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OPEN SESSION - VOULUME II

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Gaithersburg, Maryland

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Dr. Susan Runner
Angela Blackwell
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P R O C E E D I N G S
Welcome and Introductory Remarks

MS. SCOTT: Good morning. Welcome to the Dental Products Panel Meeting.

My name is Pamela Scott. I am the Executive Secretary for the Dental Products Panel. Before we get started today, I would like to read into the record our conflict of interest statement for May 11, 1999.

The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of an impropriety.

The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employers' financial interest. To determine if any conflict existed, the agency reviewed the submitted agenda and all financial interests reported by the committee participants.

The agency determined that no conflicts exist. However, we would like to note for the record that the agency took into consideration a matter regarding Dr. Willie Stephens who reported an interest but no financial involvement in a firm at issue.

The agency has determined that Dr. Stephens may participate fully in all deliberations. In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants should excuse him or herself from such involvement and the exclusion will be noted for the record.

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

Also, I would just like to read, again, the appointment to temporary voting status. Pursuant to the authority granted under the Medical Devices Advisory Committee charter, dated October 27, 1990, as amended April 20, 1995, I appoint the following people as voting members of the Dental Products Panel for this meeting on May 10 and 11, 1999; Dr. Leslie Heffez, Dr. Diane Rekow, Dr. Peter Bertrand, Dr. Richard Burton, Dr. Willie Stephens, Dr. Steven Li, Dr. Harry Skinner, Dr. Gilbert Gonzales.

For the record, these people are special government employees and are consultants to this panel under the Medical Devices Advisory Committee. They have undergone customary conflict of interest review. They have reviewed the material to be considered at this meeting. Signed Dr. Elizabeth Jacobson, Acting Director,

Center for Devices and Radiological Health, May 6, 1999.

One last item. I just would like to reintroduce our panel members for today. The panel members are listed in the back of the agenda booklet that you received.

We have Dr. Janine Janosky who is acting as our chair today. She is an assistant professor with the University of Pittsburgh. We also have Dr. Mark Patters who is the Chairman of the Department of Periodontology at the College of Dentistry at the University of Tennessee. Our consumer representative is Dr. Donald Altman who is the Chief of the Office of Oral Health with the Arizona Department of Health Services.

Dr. Alton Floyd is our industry representative. He is the President of Trigon Technology in Edwardsburg, Michigan. Our patient representative is Ms. Theresa Cowley who is the President of the TMJ Association.

We also have with us today Dr. Peter Bertrand who is the Director of the Orofacial Pain Clinic and a Specialty Advisor for Oral Facial Pain with the National Naval Medical Center and Dr. Richard Burton who is an assistant professor of oral and maxillofacial surgery at the University of Iowa Hospitals and Clinics.

We have Gilbert Gonzales who is associate professor of neurology at the Memorial Sloan Kettering Cancer Center with Cornell University and Dr. Leslie Hefez who is the professor and Department Head of oral and maxillofacial surgery at the University of Illinois at Chicago.

We also have Dr. Stephen Li who is a senior scientist with the Department of Biomechanics and Biomaterials at the Hospital for Special Surgery and Dr. Diane Rekow who is the Chairperson of the Department of Orthodontics at the University of Medicine and Dentistry of New Jersey.

We have Dr. Harry Skinner also with us today who is professor and Chair of the Department of Orthopedic Surgery with the University of California at Irvine. And we have Dr. Willie Stephens who is an associate surgeon for the Division of Maxillofacial Surgery at Brigham and Women's Hospital.

Again, our FDA participants for today are Mr. Timothy Ulatowski who is the Director of the Division of Dental, Infection Control and General Hospital Devices with the Office of Device Evaluation. We also have Dr. Susan Runner who is the Branch Chief for the Dental Devices Branch within the Division of Dental, Infection Control and General Hospital Devices.

We have Ms. Angela Blackwell who is a biomedical engineer also with the Dental Branch within the Division of Dental, Infection Control and General Hospital Devices and Dr. Murty Ponnappalli who is a mathematical

statistician with the Division of Biostatistics in the Office of Surveillance and Biometrics.

Thank you very much.

I will turn it back over to Dr. Janosky now.

Open Public Hearing

DR. JANOSKY: At this time I would like to open the public hearing. Are there any requests?

[No response.]

DR. JANOSKY: So, I am correct in assuming no one is requesting to speak during the open public hearing?

Okay. Given that the case, then, we will move on.

At issue today is a review of a premarket approval application by TMJ Implants, Incorporated.

First, we will have the industry presentation which is scheduled for one hour. Currently, I have 8:10, so it will go from 8:10 to--oh, excuse me, we do have letters, so let's continue then with the open public hearing.

We have two letters that were sent to the FDA which Ms. Scott will read into the record.

MS. SCOTT: A copy of these two letters are included in the folder that the panel received.

This was received by the Center and it states: "This brief document is in reference to the open public hearing testimony on temporomandibular joint prostheses. As a surgeon who has devoted a significant percentage of my practice to the surgical management of organic temporomandibular joint disorders/diseases I can offer my humble opinion that one of the most successful and well-researched contributions to the surgical practice of rebuilding the severely diseased jaw joint has been the CAD-CAM technology to use a chrome cobalt implant to replace vital portions of the temporomandibular articulation.

"In my own experience the metal/metal (chrome-cobalt) custom TMJ prosthesis has been uniformly well tolerated by patients who have had multiple surgeries or arthroplasties with or without autogenous or other alloplastic devices to attempt to recreate a functioning jaw joint.

"The very nature of the custom joint eliminates attempting to modify autogenous or alloplastic (off the shelf) devices to fit a given patient. These implants simply are designed for the individual patient and must remain available to salvage the lives of patients who had lost jaw joint function for reasons of arthritis, ankylosis, trauma, or neoplastic disease.

"With the notable exception of the Christensen and custom-made total joint prosthetic devices, there simply is nothing available in the technical surgical

marketplace to off the patient who has an "end-stage" jaw articulation. Patients who have lost function and have severe pain syndromes can have a significant restoration of function and an amelioration of their pain by reconstructing their diseased jaw joints with the Christensen prosthesis.

"I am aware that the above information is anecdotal and my conclusions do represent the results of a formal scientific study. However, any hearing regarding the efficacy of a surgical device should at least reflect opinions of surgeons with some experience (in this case 30 years) who must deal with the suffering of individual patients, not groups or populations in a laboratory environment. Both of these kinds of inquiry are necessarily important and each should have appropriate weight in any decision, which would change the availability of a surgical device.

"Kindest regards, Dr. Guy A. Catone, Associate Professor, Department of Surgery, Division of Oral and Maxillofacial Surgery, Allegheny University of the Health Sciences."

The second letter that we received that we were requested to read during the open public hearing is from Dr. William Buck. It reads as follows:

"This letter is for open public hearing testimony on temporomandibular joint prostheses. I have been exposed to the Christianson total and partial joint system for approximately eleven years. The Christianson joint has had an excellent track record in a field of other total joints that have fallen out of favor because of chronic failure.

"I have used the Christianson total joint, partial joint, the stock joint, the custom made joint and the metal head to metal fossa joint with success. This procedure is always reserved to a last ditch effort to give the patient function of her jaw when all else has failed. It is used when a bone graft has failed and has no hope of future success. In my patients, there was no other alternative for them to have normal life function.

"The evidence is clear that the Christianson joint is proven successful over a period of greater than 25 years. Newer joints have come and gone, but the Christianson is a well proven device that is absolutely needed for severely damaged temporomandibular joint patients. There is no other reasonable alternative. Please let me know if I can answer any other questions."

Signed, Dr. William Buck.

Also, I would like to note that the Center did receive numerous other letters regarding this particular meeting, and if any of the panel members would like to see those letters, we have copies of those available. Some of them also have been copied for you and placed in

your packet, but there is another stack that we have available also. Those letters did not specifically request to be read into the record at the open public hearing, but they available if you would like to read them and if you would like to see them.

Thank you.

DR. JANOSKY: Are there any requests to speak during the open public hearing?

[No response.]

DR. JANOSKY: At this time, we will close the open public hearing.

It is my understanding that Dr. Runner has some comments for us before we move into the industry presentation.

DR. RUNNER: Good morning. Just a reminder from what we discussed yesterday, because of the terminology that is confusing with these devices, we have determined that TMJ implants will be the generic device type, TMJ Concepts is the device we considered yesterday, and the Christensen device is what we are discussing today, just to avoid confusion.

DR. JANOSKY: At this time, the industry presentation lasting for one hour. I have 8:20 on my watch, so until 9:20.

Industry Presentation

DR. CHRISTENSEN: I am Dr. Robert Christensen. I do have financial interests in this company. I want to thank Dr. Runner and Dr. Janosky and Dr. Ulatowski, and all the panel members for this opportunity to come before you.

My beginning in oral surgery started about 50 years ago, and that first 10 years was kind of an interesting time to do all sorts of surgery on that joint, from fracture repair, but also condylectomies and meniscectomies, and you name it.

During that time, I wrote several articles regarding arthroplasty of this joint, but about 1960, I realized that something better needed to happen, and I came up with the idea of replacing this joint, both in a partial way and in a total way, and began to see my patients do very, very well. As a matter of fact, a chapter written in a book called "Oral Implantology," which I wrote in 1967, I talked about the first five or six years of arthroplasty of this joint using this alloplast.

In that time, I had done about 60 partial joints and a number of total joints, and I talked about the 60 partial joints as that I had not had to reoperate one of those during that period of time with the exception of one that overgrew bone.

I am not going to give you much of a story this morning because I have got a panel here that can do a

better job than I can do, but I would like to read you part of a couple letters that were sent to me at that time.

One was from the founder of arthroplasty of the hip. I think the doctors here of orthopedics would agree with this. It is from Dr. Otto Aufranc, and in May of '63 said: "This is a real contribution to the art of surgery and the correction of disabled joints. I have no suggestion to add to this except to compliment you on your good work."

J. Vernon Luck, who the orthopedic hospital in Los Angeles is named after, in January of '64 said: "I learned a great deal about temporomandibular joint arthroplasty that I did not know before. This subject is dramatically presented in your film."

I think, having said that, I must say too that I feel the way the patient advocate groups do too. I have suffered with those people 50 years to see them get healed, and that is why I started to develop a technique that works.

I think as you see this information, you are going to see that there is some very good information along this line. Have we done everything? No, probably have not, but we have come a long way in the last 40 years.

I would like to introduce Mr. Jim Morgan.

MR. MORGAN: Thank you, Dr. Christensen.

[Slide.]

Good morning. My name is Jim Morgan. I am the Director of Quality Assurance and Regulatory Affairs for TMJ Implants, Inc.

Before I get into my formal presentation, I would just like to echo some of the Dr. Christensen's words relative to what Dr. Zuckerman said yesterday along with Mr. Clark and Ms. Brown and Ms. Cowley.

We have heard and understand your concerns and we appreciate the need for prosthetic alternatives in the treatment of temporomandibular joint disease. Indeed, it was the recognition of this need which inspired Dr. Christensen's invention of the Fossa-Eminence and Condylar Prostheses in the 1960s.

It was his desire for a long-term solution that prompted the selection of the materials used in these prostheses, and while we don't claim to cure disease, you will see from our data that our devices can improve the patient's condition.

[Slide.]

Along with Dr. Christensen and our presenters and staff, we are grateful to have the opportunity to present our products to you today.

Permit me to introduce to you the remainder of our presenting staff: Dr. James Curry, clinician in

private practice; Mr. Al Lippincott, biomaterials consultant for TMJ Implants, Inc.; Mr. Doug Albrecht, Manager of Clinical Affairs; Mr. John Durnell, Operations Manager; Ms. Candace Cederman, regulatory consultant for TMJ Implants, Inc.; Dr. James Murphy, Professor of Biostatistics, University of Colorado Health Sciences Center, and consultant for TMJ Implants, Inc.; Dr. Subrata Saha, Professor, Department of Bioengineering, Clemson University, and consultant for TMJ Implants, Inc., and Dr. David Gerard, cell biologist and Director of Research, Department of Oral and Maxillofacial Surgery, University of Tennessee, and consultant for TMJ Implants, Inc.

[Slide.]

We are here today to consider the market continuation of a temporomandibular joint prostheses and accessories which have been in commercial distribution for over 35 years.

The TMJ Fossa-Eminence prosthesis may be implanted as a partial joint replacement, and the TMJ Fossa-Eminence prosthesis and TMJ Condylar prosthesis may be implanted together as a total joint replacement.

[Slide.]

We will demonstrate the safety and effectiveness of our devices when used in accordance with their labeling by introducing you to non-clinical test data presented by Mr. Al Lippincott, and clinical data presented by Mr. Doug Albrecht and Dr. James Curry.

I believe that Mr. Ulatowski has advised you regarding valid scientific evidence. As you know, valid scientific evidence includes evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human clinical experience with the marketed device. Our sources of data to be presented qualify as valid scientific evidence.

[Slide.]

The TMJ Fossa-Eminence Prosthesis may be indicated for use in cases of internal derangement, meniscal perforation, adhesions, or ankylosis of the temporomandibular joint where conservative therapies and treatment plans are not, or are no longer, indicated.

The TMJ Fossa-Eminence Prosthesis may be used in a partial joint replacement or with a TMJ Condylar Prosthesis in a total joint replacement procedure.

[Slide.]

The TMJ Condylar Prosthesis may be intended for us in conjunction with the TMJ Fossa-Eminence Prosthesis whenever total joint reconstruction is indicated or conservative therapies and treatment plans are not, or

are no longer, indicated.

Such indications for total joint reconstruction could include correction of deficiencies in the natural condyle in cases of serious adhesion, condylar destruction, ankylosis, avascular necrosis, intrinsic bone disease, congenital disease involving the temporomandibular joint, rheumatoid arthritis, osteoarthritis, foreign body giant cell reaction, previous failed implant surgery, or other pathology with resultant occlusal or function deficiency.

[Slide.]

The Fossa-Eminence and Condylar Prostheses are preamendment devices which have been manufactured and sold in commercial distribution since 1961 and 1965 respectively.

Our products are marketed in the United States, Canada, and the European Union, with a Notice of Compliance from Health Canada, and CE Marking Authorization from KEMA, a notified body in the European Union.

In addition, our facility is ISO 9001 and EN 46001 certified.

[Slide.]

It is estimated that over 14,000 devices have been implanted in approximately 6,700 patients over the past 38 years. Since 1993, when TMJ Implants implemented device tracking, 4,156 patients have received 9,152 implants.

[Slide.]

The TMJ Fossa-Eminence Prosthesis System are offered in 44 left and 44 right sizes to allow the surgeon to choose the device which most closely fits the individual patient's anatomy.

It is designed to provide a smooth surface for articulation with either the natural condyle in a partial joint replacement or with a TMJ Condylar Prosthesis in a total joint replacement procedure.

The prosthesis is manufactured from cobalt-chrome molybdenum alloy and is secured to the zygomatic arch using cobalt-chrome screws.

[Slide.]

The TMJ Condylar Prosthesis Systems, Universal and Christensen/Chase, with three lengths available, 45, 50, and 55 mm, are designed to seat against the TMJ Fossa-Eminence Prosthesis.

The Universal Prosthesis is designed to be used on either the right or left side. The Christensen/Chase Condylar Prosthesis is manufactured specifically for either the right or left side. Note the angled extension on the distal portion of the flange, allowing the physician to more closely follow the patient's natural mandibular structure and to provide anchoring options in

the absence of bone.

The body of the Condylar Prosthesis is manufactured from cast cobalt-chrome molybdenum alloy while the head of the Condylar Prosthesis may be either cast cobalt-chrome molybdenum alloy or polymethylmethacrylate PMMA. These materials are commonly used in orthopedic implants and PMMA is also used in intraocular lenses.

The prosthesis is secured to the ramus of the mandible with cobalt-chrome bone screws. The Fossa-Eminence Prosthesis and all models of the Condylar Prostheses are supplied to the user in kit form.

[Slide.]

These kits consist of sterilized prostheses, screws, and drill bits. Separate sterilizable sizing systems are available to aid the surgeon in the selection of the appropriate size and shape of Fossa-Eminence and Condylar Prostheses. A sterilizable instrument kit consisting of screwdrivers and holders is also part of the system.

[Slide.]

If there are significant bone loss, trauma, or other special circumstances whereby the standard stock sizes and shapes of prostheses are not suitable, a surgeon may request that the Fossa-Eminence Prosthesis or Condylar Prosthesis, or both, be cast to fit the patient's specific anatomical structure.

[Slide.]

In the case of the TMJ patient-specific condylar prosthesis, only the flange portion is adapted to the patient's anatomy. The articulating surface, either PMMA or metal, is identical to the standard condylar prosthesis.

[Slide.]

We believe that you will agree with us that the TMJ Implants, Inc., Fossa-Eminence and Condylar Prostheses are safe and effective when used in accordance with their labeling.

Permit me to introduce Mr. Al Lippincott, who will discuss the results of our non-clinical testing.

MR. LIPPINCOTT: Thank you for the introduction, Jim.

[Slide.]

Again, I am Al Lippincott of Engineering Consulting Services, Inc., from Minneapolis, Minnesota. I am here as a representative for TMJ Implants, Inc., and have been asked to present the non-clinical testing of the Christensen TMJ device.

I have no financial interest in the company, and act as a paid consultant on the company's behalf. My experience is in the manufacture, design, and research of orthopedic implant devices, and since these TMJ devices

are comparable in materials and also function as a load-bearing joint, the company has requested my services as a bioengineer adviser.

[Slide.]

I will present to you today the following four areas of nonclinical testing for the safe use of the Christensen PMMA on metal, and metal on metal, TMJ devices. These four areas, as you see, are materials, device design, mechanical testing, device retrievals with various subtopics.

Due to time constraints and to move quickly through the presentation, I will only describe the purpose of each subtopic test and follow with a short summary of the test result.

[Slide.]

For the majority of the mechanical testing, TMJ Implants, Inc., chose to use the Christensen/Chase condylar prosthesis mated with a TMJ fossa-eminence prosthesis. The 55 mm Christensen/Chase prosthesis provides the longest moment arm and is the thinnest in standard thickness of the stock devices.

For the fossa component, a larger size was chosen to provide a single point contact representing the highest load, whereas, the majority of the fossas used in vivo are multiple point contact.

For the patient-specific devices, the condyle and fossa thickness is the same as, or greater than, and screw hole placement and dimension is the same, or greater than, the stock devices. The condylar head geometries of both the patient-specific and stock components are identical.

This Christensen/Chase and large fossa component represent a worst case condition applicable to all implant versions.

[Slide.]

The purpose of the biocompatibility test is to confirm that the materials cobalt-chrome moly and PMMA used to produce the TMJ devices by TMJ Implants, Inc., will meet biocompatibility standards according to ISO 10993. These materials have greater than 50 years of medical implant use as supported by laboratory testing and extensive literature documentation.

The following tests were run to support the material biocompatibility. The results of the testing show no unanticipated findings and supports the biocompatibility of the implant materials as manufactured by TMJ Implants, Inc.

[Slide.]

The purpose of this animal test was to determine the host tissues and blood effect of cobalt-chrome moly and PMMA particulate when injected into animal TMJ joints. Parameters of the testing are shown. Wear

particles used in this animal test were generated from pin-on-disk testing.

[Slide.]

The results show a mild to moderate early reaction to the particles where the particle-injected joint was indistinguishable from the opposite side, a saline-control joint, at greater than three months for PMMA and at greater than six months for cobalt-chrome moly.

There was no evidence of foreign body reaction or giant cells in either material in both blood chemistries and histology of organs were observed as normal with no pathology of sequestration of PMMA or cobalt-chrome moly materials.

[Slide.]

The PMMA acrylic and cobalt-chrome moly metal materials are received from raw material vendor sources as certified to ASTM and ISO medical standards. These standards are validated with the additional testing as shown.

All materials produced by TMJ Implants, Inc., have met the specific medical industry standards.

[Slide.]

The purpose of this next test was to examine and evaluate the metal microstructure and polished articular surfaces. Metallography analysis shows that the microstructure is a dendritic structure with minor porosity, which is typical of a manufactured cast alloy process. Also, random minute scratches, as detected under magnification, are observed on the articular mirrored polished surfaces, again representing the manufacturing polished process and is typical of a highly polished surface.

[Slide.]

The purpose of the FEA analysis was to model stress distribution within a condyle and fossa component.

The following implant type combinations were modeled. The results of the modeling with the condyle show maximum stresses at the uppermost screw holes, while maximum stresses in the fossa decrease with increased use in the number of screws.

[Slide.]

