different way. So, I am not sure that it is appropriate really to have ultrasound bone healing devices in the same guidance document as an implantable device, for instance.

In terms of controls, I guess that is another big issue and problem, whether you can use a patient as his own control, and it seems to me that there are two issues or two ways you can look at it. You can say, "Do they continue to have **a** non-union or are they non-union or what is the rate of change of that state of that union?" and if you were looking at a patient every day, and let us say ideally you

could take a histological section every day, you would probably have a very good assessment of not only the state of the non-union but, also, the rate of change over time.

You cannot do that. You probably do x-rays every couple of months to check. So, your time periods are very large apart. So, it is hard to judge the change in time, but I guess what I am getting at is if you had a good way of assessing the change in the state of the non-union over time you could get to a level where you don't see much change in the non-union state and use that as your time frame for doing a treatment.

Now, I have told you more than I know.

DR. RANGASWAMY: May I make my comments now or after you go around?

DR. BOYAN: Oh, no, this is your chance to do it.

DR. RANGASWAMY: A couple of things I would like to comment on that people have brought up, the issue of historical data. Historical data can certainly show you that the device is safe, but it does not necessarily show you that the device is effective, and I will use an example. In the JBGS we published a meta analysis article on treatment of closed fractures of the tibia.

We normally don't publish meta analyses but we decided to do this one just to show the problems of defining conclusion of whether cast treatment, an iron rod or open

reduction, which is more effective. None of the literature tells you that either is more effective than the other. You need to remember that. It is very easy to be fooled by the data.

Secondly, for instance, I think Heckman did an article on ultrasound and the management, the treatment of tibial fractures. I believe it was December 1994 that it was published, and he does show that ultrasound decreases the time for healing, but he doesn't necessarily show, doesn't answer the question that it is good for non-unions. He doesn't necessarily show that it should be used in the treatment of fresh fractures of the tibia. He, himself, **says** that . I questioned him on this many times.

The third comment I would like to make is towards the statistician's comments. I don't think when I was talking of a clean study, I think in the spine you have to be very careful because whether you do an anterior fusion, a posterior fusion, a posterolateral fusion, an interbody fusion, whether you put an instrumentation, how meticulous you are, and I used to be a spine surgeon, the difference in how meticulous you are in obtaining an arthrodesis of the spine or whether you are a shoddy surgeon who doesn't do very well, doesn't do the technique very well and depends on the instrumentation and bone graft and external stimulation to get to your bone healing those make very big factors.

so, I think that those are variables that should be allowed in it. I agree you can never have a clean study as said earlier, but I think you should make an attempt to do that, and my last comment was in a dog femur fractures heal very quickly, and dog years are different from human life years, and so, if you are looking at 3 months in the dog for a non-union I think yes you are correct in saying that the histology will look the same, but I cannot think that you can use the exact analogy.

I think in the clinical situation to define non-union we have got to go back and have to look at serial x-rays and say that that might be a better definition, but if you look at serial x-rays and over so many months you absolutely see no signs of healing on the x-ray, no evidence in newborn formation and clinically you find evidence for non-union, persistent, you know, movement at the fracture site, then I think you may have enough evidence to say that you have an -- you cannot still say that it is a non-union until you see the clear-cut signs on the x-ray, but you can at least say that you have a delayed union.

The problem has come in I think when you talk of the practice of medicine is that so many physicians in practice ask to use the stimulators which are very expensive, and these increase the health care costs without enough proof that they are really effective or necessary all

the time.

They are being used for patients with delayed unions, etc. In spinal fusions I have talked to spine surgeons around the country and I think opinion is equally divided. There are some chaps who will say, “I never use the stuff. I don’t think it really does anything, ” and another says, “Well, it is a Workman’s Comp patient I want to use it,” hardly a scientific reason for using a device, and so, I think you need to keep all this in mind when you look at it, and I agree that you cannot get a clean study, but you still have to try for it.

DR. BOYAN: Dr. Skinner?

DR. SKINNER: I was trying to debate whether I should say something or not. Maybe I had better not.

DR. BOYAN: Go ahead.