The purpose of this next study in design is to assess in-vivo kinematics and kinetics of the TMJ by computer analysis, fluoroscopic videos, and bite force. Fifteen patient subjects, there were 5 normal TMJs, 5 fossa-only TMJs, and 5 total TMJs were evaluated.

The results from the study show that the relative applied force and average applied torque at the TMJ for normal subjects was greater than that of patients with either a partial or total TMJ joint replacement, and four of those subjects with total TMJ joint replacements,

minimal translation occurred, indicating that these total joint replacements only rotate and do not translate.

This study also demonstrates the significant decrease in TMJ joint loading from a normal subject to a diseased partial/total joint subject by almost a factor of 4 times. This study is also the only documented source that I know of comparing normal TMJ subjects to diseased/implant replacement subjects.

[Slide.]

The purpose of this final study in design was to demonstrate the point contact interface and stress between condyle and fossa components. The results of the study confirm that contact areas increase in size with increasing loads. The average measured contact stress was well within each respective material's yield strength.

This average point contact stress in the TMJ metal components is comparable to contact stresses measured in orthopedic mating congruent hip prosthesis.

[Slide.]

The purpose of this first study under mechanical testing was to determine the maximum load to failure of the TMJ implants as a static load to failure with 3 point bending across the laser mark section.

In the PMMA on metal testing, an average failure load of 365 pounds was recorded at test completion with fracture of the cobalt-chrome moly fossa component in three of the five tests.

In the metal-on-metal testing, an average failure load of 465 pounds was recorded with stopping the test due to screw pullout and bending of the condylar device. Three point bending across the condyle laser marking resulted in failure at an average load of 217 pounds.

Note that the above failure loads on all TMJ devices are values well above TMJ condyle loads observed in vivo as documented in the literature. I will discuss typical in-vivo TMJ loading conditions in the following testing.

[Slide.]

The mechanical testing of dynamic fatigue under physiological in-vivo type conditions was conducted for 5 million cycles. A loading condition of 2 to 35 pound cyclic load was used for the test. This loading condition is supported by the work of Brennon, et al., in laboratory testing measuring direct loads on the TMJ condyles of primates and adjusted to human levels following the work by Smith.

These loading conditions are comparable to various mathematical calculations as determined from the literature.

[Slide.]

Results of the dynamic fatigue show that no test units fractured or showed signs of fatigue failure under these physiological conditions after 5 million cycles. All components maintained mechanical stability and rigidity throughout testing.

This dynamic fatigue testing is intended to characterize physiological performance in chewing forces of hard foods. It was felt that there was no need to generate a stress to failure to number of cycles or S-N curve due to the low forces exhibits in painful diseased and/or prosthetic TMJ joint in comparison to the high static load to failure values as previously reported.

[Slide.]

The final mechanical testing with cyclic wear was performed under similar physiological conditions as the dynamic fatigue testing. Parameters for the testing are based on FDA guideline documents.

As discussed at yesterday's panel meeting, where a 20-pound constant load was used for wear testing, cyclic loading in our test was adjusted to attend a 35-pound load range again supported by the work of Brennon and Smith with a jaw movement at a 30-degree, single axis arc motion for a test duration of 2 million cycles.

Particulate wear volume was measured using a profile analysis system taking measurements of the articular wear surfaces at the beginning and conclusion of the test. Completed wear measurements of the metal-on-metal result in a 0.194 mm³/million cycles, volume material loss as compared to a greater wear loss on the PMMA-on-metal of 1.64³/million cycles.

All test units showing wear had a striated uniaxial wear pattern surface with no wear through of any of the components. As a comparison, the wear of orthopedic hip implants of a metal polyethylene combination yield volume material losses anywhere from 40 to 130 mm³/million cycles. This is a factor of 24 to 80 times the amount of hip implant particulate wear generated over these TMJ devices.

[Slide.]

This is a photo of the wear test station with the outer container removed for viewing purposes. The TMJ implant devices are placed and loaded anatomically, here with the condylar unit, and here with the fossa unit superior to the condylar head.

The fossa rotates in the 30-degree arc motion in relation to the stationary condyle. Cyclic load is transmitted vertically throughout the condyle. The testing protocol is more physiological and more representative of in-vivo conditions than pin-on-disk testing.

[Slide.]

This last slide on the retrieval analysis will describe the wear zones and surfaces of explanted devices. Examination was conducted on metal-on-metal specimens up to a five-year in-vivo duration and with PMMA-on-metal up to 11-year duration.

Removal of the devices was due to pain resulting from fibrous adhesions or ectopic bone formation. The wear zone on the PMMA acrylic heads was larger than that of the metal-on-metal wear zones as is to be expected with the softer material and as what is shown by laboratory testing simulator wear studies.

The surface finish of the retrieval zones on both the PMMA condyle head and metal-on-metal surfaces was smooth and polished to the naked eye. Under magnification, the wear surfaces had multi-directional scratches representing multi-axial movement as a result of abrasive wear. No wear-through of the retrievals was observed.

[Slide.]

A similar size wear zone area of both retrievals and laboratory test acrylic condylar heads were observed.

Comparable acrylic material height loss of both the retrievals and test specimens were measured.

In the retrieval components, no major surface irregularities were noticed with this being the retrieval, whereas, material yielding was noted in the laboratory test components. These major surface irregularities on the test units show a comparable or higher load condition used in the testing than that shown on the PMMA materials.

Comparison of metal-on-metal retrievals to laboratory testing units show less wear with the retrieval implants.

[Slide.]

In summary, materials manufactured for the Christensen TMJ devices are biocompatible and conform to medical implant material standards.

2. Animal testing indicates the materials elicit no foreign body reaction to tissue.

3. The design of the Christensen TMJ devices were analyzed using FEA kinematic/kinetic modeling and contact stress analysis yielding commonly expected and safe results.

4. Load-to-failure testing shows a 6 to 10 times safety factor in Christensen TMJ device survival over in-vivo physiological loading for dynamic and cyclic wear laboratory testing.

5. Particulate wear volume of the Christensen TMJ implants are a factor of 24 to 80 times lower than wear volumes as generated in orthopedic hip implants.

6. No device failures were observed in the dynamic fatigue or cyclic wear testing. Finally, because

we chose the worst case combination of representative implant test devices, all testing is applicable to all implant types, specifically, the fossa only, the PMMA-on-metal, the metal-on-metal, and the patient-specific of the Christensen TMJ system.

Now, I would like to introduce Mr. Doug Albrecht, Manager of Clinical Affairs of TMJ Implants, who will present the various clinical studies.

MR. ALBRECHT: Thank you, Al.

[Slide.]

As Al said, I am Doug Albrecht. I am Manager of Clinical Affairs for TMJ Implants, Inc.

Today, I will be presenting a compilation of data from a variety of data sources that we believe to be valid scientific evidence supporting the reasonable assurance of safety and efficacy of the Christensen designed TMJ prostheses.

[Slide.]

Recognized sources of data for preamendments devices as defined by the FDA can be anywhere from well-controlled clinical studies to significant human experience including marketing and MDR history.

The Christensen prostheses have been available for over 35 years, and TMJ Implants has been manufacturing the Christensen prostheses for approximately 10 years. A significant portion of the data presented today will be from significant human experience, marketing and MDR history from TMJ implants obtained over the past 11 years. Additional data will be presented by a partially-controlled, retrospective study and an ongoing prospectively-controlled clinical trial.

[Slide.]

The objective of today's presentation is to demonstrate that the Christensen designed TMJ prostheses are safe and effective in the majority of patients through the evaluation of pain reduction, improvement in interincisal opening, and the evaluation of adverse events.

The analyses presented today will be from patients who have supplied clinical data implanted with the Christensen prosthesis, those implanted with either a partial joint or total joint replacement, those implanted with either a metal head or PMMA head condylar prosthesis, or those implanted with a patient-specific total joint.

In most of these studies, data was also collected on diet restriction and interference with life.

While analyzing the pain data along with the diet restriction and interference with life, we found that regardless of the source of data, the same pattern of improvement from all three parameters was seen.

Therefore, in consideration of time, the data

presented today will be that of pain reduction and improvement in interincisal opening, with the understanding that similar patterns of improvement were seen with both diet restriction and interference with life.

[Slide.]

The measurement of TMJ pain, diet restriction, and interference with life were measured using a 10 cm visual analog scale. Ten cm was chosen based upon the results of Seymour, et al., who determined that scales of 10 to 15 cm had the smallest measurement error.

With these scales, the left side represents either no pain, diet restriction, or interference with life, and the right side of the scale represents the most pain imaginable with the inability to eat solid food and the most severe interference with normal daily activities.

Again, this terminology was chosen and shown to be the most suitable by Seymour, et al.

[Slide.]

These scales are marked by the patient and are a commonly accepted method of recording pain and other subjective parameters.

[Slide.]

Interincisal opening was measured using a Therabite scale, and these data are presented in millimeters.

[Slide.]

The data being presented today have come from the following sources of valid scientific evidence. This slide represents the baseline demographics from these sources. I will be focusing my presentation on the first three studies listed, as these provide the strongest evidence of safety and effectiveness.

As you can see from the baseline data, age, gender, and pre-op pain and opening values are consistent across all studies.

[Slide.]

As the registry tracks all patients receiving the Christensen-designed prosthesis, patients from the other studies may appear in the registry, however, the data being presented from the other studies was collected and analyzed independent of the registry.

[Slide.]

The TMJ Implants registry began in September 1993 in response to the device tracking regulations. A secondary function of the registry is to collect and store data on the progress of each patient implanted with the Christensen device. Baseline or preoperative assessments of pain, diet restriction, and interincisal opening are requested at the time of device registration.

On a monthly basis, additional requests are sent

to either the implanting or following physicians to obtain the most current data related to the pain, diet restriction, and interincisal opening.

This is a voluntary system and physicians are not required to complete and return the forms. Since the same group of patients therefore is not represented at each time period within the registry, we conducted cohort analyses targeting patients who reported data at the same specified time periods.

The goal of cohort analyses is to demonstrate similar patterns as seen with the cross-section data. For all subgroups of patients analyzed, cohort analyses for pain and opening were conducted, first, a repeated measures analysis of variance F test which tests for overall patterns and then repeated measures analysis of various tests of contrasts, which tests the difference between mean pairs were used for these cohort analyses.

For each subgroup of patients presented today, cross-section data will be overlaid with cohort data in order to demonstrate similar patterns of improvement.

The following slides are the results of our analysis of pain reduction.

[Slide.]

This first slide represented a cross-section analysis of the reduction in pain from the registry through five years implant duration. These data represent all patients who provided at least preoperative pain data.

A significant reduction in TMJ pain is demonstrated through five years, starting at one month post-op, and that pattern maintaining itself out to five years implant duration.

Although these data are cross-section representation, the mere numbers of patients reporting at six months, which is well over 1,000, and at two years, which approaches 500, tells the story that patients do achieve a significant reduction in pain from the use of these prostheses.

[Slide.]

This cohort analysis includes 284 patients, each having preoperative, six-month, and two-year pain data. A significant pattern in the decrease in pain scores, as well as a significant decrease between pre-op to six months and pre-op to two years was demonstrated.

The difference in pain scores between six months and two years was also significant albeit the change was a slight increase of only 0.3 cm. It is not considered to be clinically significant.

[Slide.]

This slide compares the cohort data to the corresponding cross-section data with the number of patients in the cross-section indicated at each time

period. As you can see, there is virtually no difference between the 284 patients included in the cohort analysis and those from the cross-section analysis.

[Slide.]

A second cohort analysis included 60 patients each having pre-op, one month, six month, 12, 18, 24, and 36-month pain data, applying the same statistical methods, a significant pattern in the decrease in pain scores, as well as a significant decrease between the pre-op and all other time periods was demonstrated.

A reduction in pain between the post-op period and all subsequent periods was also significant. Again, a comparison of the cohort and the cross-section data is presented, and again there is virtually no difference between the 60 patients included in the cohort analysis and those represented in the cross-section analysis.

[Slide.]

This slide represents the reduction in pain from patients implanted with a fossa-eminence prosthesis or partial joint replacement, and those implanted with a condylar prosthesis mated against a fossa-eminence prosthesis or total joint replacement.

The cross-section data, as demonstrated by the solid lines, demonstrates a pattern of pain reduction for both groups, similar to all patients presented earlier. The cohort data represented by the dotted lines includes 51 patients with partial implants and 31 patients with total implants. The cohort data demonstrates a similar pattern of pain reduction through three years implant duration.

[Slide.]

This slide represents the reduction in pain from patients implanted with a condylar prosthesis with a metal head mated against a fossa-eminence prosthesis or metal-metal total joint, and those implanted with condylar prosthesis with an acrylic head mated against a fossa-eminence prosthesis or a PMMA total joint.

The cross-section data are represented by solid lines, the cohort by dotted lines. The cohort data includes 36 patients with metal-metal implants and 27 with PMMA metal implants. There is a significant reduction in pain from both groups of patients through four years implant duration.

[Slide.]

This slide represents the reduction in pain from patients implanted with a patient-specific total joint replacement. Again, a significant reduction in pain is demonstrated with both the cross-section data and the cohort data. The slight rise at three and four years is most slightly attributable to the low sample size at these time period.

The following is the results of our analysis of

interincisal opening.

[Slide.]

This first slide represents the cross-section analysis of the improvement in opening from the registry through five years implant duration. These data represent all patients who provided at least preoperative opening data. A significant improvement in the opening is demonstrated through five years.

Although these data are a cross-section representation, the mere numbers of patients reporting at six months and two years again, as with the pain data, tells the same story, that patients do achieve a significant improvement in opening from the use of these prostheses.

[Slide.]

This slide represents the cohort analyses of 265 patients, each having pre-op, six month and two year opening data. A significant pattern in the increase in opening for two years, as well as a significant increase between pre-op to six months, and pre-op to two years was demonstrated.

There is virtually no difference between the data from 265 patients and the cross-section data.

[Slide.]

In this cohort, 55 patient with opening data at pre-op, one month, six, 12, 18, 24, and 36 months are presented. Applying the same statistical methods, a significant pattern in the increase in interincisal opening was demonstrated with similar patterns demonstrated with the cross-section data.

An improvement, although not statistically significant, was seen between pre-op and the one month period. Although pain is significantly reduced immediately post-op, it appears that significant improvement in mechanical function may take a little longer.

This may be the result of a number of variables including, but not limited to, disease state, age of the patient, the time it takes the muscles that were manipulated or cut during surgery to heal. However, this cannot be confirmed with our existing data.

[Slide.]

Comparing the preoperative period and the postoperative period to all other post-op periods, a significant difference was also demonstrated.

[Slide.]

This slide represents the improvement in opening from patients implanted with a partial joint replacement and those implanted with a total joint replacement. The cross-section data, as demonstrated by the solid lines, demonstrates a pattern of improvement for both groups similar to all patients presented earlier.

The cohort data represented by the dotted lines includes 45 patients with partial implants, 29 patients with total implants. The cohort data demonstrates a similar pattern of improvement through three years implant duration.

[Slide.]

This slide represents the improvement in opening from the patients implanted with metal-metal total joint and those implanted with a PMMA metal total joint. As you can see, there is similar improvement from both groups through four years with virtually no difference among the cohorts.

The cohort data includes 30 patients with metal-metal implants and 26 patients with PMMA metal implants. The slight drop in opening at three and four years again is most likely attributable to the low sample size at these time periods.

[Slide.]

This slide represents the improvement in opening from patients implanted with a patient-specific total joint replacement. Again, a significant improvement is demonstrated with both the cross-section data and the cohort data.

[Slide.]

In the PMA, we also presented data from a number of other sources which support the effectiveness of Christensen design TMJ prostheses and confirm the results demonstrated with the data from the registry.

These supportive studies demonstrate a significant reduction in pain and improvement in intercuspal opening, the pain and opening data being presented from the University of Tennessee and Dr. Hensher will be a cross-section analysis out to three years implant duration.

The pain and opening from Drs. Curry and Latta and the retrospective study will be from a cohort of patients with pre-op data and data from the last post-op visit recorded in their charts.

[Slide.]

This slide represents a significant reduction in pain from both the University of Tennessee study and the data independently collected from Dr. Hensher.

[Slide.]

This slide represents two cohorts, 44 patients from the retrospective study and 79 patients from Drs. Curry and Latta. Both groups demonstrate a significant reduction in pain based upon the mean VAS score from the last post-op visit recorded. The mean follow-up for the retrospective study was approximately two years and nearly four years for Drs. Curry and Latta.

[Slide.]

This slide demonstrates a significant

improvement in opening through one year from the University of Tennessee and through three years from the data from Dr. Hensher.

[Slide.]

This slide represents two cohorts, 170 patients from the retrospective study and 52 from Drs. Curry and Latta. Each group shows a significant improvement in opening from about two to nearly four years implant duration.

[Slide.]

The retrospective study represents a significant source of our safety data. That was the primary objective of the study. The charts of 249 patients from six oral and maxillofacial surgeons were reviewed. In order to minimize any bias on the part of the data abstractors, all clinical events regardless of the nature, severity, or outcome were recorded.

[Slide.]

Of the 334 events recorded, 56 were related to the surgical procedure, 275 were considered as either patient or disease related, and only 3 events were considered as related to the prosthesis.

[Slide.]

The 3 events considered related to the prosthesis. The 3 events considered related to the prosthesis each lasted less than one month, each patient required additional surgery to correct the problem, and all 3 patients recovered without complication.

[Slide.]

I would like to briefly touch on the controlled clinical study currently ongoing. The primary objective of the study is to assess the reduction in TMJ pain after implantation of a Christensen prosthesis. Secondary objectives include the evaluation of adverse events, diet, and improvement in opening.

[Slide.]

These data will confirm the data from all other sources presented here today. There have been 113 patients from 9 investigators enrolled to date. We are seeing similar patterns in pain reduction, lessening of diet restrictions, and improvement in opening as has been presented here today.

As you can see, the data from the pain, diet, and life VAS scores are virtually identical. Overlaid is the paid data from the registry which demonstrates a similar pattern of pain reduction between both sources.

[Slide.]

This slide represents a comparison of opening data from the prospective to the registry data. A similar pattern in the improvement in opening again is demonstrated.

[Slide.]

Additionally, the adverse events that have been reported today are similar to what we have seen in the retrospective study. There has been only one reported event that was deemed device related, and that was postoperative pain, and that is 1 out of 27 events.

[Slide.]

This slide is a chronological representation of TMJ Implants' MDR history since 1992. The MDR regulation is a very subjective tool to measure device-related events, and the company has adopted a conservative reporting philosophy.

There is no discernible pattern of device-related events, and the overall MDR incident rate is less than 1 percent.

I would like to just touch on a few of these reports here. As far as condylar fracture, we submitted 8 reports, however, upon further evaluation, we found that 1 was not a Christensen device after we had reported it, and 1, upon surgical entry to retrieve the device, found that it was not fractured after all. So, therefore, if only 8 reports were submitted, only 6 were true fractures, and the majority of them were most likely due to screw placement, where screws were not placed at the top of the condylar prosthesis, therefore, putting more stress at the top of the condylar prosthesis.

We have since revised our labeling to instruct physicians to be sure that at least 3 to 4 screws are placed at the top of the prosthesis, therefore, reducing that incident. You can see since 1996, 1997 was the one that was not fractured, so we have not had a fracture since 1996 with the condylar prosthesis.

With regard the fossa fractures, again, it is 0.1 percent incident rate of fossa fractures since 1992. The majority of them were due to manipulation of the device prior to implant, either bending the flange or increasing the size of the screw holes, therefore, compromising the integrity of the device once implanted.

Two reports were due to a monotonic stress overload, one due to a motor vehicle accident, and therefore, none were truly seen as a wear-through or any problem with the device at all.

[Slide.]

To summarize, presented today was evidence that the Christensen design TMJ prosthesis product lines are safe and effective for their intended use regardless of the source of the data analyzed, whether used as a partial joint replacement, total joint replacement, whether a metal or acrylic headed condyle, or a patient-specific condylar prosthesis, the use of these devices have been shown to provide in the majority of patients a significant reduction in pain and significant

improvement in interincisal opening.

This allows the patient to eat a more normal diet and enjoy a relatively normal lifestyle.

It has also been demonstrated that these devices are safe. The frequency and type of events reported were to be expected considering the disease being treated and the surgical procedure undertaken to treat the patient.

There have been no unanticipated adverse device effects reported. These devices have been available to treat patients suffering from severe TMJ disorders for over 35 years, and we have presented no evidence that would lead one to conclude that these devices provide an unreasonable risk of illness or injury associated with their use.

Additionally, the clinical benefits experienced by the majority of patients implanted with the Christensen designed TMJ prosthesis far outweigh the risks associated with their use.

I would now like to introduce Dr. James T. Curry. Dr. Curry is a member of the American Association of Oral and Maxillofacial Surgeons, the American College of Oral and Maxillofacial Surgery. He is a diplomate of the American Board of Oral and Maxillofacial Surgery. Dr. Curry is also past President of both the Arapaho Chapter of the Metropolitan Denver Dental Society, and the Colorado Society of Oral and Maxillofacial Surgeons.

Dr. Curry.

DR. CURRY: Thank you, Doug.

[Slide.]

Again, I am Dr. James Curry. I practice oral and maxillofacial surgery in Highlands Ranch, Colorado, with my partner, Dr. Jim Latta, and we have been together for over 20 years.

I have no financial interest in TMJ Implants, Inc. I am involved in various educational seminars in which we educate physicians as to the use of these devices, and for that I am paid an honorarium, and they have provided my expenses for this trip.

I have been involved in treating TMJ disease for 29 years, and my experience with the Christensen devices is in its eleventh year. In fact, my partner and I early on, in the mid-1980s, had considered discontinuing treating temporomandibular joint disease surgically in our practice because of the many problems we were facing.

We have been plagued, as many other oral and maxillofacial surgeons had been, with problems with Silastic and Teflon Proplast. We had also been plagued with problems with autogenous grafting methods that we had used for our patients.

We are very interested, vitally interested in safety and effectiveness of any device that we recommend for our patients for treatment of this disease. The

outcomes that we have seen in our practice have been so dramatic that we continue to use this device for treatment of severe and disabling temporomandibular joint disease.

When I was first introduced to the Christensen device, I was able to review a patient who had had a Christensen device implanted some 25 years before, and this was the primary thing that convinced me to try to device in patients in my own practice.

[Slide.]

Our treatment philosophy is based on science at this point and some of that science has been presented both yesterday and today for your consideration. It is also based on significant clinical experience.

In my own case, I am in my eleventh year of utilizing the Christensen devices for treatment of severe and disabling temporomandibular joint disease, but aside from that, these devices have been used by many surgeons for over 35 years, not to mention the several thousand devices that have been implanted in this country by experienced surgeons, as well as those who are just beginning their surgical experience.

Our treatment philosophy is also based on common sense. The materials used in the production of these devices have had long and successful orthopedic histories. The system is a simple design, it is relatively simple to place for the surgeon. It cuts down on surgical time, it provides me with the only partial joint replacement that is available to me for my patients.

The anatomical design of the fossa prosthesis protects the base of the skull from additional destruction in diseased joints following placement.

[Slide.]

I have developed some practical goals for alloplastic reconstruction for my patients, and we have already seen that we really expect moderation of joint pain, not elimination, improvement in joint function as evidenced by acceptable vertical opening and the ability for these patients to chew solid food once again.

Restoration and maintenance of facial aesthetics is critical. Restoration and maintenance of functional occlusion is essential. We want to limit the period of disability, limit the progression of the disease, and look for long-term maintenance of restored function, comfort, and aesthetics.

[Slide.]

The indications in my practice for a partial joint replacement include painful and dysfunctional internal derangements where nonsurgical efforts have failed. It also includes previous failed joint surgery failures as you can see here of various types, and other

pathology where the condyle remains healthy.

[Slide.]

Indications for a total joint replacement include destruction and loss of the condyle due to trauma, pathology of various kinds, and ankylosis.

[Slide.]

This represents my clinical experience in a group of consecutive patients, and our experience is consistent with the registry that you have already seen.

[Slide.]

We looked at opening in a group of my own patients, and it also, even when you compare the total joint with the partial joint, mirrors the information that you have already been provided.

[Slide.]

In an effort to assist the panel in understanding better some of the types of patients that I see in my practice, I want to present a few clinical case reports, and I will run through these fairly rapidly.

In the first couple of cases, I want you to pay particular attention to some of the questions that I have been asked around the country as I have presented my clinical data.

This particular patient is a relatively young female. She had had some previous surgical experiences that had failed, and in 1990, she had bilateral partial joint replacements. The x-ray slides that you see here of the right and left jaw joints, the CT scan done in 199, and what I want you to notice, yesterday, I think a really good description of the way a condyle looks is a drumstick in the glenoid fossa, and so this condyle looks a little bit like a drumstick, and this one does, too.

The question is how does a condyle, a relatively normal condyle respond to partial joint reconstruction, and in my patient population, the condyle responds very favorably. This is a nine-year, postoperative view following partial joint reconstruction.

[Slide.]

Another question that I am often asked is how does the contralateral joint respond to unilateral joint reconstruction in a partial way. This is a 10-year, postoperative picture of a CT scan. You can see the partial joint replacement on the left and no surgery on the right, and this condyle still remains relatively healthy, and so does the one on the left.

[Slide.]

As we move into the total joint arena, this case will be representative of some of the other data that you have been presented with, multiple attempts at correcting pain and dysfunction in a nonsurgical fashion, orthodontics, orthognathic surgery when the occlusion is off, finally, open joint procedure that failed, and then

in 1991, bilateral total joints.

[Slide.]

This is the Panorex view of the right ramus, the entire condyle is missing. This is the lateral head plate of this same patient showing the incredible open bite deformity, a very significant aesthetic problem. You can see telltale clues of the previous orthognathic surgery in an attempt to correct this patient's worsening bite and aesthetic considerations.

This is the lateral head plate following stock total joint reconstruction for this patient. We were able to improve her facial aesthetics, correct her open bite deformity. She had a significant speech pre-surgery, significant pain, and dysfunction.

[Slide.]

This is the same patient clinically for you to consider. What I want you to see here is the significant aesthetic dilemma that some of these patients find themselves in, not to mention the functional dilemma, the huge open bite. The only teeth that are touching are the posterior teeth.

This patient has a significant speech impediment, tongue thrusting problems, lip incompetence, and all sorts of problems associated with her significant pain and joint dysfunction.

Following total joint replacement, we have increased her facial aesthetics and corrected her dental problems, as well. This patient is continuing to be followed in my practice, and she is doing beautifully.

[Slide.]

Another typical example relates to a young female. She had had a traumatic incident with a right condylar fracture in 1980. In 1985, she was involved in another motor vehicle accident, and we did total joint replacement on the right and a partial joint replacement on the left.

[Slide.]

This represents a stock prosthesis, total joint replacement for a significant deformity resulting from trauma. Here is the glenoid fossa. This is the stump that is remaining of the condyle. This patient is continuing to be followed in our practice. I have seen her within the last month, and she is doing beautifully, as well.

[Slide.]

This is just the representation of the partial joint replacement on the opposite side.

[Slide.]

This is a young female who has been through a litany of other procedures with the Teflon Proplast replacement devices that have failed so miserably that we are all involved with now, and she underwent bilateral

temporomandibular joint patient-specific Christensen type total joints in 1995.

[Slide.]

This x-ray picture shows the immense destruction of almost the entire ramus of the jaw and the glenoid fossa area. This is a 3D reconstruction for your consideration, and you see how much bone loss has occurred underneath the previous prostheses.

[Slide.]

This is an SLA model, and you can see that both joints, both the right and left joints are completely mutilated and completely destroyed, and this the patient-specific device on the right that was designed for this patient. We designed a similar one for the other side.

[Slide.]

This is just an x-ray representation of the patient postoperatively. I have been in touch with this patient in the last two months. She lives in Houston, Texas, and is being followed at the University of Texas, and she is just doing beautifully.

[Slide.]

This gives you some idea clinically of the amount of destruction that takes place in multiply operated joint patients, as well as those who have had previous failed alloplasts, and the way we have been able to reconstruct them.

[Slide.]

This is an example of bony ankylosis. I know we have talked a little bit about ankylosis, and just for your consideration.

When we see total bony ankylosis, it is an incredible thing. The mandible fuses to the base of the skull. These patients many times can't move in any direction. There is no way they can have a general anesthetic for any kind of normal surgery without severe risk to life and limb. They can't have any dental work done. They can't get their mouths open at all.

This is a clinical picture of this case, and you can see there is just a mass of bone there and no anatomy at all.

[Slide.]

One of the beauties of the design of this particular joint prosthesis, and whether you are going to do a patient-specific design or whether you are going to do a stock replacement, we have available to us templates for reconstructing the glenoid fossa, and we use these templates. They have holes through them in several different places, so that we can actually reconstruct the glenoid fossa for these patients.

[Slide.]

As you see, we are continuing our surgery here,

and then we do a total joint replacement. I would like to make a comment about the design, as well, from a clinical perspective. The oval shape of the condylar head makes it very easy for the surgeon when he is placing the ramus device, which we have to attach to the ramus of the jaw, and those jaws come in various configurations. They may be slanted one way or the other, and the real nice thing about this is that if you have to slide this around a little bit to get it to fit properly and to get solid contact, you don't change the dynamics of the joint itself.

[Slide.]

This is an 11-year explant. I would like for you to see clinically, this is PMMA head and a fossa liner, and this is what the bone looked like after we took the prosthesis out. All of this tissue was biopsied. We found no giant cell reaction, and the bone is just beautiful underneath these prostheses.

[Slide.]

This is the replacement that was done for that patient.

[Slide.]

In conclusion, I would like to offer that alloplastic devices are needed by surgeons and patients alike to reconstruct a variety of diseases affecting the temporomandibular joint system. No other device is currently available for me that will so effectively and safely partially replace the diseased temporomandibular joint.

These devices are simple to place, reduce surgical time in my hands, and revision surgery, as you have seen, is pretty simple to do because the bone is really maintained underneath the devices, and clinically, I have not seen a single case of giant cell reaction or bony erosion, and I encourage this panel to recommend the continuing availability of the Christensen designed prosthesis system for my patients who are suffering from a disabled joint.

Thank you.

MR. MORGAN: Dr. Janosky, if I could just summarize very quickly, your decision today, as Dr. Curry has said, is whether or not a product first introduced in the 1960s will remain in commercial distribution.

Your decision impacts the surgeons' and the patients' choice in alloplastic devices and treatments. We trust that you will agree with our conclusion that the TMJ Implants, Inc., prostheses are safe and effective when used in accordance with their labeling and that you will agree to continue to allow this choice of treatment in temporomandibular joint disorders.

We encourage you to vote to approve this device for continued commercial distribution for the sake of the

patients suffering from temporomandibular joint disease, for the sake of the surgeons seeking, as Dr. Curry has stated, the only viable alternative available to certain patients, and for the sake of the public health.

Thank you.

I would like to pass around some samples if that is all right.

DR. JANOSKY: At this time, are there any questions from panel members for the sponsor? If there are, I ask that you state your name before asking the question, please.

DR. HEFFEZ: Leslie Heffez. I have a question for Dr. Latta.

In your mind, what are the specific indications for an eminence-fossa replacement only?

DR. CURRY: Dr. Curry, Dr. Latta is my partner.

DR. HEFFEZ: Sorry.

DR. CURRY: And he is much less gray-headed than I am. Would you repeat the question? I am sorry.

DR. HEFFEZ: Dr. Curry, could you please tell me what are some specific indications for eminence-fossa replacements only?

DR. CURRY: The specific indications are when the joint is diseased and has not responded to nonsurgical care, and the patient is debilitated to the point that they have a functional disorder and/or concomitant pain disorder that has been shown to be joint related, in the joint itself, and if we have documented evidence of internal derangement, and the condylar head remains healthy, at least in the testing that we are able to do, then, we believe partial joint reconstruction early on is the treatment of choice.

DR. HEFFEZ: So, let me clarify. You are stating that the condyle is in normal configuration, anatomical configuration, yet, what is going on in the eminence that leads you to place the implant at the site of the eminence-fossa?

DR. CURRY: Well, there may be no MRI or radiographic evidence of significant destruction even of the eminence, but sometimes there is, and the other joint elements, the interarticular disc, if there is functional problems and serious adhesions, we place the fossa-eminence prosthesis to, number one, protect the base of the skull, and, number two, to reduce the likelihood of adhesions postoperatively in ankylosis.

DR. HEFFEZ: You are taking out the cases of ankylosis. I would like specifically to know if the eminence in your mind, in your experience, can undergo degeneration and the condyle not undergo degeneration, and this leads you to the placement of this eminence-fossa implant.

DR. CURRY: Yes, that occurs occasionally, as

well, and that would be a specific indication.

DR. HEFFEZ: How frequent do you see the need for placing an eminence-fossa device without placing a condyle device?

DR. CURRY: In my clinical experience, about 60 to 70 percent of the patients that we do open procedures on are indicated for partial joint replacement rather than total joint replacement.

DR. HEFFEZ: What type of procedures would that patient have undergone prior to placement of this eminence-fossa device, or is this a primary surgical procedure?

DR. CURRY: It can be a primary surgical procedure. In my hands, if a patient has not been multiply operated, I won't hesitate to put the fossa prosthesis in at the first surgical insult. We are making every effort to reduce and eliminate eventually the multiply operated patient from our practices.

We have seen over and over again that multiple procedure after multiple procedure results in nothing but failure for these patients.

DR. JANOSKY: Ms. Cowley.

MS. COWLEY: Theresa Cowley, TMJ Association.

I notice in your promotional materials that you are actually encouraging that patients have one surgical procedure, if that. I would like to know how you ethically can espouse this when, in your instructions for use, you say, "Although total temporomandibular joint replacement is an option in patients," and so forth, "the long term outcomes with currently available total joint implants have yet to be determined," and your studies are actually voluntary on the part of the physicians.

MR. MORGAN: Jim Morgan. I think that Dr. Curry has responded to the early procedure aspect of it, that there are certain indications clinically that would be beneficial for the patient. In addition, there is certain aspects of our labeling that are required by the FDA, I think you read just part of that, and our objective is to assist the temporomandibular joint disease patient to improve their condition, and we leave it to the clinician to make final determination as to when to exercise that discretion.

MS. COWLEY: Can I follow up? What instructions do you give your clinicians when a device fails, who are they to report it to? Apparently, I saw 60 MDR reports.

We have approximately twice that in our registry, and a lot of people in this country don't even know we exist.

MR. MORGAN: I guess the question deals with filing MDR reports. We believe that we have taken a rather conservative regulatory approach towards filing MDRs, that is, if there is some question as to whether or not we would be required to file an MDR, generally, we do

file.

So, when we obtain information, we evaluate that information relative to the MDR regulation, and we believe make the appropriate determination to file.

MS. COWLEY: Can I follow up? What happens to the devices and who do you deem owns the devices once they are explanted?

MR. MORGAN: When devices are returned to us, we perform an evaluation on those devices, and we retain them in our archives. The question of ownership, I don't quite know how to address.

DR. JANOSKY: Dr. Rekow.

DR. REKOW: This is Diane Rekow. I have a real simple question. What is a device? When I start adding things up, I end up with more devices than patients times 2?

MR. MORGAN: What we are really talking about is a system, and we have a partial joint system that consists of the fossa-eminence device, along with the screws and accessories to implant that device, and we have a total joint system that consists of the fossa-eminence and the condylar prosthesis.

Within that, there is a condylar prosthesis with a metal head and one with a PMMA head. Finally, we have perhaps one would consider another subset, and that is that there are patient-specific devices, which may be either be either fossa-only or fossa and condyle with metal or PMMA.

DR. REKOW: I understand that, but, for instance, in the literature that we had, you had 3,914 patients with 8,600 devices, but 3,900 patients only have a total of 7,800 joints, so I got confused about what you are counting in the numbers that you report.

DR. CHRISTENSEN: I am Dr. Christensen. Per patient on the average we are seeing about 2.2 devices. It could be a fossa, it could be a condyle, or it could be a fossa on one side, a fossa on the other side, so when we report different numbers, that is sort of how it goes.

You could have a partial on one side, you could have a total on one side, you could have a total on both sides, and if you had a total on both sides, you would have basically four devices. I think that is maybe where the confusion is.

DR. REKOW: I was thinking of a total joint being one joint, but it is two pieces.

DR. CHRISTENSEN: That is correct.

DR. JANOSKY: Dr. Patters.

DR. PATTERS: I would like the sponsor to address the MDR issue. The panel has been provided with information from FDA that between 1984 and June of 1998, 434 MDRs were filed regarding the generic TMJ implant; 75

percent of those were Silastic or Proplast Teflon, however, 14 percent were the Christensen implant.

Then, after those two were taken off the market, the Proplast Teflon and the Silastic, from August of '96 until May of '99, there were 63 MDRs filed, and 65 percent of those were Christensen devices.

Do you find that alarming at all, and can you comment in the significance of it?

DR. CHRISTENSEN: I think if you looked at what we projected up there, the percentage of MDRs or events listed per the population that doctors have operated on is less than 1 percent. Most of them are less than half of 1 percent. That generically, or not generically, but globally, should tell something.

Jim?

MR. MORGAN: I have nothing to add.

DR. PATTERS: One additional question. Based upon your total clinical data, can you at least give estimations of the percentage of implants placed that the patient did not improve? Not necessarily those which failed mechanically, but that the patient did not report any improvement in the measured parameters?

MR. ALBRECHT: Doug Albrecht. We did look at that, and we looked at patients whose pain or opening did not improve at each time period throughout the continuum, and overall, approximately 5 to 6 percent of patients did not have a VAS score lower than their baseline or intercisoral opening higher than their baseline at six months, 12 months, and every six months after to three years implant duration.

So, on that, approximately 95 percent of the patients do show an improvement in their pain and their function post-surgery.

MR. MORGAN: Could I just add something to that?

In that time period, we were essentially the only marketer or certainly the primary marketer of the device at that time. That might also be a reflection of the percentage of MDRs filed.

DR. JANOSKY: Dr. Heffez.

DR. HEFFEZ: I have a follow-up question to Dr. Patters' question.

Have you looked at specific diagnoses of the patients, for example, the Proplast Teflon patient, as far as its failure rate as opposed to just if you have already treated patients for primary, with these devices as primary surgeries, it muddles the data. So, if you could look at just the Proplast Teflon patients and advise us on your data.

MR. ALBRECHT: Yes, we have looked at those patients with history of Proplast or Silastic, and we have shown--I have slides if you would like me to put them up or I can just annotate--we have seen the same

type of improvement in pain and the same type of improvement in opening for those patients.

DR. JANOSKY: A question from Dr. Burton.

DR. BURTON: This question is for Dr. Christensen. I am still sort of curious, though. You have a multitude of treatment options that you have developed here, but there doesn't seem to be any kind of guidance that I could see in terms of between metal-on-metal, PMMA-on-metal, or the now your custom, which didn't seem quite as well defined in terms of indications or differences between these various systems and your utilization.

DR. CHRISTENSEN: The use of this patient-specific, of course, depends upon the amount of anatomic structure there as to what we need to anchor that to, to the bone, and make it one that would hold up.

The use of the metal versus--and that the physician choice really--but the use of the plastic versus metal, we are attempting to, of course, reduce any wear that we can and get down to as small amount as possible. I think in several articles, like the Sulzer article, and so forth, that talks about the metal versus, say, other things, such as polyethylene, being anywhere from 20 to 100 times less wear debris, and we are finding that I think in our studies, too.

DR. BURTON: Thank you.

DR. JANOSKY: A follow-up question from Dr. Heffez.

DR. HEFFEZ: Again, a follow-up question. Could you give us data on the percentage of patients that were operated as primary surgical procedures and the percentage in which you placed in either of these devices in mutilated joints?

DR. CHRISTENSEN: Anecdotally, it's a little bit more than anecdotally, but he will have the real answer, but in my practice, when I saw internal derangement and perforation of that meniscus, I realized that meniscus will not repair itself, and I put in the fossa-eminence implant and partial joint, those patients almost never had to be reoperated. We are seeing a group of people now that have been operated in many ways, and that, of course, compounds the problem.

Fortunately, I think our results--and he will show you--are quite significant in both areas.

MR. ALBRECHT: Doug Albrecht. To respond to Dr. Heffez' question, in our clinical report, which was included in the PMA, on page 4.9 of the clinical report, we reported from the University of Tennessee study patients who had been multiply operated versus patients who had been operated for the first time, and both of those, we looked at pain and opening for those groups of patients, and we found similar results although the

patients that had been multiply operated did have higher pain scores, but both groups of patients did show improvement postoperatively.

DR. HEFFEZ: What wasn't the question. My question was how many patients were treated as a primary disease and how many were treated in mutilated joints. Do you have that data for the total amount of patients that you reported? If not, if you only have it for the University of Tennessee study, could you say it for the audience?

DR. ALBRECHT: Yes, for the University of Tennessee study we had 211 patients that had been multiply operated, and 109 patients who were operated for the first time, and again both groups of patients showed improvement after surgery, however, the multiply operated patients did have higher pain scores.

DR. JANOSKY: A question from Dr. Skinner.