DR. SKINNER: Okay, we are apparently having trouble defining a non-union, and you know we are pretty good at defining what a union is. A union is something that shows signs of healing on an x-ray. It has no tenderness to palpation. There is no pain to stressing it, and there is no motion at the fracture site, and it has had adequate time to heal more at that particular site, and happily in orthopedics things are fairly simple. Most things in orthopedics go by the 4 to 6 rule. So, skin heals in 4 to 6 days. Finger fractures heal in 4 weeks, Cones’ fractures 6

weeks, humerus fractures 4 to 6 months, tibia fractures 4 to 6 years, femur fractures 4 to 6 months, but that is the old days, and we have gotten better at treating fractures.

So, those numbers aren't as accurate as they used to be once, and typically when I was a resident 9 months was what it took to define a non-union of a humerus. No one ever operated on a humerus until it was 9 months old, and by then it was almost impossible to operate on. So, you didn't operate on it anyway.

So, the patient lived with it. So, I think what we can say in terms of trying to define a non-union, and what I would throw out as a possibility to have people throw stones at is that there has to be motion at the fracture site unless there is metal in the site holding it together. There has to be evidence on x-ray, CT or tomos to show non-union or failure of bridging callus. There has to be pain to palpation. There has to be pain with stressing the area, and there has to be a minimum of 3 months of no progression in radiographic scientific healing by an independent observer.

Now that leaves you with a group of patients who have a probable non-union, certainly a delayed union, and that 3 months could be before, start before the expected time of healing.

At that point I think that you would have to have real controls, and as Dr. Larntz alluded to, you could

always go back to the standard treatment for non-unions which is bone grafting, randomize them into the two groups. One is electrical stimulation. One is bone grafting. That is a way to take care of the problem.

Other than that I really don't have much to say about this particular problem.

DR. BOYAN: Thanks.

Okay, is that everybody? We are all the way around. FDA, do you have any comments you would like to enter into the general discussion?

DR. WITTEN: There was another question brought up by one of the sponsors that if anyone had some comments on we would be interested in hearing.

DR. BOYAN: I guess I missed it. I thought we had covered this. You are about to share it with us.

DR. WITTEN: I am about to tell you.

One of the sponsors said that they would like to make mechanisms claims based on in vitro data, and we have been wondering about this, what type of mechanism claims could be demonstrated by in vitro data and what type of data would that be?

There may be no comments. I just want to throw that out.

DR. BOYAN: I guess I would address it, but I would like to disclose something as I address it. Let me

think how I would like to phrase it. Right now the disclosure I want to make is that I have done studies like this and will be doing studies like this in the future trying to understand how it is that manipulating non-union cells in a variety of ways might make them behave in a more normal manner, more commensurate with normal healing.

I have looked at non-union cells. These are cells that come from chronic non-union tissue from both humans and dogs and tried to understand how it is that, what makes them a non-union cell, why is it that they produce a non-mineralizable matrix instead of making normal bone matrix, why they behave more fibroblastic instead of behaving more osteoblastic or even more like **a** cartilage cell which is going to go through an endochondral developmental pathway. so, I have looked at how they respond to growth factors. I have looked at how they respond to hormones, and I have looked at how non-union cells respond to -- at present I am looking at how they respond to pulsed electrical magnetic fields, but I am not wed to any one particular mechanism of manipulating the cells. I am just trying to understand what makes a non-union cell do what a non-union cell does.

Non-union cells are not the same as cells that would normally be healing a defect. We have published in the literature how cells, at what point in a craniotomy does a cell achieve a non-union phenotype in the craniotomy of a

rat . By day 17 the decision has been made biologically for a chronic non-union to be established. This is very, very rapid, and I admit that rats are not dogs, and dogs are not humans, but when the decision, the biological decision for a chronic non-union has occurred by day 17, you have to ask yourself why -- part of the reason why we are having to wait to 9 months is we don't have the right diagnostic tools of determining when the actual decision for a chronic non-union was established biologically at that site in the human.

In a dog it is around 3 months, 12 weeks, and at which time that tissue is really going to be chronic non-union tissue. It is not going to suddenly start to support bone formation.