DR. SKINNER: I have two questions. One was regarding the wear debris studies that you did. That was polymethylmethacrylate that you put in a rabbit's joint. Do you have any idea what the wear debris particle size distribution and size was?

MR. ALBRECHT: I think I will direct that question to Dr. David Gerard who did that study.

DR. GERARD: David Gerard. I don't have any financial interest in this company although I performed two animal studies for this company.

The particles that we looked at were ranging from 50 to 250 microns in size and were irregular in shape, and they were injected into the joints, the TMJ joints of rabbits, and on the contralateral side, saline was injected as a control.

DR. SKINNER: Do you have some rationale for using such large particle sizes?

DR. GERARD: The particles we used were actually generated from wear studies, and in analyzing the size of those particles--this study was done in '94, at that time we didn't fully appreciate the importance of very small particles--and we analyzed the size of those particles using SEM and just a settling technique, and so we may have had small particles in that sample that we did not see, but I cannot say that for certain.

But if you look at the wear pattern, for example, on the test condyle versus the retrieved condyle, you will see that the wear patterns are very similar, and that would indicate to me that particles generated in a wear test would have the same range of sizes as particles that you would see in vivo.

DR. SKINNER: And that was a single injection rather than a continued injection?

DR. GERARD: Yes, it was a bolus rather than continuous generation, yes.

DR. SKINNER: A second question was regarding the clinical data. The cross-section and the cohort data overlapped, didn't it?

MR. ALBRECHT: Yes, they did. They pretty much mirrored each other.

DR. SKINNER: No, no, overlapped. There were the same patients in each group.

MR. ALBRECHT: Yes, the subset, the cohort was a subset of the cross-section data for patients with complete data at every time point presented.

DR. SKINNER: So, the cross-section data included the cohort group.

MR. ALBRECHT: That is correct.

DR. JANOSKY: A question from Dr. Gonzales.

DR. GONZALES: This is a question for Dr. Doug Albrecht regarding the way the pain scales were performed.

First of all, I understand that you performed 10 cm pain scales on these patients. In the prospective study, I understand in the handout that was given, that yes/no scales and also 5 cm or 5 point scales were also performed.

The other question is why the dropout or reduction in the number of patients in the second cohort.

You start off with 1,794 patients. At two years, you are down to 447, and three years, 234 patients.

Was that based on the fact that was a questionnaire that was sent to patients and you just weren't getting the return on those questionnaires?

Finally, when were the patients required or asked to fill out the questionnaires in terms of when they were measuring their pain, when were they asked to measure their pain since pain is not--it is rare that pain is a consistent, constant painful symptom. Oftentimes these patients will have pain after eating, during eating, or at other times. I am interested in finding out what the questionnaire instructed the patients, how they were instructed to fill out the questionnaires.

MR. ALBRECHT: Just to clarify, you indicated that we just used yes/no in the prospective study. We collected yes/no data from the retrospective study.

Let me just clarify the types of studies, and then I can answer your questions. We did the retrospective study primarily to collect adverse event data. While we were in the patients' charts, we also collected data on pain and opening.

Yes, we did find that in a number of cases, the notes in the physician's chart did not always indicate a pain scale. They said yes, I am still having pain, or no, I am not having any pain. We probably underestimated the amount of data like that in the charts, but we had to

record it, and we had to analyze it somehow.

That purely is a retrospective evaluation. We just recorded what was written in the physician's charts at that time.

To answer your question regarding when the questionnaires and when the patients filled them out, for the prospective study, which is currently ongoing, those visual analog scales are filled out by the patient when they are seen in the office by the physician.

The forms state to ask the patient to rate their pain, diet, and life problems averaging over the last month, how have you felt over the last month, and they are to mark on the scale what that value is.

DR. GONZALES: And the dropout of patients?

MR. ALBRECHT: The dropout of patients from the registry. Again, the registry, the primary function of the registry is for device tracking. We initiated trying to track the progress of patients on a voluntary basis since 1993, and again it is not a complete cohort.

There is dropout because, number one, it is a voluntary system, that we sent the questionnaires to the physicians on a monthly basis. If the physician wishes to return the questionnaire to us, he does, and we record the data. So, it is not designed as a clinical study to be active in that sense. It is to give us a sort of feel of how patients are doing over time. That is the reason for the dropout, plus we are continually enrolling, so your pre-op patients are going to be higher than your patients out to four or five years.

DR. GONZALES: But this study is giving you a feel of how these patients are doing, and unfortunately, when one fifth remain after a two-year period, the feel that you are getting is from those patients who are actually filling out the form, and since it is being stressed that these patients are continuing to do better over time, and you are not really capturing the majority of these patients, so an impression to be made regarding this is very difficult to make any statements when, again, four-fifths of the patients are not really being measured.

MR. ALBRECHT: And we understood that, and that is why we conducted the cohort analyses where we looked at patients who provided data, at every time point, versus having a cross-section of data where patients do not report data at every time point.

As you can see from the presentation, the cohort data mirrored the cross-section data almost identically all the way through, and even with our prospective trial in which we are measuring those patients on a prospective basis in a clinical study, when compared to the registry data, we are still seeing the similar results.

DR. GONZALES: Thank you.

DR. JANOSKY: A question from Dr. Li.

DR. LI: We have a couple of questions on the nonclinical data that was provided.

First, the PMMA that you appear to be using is clearly different from the bone cement used to fix total joints, and I didn't find all the properties, although they might have been in there.

Could you describe a little bit the difference between the PMMA you are using now and the PMMA we typically use as a bone cement?

MR. LIPPINCOTT: Thank you for identifying that, Dr. Li. Yes, it is different. The material characterized in the Christensen device has a similar chemical composition except that this does not have a radiopaque identifier, such as barium sulfate or zirconium oxide, and it is a common material that is used in the lens industry. It has got a long history of use.

Also, this device is premanufactured compared to the acrylic that is used in orthopedics from the standpoint that you have total release of the monomer that is used to solidify the material. That is also further released through gamma irradiation of the product to make sure that it is fully released because it is tissue destructive.

DR. LI: In particular, I was interested. There is one component that is very different from bone cement.

I think it is the dimethacrylate that is in the powder, that is used as a cross-linking agent. I would guess that the effect of that cross-linking agent would be it perhaps would lower wear, but actually would reduce the fracture toughness.

So, my question is what is your fracture toughness of your PMMA versus bone cement either in terms of the K1C or a J or a materials fracture number? I didn't see that in the application.

MR. LIPPINCOTT: Well, we have done testing such as tensile testing.

DR. LI: I am looking for a fracture toughness.

MR. LIPPINCOTT: Like a Charpy-impact test?

DR. LI: No, I am looking for a fracture toughness value, actually, the inherent fracture toughness of the material. It is typically provided either as a critical J or a critical K value in the ASTM vernacular.

MR. LIPPINCOTT: Unfortunately, we don't have that information.

DR. CHRISTENSEN: We did do a static load test on that in which we put about 790 pounds or 800 pounds or maybe 900 before the thing ever fractured.

DR. LI: I understand. That just isn't the same as a fracture test, that is more of a total device test.

It was more of a materials question.

In your finite element modeling, did you allow for the creep of your methacrylate as part of your model or did you consider it as a rigid body?

MR. LIPPINCOTT: We considered it as a rigid body.

DR. LI: Because the deformation of your PMMA also, the other substantial difference appeared to be the deformation under load, which was substantially higher than bone cement, so I guess the question would be the appropriateness of modeling that material as a rigid body.

MR. LIPPINCOTT: I really couldn't answer that for you.

DR. LI: What did you use as a failure criteria in your modeling? In other words, you appeared to calculate stresses, and you made some little--I forget the phrase--but that you didn't get near the yield point and thus considered that an appropriate safety test, but without knowing the fracture toughness value or the fatigue values, how could you actually assess from the finite element model that it was safe using that method?

MR. LIPPINCOTT: Well, we modeled simulating loads in the FEA, and what we did is we looked also in comparison to the wear testing as far as how the material yield with certain loads that we used on it, and as well we did a tensile test on the material, which typically there is very little yield, if anything, in the material. You usually have a tensile and elongation factor.

DR. LI: So no other failure criteria other than tensile and yield were used in your FEA.

MR. LIPPINCOTT: That is typical, yes.

DR. LI: Speaking of the wear test, I had a couple of questions. You have got two different wear tests. One is a pin-on-disk, and one that was supposed to be a little closer to the anatomical case.

Did you get the same particle size in both of those tests?

MR. LIPPINCOTT: We did not evaluate the particle size as a comparison between the two tests. Now, the particles that were used in the rabbit study were for the pin-on-disk test.

DR. LI: As Dr. Skinner pointed out, those were rather large compared to the particles we are now currently worried about.

And the fluoroscopy data, working with the same group and total knee replacements, we find a very large mismatch between where the fluoroscopy says the components are relative to each other versus what we find in the retrieved components.

In other words, in the fluoroscopy of total knee replacement using the same group, the fluoroscopy data will tell you through a range of motion where the femoral

component was relative to the tibial component.

Then, you compare that information to where the components had to be because you see the damage in your hand of the retrieved component. There is actually poor match between the fluoroscopy kinematic locations and the retrieved device locations.

So, my question is seeing as how you seem to have gotten some retrievals, what is the comparison of the location, the fluoroscopic locations versus your retrieval damage locations?

MR. LIPPINCOTT: I would say that because of the configuration of the fossa component, that there is a sulcus, a cavity, that the head would fit into, we are seeing comparable locations from the study, because it is almost self-centering as far as its finding its center in this location.

DR. CHRISTENSEN: You won't be able to evaluate accurately, I don't believe, Dr. Li, the fluoroscopic picture of that in the patient versus that in the explant. It is complicated because of the whole skull, because of the metal, and so forth.

DR. LI: Understood. Actually, that was my point.

I think it was Volume 4, page 847, let me read this because I was kind of surprised that it was here. It says, "The wearing of the PMMA head may progress to the cobalt-chrome retaining post embedded with the PMMA head. After that time, the working mechanism would be a single point, metal-on-metal contact with the resultant lower wear of the metal-on-metal devices."

My question is do you actually believe that, and, if so, how could that possibly be, and did you actually verify that independently somehow?

DR. CHRISTENSEN: I would like to add that, and I think Mr. Lippincott will, too, clinically, from the explants, and so forth, we have seen occasion where the plastic head comes down almost never to the metal, maybe one or two cases at most, but if it ever does, that was put in there for a reason, to be of a highly polished mandril or point that this implant could fit on. We have never seen damage to the fossa or that metal strip, and it would slow down at that point.

MR. LIPPINCOTT: I would like to comment also, that by the time you get down to the post, the acrylic is conformed to the shape of the fossa, okay, from wear, and so your contact stresses are distributed quite more out on a larger area, so you wouldn't expect to see the higher contact on the metal post.

Granted, there may be some load transmitted to the post, but I think it would be very minimal.

DR. LI: Have you verified that?

MR. LIPPINCOTT: I don't know how you would

verify that.

DR. LI: Well, that was my question actually.

DR. CHRISTENSEN: In our wear testing, have never taken it, in the time of 10,000 cycles we have run, has not gotten it down to the post. That is only a millimeter and a half in thickness.

MR. LIPPINCOTT: In our wear test, the worst wear test, which showed the greatest wear, typically, we have a millimeter or 40,000ths to 60,000ths difference in height between the post and the top of the acrylic, and in that wear test, we had wear of about half a millimeter as a worst case with the five test components that were tested.

DR. LI: Back to the wear test, the anatomical wear test, you have a statement in there that you thought the surface profiling was more accurate than a weight measurement. Yet, if I read my details right, the weight measurements were done with a balance that actually couldn't possibly weigh the wear that you were getting.

So, my question is although it may be true the surface profiling may be more accurate, how did you actually determine that given that you had no weight measurements to compare it with?

MR. LIPPINCOTT: Well, we did have weight measurements to compare it with. This was done by an independent lab. This was Rose, who you are familiar with. I think they are relatively new in doing this type of work, and unfortunately, we had some discrepancies in the weight measurements that were taken.

We did take measurements every quarter of a million cycles, and unfortunately, we got weight gain at the beginning of the test, and then in many cases, especially on the condyle units, they did level out and we did have loss.

Now, we did have the fossa component on the metal-on-metal, and we compared that to the surface profile analysis that we also used as a fail/safe method to check before and after the test, and we did get very identical or comparable mass loss measurements with weight versus profile as a comparison, so that validated us using the surface profile method.

DR. LI: Just a couple more, if you will indulge me. How does the physician choose whether or not to use a metal-on-metal or a metal-on-methacrylate component, and why do you have the choice?

DR. CURRY: I am Dr. Curry. In the early stages of my experience with this prosthesis, I was using all PMMA-on-metal joints, and I think part of my reasoning is from unfounded fears that had been generated through discussions that I have had with my colleagues, problems with previous alloplasts like Teflon and Proplast, and I was fearful of particles generated from PMMA wear, and so

I have switched to the metal-on-metal joint just from that fear although I will say that as it stands now, probably 70 percent of the patients that I have operated have PMMA-headed condyles.

My partner and I made an anecdotal decision early on that patients that had had pre-existing alloplastic failures involving Teflon and Proplast and/or Silastic, we went to the all-metal condyle for those patients early on and have been very happy with that.

So, it is patient and doctor choice. Sometimes we have patients that say I don't want any plastic, so for that reason we will use an all-metal condyle.

We also consider--and I think you brought this point up yesterday, Dr. Li--we are dealing with overall a fairly young patient population when we compare the population of total joint replacement in the temporomandibular joint to total hip replacements and total knees. Although you have made the comment that your patient age population or the age of your patient population is being reduced over the last few years, our average age of our patients is in their forties, if you look at the demographics over the entire world, and my sense tells me that metal-on-metal is potentially stronger and potentially will last longer than a metal-on-plastic, but that has yet to be proven.

MR. LIPPINCOTT: I would like to make a comment on that also. With my background in orthopedics, I am very familiar with the complications with lysis. That has been one of the ongoing things in the last 10 years that has confronted the orthopedic surgeon and is a very big concern.

So, there is, you know, now in orthopedics a need to examine materials and what particular wear debris does, and they are examining sizes, accumulation of debris, how the material reacts in the tissue, et cetera, et cetera, and so this company has taken the measure to go along the orthopedic route and consider that also, and so has incorporated various testing parameters to look at that.

In this cyclic wear testing we did do using the same identical physiological conditions, we did see a lower amount of wear and particulate generated compared to the acrylic, but understand that also from histology sections that have been retrieved, from those retrievals we have not seen a foreign body reaction to the acrylic, and although acrylic was abandoned in orthopedics 30 years ago from the Judet prosthesis, that was abandoned I think more due to mechanical failure rather than wear, although wear was identified. They did not have the means at that time to characterize the wear and what it was doing to the joint.

But they did not see the lysis back then like

they see today with those acrylic Judet prosthesis.

DR. LI: Although those failed by loosening before osteolysis could catch up with them, but there was wear.

MR. LIPPINCOTT: There was wear, there was most definitely wear.

DR. LI: In the last 35 years, have you ever monitored metal serum levels from urine samples, from metal-on-metal devices, because when you do that from patients, even with metal polyethylene components, there is increased level of metal, for instance, in their urine and even elevated more in metal-on-metal total hips.

MR. LIPPINCOTT: I think I will direct that question to Dr. David Gerard.

DR. GERARD: I don't know of any clinical trial or any clinical testing that has specifically been done on these patients to monitor either acrylic or metal in either blood serum or in urine, although in the animal studies we did monitor normal blood chemistry, as well as blood hematology looking for these particles, as well as looking in organs, the major organs and in the lymph nodes.

DR. LI: Although with the size of the particles you used, they are unlikely to migrate.

DR. GERARD: But I would go back again to say that the size of the particles--the particles were generated from a wear test, and so there may have been smaller particles in there that we did not see.

The other thing I would point out is if you look at the histology especially with PMMA--and Dr. Mercuri showed his slide yesterday of PMMA in tissue--you saw large particles, and you saw no foreign body reaction.

I have looked at over 400 joint tissue samples from temporomandibular joint patients, not all of those obviously with PMMA, but with other disease processes, and giant cell reaction is a very obvious thing to see. It is not something that you have to hunt for, and we do not see that either in the animals or in the retrievals that we looked at.

DR. LI: Thank you. One final question, the same question I asked the folks yesterday. Have you done any measurement of the relative micromotion or stability of your implant against the bone, because I think that these implants are fixed with numerous screws, and often micromotion of an implant against the bone is what leads to pain, and so the question is, have you ever checked the relative stability of your implant in cadaver studies or in any other way?

MR. LIPPINCOTT: No, we have not, and I would assume if we see--of course, it is hard to judge that in these type of patients because of the pain complications that they have, and whether that is one of the factors

from micromotion--now, in many cases, the reason for retrieval is not from loosening of the screws or loosening of the device. It is typically due to pain from heterotopic bone or fibrous adhesions. So, we don't see that.

DR. JANOSKY: A final question from Dr. Skinner.

DR. SKINNER: Just one more question.

Were any of these human studies, were any of that data collected with an OPRR-approved, IRB approval? Especially, the fluoroscopy I am particularly concerned about.

MR. ALBRECHT: The ongoing prospective study right now is being conducted with IRB approval at every center. With regard to the fluoroscopy, I don't understand or could you be more clear with that question?

DR. SKINNER: There is obviously some inherent risk in doing fluoroscopy on normal patients and patients with TMJ problems with implants in, and that sort of thing should be done with an IRB approval, preferably with an OPRR/IRB approval.

DR. CHRISTENSEN: I don't think other than the kinematic study, that we have been involved much, Dr. Skinner, in fluoroscopy of this joint other than maybe Dr. Curry might want to add to that, to examine those patients.

DR. CURRY: I don't have IRB approval, and I don't do fluoroscopy on all of my patients. I will say that following patients with total joint prostheses, particularly when you have metal-on-metal, is sometimes difficult with standard radiographic techniques, and occasionally I will take my patient to my hospital and do a short fluoroscopy and take a still picture because I get a better view of the components, where I can angulate the patient where I feel that I get the best view rather than just sending them over a standard x-ray.

DR. SKINNER: But weren't there studies done with Doug Dennis' group looking at these patients under fluoroscopy, actually cinefluoro? Maybe I misread something.

MR. ALBRECHT: I am sorry, I was speaking to Dr. Gerard. Could you repeat the question, please?

DR. SKINNER: Weren't there studies done with Doug Dennis' group doing cinefluoroscopy on some of these patients?

MR. ALBRECHT: Not that I am aware of, no.

DR. JANOSKY: At this time, we will take a 15-minute break, returning at 10:25.

[Recess.]

DR. JANOSKY: We are continuing with the FDA presentations. There will be presentations by Dr. Susan Runner, Ms. Angela Blackwell, who is a biomedical engineer, and Dr. Murty Ponnappalli, who is a mathematical

statistician.

FDA Presentations

DR. RUNNER: Good morning. I am not going to repeat my comments from yesterday on the history of TMJ Implants, but those should be taken into consideration, as well, today.

[Slide.]

TMJ Implants, Inc., or the Christensen device has submitted a variety of data in support of the Premarket Approval Application for the various configurations of their temporomandibular joint prosthesis.

These include the total joint with a metal-on-metal articulation, a total joint with a PMMA-on-metal articulation, and glenoid-fossa prosthesis, and the patient-specific total joint with either a metal-on-metal or a PMMA-on-metal articulation.

The data, as you have heard, comes from a variety of sources including case studies, retrospective data, significant human experience, partially controlled studies, and a controlled clinical study that is now in progress. Endpoints in their studies included pain, function, intercisal opening.

Review of the data reveals that many of the data points on patients are missing at various time points. There also does not seem to be a sufficient number of data points to analyze data consistently beyond the 18-month point in a consistent fashion. The sponsor has thus analyzed some of the data into different cohorts to reveal patterns of success.

It is difficult, however, in our clinical review of this data to separate out the various endpoints on patients into pain, diet, and intercisal opening and get a clear picture of the relative success or failure of any one implant in the sponsor's armamentarium.

In our opinion, the sponsor has not adequately separated the various implant types, i.e., partial versus total, all-metal versus PMMA versus patient-specific, in terms of the types of results that were achieved in the clinical studies.

The prospective study does have plan for collection of data that could delineate effectiveness of the individual implant types, however, data from this study is incomplete.

The engineering reviews, which you will hear more about in a few minutes, have indicated deficiencies in the way the sponsor has developed data on dynamic fatigue and wear. These deficiencies relate to the absence of information on failure of the device and inappropriate loads during wear testing.

[Slide.]

The MDR reports on this device include reports

of failure including breakage of the condylar element and reports of wear-through and fracture of the fossa element in the metal-on-metal version of the appliance.

[Slide.]

Given the inappropriate nature of the engineering data and the equivocal nature of the clinical data, the data on failures and the concerns about safety related to these failures, I feel that the following items need to be addressed by the company.

TMJ Implants, Inc., has four major configurations of its TMJ prosthesis: the fossa-eminence prosthesis alone or partial; the total joint with PMMA condylar head; the total joint with all-metal configurations; and the patient-specific total joint.

The sponsor has not provided adequate separation of the data regarding safety and efficacy of these different configurations for the intended use as presented. The sponsor should provide data that addresses these implant types separately.

In summary, the sponsor should provide data on sufficient number of patients to demonstrate safety and effectiveness over at least a three-year time period.

Ms. Angela Blackwell will now proceed with the more detailed engineering review.

[Slide.]

MS. BLACKWELL: I am going to present the engineering review of TMJ Implants, Inc., PMA.

There were two engineering reviewers for this PMA, myself and Dr. Gary Fischman from the Office of Science and Technology.

[Slide.]

The sponsor has deficient fatigue and wear testing based on our engineering review. In my presentation I will outline a summary of the data that was presented.

[Slide.]

The dynamic fatigue testing presented tested only two of the four configurations. It was tested at 2 Hz for 5 million cycles, in bovine serum, with a sinusoidal load of 2 to 35 pounds

[Slide.]

There were no failures and no S-N curve was generated.

[Slide.]

Literature references show a maximum bite force in the range of 300 pounds and an average bite force of 35 pounds.

The TMJ surgical patient would have a decreased bite force secondary to loss of muscle attachment.

[Slide.]

But a load of 35 pounds gives no safety factor above the reported average bite force.

The partial prosthesis (the fossa used alone) needs to be tested in fatigue. Due to the fact that it is opposed by a natural condyle, the fatigue data on the partial model cannot be extrapolated from one of the total joint prosthesis.

Justification for not testing the patient-specific model is also needed.

[Slide.]

Wear testing was conducted on the same two models as the fatigue testing, for 2 Hz, 2 million cycles, in bovine serum, with the same load, sinusoidal 2 to 35 pounds.

There was a comment earlier about that the load was sufficient. The problem with the load in this case was not the weight per pounds, it was the fact that it was a sinusoidal load, and for worst case for wear you want a constant load.

[Slide.]

The surface profile analysis showed a change of 0.197 mm³/million cycles for the metal-headed condylar prosthesis and a change of 1.64 mm³/million cycles for the PMMA-headed condylar prosthesis.

[Slide.]

The testing needs to be redone with a higher average load, constant as opposed to sinusoidal.

Justification for not testing the patient-specific model is needed, and wear testing is needed for the partial joint prosthesis (fossa used alone). The same problem as before, because it has a natural condyle opposed to it, it is a different situation.

[Slide.]

Pin-on-disk testing was also presented although this was a little unclear. I had previously looked at a report in a 510(k) that was pin-on-disk testing, but that report didn't appear in the PMA. There appeared to be one that was similar that went for a longer period of time, but when the reports were compared, the data points didn't match up. So, it must two different tests run by the same lab.

But both of the tests used a 50-pound load.

[Slide.]

Both reports showed that the volume and weight they reported would remove a large portion of the PMMA head in 2 million cycles. If the test was run out to 10, it is possible that the metal posts would be exposed.

I know there was a discussion about that earlier, about the metal posts being exposed, and from our point of view, if the head was worn off and the metal post was exposed, that is a failure.

[Slide.]

The fossa and condyle are not matched components

- they usually demonstrate point contact.

[Slide.]

Orthopedic literature suggests that close tolerances and a tight fit are necessary for a good total joint, particularly on metal-on-metal systems.

[Slide.]

The company needs to address this concern and justify why the design has not changed to address this issue.

Thank you.

DR. PONNAPALLI: Murty Ponnappalli.

[Slide.]

I am going to look at the statistical aspects of this submission.

[Slide.]

As you know by now, there are several different sources of data given in this submission. Those are given in this slide.

The primary efficacy parameters in this study are reduction in pain, measured in 10 cm VAS, and interincisal opening, measured in mm.

The secondary efficacy parameter is reduction in diet restriction, measured in 10 cm VAS.

[Slide.]

In my opinion, not all of these throw much light on the effectiveness of the device. My concentration is going to be on the effectiveness because the safety data are not amenable to statistical analysis.

In my opinion, the data from registry given here, are given in this slide, the most important to determine the effectiveness. The first one is Cohort 1 of 284 patients. These 284 patients, there is data on pre-op levels, 6-month level, and 24-month levels of pain.

The study is done on this cohort by means of the so-called repeated measure ANOVA F-test. These are repeated measures because the same patients are observed for all different time points, and that gives significant difference. Because there is a significant difference in the sample averages given in the first row.

They are decreased over 24 months. It is a reasonable conclusion to make that the pain level decreases. Also, another important point here is the comparison between pre-op levels and cross-section mean.

For example, for this cohort it is 7.7 as the pre-op, and the cross-section mean is 7.9. They are fairly close, very close, in fact, and the same thing is true of 6-month and 24-month.

But there is a limitation to this because the cross-section mean 7.9 is not based on all the 4,000 patients, approximately 4,000 patients. It is based on approximately 2,000 patients, only about half of them,

because the remaining ones, we don't have data on the remaining ones.

This could introduce some bias, but because of lack of data if you regard these 284 patients as the whole sample, then, the result is favorable. The conclusion is that the pain level is decreasing.

[Slide.]

Then, we go to Cohort 2-pain. Here, we have many more time points. There are only 60 patients. You can see from the row here. But it is because there are many more time points, and this is a subset of the Cohort 1, this cohort of 60 patient is a subset of Cohort 1.

Again, we again perform repeated measures ANOVA F-test, which gave a highly significant p-value which indicates the pain level is decreasing. Again, you can see from the row of means and the cross-section of the means that these two in every case, at every time point, almost every time point, these two are pretty close to each other.

[Slide.]

So, these were about pain. Now we go to the opening. It turns out that the data are at pre-op, 6 months, and 24 months are available on 265 patients. Again, we use repeated measures and ANOVA F-test. It showed highly significant value and a reasonable conclusion is that the opening is increased this time, because we can see that it is increasing.

Again, compared the pre-op level of the sample with the cross-section mean, a sample mean with the cross-section mean. It is fairly close to each other. Again, that limitation to the cross-section mean applies. It is not the whole set of patients, but approximately only half the patients.

[Slide.]

It still is the same with Cohort 2. The number of time points is much larger. We go up to three years, and the repeated measures and ANOVA F-test shows highly significant difference, and the limitation again is that for the cross-section mean we don't have the data on all the patients.

[Slide.]

Our review team thought that the data should be subdivided into metallic condyle, PMMA condyle, and patient-specific prosthesis. So, we asked the sponsor to analyze these subsets, so this gives the data on metallic condyle.

Note that this is not a cohort. If you look at the numbers you see that they go on decreasing. It is not the same cohort of patients. The patients there at one month, some of them are there at six months, and some of them are not there. The patients at six months, some of them at one month, but some others were not there.

Statistical analysis of data of this type is rather difficult. We cannot use the ANOVA F-test, for example, because there is difference. We cannot use repeated measures in ANOVA F-test because it is not the same cohort.

But if you look at the first row, for example, the pain level is decreasing, but there are statistical limitations to this conclusion, as I just pointed out. The same thing about diet, the same thing is about opening. To test it statistically is difficult.

[Slide.]

Now, I go to patients with PMMA condyle. The situation is the same here. It is not the same cohort as you can see from these numbers here. But in the sample, you can see that the pain level is decreasing up to 12 months. At 12 months it is somewhat stable.

Diet, when I say diet I mean diet restriction, diet restriction is decreasing up to approximately 12 months, and from there it is stable. Opening is increasing up to I would say approximately 12 months, and then it is stable. Again, statistical tests for statistical significance are difficult.

[Slide.]

Now, I go to patients with patient-specific prosthesis. Also, you can see from the numbers again that it is not the same cohort, and also that pain is decreasing in the sample. We don't know whether it is statistically significant or not up to approximately 12 months, and stable after that.

Diet restriction is also decreasing over the time period until up to 36 months, and opening is increasing again up to approximately 12 months, and then it is stable.

[Slide.]

There is also prospective study, but it is incomplete. I wouldn't give too much weight for this, but it cannot be ignored because the number of patients is approximately 90 or 100, so I wouldn't like to ignore it completely. You observe back again in the sample the pain level is decreasing up to approximately 12 months, and it looks like it is stable after that. Diet restriction is decreasing again up to approximately 12 months, and remaining stable after that, and opening, there is a little bit of puzzle. Opening, there is no significant improvement in the opening as you can see from the numbers there. There is no significant opening in the prospective row in the study, but it is incomplete and I don't regard it as important as the cohort study from the registry.

My final comment, judging from the data on Cohort 1 and Cohort 2, pain and diet restriction seem to go down after the implant, and opening increases up to 12

months and then stabilizes. This is true also for metallic condyle patients, PMMA condyle patients, and patient-specific prosthesis.

From the interim analysis in the prospective study, pain and diet restriction decreased up to 12 months, but opening remains the same.

Thank you.

DR. JANOSKY: Are there any panel questions for Dr. Runner, Dr. Ponnappalli, or Ms. Blackwell? Dr. Li.

DR. LI: I would like to ask Ms. Blackwell, did you also look at the retrieval wear patterns compared to the wear test wear patterns? There were some photos in my review packet, but they were like xerox copies of photos.

MS. BLACKWELL: I also had the xeroxes, and so I wasn't really able to tell enough to analyze it. So, that would be interesting, but I couldn't tell, and there are different patterns apparently for the different condyle types. So, that would make things even more complex.

DR. JANOSKY: Dr. Patters.

DR. PATTERS: Mark Patters for Ms. Blackwell.

Do you believe that there is a fundamental engineering difference between the patient-specific implants and the presized implant that would require separate testing?

MS. BLACKWELL: Yes, there is a difference. Most of the patient-specific ones are wider at the bottom, so the loading will be different, but that doesn't necessarily mean that patient-specific would be worse. It could be better because it is bigger. But they need to perform some type of justification to engineeringwise to show that the worst case would not include the patient-specific.

DR. PATTERS: Thank you.

DR. JANOSKY: I have a question for Dr. Ponnappalli. If I take a look at the two overheads that you had presented, the first one being Cohort 1-pain, the second one being Cohort 2-pain, is the Cohort 2-pain, if I look at the means for the Cohort 2-pain compared to the cross-sectional mean, it seems to me that the means for n equals 60 are uniformly lower for pain, most likely not statistically lower, but I see a lesser number.

If I take a look at your Cohort 2 for opening, and again if I take a look at the mean for Cohort 2 and your n of 55, and I look at the cross-sectional mean, if I do that comparison again, I see that the opening for the Cohort 2 is again across the board larger or higher number than for the cross-sectional mean.

Given those two pieces of information, do you have any other information or could you address the issue that the patients that continue, so the patients in these

two cohorts that have up to 3 years of data are different than patients that do not continue.

That is an issue that we were dealing with previously and it is one that sort of is within this same data set in multiple studies, that I wanted to get some clarification about.

DR. PONNAPALLI: As I said yesterday, there are problems in comparing the means of a subset and the whole population, as you know, but from the sample data you made an important observation, that for pain, in the subset of 60 patients, the mean is almost consistently lower from the whole population, and for the opening it is consistently higher. I have no explanation for this, and I cannot perform a statistical test.

DR. JANOSKY: I am just asking based on that, it appears to me--what it's played out or not we haven't analyzed it, and I am assuming that the sponsor has not analyzed it--is that the patients that continue are starting with less pain, starting with a wider opening, and then they are being consistent across time compared to the cross-sectional patients.

MS. BLACKWELL: Dr. Janosky, it was also of interest to us to know how many of the patients in the two cohorts for pain and opening were which type of implant, because that could also give us the reason for why the pain was lower on average. You know, if out of 60, 40 of them were one type, that distribution could be important.

DR. JANOSKY: You don't present that information.

MS. BLACKWELL: We don't have that information, no.

DR. JANOSKY: Oh, you don't have that information.

MS. BLACKWELL: That was one of the items we were missing.

DR. JANOSKY: I am very interested in this group because that seems to me that the ones that have the most complete data, and perhaps that would give us some information about at least two to three years effectiveness.

DR. JANOSKY: Dr. Burton.

DR. BURTON: Dr. Ponnappalli, do you have a feeling when you look at the data on the prospective study, when you get out to 18 months, there is only 9, that has an n of 9 for pain and diet, is that because of the fact that it is prospective, only been going on for a period of time, so there is only nine.

How many does that 9 represent out of the total enrolled that could reach 18 months, because they have a very, very high dropout rate in their other groupings prior to that, and they continue out to about usually

less than 30 or 40 percent at about 18 months, and by the time you hit 36, they are all down around anywhere from 4 to 8 percent, but do we have a feeling for, in the prospective study now, what percentage they are retaining as they start to reach some of these milestones?

MS. BLACKWELL: I don't think we have that information.

DR. BURTON: I am just trying to get a feeling, if the prospective study is going to be able to get that.

DR. PONNAPALLI: No, we don't.

MS. BLACKWELL: The prospective study is not under IDE or was not reviewed by us prior to submission in the PMA, so we are not really sure how many patients are going to be in there. I think it was 180 or so, but that wasn't real clear. It also didn't stratify between, as far as out the number of 180, how many of which devices.

DR. RUNNER: Possibly the sponsor could answer that question.

DR. BURTON: Could you give us any idea of how many patients you have, what your dropout rate is in the prospective study now as you start to reach 12 and 18 months where, again out of your n of 95, you have 28 and 9, is that because there are only a small number of patients who have reached those milestones, and you have basically a large number still remaining that are being followed or have you already had high losses?

MR. ALBRECHT: To answer the first question, the number of patients we expect is 138 patients total with 62 being partial strata and 76 being of the total strata. The data presented in the PMA is presented up on the slide. The FDA did indicate that we were allowed to update those patients that we presented in the PMA with a little bit longer term data for our presentation today, and that is the data that I presented.

Percentage dropout, I think is small at this point. We did allow for that in our sample size calculation. I cannot tell you specifically the percentage of dropout at this point, but those numbers out at 12 and 18 months are somewhat higher than what is originally reported in the PMA submitted in January.

DR. BURTON: Thank you.

MS. BLACKWELL: I have a question for you. If you have 70-something patients and you are splitting that between three different models of total, how are you going to get a statistically significant number for each?

MR. ALBRECHT: We will have to analyze the data when we finish the study and see, and it is possible if we don't have statistical significance at that point, we may have to expand the study.

DR. JANOSKY: Additional questions for FDA?

Dr. Bertrand.

DR. BERTRAND: Can I address a question to the sponsor?

In the prospective study, the initial openings are rather good, at 31.5 mm, and they don't seem to increase, and according to some information, maybe 70 percent of those patients only had a fossa implant.

In this particular group of patients, how is it determined that the joints themselves are actually the pain sources before the surgery was started, initiated? What diagnostic criteria for the fact that it was actually the joint was the pain source?

MR. ALBRECHT: We did have specific inclusion/exclusion criteria to be included in the study. Patients were enrolled if they had a pain greater than or equal to 4 and/or opening less than or equal to 15 preoperatively at their baseline.

They also needed to have one of a variety of different other joint problems that the physician had to look at, and if the patient had that problem, they were included in the study.

As far as how the physician diagnosed that, I cannot answer that question. I am not a physician.

DR. BERTRAND: So, we don't know if we have, say, an auriculotemporal nerve block done to anesthetize most of the joint to see if nose resection towards the brain had an impact on the patient's level of discomfort. That is not part of the diagnostic criteria then?

MR. ALBRECHT: That was not part of the inclusion criteria for the study.

DR. BERTRAND: But many of these patients, if they had a fossa implant only, were a substantial number of these patients first-time surgeries, is that my understanding, a third of them?

MR. ALBRECHT: Approximately a third of them probably are first-time surgeries, yes.

DR. JANOSKY: Dr. Gonzales.

DR. GONZALES: Just a follow-up on what Dr. Bertrand said. The patients who preoperatively are being evaluated, and specifically those patients with a great deal of pain, somatic pain, pain in the joint, we would anticipate that a pathological joint, which is reviewed for somatic pain, pain from the structure itself, would improve with removal of the joint, but there is a subset of patients who have neuropathic pain, pain from the nerve itself, where, in fact, doing procedures on those individuals is contraindicated because you can actually make them worse, you turn a neuropathic pain condition into a condition called anesthesia dolorosa or a number of worsening neuropathic pain states.

I think it is important to get some information about the kind of pain these patients have, and I really haven't heard a lot about the characterization of the

pain other than a pain scale is filled out, and that pain could be their average pain for the prior month or at the time.

It is very difficult, and I know it is very, very difficult to do adequate pain studies because you have an enormous number of factors with these patients. You have the psychological factors that you have pre-morbid or post the implant that can occur with the patient who has sustained pain.

You have all of these issues about the changing of the pain and how it alters and it modifies, and its incident, but I think you could narrow it down to some very, very simple straightforward questions or details about the quality of pain to at least find out if there is a neuropathic, and it is fairly simple, straightforward to ask about is there a burning quality, not just is the pain right here or that it hurts when it moves, but is there a burning quality, is there dysesthesias, does it move, is the pain, is it hyperalgesic, is it displaced pain, is there a shooting, stabbing, lancinating pain.

There are questions that can be asked that will characterize that, because I think my concern is that for whatever the number may be of patients who have neuropathic pain, those patients should not have any kind of procedure, and that goes for everything in terms of you are talking about procedures for nerve root compression in the lumbar spine or cervical compression or peripheral nerve compressions elsewhere, in other parts of the body.

So, I think that one concern I have is that there isn't enough information about just the quality of pain. Again, that could be characterized I think very easily with some statements at the time that the questionnaire, if that is what you have and what you have going on here, is some questions about the quality of pain.

Again, that could be characterized I think very easily with some statements at the time that the questionnaire, if that is what you have and what you have going on here, is some questions about the quality of pain in addition to is the fact that it hurts there in the joint.

So, I don't know that that was, in fact, not having seen all the details of the questionnaire, but were questions like that ever posed, and what are the concerns by the company of neuropathic pain and replacing joints and operating on those individuals?

MR. ALBRECHT: You make a very valid point. Pain is a difficult symptom to address and to understand with patients. We are trying to characterize at least the patient with the study. We are obtaining medical

history, previous medical history before they are even enrolled in the study. I am talking about the prospective study now.

We will hope to have some idea of what type of problem the patients had, their previous medical history, how many surgeries, how many insults to their joint they have had prior to entering the study, and therefore, hopefully, have some sense of an understanding of what kind of pain they are having.

I cannot answer or address your concerns with regard to neuropathic pain, and so forth, and how the physician and the patient interact when they discuss that. All I can say is that when we instituted the study, the patients are given the VAS scales to fill out, and they should be instructed by the physician to give me your average pain over the past month or if you are really feeling bad now, please mark it on this scale.

If you would like further information, maybe Dr. Curry could add some light onto how he deals with his patients, and so forth.

DR. CURRY: I am a participant in the prospective study, and I can only speak for my own practice. We have the same exact concerns that you do, but even beyond that, if you do an auriculotemporal nerve block, that alone won't really isolate the pain. If we lucky enough to be able to inject the joint directly and miss the auriculotemporal nerve, the anesthetic is nonselective in terms of whether it anesthetizes the fossa component of the joint, the mandibular condylar component of the joint or the soft tissues that are in between those two structures.

So, we have, as clinicians, a very, very difficult time sometimes characterizing the pain that you have described, and we make every effort to try and isolate the source of the patient's main complaint as relates to pain, and sometimes that is exceedingly difficult.

DR. JANOSKY: Additional questions for FDA? Dr. Patters.

DR. PATTERS: Could I address the sponsors? Thank you.

From what I understand, there seems to be a fundamental disagreement between FDA staff and the sponsors as to how both the engineering data and the clinical data need to be presented. FDA staff makes a strong argument that you need to break the engineering data down and test the individual configurations, and you need to treat the clinical data based on the configuration.

You apparently disagree. I think I understand FDA's rationale. I would like to hear what your rationale is for not breaking them down into individual

configurations.

MR. MORGAN: Jim Morgan. I can address some of that, and then I may ask some assistance from my colleagues.

It seems that some of FDA's concern is the breakout of the information and the presentation of it from a clinical standpoint, as you say. I believe in our presentation, we saw that we did break out fossa-only, and then total joints with PMMA heads and total joints with metal heads, and then I believe we also broke out patient-specific, and those are the four.