In a human it may take longer, and a lot of that depends on a lot of factors in all three animal models, rabbit, also.

so, the answer is yes, you can start to make claims about how cells respond. You could say that in vitro this cell responds this way. Whether or not you can make a mechanistic claim based on in vitro data about anything in an actual human is amazing at the state of the art in which we now live.

You could make the statement clearly that that is what happened in vitro just as you could make the statement that parathyroid hormone makes a cell do whatever it makes

it do in vitro, just like you could say that cells living on titanium surfaces do something in vitro. When you put those cells back into the animal where they are surrounded by lots of different cells and many different signals then they would ever see in cell culture you have a whole different story.

so, if a company came to FDA and wanted to make a claim about what non-union cells did when they were exposed to a certain stimulus in the cell culture that would be factual, and I think they could make that. Whether or not that could be at this state of the art transferred into a major statement about the mechanism of non-union healing in response to a particular stimulation is really open to an awful lot of discussion and it goes way beyond the expertise right now of this Panel or of the scientific community in general.

That is my opinion. Nobody else has the courage to speak up I guess.

DR. RANGASWAMY: We all agree. We agree with you .

DR. BOYAN: So, if there is anybody that doesn't go with that opinion so state your name, admit who you are and --

(Laughter.)

DR. BOYAN: Does FDA want to add anything to what

I just said?

Would the sponsors like to say something?

MR. TAGGERT: Mike Taggert, EBI. I would just like to state that I didn't say, "A claim" per se. If you pick up a PDR, and you look at a drug there is a section in there that talks about potential mechanism of action. It may work as a beta blocker or it may do this; it may do that. They don't necessarily know the mechanism of action, but in the labeling they are allowed to state in there that it may be this or it may be that.

When people use a drug or when people use a device they may want to know how it works, but if you cannot tell them the in vitro data that it is based on or possible animal studies that it is based on how could a doctor possibly make a decision that he would like to use it?

So, it is not necessarily to make a claim. It is just a potential mechanism of action, and it wasn't intended to be as a claim per se.

DR. RANGASWAMY: May I make a comment?

DR. BOYAN: Yes.

DR. RANGASWAMY: I think when you put in mechanism of action it is interesting. When I think Hialgan(?) came onto the market and despite the fact that it is put down this was what it is effective for osteoarthritis, the way the salespeople come around and do their pitch and with the

data that they have, they don't really identify for you clearly the patient population that were supposed to be using it.

so, I review stuff around the country, and you get requests for this in totally in appropriate patients, patients who needed a total, obviously need a total joint.

DR. BOYAN: Wait, I don't think we can talk about it in that format.

DR. RANGASWAMY: No, but I was just saying that if you put something in and you don't really clearly define it and if you allude to it then it can be misinterpreted to mean something else, and I think that is always a matter of concern.

DR. BOYAN: Yes, but I mean as strongly as -- this is Boyan again and as strongly as I made my statement I do have to say that to present data that is in a peer-reviewed publication as information to people I think is perfectly legitimate, and I think that to state that that information if it is peer reviewed and it is in a technical document I think that is an entirely different situation, and I think more companies should consider that as a way of getting that information out as an alternative.

It is, once it is peer reviewed once it has been established that the study was done in a scientific manner and what the data are and it is not overinterpreted, that is

a perfectly legitimate position to take.

MR. TAGGERT: I think that is the point though. Right now, we cannot really do that, and --

DR. BOYAN: You cannot do it in the labeling is what you are saying.

MR. TAGGERT: Right. We cannot do that in the package insert or --

DR. BOYAN: But you know some security for you is that some of our clinicians repeatedly tell us on this Panel that they don't read the package insert.

(Laughter.)

MR. TAGGERT: I have heard that, too, but that is what we are looking for is some mechanism to do that. So, I mean if you could suggest a mechanism, we would appreciate that.

DR. BOYAN: A technical report they think would be a perfectly appropriate way to do it.

Okay, any other comments from the Panel?

Yes, Dr. David?

DR. DAVID: I would like to change the topic a little bit and go to the organization of the document. I think the document is well laid out and some of the comments that were made about implantable versus non-implantable differentiation can be addressed by reorganization of the existing material here.

For example, on Page 3 we have a section calling to invasive devices requiring information about sterilization of material, a question that the panel was asking about in Page 5. Instead of invasive devices we are addressing the description of implantable devices. So, I think there is some inconsistency as far as definitions. I think the organization needs to be clearer as far as implantable versus non-implantable devices and it will be easier to follow.

Also, the issue of characteristics and I am referring to the physical and electrical output characteristic of devices, they are left to be described in a vacuum, not under certain conditions, i.e. , simulated loads are no described, not defined, and I think they need to be addressed as we all know that from tens(?) to the fibrillators and so on the output is changed by the load that is presented to the device and it is important to put that as part of the submitted material.

There is a part here, I think it is the capacitively coupled devices that is just hanging without proper sequence and doesn't have a numerical value or alphabet addressing the location in the article, so, again, talking about the organization of the document.

DR. BOYAN: Thanks . I think we have had such a very complicated discussion here, and the overall tenor of

the discussion is that the guidance document is well written. We have identified some areas that we think it could be improved, that it does lay out the issues very nicely, that we have had pretty thorough discussion on what is a non-union, and I think FDA has heard it.

I would like to go to FDA's questions very quickly and take each one up and just go around the room very quickly to identify if there is any other information we need to provide FDA that maybe these will jar our memory.

Dr. Aboulakia?

DR. ABOULAKIA: Barbara, this might avoid me from asking a lot of questions as we go through the individual questions. I just want to get a sort of a group sort of consensus of whether we think we as a group need to treat these separately. In other words, I feel like we are looking at two very, very different items. If I am the only person who thinks we are looking at two very, very different items, then I probably won't have much to add and I won't keep raising the same question over and over and over again. So, does that apply to both or just one or to the implantable versus the one that is not implantable?

DR. BOYAN: All right. The argument then is that there should be two separate guidance documents. Is that what you are trying to suggest?

DR. ABOULAKIA: For me personally I think they are

radically different and require very different protocols for evaluation, standards, definition, whether one represents a material risk or not, what the potential complications, side effects, indications --

DR. BOYAN: Would you be willing to accept a subheading under the overall? BGS might be a good, not a good terminology considering that it is, also, used by FDA as bone graft substitutes. They might want to think about that but maybe as a subcategory under this general one for implantable devices so that there need not be two completely separate guidance documents.

DR. ABOULAKIA: Yes, absolutely, and I won't have much to say which will save another 10 minutes, but then might we, also, at some point make a recommendation to industry about what our thoughts are regarding what we would require if it is indeed different for a non-implantable bone growth simulator?

DR. BOYAN: So, how can we phrase that? I guess put that forth to FDA just as a statement that we would like you to at least consider that there are two separate issues. Several people raised it as we went around the room that the implantable device has its own distinct set of issues and that that be set apart in the guidance document so that anybody that is looking at the guidance document be really aware .

DR. DAVID: That was the point I was making, just reorganization.

DR. BOYAN: Okay. So, I don't think that comes up as a separate issue. So, we would like to make that as a statement to you, FDA, from the Panel to you.

Okay, the first question is l-year follow-up at what --

DR. WITTEN: May I make a suggestion just in the interests of time?

DR. BOYAN: Yes .

DR. WITTEN: I think the first two questions can kind of be handled together. The first one is l-year follow-up after completion of treatment of bone growth stimulator the appropriate follow-up time frame for non-union, and that is meant to be of long bones and the second question is, maybe you can switch to that, here are some other conditions. What is the appropriate time frame for follow-up after completion of bone graft stimulator treatment for these other conditions, and I think most people have already answered the first question.

DR. BOYAN: I think they have, too.

DR. WITTEN: So, it might be simpler just to ask if there are any considerations that would change that answer for any of these other conditions.

DR. BOYAN: So, let us ask that question. Would

anybody like to identify an alternative time to a l-year follow-up for any of these other conditions following treatment? If you exist, identify yourself.

DR. ABOULAKIA: I guess I would. I hate to do it but OA and ABN, I don't think we know what the natural history of OA and ABN is and a year does not define the natural history of that, and osteoporosis I don't know what you are looking for as an outcome measure. Are you looking at increased bone mineral density? Are you looking at the number of fractures? So, you know for everything except the bottom line I am okay with it.