If necessary, we would be glad to set up again and show those slides. In fact, I believe that even Dr. Ponnappalli in his analysis pointed out metal-on-metal, PMMA, and patient-specific, so we think we did satisfy what the FDA was interested in.

In terms of the nonclinical testing, we admit that we did not do, for example, fatigue testing at very high levels. What we chose to do was physiologic testing, which I believe that Mr. Lippincott addressed, and we can go into detail again, and would be glad to do that.

I think we disagree on relative to nonclinical testing is the definition of a failure on a PMMA head. Our design is such that within the PMMA head, we have a post, the tip of which is highly polished, as polished as that on the metal-on-metal head, so that should the PMMA wear down to the post, the post, along with the residual PMMA, which by that time has conformed at least partially to the form of the fossa, can articulate and help bear the load.

So, we do not consider wear of the PMMA head to the metal as a failure. The device will continue to function and to articulate.

If there are specific questions, I would be glad to try and answer them or defer to my colleagues.

DR. JANOSKY: Additional questions for FDA? Dr. Skinner.

DR. SKINNER: No.

DR. JANOSKY: Additional questions for FDA? Dr. Floyd.

DR. FLOYD: I have got a couple of questions. Maybe I misunderstood, but I almost thought I heard in Ms. Blackwell's presentation, she raised a question about the design of the joint, and suggested that it should be more like other orthopedic joints.

TM joint is a very unusual joint. It must not be locked in a lateral direction. It has to rotate. Otherwise, the function that we are trying to restore in the patient couldn't exist.

The other thing that surprised me a little bit was the question about wear on a fossa implant only,

because if I understand what is being done clinically here, not on new surgery obviously, but if I understand what is being done clinically here, we are talking a fossa implant being done if there is a healthy intact condylar head.

Now, if there is an intact healthy condylar head, it has got to be covered with cartilage, and if it is covered with cartilage, firstoff, it is a soft, compressible material that, under compression, exudes long-straying lubricating materials, and I really have difficulty understanding why there is ever a question about that kind of surface wearing through a metal implant.

DR. JANOSKY: Ms. Blackwell, would you like to respond?

MS. BLACKWELL: The question with the fossa was not for the fossa, it was for the condyle. We have reports of the top of the condyle being destroyed by the fossa-eminence. Those are telephone reports only. So, we were requesting information, you know, validation whether that is true or not, but that issue wasn't addressed at all in the PMA.

The question about design, the comment was about the fact that they haven't used any modern technology at all. The technology they are using is sixties technology, and we have some questions. For instance, he was talking about wearing the top of the PMMA head, so that it mates better with the fossa, well, if that is the purpose, why don't they just make them mate to begin with instead of having it wear off and the particles ending up in the patient. That was the question we were looking for an answer.

The company says that it wears off and it mates better with the fossa. Why don't they make it that way to start with? They haven't addressed that.

MR. MORGAN: I believe that there are two or three issues that Ms. Blackwell brought up. One deals with sixties technology versus more recent technology in terms of design. I think our response is that we have a design that works, works in nonclinical testing, it works in clinical testing, it works in the field in the patient.

Also, in terms of the PMMA heading wearing and conforming more to the fossa, there is a need, we think, for sufficient room for the condyle to rotate and translate in relationship with the fossa, and a close conforming fit similar to, say, that of a hip implant, might not afford that kind of liberty needed for that kind of rotation and translation.

Ms. Blackwell, I believe there is one other point that you had made? I thought you had made three points. You had mentioned getting telephone reports of

condylar head being destroyed. We have not had any reports of that. We are not aware of any. We simply can't respond to it if we don't know about it.

DR. CHRISTENSEN: May I add something to that? Is that all right?

DR. JANOSKY: Yes.

DR. CHRISTENSEN: I have seen the normal condyle 38 years later against fossa-eminence implants on several patients, still functioning the way I put them in that many years ago.

DR. FISCHMAN: Dr. Gary Fischman, Food and Drug Administration.

Dr. Floyd, part of that issue with respect to the orthopedics industry had specifically to do with the materials and what the materials were being used for, and that, to some extent, addresses the PMMA in this particular aspect, in this particular function.

The question is, is it really working, and without having any basis in any parallel uses or any other predicate uses, it is hard for us to assess that given the situation at hand.

DR. JANOSKY: Additional questions for FDA? Dr. Li.

DR. LI: Two questions for the sponsor. I am concerned a little bit about the histology reports especially from tissues, the periprosthetic tissue.

If your wear rate is on the order of--was it 1.6 mm³ for the PMMA? I back of the envelope calculated if the average particle size was 1 micron, that is 100 billion particles, which is low relative to polyethylene, but it is still billions of particles, and the fact that you don't see any under histological sections, for one who does histological sections, it seems like it might be more a reflection on your histological technique rather than the actual absence of particles.

The same thing would hold true for the metal particles. Even though the wear would be half or a quarter, we are still talking billions of particles, and the fact that you see none kind of puts the whole histology in question.

Could you comment on that?

DR. GERARD: David Gerard. As far as the PMMA, I am sure you are aware as during decalcification and processing, the PMMA is leached out, and so what you actually see are ghosts or where they had been, where those particles had been.

Again, we did not see any giant cell reaction to those particles, but we did see particles associated with mild inflammation at early time points, one through three months.

As to the fate of those particles later on, I cannot tell you what happened to those particles although

there is some evidence that particles such as that could be dissolved and processed through the system.

I guess that is what I would say about the PMMA.

As far as the chrome-cobalt, we saw a little bit more of a reaction early on, a stronger inflammatory reaction. We did see particles in the joint space at one month and two months, and by six months we did not see particles any longer, and I cannot tell you the fate of those particles. I don't know what happened to those particles.

DR. LI: So, do you believe it is not wearing or you just believe that you actually just didn't see them in the sections that you are talking?

DR. GERARD: We did serial sections.

DR. LI: Right. So, my question is do you believe actually wear is not happening?

DR. GERARD: No, no, no. Now, this is animal studies where we have injected particles.

DR. LI: Okay. How about from patients, from periprosthetic tissue from patients?

DR. GERARD: Most of the patients that I have looked at that have had PMMA heads in total joints have had prior surgeries, as a matter of fact, all of them, so the material I see is not, as far as I can tell, chrome-cobalt, because I have done elemental analysis on these particles in some cases, and because PMMA is leached out, I cannot tell you definitively whether or not PMMA was there.

DR. LI: Again, taken from total hip and knee replacements, even around metal-on-metal total hips, particles can be relatively easily identified.

DR. GERARD: Yes.

DR. LI: So, if you used the appropriate histology, so I guess--the whole thing on the particles from tissue, that you find none I find rather disturbing.

DR. SKINNER: Could I comment?

DR. JANOSKY: Yes.

DR. SKINNER: I hate to take the company's side on this, Steve, but I think we are talking about a small joint with relatively low wear rate production, and based on that, I think that the orthopedic literature supports a threshold, that if you don't get to a certain rate of production, you often don't get much of a tissue reaction because it is carried off in the--

DR. LI: I am not looking for a tissue reaction, Dr. Skinner, I am looking for just the presence of the particles. So, the wear rates they report for metal-on-metal for their joint is in the range of the metal-on-metal total hips where we do find the particles.

I am not looking for a tissue reaction, I am just looking for the particles.

DR. GERARD: Can I respond to that? The only

joints that we have looked at that have been retrieved histologically have had PMMA heads, and I would expect that metal particles would be virtually nonexistent because of the softness of the PMMA head articulating against the metal. I don't think we are going to be generating many, if any, metal particles. We may be generating some.

Now, we do see PMMA. We do not see it associated with a giant cell reaction, just with a mild inflammation.

DR. LI: My final question. On metal-on-metal total hips with also a similar long history, we have learned that there are design factor issues that make a good or worse metal-on-metal total hip articulation, that have to do not only with the area of contact, but the location of that contact.

Back of the envelope from what you provided, your device seems to go contrary to all of that experience, so I guess my question is, why are the design considerations that are so critical for a total hip application, appear to be absent completely, for instance, in your--well, let me ask you actually if you can limit that even to just your nonclinical lab data, why your results are so different, because like on a metal-on-metal total hip replacement wear simulation, even though the wear is low, the chamber is often blackish from the release of the few particles that you get, and you don't seem to be getting any of that.

MR. LIPPINCOTT: First of all are movement more along the lines of knee movement rather than a congruent movement as a hip. From the standpoint that there is translation in rotation, as well as arc movement, and so it is a complicated movement similar to a knee, and so if you do confine the design so that it is congruent, like a hip, you may introduce other factors, such as joint stresses that are transmitted to the prosthesis that could cause further loosening.

So, for that reason, TMJ Implants has followed the line of going with less contact to allow for that movement, if the movement is there.

Regarding the particulate debris, I am familiar with some of the literature in the orthopedics regarding a threshold level that Dr. Skinner mentioned, and the wear volumes were seen from the testing were down to 0.2 mm³/ million cycles.

I see that as even lower than some of the metal-on-metal testing that has been done in the laboratory, which is up to 0.5 to 1 to 4 mm³/million cycles. So, we may, in fact, not see that debris because of the threshold level that the body is able to take care of and excrete it some way.

DR. JANOSKY: Dr. Heffez.

DR. HEFFEZ: I have two short follow-up questions. I will reverse the order because you just mentioned that this joint closely parallels the knee, and you indicated translation of movement, but earlier in your presentation, your company's presentation, you indicated that there was only rotational movement or minimal translational movement.

Could you clarify that and could you also indicate if any jaw tracking methods were used in order to classify how far lateral movements were?

MR. LIPPINCOTT: Much of the movement that we describe is from a fluoroscopic study that we did, again on a normal versus fossa-only versus a total. What they did see in that motion study was definitely less movement and more just arc movement on the total versus even the partial versus even the normal, and granted that you don't have as much motion with the total as you would with the normal, but I feel there is still some motion there because in our retrieval studies that we did, in analyzing the surfaces through SEM high magnification, we saw multidirectional scratches. We did not see uniaxial scratches. So, that would indicate to us that there is more movement in there regarding translation rather than just arc motion.

DR. HEFFEZ: Will you get multidirectional scratches if you had arcing on an irregular surface?

MR. LIPPINCOTT: I don't think you would because in the study that we did with the metal-on-metal, and I didn't show you that, but we had uniaxial striated marks, and there we, of course, looked a worst case scenario with point contact rather than multiple contact.

DR. HEFFEZ: But the surface you were working against was smooth as opposed to irregular.

MR. LIPPINCOTT: It was smooth from the standpoint that it was polished, but there were irregular curvatures against it. It wasn't totally congruent.

DR. HEFFEZ: My second follow-up question is the histological studies didn't indicate any foreign body reaction, but on your MDR report you indicated eight cases of foreign body reactions. Could you clarify that?

MR. ALBRECHT: To respond to your question, Dr. Heffez, yes, we reported eight foreign body reactions, MDR reports. Six were unconfirmed, two of them came through us through Freedom of Information or the device tracking network, DEN, two reported to us by physicians did not provide us any additional information surrounding the issues at hand. We were not able to get pathology or anything from them despite repeated requests.

We have two that are still under investigation now. We are waiting for pathology results at this time.

One of those eight was found to be a residual reaction to Proplast Teflon and not from our implant, and one was

found to be residual reaction to previous Silastic, and not to our implant.

DR. JANOSKY: Dr. Skinner.

DR. SKINNER: Just to follow up on that cineradiographic study I mentioned earlier, you did the fluoroscopy. Was that done with an IRB approval, which you said wasn't done before?

MR. ALBRECHT: I would like to clarify my statement from before the break. I did not recognize Dr. Dennis' name when you mentioned that. Yes, that study, Rose Medical did do for us. To my knowledge, IRB approval was not obtained, but I could confirm that, whether it was or was not.

DR. JANOSKY: At this time, we are going to move into the open committee discussion with presentation by panel members.

The first panel to present will be Dr. Diane Rekow followed by Dr. Leslie Heffez.

Open Committee Discussion

DR. REKOW: I am sure that everything that I have to say is not going to be a surprise because I think all of the points have been discussed, but if you will bear with me, I will review a few of them.

The wear tests, of course, are an issue, and the wear tests do show wear zones, but little mention is made of the particle sizes in the information as we received it. You did discuss that this morning, and the debris apparently had some characterization, though it may or may not have been complete.

I understand that with today's knowledge base, things might have been done differently because some of these tests were done some time ago, and we have learned a lot, fortunately, since then, but we have also learned the importance of some of those things, and the size and extent of the debris and the physiologic effects that it can have, so there is some interest in better understanding of what is going on and the relationship between the particles, their volume and their size that is implanted in the animals and the responses that you get from those.

A lot of that has been said, and I will just let that sort out.

In the fatigue testing, too, it might be wise to try to collect some of the debris as part of that test, you sort of get that for free, and as you are doing the fatigue, you might as well collect those particles and look at those, as well.

There is lots and lots of choices and combinations of sizes and devices that have been implanted, and there has been some discussion about that.

In the engineering data that you present, you talk about worst cases, and certainly that is a reasonable approach,

and every engineer is going to approach it as a worst case, but I think that some verification of some sort that you do indeed get the same results on smaller numbers of samples perhaps with different combinations would relieve some of the concerns that other people have.

On the fatigue problems, I think that one of the issues that perplexes me is the fatigue degradation. You are putting these in patients that are likely to have them for a very, very long time or hopefully, will have them for a very, very long time, and you have a casting, and you have a metal, and it is hard to see any internal flaws could potentially be sites of subsequent fracture.

So, at some point along your fatigue testing, I would be more comfortable, and I think other panel members would be, if we saw what the post-fatigue strengths were of some of these pieces.

I want to talk a little bit about your finite element model. It is certainly not critical in your decisions, but there is some points that I would like to make. On one of your pages, on page 960, one of the people that was involved in the development makes a mention that the stiffness of the bone base structure and the mandible is not known, and that information is appearing in the literature, and it might be wise, depending upon what you want to do with your model, to integrate that information as the bone implant interface, because that certainly will strengthen your predictive models if it is done right, of course.

There is also some concern in some of the mechanical testing, your measurements basically that were done, there was a lot of variation in the stem thickness, screw hole diameters, countersink diameters, and depth, and the shape of the holes.

Those could potentially, those two metric changes could potentially change your finite element results, and perhaps you might want to look at the sensitivity of your model to those changes. It may be important, it may not be important. It also may make a difference in some of your predictive value on your patient-specific stuff where the thicknesses of various components may change, and the geometry may change.

The impact of those is really going to impact what it is you want to do with the model and how much you want to use your model to predict other things, and if you want to use that, because if it is a cheaper way to do testing, you need to be very clear about what some of those sensitivities are, so you can address those issues.

You also might want to address some of the questions that Dr. Li brought up about the creep of the PMMA and what you really are using as your failure criterion in the model. That may have been there, I

don't remember seeing it.

One thing I forgot to say when I was talking about the fatigue strength, the post-fatigue strength. That would be less of a concern to me if one of the three samples that you were using for getting your materials properties to the finite element model hadn't failed before the tests were done in the load to fracture tests, apparently had failed at some relatively low value, and so that raised a flag that I needed to think about the inclusion problem.

That came up on page 990 where you are talking about where you were getting the properties for your finite element model. In those tests, there were three rods that were tested, and one of them failed prematurely.

I think anything else has been said in greater length than needs to be repeated.

DR. HEFFEZ: I was asked to review this PMA. I won't belabor all the points. I will try to highlight maybe some points that weren't discussed yet and rapidly go over the points that have been discussed.

I was asked to evaluate several designs and several devices. There is TMJ fossa-eminence separate from the TMJ condylar prosthesis. The TMJ condylar prosthesis is always used in conjunction with an eminence prosthesis.

DR. REKOW: While you are waiting, can I add one thing, because I had it in my notes and glossed over it, which I should not have, because the bone response to the fossa, I think is a test that does need to be done, at least some laboratory testing to show what wear you are going to get with the bone opposing the fossa. I am sorry.

DR. HEFFEZ: These preamendment devices were used now for some time, since 1960, in human use since 1961, and the condyle was used since 1965. I think the strongest suit for these devices is longevity as opposed to the accuracy of their effectiveness data.

[Slide.]

One of the difficulties that exists, as has already been discussed, is understanding the data, not only from the different types of devices that have been tested, and you can see these listed without actually specifically describing them, but also the indications for use of each of the devices. That is, I believe, a primary problem or weakness is that in many cases, these devices were used, especially the fossa-eminence device, in a primary surgical procedure, not as a salvage procedure.

[Slide.]

As indicated, the indications for sole use are not clear for the fossa-eminence device, the condyle

head. There is several devices, but the condyle can appear as a chrome-cobalt or PMMA.

One of the concerns that I didn't feel comfortable with was the PMMA definitely demonstrated greater wear, and it wasn't really clear why the company persisted with the marketing of it, especially since it indicated in its own PMA that many surgeons are gravitating towards the chromium rather than the PMMA.

[Slide.]

The tumor registry was performed as serial data was not provided per patient. I won't belabor the statistical analysis, we ended up discussing that.

[Slide.]

The company states the loosened implant percentage was less than 1 percent, however, it didn't really explore all the MDRs. The data presented as MDRs is a little confusing. It is indicated, for example, eight foreign body reactions, and yet there is a lot of clarifications made on the basis of the company.

We can accept certain anecdotal data from the company, then, we have to accept certain anecdotal data from other sources. The TMJ Association indicates that they have received greater MDR reports than the company actually describes.

[Slide.]

Foreign body reaction, allergic reaction. Nickel content is always a concern. This is not routinely tested on patients, however, with such a surgery it seems like it should be even though the percentage is low routinely done.

[Slide.]

Trace ions. Clearly, there is wear pattern, and we are not identifying where the wear pattern is. We know that there is wear pattern, but we haven't identified the wear particles, and so one concern is where do these particles go.

Clearly, it has been indicated in some literature that there is deposition of some particles and excretion of particles. They have found it in the reticuloendothelial system. Clearly, there are trace levels and what a threshold level that is required for the human body to tolerate is not known.

[Slide.]

Just to highlight one important item here is that material PMMA or some of the components are irradiated through gamma irradiation, and whether the components were from an engineering point of view tested following irradiation, I understand that was done, but it was not clear whether those components were aged before mechanically testing them, in other words, what the effect is with age.

[Slide.]

Not to belabor all the tests that were done, but what is important here is that certain tests were applied to the joints, however, it wasn't clear whether these were cumulative effect of all the testing was done, in other words, you subjected certain joints to dynamic fatigue, were those joints subjected to other mechanical testing. I think that is valid.

[Slide.]

As far as the wear is concerned, the most important item is in the last item that is mentioned, is even with CAD-CAM or patient-specific prostheses, you are always concerned that you don't have a perfect mate. We have to remember that you get a closer mate using patient-specific prostheses, however, we are generating a computer model based on CT scanning.

The surgeon may not exactly place that condyle exactly on the ramus in order to interface properly with the glenoid fossa. It is certainly much improved from using generic sizes, however, even with computer-generated models, there is no device that is actually holding the glenoid fossa and the ramus portion together and transporting that mechanism together, so it is secured in the proper relationship. So, we don't know what the effect of malalignment is.

[Slide.]

We talked about wear particle induced osteolysis. I don't think it was properly or fully studied by the company.

[Slide.]

Probably the middle item, the worst case scenario. I think what is important is to identify what is the range of motion that is expected postoperatively in these patients, and then test those joints with expanded forces in that particular range of motion.

Sometimes we are trying to be really good and trying to identify what the worst case scenario is, but maybe when we don't try to mimic what we actually get postoperatively, we may not be testing the materials appropriately.

[Slide.]

Again, the greatest advantage I believe of the materials, some of the devices, is longevity rather than the statistical analysis.

The last item, potential carcinogenicity, it is not clear. Definitely, the company has provided articles regarding this, and it is certainly not at all clear in the literature whether there is any carcinogenic potential, but I bring it up.

[Slide.]

We already discussed this as far as bolusing interarticular particles and the sizes of the particles that are utilized. Again, we are using a small joint,

how important is it, and I think it becomes very important to try to again. It's patient selection. If the patients were selected, not as a primary surgical procedure, but as a salvage procedure in a mutilated joint, then, you are willing to take certain risks regarding osteolysis as opposed to later rather than primary disease.

[Slide.]

The big questions are registry details. We know that there is a great fallout ratio, we mentioned that. Very important I believe is the diagnosis, why the particular patient was operated in the first place, and that is when you can interpret the data to lump in people who have had primary surgical procedures and had some devices placed with those who have had more severe disease, I believe is inappropriate. It is very hard to interpret the data.