DR. BOYAN: Are there any other comments related to this? Dr. Rangaswamy?

DR. RANGASWAMY: I have a question. Does this mean that this is part of what a plan is to use the stimulator for these conditions or are we accepting that these are, also, good indications for it? Is this an accepted list?

DR. BOYAN: No.

DR. WITTEN: The question is for the purposes of performing a clinical study how long after --

DR. BOYAN: Independently.

DR. WITTEN: -- completion of bone growth stimulator treatment should the sponsor continue to follow the patients and report.

DR. BOYAN : Right, independently of whether or not you think it is an appropriate indication, okay?

Dr. Larntz?

DR. LARNTZ: I don't have any information on the amount of time; however, I do think it might vary with studies, study population, certain indications. I am pretty sure it does, and if multiple measures are taken appropriate longitudinal analysis could in fact make it not necessary to say that you have to choose one particular time or another.

DR. BOYAN: Is that, do you think that we have adequately answered your question, FDA?

DR. RANGASWAMY: I think you are looking at the end point as union. Am I correct? So if the end point is union, that is your end point.

DR. ABOULAKIA: Except for the bottom ones.

DR. RANGASWAMY: Except for the bottom ones which don't really fit, right, sorry.

DR. BOYAN: Dr. Coutts?

DR. COUTTS: The problem is what is your treatment period. It is clear when you get a positive effect what your treatment period, when it ends, but if you are not getting a positive effect when do you end it. So, there has to be some sort of an arbitrary decision that after 1 year of treatment if you don't get a union then --

DR. BOYAN: Right, it is not useful.

DR. LARNTZ: But if you are doing something in a very elderly population that is healing very slowly it might be appropriate to be a longer period maybe depending on the particular -- 1 am just saying that if you are going to take multiple measurements you should take account of analyzing those multiple measurements to see if you have got the end point at any point along the way.

DR. COUTTS: Right . I am sure that the sponsor of a study would have some arbitrary end point that they would discontinue treatment if they didn't see an effect and then after that point in time 1 year to me would be a perfectly adequate follow-up except for the bottom line.

DR. BOYAN: Okay, next question.

For the purposes of describing bone growth stimulator or patient population please describe the clinical and radiographic indicators for defining previously failed fusions of the lumbar, thoracic and cervical spine. Are there specific risk factors that define a patient population that FDA should look at separately in bone growth stimulator studies and can a patient population be defined for failed spinal fusion where it is appropriate for the patient to act as his own control?

The first part was addressed by Dr. Larntz on the saying that -- I think Dr. Larntz needs to restate it so I state it correctly.

DR. LARNTZ: I think that the key feature of any subpopulation is that the treatment effect would differ by that subgroup and in fact, there are many, many efforts to say that we should have data on each particular cross-classification of subgroups, and that gets to be a very small, maybe a very small number of patients in any particular study and to try to get the study to be powered for each of those small subgroups is a mistake.

In fact, it is very unusual that there are such complex interactions that these subgroups act very, very differently.

DR. BOYAN: Okay, now as a corollary to that would one of the clinicians please address the risk factors that are known to affect fusion that really would affect this outcome.

Yes, Dr. Aboulakia?

DR. ABOULAKIA: Smoking.

DR. BOYAN: Smoking, yes.

Dr. Rangaswamy?

DR. COUTTS: I was going to bring up the Workman's Compensation issue again here. It may not necessarily affect healing but if you are using other indicators of success such as pain and return to work, etc., then that becomes a real issue.

DR. ABOULAKIA: And that is why I would argue that

what we are looking at is healing and not the other factors that we cannot control like motivation.

DR. COUTTS: But defining healing in the spine is very problematic.

DR. RANGASWAMY: It is very difficult to even define pseudarthrosis in the spine particularly when you have instrumentation in place. The x-rays are just not adequate. CTS, none of them are really very adequate to tell you that there is a non-union going on. So, the question comes in if they are using it just purely to produce fusion right from the beginning after doing the arthrodesis then I still have to disagree with Dr. Larntz here that I still think you have to define the population because anterior and posterior fusions are two completely different things. The instrumentation is different, the mechanism, the forces; all the things are different. So, you have two different entities. So, you have to be very careful I think in that kind of situation.

DR. BOYAN: Any other comments? Yes, Dr. Cheng?

DR. CHENG: There are a number of other factors to consider in bone healing, not just smoking. There is a tremendous number of factors and metabolic conditions, renal osteodystrophy, diabetes, any one of the drugs that involve osteoporosis, previously irradiated field, previous surgery, instrumentation, all those need to be taken into effect.

DR. BOYAN: Is there anything else that we would like to add? FDA, did we address the first part of this question adequately?

DR. WITTEN: Yes.

DR. BOYAN: Okay, Dr. Coutts?

DR. COUTTS: I mentioned this in a different discussion, but one method which has not been used in the spine but which would have great applicability would be radiostereophotogrametry. I mean you could accurately measure movement if that technique were to be used.

DR. BOYAN: If you didn't mention it, I was going to. I think that is a fair comment, that better measurement devices, better measuring mechanisms for some of these questions would, also, eliminate the question of when non-union has actually occurred.

Now, the second part of the question is can a patient population be defined for failed spinal fusion where it is appropriate for the patient to act as his own control, and I think in a general discussion that was addressed, that we did think it was appropriate under certain circumstances for the patient to be his or her own control.

Is that fair? Is there anybody that would like to argue against that?

Dr. Aboulakia?

DR. ABOULAKIA: Yes, you know I think this whole

thing with 9 months and being your own control and treatment versus no treatment group came about by the manufacturers trying --

DR. WITTEN: Before you answer this, may I just clarify something? That 9 months we were discussing is applied to long bone, and this question is about failed spinal fusion.

DR. RANGASWAMY: Lumbar spinal fusion, I assume.

DR. WITTEN : Any.

DR. ABOULAKIA: I am talking about study design. so, with long bones what they did was they took a group of patients where if you took a group of surgeons who treated long bone fractures you could come to a reasonable decision and say, “I think the chances are pretty good that this bone is not going to heal, ‘r and that is 9 months, and if it was 6 months you would probably have fewer surgeons saying, "I think this bone is going to not heal,” and if you had 3 months then fewer surgeons.

so, if I went into an orthopedist’s office and said, “Look here is the tibia fracture. Here is the x-ray at 9 months, and it hasn’t healed. What do you think the chances are that it is going to heal?” Most surgeons would say, “Gee, not very good, more than 1 percent but less than 20 percent. ”

So then they took those patients and they treated

them, and they said, “Look we have got a union rate of X," and X was more than what the surgeons predicted, and that is what that historical data is. So, then there was another approach that came along which is what Heckman did. He said, "Since we are looking at this historical sort of non-randomized and letting patients be their own control, let us do it differently. Let us prove that the device is actually exhibiting an effect, “ and he said, “Let us put it on the day they break their bone and see if it makes it heal quicker, and then we will convince people that it actually has an effect, ” and so you have two extremes of a study design, one which is immediate treatment and then one is selected treatment.

DR. BOYAN: SO, the question still remains for spine and for spine is there anybody here who feels strongly that it would be inappropriate for the patient to be his or her own control? The reality of life is I think in the general discussion we clarified that at the time of chronic non-union finding a large enough group of patients to serve as controls or untreated controls or placebo controls against another treatment group that is now going to receive whatever the bone growth stimulation is would be very difficult to achieve.

All right, next?

DR. WITTEN: Next question, is that what you meant?

DR. BOYAN : Yes .

DR. WITTEN: I would like further amplification of this one because if the answer to this is yes, I would like to hear a description of what or some indication of how that patient population could be described.

DR. RANGASWAMY: Part two?

DR. BOYAN: Yes.

DR. RANGASWAMY: You would not be able to find. I think you will have to go back and we will have to divide this . It works differently. There isn't enough data at all even to this date on cervical spine, but I do know even on the lumbar spine that you see on the failed fusion of the multiply operated back or whatever you want to call it, whichever category and again not all of them are proven to have a pseudarthrosis.