[Slide.]

As far as bite force calculation, I think it is very important to try to evaluate these patients as far as the pressures generated per patient, preoperatively and postoperatively. We have to look at some of these patients. Their vertical dimension is being changed dramatically. I believe Dr. Curry showed a slide where the patient had an open bite and retrognathia, and that was corrected using this prosthesis.

That is going to generate a lot more forces than another individual in which the joint is simply advanced, for example, as opposed to correct significantly the vertical dimension.

So, I think some pressure transducers are important in evaluating these patients. Taking data that is existing in the literature I don't think is appropriate especially in this subset of patients where there may be parafunctional habits.

[Slide.]

Again, identifying parafunctional habits is extremely important because that may be a source of pain in these patients, and it may be erroneously attributed to the joint prosthesis.

[Slide.]

I would like to indicate again that it is a heterogeneous population we are studying. There is a constellation of symptoms. We have to identify the symptoms, why we are operating the patients, and that is how the data should be presented. It shouldn't be presented by lumping it by devices or categorizing these people by categories, such as failed prosthesis or previous prosthesis.

[Slide.]

As far as effectiveness, again, I felt after reviewing the PMA that really the effectiveness of

surgery should be based on identification of the patient's specific complaints, not on a hardware. The hardware is in fixing the patient. What fixes the patient is addressing the problem, and you can address that problem in different manners. You can't attribute success necessarily to the hardware.

Unfortunately, you attribute failure, you have to consider failure due to the hardware, but you don't necessarily have to say success is due to the hardware.

[Slide.]

Presence of pain depends whether it is from loss of vertical dimension, whether persistence of inflammatory disease, whether we have removed an infectious process, whether the bite has become stabilized. These are all factors that have to be considered why the patient is demonstrating improvement or stabilizing the disease process.

[Slide.]

As far as safety is concerned, the clinician is most concerned about having an option for reconstruction other than autogenous bone. The safety as far as after reviewing the PMA and further discussions today, the safety of the polymethacrylate is not clear, and I wonder whether we have an acceptable failure rate from it especially indicating the tremendous amount of wear to the pin.

The indications for the fossa-eminence relationship are not at all clear, and I feel that we should be looking at these devices, not as a primary modality, but rather as indicated, a salvage modality.

I think the clinician has to view any hardware placed in the body of a patient, that it may have to be removed at some other time, and informed consent should be discussed.

I am not sure that the brochures currently on this implant clearly explain the problems that can occur with these devices.

[Slide.]

The last item, if we are going to have to remove that appliance or that device, we should be able to be comfortable that it is only causing localized damage rather than systemic damage, and it is not going to remove the possibility of reconstructing that patient or increased difficulty in reconstructing that patient.

Lastly, there is really no effective study control. It is not possible to have an effective study control because the patients' symptoms are varied, and the etiology for each of those symptoms is varied. The fact that the person has pain, it is nice to lump everybody up that those patients have pain, but there are various reasons why each one of those has pain.

The last item was regarding one comment that was

made that the company has seen a decrease in multiple operated patients by inserting eminence-fossa prostheses or devices. One has to wonder how would the disease have favored if no intervention was contemplated.

That was my review.

DR. JANOSKY: Are there panel questions for Dr. Hefez or Dr. Rekow?

At this time we will break for lunch. I have five to 12:00. We are going to shorten the lunch to one hour. Let's say one hour and five minutes just for the sake of remembering when to return. So, return at 1:00 p.m., please.

[Whereupon, at 11:55 a.m., the proceedings were recessed, to be resumed at 1:00 p.m.]

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A F T E R N O O N S E S S I O N

[1:00 p.m.]

Open Public Hearing

DR. JANOSKY: At this time, we are going to continue and we are going to have an open public hearing. Is there anyone that would like to address the panel?

First is with Ms. Lisa Brown from TMJ Association, followed by Mr. Kevin Clark from TMJ Association. You each five minutes for a presentation, please.

Dr. Zuckerman, you also had your hand up requesting to speak? Followed by Diana Zuckerman from National Women's Health Network.

If you would please state any financial interest in the company and/or other companies.

MS. BROWN: I am Lisa Brown, and I have no financial or involvement with any of the companies here today.

We would like to show you a few slides of patients who have received devices, maybe to just kind of reinforce a little about what we say when we are talking about patient failures to you.

[Slide.]

This is Christine from California. This is at her initial treatment.

[Slide.]

This is what Christine looked like one year before her death in '94.

[Slide.]

This is Amy. This is Amy in '95. Amy had a promising career as a model and after her TMJ implants and severe problems afterwards.

[Slide.]

This is Amy in '95. I wish that I could say at this point is that we keep in touch with Amy, that she had improved greatly, but that is not the case.

[Slide.]

This is Marilyn. She has also received devices. I think you can see some of the problems that we are having here with the device out of the skin.

[Slide.]

I believe this is Sharon.

That's all.

DR. JANOSKY: Mr. Kevin Clark from TMJ Association.

MR. CLARK: Good afternoon. I am Kevin Clark

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with the TMJ Association, and also I guess presenting personally from my own story. I have no financial interest in either company today or yesterday or any of the competitors.

We heard a lot of the successes from today's sponsor, and I guess I would like to share just one personal story of one that wasn't quite so successful, that case being the one of my wife, which I explained yesterday. She has had 6 TMJ surgeries, 5 of them bilateral.

In 1989, she had VK-2 put in and approximately one year later one side failed and which was replaced with a Christensen implant. We have had two opinions in the last year and a half by two different surgeons that both of her joints are failing and that they should both be removed and replaced, again, one being a Christensen and one being a Vitek.

She reports today that she has considerable more problem with the Christensen implant than the Vitek, which I was quite surprised by, and less movement. She has much more pain on the Christensen side and less movement on that side.

We are both very concerned about having them taken out, and we are not sure at this point what to do.

In addition, I guess some of my concerns here are what devices, and we have already kicked this around a lot today, but what devices specifically are we looking at today with the sponsor, and I am certainly not clear in my mind which exact device we are looking at.

The device that my wife has is the PMMA-on-metal, and I am not sure if that is what we are looking at today. It appears to me to be a series of products that we are looking at today, and I guess my request to the panel would be that you look at the science behind each individual device and approve only those which you find acceptable.

I have great concern with the PMMA head as the advice that we received from the two surgeons is that it has been sheared off and is coming loose toward the bottom of the implant. The screws are coming loose according to the two opinions that we received.

So, having said that, I guess that is one case. That is not the science that you have seen. You have got studies that show you differently apparently, but from what I have seen I can't tell. It appears that they are all meshed together in the science, and there is not specific science for each individual device.

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So, I will leave that alone for now. That is as much as I had to say on that.

Another concern is--and, by the way, I have the x-rays if anybody wants to see them, I don't know if that is appropriate to show them, but they are available at the panel's request--the other concern that I have with the sponsor's activities are primarily related to truth in advertising.

The company has shared with us a lot of success stories on their web page, as I have looked at it, and my wife and I were desperately searching for answers back in the mid-eighties, late eighties, and it wasn't quite as readily available as what is available today.

Fortunately, with the advent of the World Wide Web, we can now reach 6 1/2 billion people at a key stroke, which is a benefit, and also has some problems with that.

I am in the investment business myself, as I mentioned yesterday, and every piece of material that my office sends out must be scrutinized by the MESD. That is our regulatory body. We have more disclosure in my business to buy 100 shares of stock or even in the tobacco industry where you can't buy a pack of cigarettes, there is more disclosure on those two events than there is in a lifelong implant such as a TMJ device.

I would like to read parts of the web page that TMJ Implants, Inc. has put out. On their first page, "Welcome to TMJ Implants, a world leader in providing predictable alloplastic replacement for the temporomandibular joint."

On their page Products and Services, "TMJ Implants provides a complete set of stock prostheses or partial or total joint reconstruction. The implants are constructed from cobalt-chrome considered to be the gold standard for orthopedic applications. TMJ Implants is also capable of constructing a patient-specific prosthesis according to the surgeon's prescription."

My question I guess is when I read this, does the patient understand that they may end up with one of the PMMA heads on their condyle as opposed to this cobalt-chrome, and it is not clear. PMMA nowhere is mentioned in the web page.

So, again, which devices are we seeking approval for today?

On their page about TMJ Implants, they have multiple quotes from a variety of surgeons and doctors, some that are here. Dr. Curry, who spoke earlier,

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suggest that, "If can limit the patient to two or three surgeries before they have a total joint replacement, they are more likely to have success with the total joint than if we put them through 10 or 15 surgeries and then do a total joint at last resort."

I agree with some aspects of that statement, but I think it clearly says that the sponsor and the associated clinicians feel that this is a front-end device, this is not a back-end, last ditch effort to salvage a patient who has already had multiple surgeries.

Another quote under headline called Predictable, on the same page says--and this is Dr. William Garrett from Florida--"There isn't any patient that hasn't improved. It's a matter of whether they have been multiply operated, but even those patients have improved dramatically. It is an outstanding prosthesis, it works very well."

My question is how could you possibly represent this to 6 1/2 billion people and potential TMJ patients?

The choice to me is clear when I read this. I am going to go for it, and I went for it, and my wife has not improved.

So, under that or following that it says, "Over 95 percent of the prostheses sold by TMJ Implants, Inc., from 1988 to present remain in service."

I don't know if that is true or not. I assume it is, it is on their web page. You can probably tell from the studies I guess that you have seen.

Going down the page to what is entitled Preserving. This is Dr. Curry, who is with us today, and has alluded to this benefit of using the joint.

"If we need to remove this prosthesis, we can go back in, take the fossa liner out and the base of the skull is just as pretty as the day we put the prosthesis in. With most other procedures we get all kinds of distortion of the bone. This prosthesis really preserves the bone."

I am not sure how my wife Heidi is going to react when I inform her, first of all, that the sponsor does not consider the shearing off of the PMMA head a failure. Apparently that is not a failure in the company's mind.

I am also not sure how she is going to take the suggestion that I mentioned yesterday that TMJ patients are some paranoid of the system, they are paranoid of their surgeons, unfortunately, of the companies, the manufacturers, and even of the FDA unfortunately.

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So, when I suggest to her that the base of her skull is going to be just as pretty as the day she put that thing in, I am not sure that she is going to believe me, and I am not sure that she should.

I guess I would like to move on to the end of the web page, which is entitled some Success Stories or Success Stories it is called. There are six success stories which I would like to quote just a few of them, just parts of a few of them.

Tracey Finley who is age 26. "I began treatment, but nothing worked. Four years later, the Christensen procedure gave me my life back. Now, I am absolutely pain-free. I am able to enunciate when speaking and I am no longer embarrassed to be seen eating in restaurants. During the recovery, my pain level has gone from a grade 10 to 0."

Charlene Jaspersen, age 53, in Colorado. Just a portion again. "I was introduced to the Christensen fossa-eminence prosthesis and had it placed in both sides in 1990. I felt better within a week."

My wife has been through six surgeries, and I have been at the hospital for about a week each time. I guarantee you she didn't feel better within a week unless she was on morphine or whatever it was that they were giving her at the time.

"It's made a 95 percent improvement in my day to day life. Once again I feel like a normal person. I do everything and eat everything with no limitations. My jaw feels like the one I was given at birth."

A last example is a Catholic sister, age 72, in California. Again, just a partial quote of the testimony.

"Since I had the implant over 35 years ago, all symptoms have disappeared. The severe pain in my joints is gone. I'm able to eat without discomfort"-- da-da.

Thirty five years. One of my questions, is this joint still on the market, the same one that was used 35 years ago? Are we having testimony of joints that no longer exist?

In summary, I would just suggest again that the panel only approve those specific devices that are scientifically proven and stand on their own merit. I have great concern with a blanket approval for the sponsor's products which seem to be an evolving product line over a period of time.

I also feel that the company's advertising should be looked into, and just as in my business, a

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highly regulated business from an advertising perspective, that their advertising be scrutinized and promises apparently made to patients are not out of line with reality.

Dr. Christensen mentioned earlier that he had not received the phone calls that the FDA has received. On this very same web site, if you want to talk to the company, you are instructed to talk to your physicians. The company does not talk to patients, nor do they send patients materials. They deal exclusively with the physicians.

My recommendation is that the panel or the FDA would suggest then to the company that this web site be limited to the clinicians. Let them access it by password. Don't put this out for public reading if it's not available for follow-up and having a balanced approach.

Thank you very much.

DR. JANOSKY: Dr. Diana Zuckerman from the National Women's Health Network.

MS. BROWN: Lisa Brown. I just wanted to apologize for letting you know that the pictures of the people you just saw either had an all-metal or a device with PMMA, so that you would know that these people did receive an all-metal or a PMMA device.

MS. ZUCKERMAN: I am Diana Zuckerman from the National Women's Health Network.

I guess I wanted to make three points. The first point is that clearly, as we just heard from the web site and from the manufacturers, these products have been on the market a long time.

This company has been in business a long time, and so one would hope that given that they have had a lot of patients, that they would have followed them in a research study for more than 12 months, that they would have had a really good sample size that stayed in place without a high dropout rate for more than 12 months.

Yesterday, I talked about at least five to 10 years or more. Apparently, that is a standard that is too high to reach, but I don't think two or three or four years is a standard that is too high to reach, and particularly for a manufacturer that has consistently been in business and has apparently been selling the same devices for at least some of that time.

It would seem to me that at least one really good study that followed the same people, using really good measures, would tell us a lot. All of the

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mechanical data are very important, but when you do have patients getting these devices, I don't think it is too much to ask that they actually study them.

My second point. As a consumer organization, the National Women's Health Network spends a lot of time trying to explain to consumers, you know what does this FDA process mean and what does this vote mean, and if a product is being sold, does that mean it is safe and effective.

So, I would ask you on the panel, and I would ask the FDA respectfully, that it is very helpful to consumers when votes that a panel takes are really clear.

If being approved by the FDA means that it is proven safe and proven effective, it is very nice when the panel actually has a vote that says how many people on the panel believe that the manufacturer has proven this device safe, and a separate vote asking how many people believe that the manufacturer has proven this device effective, and those kinds of votes are an objective kind of piece of information that is useful for consumers to have and can be very helpful particularly when there is so much hype and so much promotional material talking about how great a device is, and, of course, every manufacturer is going to do that.

So, it is helpful to not just have a decision about how to proceed, but a clear vote as to what that means would be very helpful. I have certainly seen it in panel meetings, and it is something that the press understand and consumers can understand, so that even when products remain on the market or remain on the market under certain conditions, or when the manufacturer has to meet certain conditions, it is still helpful to have that very clear vote, is it proven safe, yes or no, or is it proven safe for two months, is it proven safe for 12 months, whatever.

I guess the last point I want to make, having participated in these kinds of panel meetings before, is that I know that there is a lot of desire on the part of panel members to keep products on the market that they see as helpful to patients, even when they are not necessarily proven safe and effective, and part of that process frequently focuses on what can the manufacturer do to improve their studies in the future or to improve how the product is used in the future.

I would just respectfully ask that FDA make it clear to panel members what it is they can and cannot do. It is very to have a whole list of, you know, a wish

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list of how a study could be so much better in the future or how the manufacturers could provide so much more useful information in the future, but I know, and FDA officials I think can easily tell you, that they are not always able to do all of these things. They have neither the resources nor, in some cases, even the authority to make some of these demands on manufacturers.

So, it would be very helpful I think for a process, that everybody be clear on what is possible and what isn't possible before you take those votes and before you make those decisions.

Thank you.

DR. JANOSKY: Are there any other requests from the public? Are there any questions from panel members for Ms. Brown, Mr. Clark, or Dr. Zuckerman? Dr. Patters.

DR. PATTERS: I would like to ask any of the three individuals that just spoke how they think the panel can differentiate between an unsafe or a poor device, and an unsafe and a poor surgeon.

DR. ZUCKERMAN: I guess I would just say that as a researcher, one of the key ways of doing that is making sure that studies look at many surgeons, just the way when you do a program evaluation, you don't study one program as conducted by one person, because one person can have a great program, one surgeon can have a lot of successes, so you want to get some sense of a typical surgeon using a device to find out if that device is safe.

From a manufacturer's point of view, of course, they want to talk about the safety of the product, but if they are not properly training surgeons to use it, or if the product is difficult to use correctly, it doesn't matter it seems to me how perfect that device is in the real world. You have surgeons that have to put it in.

So, the more people you have in your study, that is the whole point, right, of multicenter clinical trials, the more people you have, the better sense you have of what is going to happen to patients, and from a consumer point of view, that is what we care about.

DR. PATTERS: Let me ask Ms. Brown specifically. Do you have any information on the failures that you showed as to whether you believe it was a device failure or it was poor surgery?

MS. BROWN: From what patients tell us through phone calls and letters, it would very hard to distinguish between the two. As we said before, that is subjective and as you all have pointed out it is

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subjective data that we receive from the patients.

However, you know, showing these pictures, I don't think a tumor could necessarily come from a surgeon. Maybe it's possible. I think a broken device, after it has been implanted for three years, would probably not be due to the surgeon, but could possibly.

So, in looking at a lot of the data we look at from patients, it would be a very difficult decision to make as to whether--and probably not for us to make as to whether it would, you know, come from surgeons or the implants.

Our concern is that they are as safe as possible for the people who actually--you know, if your jaws were fused shut, as patients that we hear from are, and you couldn't eat, your last option would be to get that implant, to take the chance you have to eat food and live.

Granted, you know, if you are already in pain, fine, but if you are in pain and you still have a little function of your jaw left, I think between pain and functionality is a big issue, and I think that if you are in a lot of pain, but you can still chew, are you going to make the choice to have an implant? If you are fused shut, would you make the choice to implant even though you would deal with more pain?

I am really not sure exactly what to say on that, but I wish that--I will stop here. Sorry. Did that answer your question?

DR. PATTERS: Thank you.

DR. JANOSKY: Dr. Heffez.

DR. HEFFEZ: I just have a follow-up question if you could come back the podium, Ms. Brown.

In your opinion, is the public principally, their principal source of complaint is pain or lack of function?

MS. BROWN: Both.

DR. HEFFEZ: You don't find that they are separate?

MS. BROWN: They are in combination with each other, because if you take a bite of food and try to chew it, and you are in excruciating pain, how often do you think you will return to that plate of food or speak out and experience that pain over and over again?

What you will do is you will try to compensate.

You will start keeping your mouth closed, perhaps you won't eat.

DR. HEFFEZ: Is the pain they are feeling

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primarily therefore chewing function or is the pain that they are complaining of primarily spontaneous with or without function?

MS. BROWN: Since we hear from so many, I couldn't tell you, but it is all of the above, it is D.

DR. SKINNER: Could I ask a question also? I am an orthopedic surgeon, and I do mostly hip and knee surgery, and I put in total joint implants similar to these in some respects.

I get an occasion patient, despite putting in a total knee, I tell them not to go skiing, I tell them not to play tennis, and the patient insists on doing that.

Is there some analogy that can be drawn to this implant, that the patient perhaps has some effect on the survival of the implant?

MS. BROWN: Most that I have heard from, I think they are fully aware. I really don't think that we have patients that are taking a big bite of an apple two days after their implant, not even two months after their implants. Most of them aren't doing that two months after an open joint surgery.

As far as being advised by their surgeons, I think that they are advised by their surgeons to take special care, and I think they do take the special cares.

I think their frustration comes in when the problems start recurring, and they have done everything that they know, that their surgeon has said, and their doctor has recommended to make them better.

DR. HEFFEZ: I have an additional follow-up question. If you state they are having problem with function, is the problem a function of their opening or their biting?

MS. BROWN: It could be both.

DR. HEFFEZ: Which is the principal complaint of the patient? The reason why that is important to understand is that most of these companies end up studying how much a person opens, but nobody is ever paying attention to the biting force, and the reduction in biting force, whether biting force gradually increases following surgery.

So, the importance is to direct the treatment to the patient's symptoms. So, is the patient's chief complaint primarily that, in your opinion, that they are unable to chew or unable to open their mouth?

MS. BROWN: Well, as I said before, I think it could be both in the respect that you have people whose musculature, for instance, an atrophied muscle, if it did

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not have any muscle tone at all, would it not sag, would there not be any structure here?

A lot of people, just the spasm of it to begin with, the spasm and the other things that are going on in their face, can cause force to that joint or at least they complain of forcefulness, the feeling of this into their faces, I feel tightness, I feel pulling, I have spasms. This is in a non-movement situation.

I think that they complain more about it when they are talking or chewing, that this increases, but they could be relaxing and still have that muscular force that they tell us about, the spasms, that they say feels like it is ramming my jaw into the back of my head.