We don't know that, and that is part of the problem is the question is when you say can they serve as their own control, then you have to base this on the fact that the same factors that everybody just negated in terms of pain or no pain, Workman's Comp, all those issues unfortunately are part of the reason that the patient is being considered a failed spinal fusion case, and even though they don't see a pseudarthrosis that is the real world.

That is how people are defining it, that this

patient may have a pseudarthrosis someplace and that is why the patient is complaining of pain.

So, the pain and all those other patient outcome factors are not going to be included in the equation of evaluation of outcome, but it is in defining that patient to include that patient as part of the inclusion criteria it seems strange because then how do you define that it is successful. So, I think it is difficult to say that you can use that same person as a control then.

DR. BOYAN: Dr. Rangaswamy, can we use the same criteria and tune in here Dr. Skinner because these are your criteria, that there is motion, pain at palpation, pain at stress, 3 months of no progression in healing and you had one other criteria, and I missed it.

DR. SKINNER: Three months of no progression.

DR. BOYAN: Three months of no progression in healing, pain at stress --

DR. RANGASWAMY: On the x-ray.

DR. BOYAN: On x-ray, yes. You mentioned no progression in healing on x-ray. Pain at stress is what I wrote down from what Dr. Skinner said, pain to palpation, motion at fracture site or motion at --

DR. SKINNER: Non-union site.

DR. BOYAN: Non-union site, and you had one other criterion, and I really did miss it.

DR. SKINNER: I cannot remember what it was just now, but I think when you come to look into the spinal fusion I don't think even the most aggressive spinal surgeon wants to go in and operate on a spine before, certainly before 6 months if they think it is a non-union.

so, I think that you have got to start thinking about 9 months and a year and at that point a bone scan starts to be helpful. So, bone scan evidence of a pseudarthrosis can be helpful at that point and flexion extension films would potentially give you some help there, depending on what is in there in terms of instrumentation.

DR. BOYAN: Okay, is that better for you?

DR. ABOULAKIA: Dr. Rangaswamy, I pride myself on my lack of knowledge of spinal surgery. So maybe you can answer. Don't many of the papers that talk about non-union break it up into three categories, definitely not healed, definitely healed or probably not healed?

DR. RANGASWAMY: Not just spinal, just non-unions in general, that is how we define it, right.

DR. ABOULAKIA: But if a clinical study were undertaken they might have to use more flexible terms than black or white and which side it graded on.

DR. BOYAN: All right. We should move to the next question. Should bone growth stimulator study design specific -- that are each type of fusion procedure

indication and levels of use involved --

DR. ABOULAKIA: We are still on spine?

DR. BOYAN: We are still on spine and I think that in the general discussion we heard the answer was yes. Did I get that correct?

DR. ABOULAKIA: Yes.

DR. LARNTZ: Could I say that I think it is really important to understand is the treatment effect different by these variables, not is there a different rate of success. That could be true, but in fact do the treatment effects go different at the different variables, and I think you will find that much less often than you will find different rates of success by these indications, and so controlling for the level of success is important in the analysis, but in fact designing and thinking that you are going to have entirely different effects for each combination of these things makes terribly large studies and usually does not find out anything different than you would find out by assuming the effect is proportionally the same in the various groups. So, I have said that again, and I will stop saying it.

DR. BOYAN: No, that is okay. Please note that that caveat or that comment goes in with the discussion from a clinical point of view.

Important design parameter modifications which need animal and/or clinical data to support a change in bone

growth stimulators with implantable electrical devices, capacitively coupled electrical devices and ultrasound devices.

So the design parameters that came out in the general discussion had to do with the material, what it was made out of, whether it was going to be a chronic implant or simply an acute implant, whether there was plastic, whether there was potential for particulate, the method of sterilization. Does that cover all the various things that we discussed?

DR. LI: I would add shelf life to that.

DR. BOYAN: Shelf life. We were interested in soft tissue damage, as well as any damage that might be to the bone itself.

Yes, Dr. Coutts?

DR. COUTTS: Batteries.

DR. BOYAN: Batteries.

DR. DAVID: The whole issue of the output should be or if you are changing the output there is definitely tissue response that relates to that, so, that definitely in the initial category the amplitude and wave shift of the output .

DR. BOYAN: Okay, any change in output. Any other additions?

DR. SILKAITIS: Dr. Boyan, this is Ray Silkaitis.

When we say, "Design parameters," inside the box that can change as long as the output is the same; we wouldn't require animal studies. It is only when --

DR. SKINNER: Yes, output is the square wave to a sine wave.

DR. SILKAITIS: Exactly, okay.

DR. BOYAN: In this particular instance I think this brings in the issue right now that is being raised by Dr. --

MS. KEITH: If I might, our major concern was more with design changes that changed the sort of electrical outputs of the devices and whether or not you thought that we should see animal or clinical data when that happened.

So, if you changed the surface area density, current density or the current density in an implantable device would you want to see animal data or clinical data to support that change or if in a capacitively coupled device you might want to see data if the voltage was changed or the current or the current density was changed and with an ultrasound would you want to see it if the frequency or the pulse width or the temporal maximum power was changed or if there was some other kind of design feature that went along in that area that you were aware of that you thought if it was changed we should be seeing clinical or animal or both.

DR. BOYAN: Many of those questions in my

estimation could be addressed with animal data, and then I would like to have Dr. David make a statement.

DR. DAVID: Tissue excitation in relationship to any one of those different technological principal devices, the ultrasound, the ultrasound capacity coupled electrical device or electrical stimulation is a known phenomenon. So, my response to the question before took that into consideration and I said that we should have animal data for those changes.

DR. COUTTS: It is my understanding that the manufacturers use specific signals and claim that the effect is related to that signal so that any change in the signal would in my mind fairly require that there be a new set of evidence that that is effective for what they want to claim.

MS. KEITH: Would there be under any circumstance where you would want to see clinical data for that or do you think that in most circumstances animal data would be sufficient?

DR. BOYAN: Does anybody want to make a comment about that?

DR. DAVID: The two issues of safety and efficacy will require that there will be clinical data to support that as well.

DR. LI: With the odd exception if some very strange or never-tried-before material was used, an

implantable material.

DR. BOYAN: Yes, I think this Panel wants that clear that we want you to consider the material that might be implanted and not --

MS. KEITH: In a normal review cycle that is certainly considered, and if it is truly new it would require data.

DR. LI: This is not specifically laid out in the guidance document.

MS. KEITH: Okay, thank you.

DR. COUTTS: This discussion has centered around the signal, right?

MS. KEITH: Yes, the outputs.

DR. GILBERT: I guess I would have to chime in at this point and say that the signal and the delivery of the signal with the metal electrode lead may very well change the behavior of that lead via corrosion mechanism, electrochemical mechanism. That would, also, have to be considered.

DR. COUTTS: But that could be resolved with animal data. You wouldn't need a clinical study necessarily.

DR. BOYAN: Next question? That was the last one. That is it. We are done. Wait, we have wording here. Nothing is ever done just outright.

I am going to turn the floor over to -- oh, we

have to do this. FDA, did we answer these questions to your satisfaction?

DR. WITTEN: Yes, thank you.

DR. BOYAN: Sponsor, this is your last chance. Is there anything you would like to add before we close the proceedings?

Okay, I turn the floor back over to our Executive Secretary.

MR. DEMIAN: I would like to thank all the Panel members for their time and effort and energy in reviewing this material and the participants on this FDA Panel.

All your efforts are truly appreciated. At this time I would like to remind all Panel members that if you want the review material, any notes, you may have taken destroyed, please leave it in front of your seat with your name card on top of it. Please know that if this information is presented to me as Executive Secretary it will be entered into the record.

I would like, also, to remind all Panel members that you have the choice between either personally destroying any material you have received or shipping your review material back to FDA using a Fed Ex label enclosed within your blue folder.

Regardless of how you get rid of your review material please return the certification sheet that has been

provided in this blue folder.

Thank you.

Dr. Boyan?

DR. BOYAN: The meeting is adjourned.

MR. DEMIAN: Dr. Witten?

DR. WITTEN: I would like to just thank the Panel, also, and the sponsors and the FDA staff.

(Thereupon, at 3:40 p.m., the meeting was adjourned.)