DR. HEFFEZ: The question specifically was does the patient come to you and say I cannot open my mouth, that is my major complaint, or do they come to you and say I cannot chew?

MS. BROWN: It's both.

DR. JANOSKY: Ms. Cowley.

MS. COWLEY: If I take time to respond to several of the questions Dr. Heffez has, will you penalize me from asking my questions? Okay.

First of all, somebody asked a question about the surgeon whatever, I think you have a term for that, whether it is the surgeon's fault or the device's.

Obviously, any device manufacturer should have an impeccable training program for any surgeon that is going to be implanting their devices. However, a model of the PMMA head that we know of, that was on the market in--I don't know when--but the patients told us that at some point the PMMA head just lopped off the platform, there was not a screw going up the center.

So, you would have the PMMA bobbing around in the space. Okay. So, I don't know if that's the surgeon, but if the thing breaks off, the blob breaks off, that's a device.

Dr. Heffez, in fact, this is quite interesting, in the last month--well, first of all, a lot of doctors tell their patients you can do anything after you have this surgery. However, one of the manufacturer's surgeons actually tells his patients never eat food, you must only drink Ensure, and so forth. So, that is one of the surgeons.

However, Dr. Curry's partner, in the last month, I heard from a patient who was--Dr. Curry's partner was trying to entice this patient into having a surgical procedure by explaining to her husband how this was going

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to enhance his sex life. So, obviously, if can do that, you can probably eat apples, I don't know.

As far as pain goes, you ask a very interesting question, because I think in my own situation, I have identified about nine different types of pain. You have the pain, the skin, so you have just scraped your skin on the ground from just the edematous swelling, you have streaking pains from the joint, you have, for implantations, we have the submandibular preauricular lymph node pain, you have burning mouth from the loss of vertical dimension, and you have allodynia, and you have every type of pain.

So, if the patient even called us on a particular day and said I can't bite into an apple, would say, you know, are you crazy, get the knife, you never should do that anyway.

So, you know, is it biting, is it chewing, is it whatever, I mean, heavens, first of all, we don't have the science on that, so we don't know. So, you know, in answer to that question.

Should I continue with my others? I have questions of the FDA.

DR. JANOSKY: Excuse me for one second, please.

No one else is requesting to speak from the public, am I correct?

DR. HOFFMAN: My name is Dr. David Hoffman. I am an oral and maxillofacial surgeon.

DR. JANOSKY: Excuse me. Do you have financial interests?

DR. HOFFMAN: Yes, I do.

DR. JANOSKY: Can you please state those for us?

DR. HOFFMAN: I am the co-developer of a joint for Endotech, which is one of the joint companies making a prosthetic joint, and I will be paid potential royalties.

What I wanted to do is hopefully, just for the purpose of the record that is being recorded today, that having had a large experience in putting total joint prosthesis in, that I wanted to make sure that it was at least documented that in doing such, these are not isolated events, and they are part of a total health care delivery system, and even though the information that is being delivered is important, very important, that one of the problem I see is that it is not just the FDA and the manufacturer and the surgeon, that is the health care delivery that falls often short, in particular the HMOs, and I know that this is a little bit supercilious, but I

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want to again stress that patients undergoing these situations, in terms of range of motion, pain control, deciding who is a good candidate often are shortchanged because their insurance carriers aren't helping with the total package.

You can't look at a patient in terms of a joint rehabilitation without having them have rehabilitation after surgery, and it's not the onus of the manufacturer or the surgeon, but there is a definite problem existing in the United States today that my patients, a good percentage of them, are denied the total health care package which makes them successful, and that is probably as important a consideration.

I realize there is not much this panel or the group can do, but it should be noted that a patient who has had this surgery, and not permitted to seek pain management either before or after surgery, not reimbursed for their physical therapy, and not reimbursed for a whole host of other things that they need, such as CPM machines, if you choose, often may very well be looked at as a failure, when, in fact, it has nothing to do with the equipment, the surgeon, or the regulatory bodies, it's purely a function that they ran out of health care financing or they never had it available to them.

Thank you.

DR. JANOSKY: At this time I would like to close the open public hearing and move on to the open committee discussion and vote.

I would like to organize the open committee discussion and vote by first addressing any final questions to the FDA, and then any final questions to industry.

So, final questions to the FDA, for Dr. Runner or Ms. Blackwell, Dr. Ponnappalli.

Open Committee Discussion and Vote

MS. COWLEY: I have a question. What is the intent of device tracking, and is evidence of a reliable device tracking system inherent in the PMA package, is it a part of the PMA package? And if not, how can a TMJ patient be assured they will be notified in the event of identification of a product defect?

MR. ULATOWSKI: The tracking of devices, the follow-up on implants, that opportunity is available in the PMA process to what extent we feel is appropriate in order to track those devices farther out, and then for follow-up purposes, and I am not sure if that was an element of yesterday's conditions, but that is certainly

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on the table for discussion.

MS. COWLEY: I think the patients would feel very comfortable if our companies were at least tracking us, to find us in the event that we all get osteolysis in five years of something.

Secondly, does the FDA have a copy of the Christensen prospective study protocol as part of the PMA, should you have, as well as a copy of the patient consent form?

MR. ULATOWSKI: I am looking at Dr. Runner for a nod yes or no on that. We do not have the prospective study, but that would not be a requirement under our regulations in any case.

MS. COWLEY: It is not, so you would not.

MR. ULATOWSKI: It is? I am not sure if we have the entire protocol.

DR. JANOSKY: Are you going to address the issue as to whether it is contained in the PMA or not?

MR. ALBRECHT: Yes, the prospective study protocol is part of the appendix of Section 6B of the PMA.

MS. COWLEY: So, you do have it.

MR. ULATOWSKI: Yes.

MS. COWLEY: You all. I mean I didn't get it.

MR. ULATOWSKI: Evidently. But I think a point to be made is prospective studies for these types of devices, these 515(b) devices does not require FDA preclearance because they are marketed products, and they are exempt from our investigational regulation.

MS. COWLEY: Should I continue with questions of the manufacturer?

DR. JANOSKY: The questions are for FDA at this point. We can return back to the other.

Additional questions from panel members for FDA?
Dr. Heffez.

DR. HEFFEZ: Can they voluntarily provide that?

MR. ULATOWSKI: Voluntarily. People submit protocols to us all the time for comment, so that is certainly open for consideration, but formally, they are exempt from our investigational regulation.

DR. JANOSKY: Dr. Stephens? No.

Additional questions for FDA?

At this point, I would like to move to additional questions for the sponsor, if panel members have additional questions for the sponsor. Dr. Stephens.

DR. STEPHENS: I have a question that I would like to ask Drs. Curry and Christensen.

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On the fossa prosthesis, is it indicated as the primary treatment for first-time operated internal derangement, is the typical patient with an anterior displaced meniscus with MRI documentation for which you feel that that is the etiology of their pain or dysfunction?

DR. CURRY: In my practice it is, yes.

DR. STEPHENS: Dr. Christensen, is this the company recommendation?

DR. CHRISTENSEN: Our history has certainly shown that as a primary surgical treatment for diseased joint, it is very, very effective. That first operation is the time you get to have the greatest ending or the greatest time of no more surgeries, and I can tell you from my experience of 40 years, that that is the great place to have it, but you don't do it, as Dr. Heffez would surely tell us, you don't do it on a joint that you don't know that you have got some problem.

Did that answer for you?

DR. STEPHENS: I think so. This is the typical patient who would otherwise have a meniscus plication.

DR. CHRISTENSEN: I certainly found plication was not the answer, but if I put a fossa-eminence implant in there, that was the answer, statistically, too.

DR. CURRY: Let me amend my statement to you a little bit because there are certainly other treatments that are available for some of our patients, for instance, arthrocentesis and arthroscopy, and certainly, under certain circumstances, those would be recommended before an open joint procedure is done.

DR. STEPHENS: Patients who have the fossa prosthesis, do you have any sense of how many of those patients will go on to total joints, and patients where there is not an indication of early DJD?

DR. CURRY: Yes, I do. In my own practice, 14.4 percent of my patients have moved from partial joint reconstruction to total joint reconstruction. There is a reference in the literature, in 1990, out of the University of Pennsylvania, Peter Quinn's bunch, when he was doing a Christensen joint prosthesis, he had about a 12.2 percent conversion rate from partial rates to total joints.

As my partner and I looked at our series of cases, we found that in the early stages of our learning curve for doing joint prostheses, in an effort to be more conservative, we did more partial joint reconstructions early on even in cases which today we would do a total

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joint procedure on to begin with.

A couple of reasons for that. We have learned since the middle 1990s, that the more procedures that a patient has, the less likely they are to have a successful outcome no matter what we do to them. So, in an effort to cut back on the number of surgeries a patient is likely to have because of the disease process in rescuing this disabled joint, we do a partial joint reconstruction when it is indicated, and hopefully a total joint replacement when it is indicated.

DR. STEPHENS: In these patients who go on to total joint replacement, what is your sense, what is the typical diagnosis that is made at the time that you are progressing, are they principally DJD or are there other causes?

DR. CURRY: I am not really sure I understand. In a significant number of our earlier patients that we were treating with partial joint reconstruction, were Teflon Proplast failures and other alloplastic failures and other joint failures, and if the condyle radiographically and/or clinically had any chance of survival, it was our protocol to try and maintain the patient's condyle, and if, in fact, the partial joint reconstruction did not meet our expectations and/or the patient's expectations, and further clinical evaluation of that patient indicated continued joint pain and/or continued joint dysfunction, then, we would either recommend a total joint at that point or do a revision arthroplasty and maintain the partial joint.

DR. STEPHENS: The patients that I am thinking of are patients who have only a meniscus displacement primarily in an otherwise healthy joint, that looks normal, and the only problem is a displaced meniscus, I am interested in the number of those patients that you think go on to a total joint, and what kind of problems led to them needing a total joint?

DR. CURRY: I don't have data on that. My sense clinically is that we very rarely, very rarely see an early case like that, that has to go on to more than the initial surgical insult in my hands.

I can't speak for other surgeons, and I think there are some things to be considered there, but in my hands, early recognition of a failed joint beyond which nonsurgical intervention has been totally ineffective and/or even arthroscopy sometimes and arthrocentesis has been ineffective.

We know from studies that disk position is very

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controversial, and we have also known from studies that replacement or repositioning the disk surgically and nonsurgically has been shown to be absolutely unreliable.

Up to 86 percent of repositioned disks, surgically and nonsurgically, are imaged two years after their procedure, and they are out of place again.

So, disk position doesn't mean as much to me now clinically as it did five, 10 years ago.

DR. STEPHENS: Another question I would like to ask Dr. Christensen. When the company decided to add the all-metal joint to the inventory, can you give us a sense of what the company's impetus was for doing this, and were there were reports from surgeons of feeling that perhaps there were problems that might have been related to wear debris, inflammation around the joint, that kind of thing?

DR. CHRISTENSEN: That is a good question, Dr. Stephens. Oh, I think over the years we have probably heard from people that were concerned about the PMMA because it is a little bit softer, but over the years I have not seen a problem with it. In fact, it will flatten off and smooth down. But anything that we can do to minimize wear totally will help, and we had a number of doctors that were utilizing, as well as myself, utilizing metal, and the results have been very good with that.

I think over the long haul, if we look at the thing 20 years from now, we are going to find that metal is going to do very, very well.

Did I answer your question?

DR. STEPHENS: So, there was not a push by users of the joint--

DR. CHRISTENSEN: No. There are a lot of doctors that still liked, preferred using plastic versus metal. It is a doctor's choice.

DR. STEPHENS: If there is a new surgeon who is going to use the joint system, and if they were to inquire to the company about the joints, which ones they ought to use in a particular situation, what would you tell them about indications for one or the other?

DR. CHRISTENSEN: I would like to answer that slightly different, if I could. We really encourage our courses which we put on in various parts of the country at various times during the year, we encourage the surgeons to be there. We put on really an excellent course, and try to bring in all the data that we have, and all the data of surgeons that use it. There are

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several hundred doctors that utilize this technique, so it is not just 1, 2, 3, 4, 5.

The results you have seen up there today have all come from these hundreds of doctors doing it, so it isn't particularly a single doctor doing it, but would we--was your question how would we recommend?

DR. STEPHENS: What would you tell a new surgeon who is inquiring about the system the difference between the two and what instances, how one would consider one or the other?

DR. CHRISTENSEN: I think in our courses we have probably got the greatest evidence of that, but it is really doctor choice. Both will work. One has a little bit more wear than the other, and beyond that, I think that is about it. We have not seen foreign body reaction or--I have not seen osteolysis to either one of these implants in all these years. Occasionally, you will see an AVN of a condylar head that would occur whether you did anything or not. That is very rare, too.

DR. STEPHENS: On the PMMA head, have you had joints returned where they have worn down to the pin?

DR. CHRISTENSEN: If we have, it has probably been one, and I am not sure that that happened. Even if it does, it is highly polished that it would make no difference, it would stop right there. It would take forever to wear much beyond that point.

DR. STEPHENS: Have you had fractures of the head above the shoulder of the joint?

DR. CHRISTENSEN: No, I know of one case in which this patient had about 25 surgeries before, kept getting heterotopic bone, and they went in and cranked this jaw open and open and open and open, did it on a TV program, did it everywhere, and that one did break off, right. That's the only one I ever heard from.

In regards to the patients on the web site, that Mr. Clark talked about--and I am not criticizing--those patients, I know them personally. What is said in there is absolutely true, what is on that web site.

DR. STEPHENS: Thank you.

DR. JANOSKY: Dr. Li.

DR. LI: A question for the sponsor. You have multiple sizes. What is it, 45 sizes, I think, is that per side, left and right sizes? Are the sizes interchangeable? Is it possible for the physician, for instance, to use--I will just make up, I don't know how you catalog them--but a size 1 condyle and a size 45 fossa component, and if there is an opportunity, are

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there combinations that, in fact, should be disallowed because wear rates would be affected or impingement would be affected in some way?

MR. MORGAN: Jim Morgan. Dr. Curry may want to comment on part of that. The stock system is what you are referring to. We have 44 right fossas, 44 left fossas, and then we have Universal and Christensen/Chase condyles in three sizes, 45, 50, and 55 mm.

Those can be used interchangeably, that is, you could take any one size of Universal condyle and fit it to any of the fossa.

DR. LI: My question is do they perform differently, in other words, are the contact areas the same, are the loads the same, is the wear the same if you mix and match?

MR. MORGAN: Contact areas could be different. You could have, for example, one point of contact, which is what we consider to be our worst case testing scenario. It is possible to have two or three point contact.

DR. LI: A question on your packaging or sterilization. You gamma-sterilize your components?

MR. MORGAN: That is correct.

DR. LI: And you do that in air environment, just in a normal package?

MR. MORGAN: They are double packaged in PETG with Tivek.

DR. LI: But in air, it is not evacuated or flushed with--

MR. MORGAN: That is correct.

DR. LI: Do you have any data on the aging of the PMMA as a function of time, sterilizing under those conditions?

MR. MORGAN: We don't have specific aging data. We do have pre- and post-sterilization test data.

DR. LI: It is quite possible, though, if you have an inventory that is a few years old, the properties are significantly changed with aging, which occurs with every other polymer. I wouldn't see why it wouldn't happen with the PMMA.

MR. MORGAN: We have not performed specific aging testing.

DR. LI: Thank you.

DR. JANOSKY: Question from Dr. Altman?

DR. ALTMAN: My question really involves information to the patient. I noticed in the back of I think the last book that we received, there is a TMJ

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patient brochure draft that I hope will forever be a draft. I think the information here is understandable to myself because I have a dental degree, but I don't think a patient that doesn't have a dental degree would even understand this information, and would not be of use.

My point is that I think that any information that goes to patients really needs to be down on a fifth or sixth grade level. That is what patient information educational information should be written at.

But a bigger concern also sort of tags onto Mr. Clark's and that there really isn't a way for the consumer to contact the company to receive information, and I find that a little bothersome that there is not, if not so much a patient advocate at your company, somebody that could answer nonsurgical questions, if you will.

I mean I see some problems with giving out clinical information, but for there to be a web site to give information and to have a brochure, to give information and not be able to seek clarification other than having to go to a surgeon, I find a little bothersome.

What is the reason for that?

MR. MORGAN: Let me address the sixth grade level thing first. That is something that the FDA has identified, and we will be addressing in that labeling.

Relative to communication with patients, our policy has been to encourage patients to seek medical advice from their surgeons and discuss these issues with them as opposed to the manufacturer.

DR. ALTMAN: But yet you will distribute the information or they can get it from the web. For some reason I have a disconnect with that.

You will give them just enough information, but then you are going to refer them to a surgeon if they want any sort of clarification. It seems to me that there should be some way that they could, you know, be answered, have answers to frequently asked questions, if you will, that are not surgically related, but there might be a question about, you know, just simple indications or--I can't think right offhand.

I guess I am concerned that that is the policy, understand it as the policy. I just want to register my concerns with that.

MR. MORGAN: We can certainly revisit that.

DR. JANOSKY: Dr. Burton.

DR. BURTON: Just in some of the comments that I heard you make earlier--and I am not sure which one of

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the individuals made this--said that the only explanted devices had been PMMA head devices, is that correct? You have had both metallic condyle, all-metallic, and PMMA heads that have been returned to the company as explants?

MR. MORGAN: Yes, I think that is correct.

DR. BURTON: I had heard that comment earlier, that they said, well, the only things we have seen that have come back have been PMMA heads.

MR. LIPPINCOTT: We have had it up to five years explant of metal-on-metal, and up to 11 years explant of PMMA.

DR. JANOSKY: Dr. Patters.

DR. PATTERS: I would like to address Dr. Curry, if I could. Dr. Curry, you apparently have great experience at placing temporomandibular joint implants. I would have to assume you also have some experience at explanting others, not necessarily the Christensen implants, but others.

In your experience, when dealing just with metallic implants, not the Proplast Teflon ones, when a patient comes and you advise them to have the implant removed, and you explant them, do you think the reason for failure is more often failure of the device or some iatrogenic failure based on how the device was placed originally by the surgeon, certainly not yourself.

DR. CURRY: Certainly not.

DR. PATTERS: Certainly not.

DR. CURRY: Most of the devices that I have explanted, that are metal devices, had Proplast attached to them, and so the major issue that I have seen with other devices that are metal have had the Proplast attached to them, as well, and so I see a huge device failure on that basis.

I have explanted one fractured Christensen device that had been in for 11 years. I showed the device earlier in the day. The screws were all still tight, the only problem was the device itself had a fracture in it, and it was relatively simple to take it out and replace it with a new device. The bone was beautiful underneath it.

So, that is the only Christensen device total joint that I have taken out for that length of time. I have done two or three other revision cases in patients who have had problems, either posttraumatic or what have you, and I have seen one PMMA head shear off, but it was an iatrogenic placement on my part, and so when I look at a case like that, I question in my mind whether that is

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surgeon related or device related.

Certainly the patient is having a problem related to the device, but the device failed because of something that I did. I have bent the--maybe the company won't listen to me for a minute--I have bent the flange on the fossa liner early in my career trying to get it to fit just a little better, and have fractured that off and reported that to the company, and that has been reported as an MDR. That is not a device failure, that is a surgeon making a bad choice.

DR. PATTERS: Have you seen any of the dramatic failures, such as Ms. Brown presented?

DR. CURRY: You mean with the Christensen device?

DR. PATTERS: No, sir, just in your surgical experience.

DR. CURRY: Yes, sir, I have.

DR. PATTERS: In your professional opinion, are we most often looking at a device failure or are we looking at some iatrogenic failure? There are good surgeons, there are bad surgeons, as I am sure you will agree.

DR. CURRY: I do agree, and I have seen a little of both. The kind of failures that I saw earlier in the afternoon have been--every one of them have been, in my opinion, device related, but they have had Teflon and Proplast associated with them and/or Silastic, and the tumor that was shown earlier, I have seen a case like that, and that was giant cell reaction to Proplast Teflon, and that is all I have seen from that standpoint.

DR. PATTERS: Thank you.

DR. JANOSKY: Ms. Cowley.

MS. COWLEY: I believe you answered the question this morning, but perhaps I wasn't terribly clear. I think the issue of who owns the device is very important, particularly when we have implant failure, and we consistently hear complaints from patients that a device suddenly disappears from the OR, nobody can find it, oh, it was sent to the manufacturer.

The patient then requests the device from the manufacturer or their lawyer does, and it's lost, or as in one case, a totally different, new, banged-up device was returned and presented as theirs.

Is there a consistent policy that your company has, do you respect the right of the patient? I mean to the best of my knowledge, we don't sign a sheet saying that this is, you know, Christensen rent a device, it's

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we buy it, and even though it can be sent back to the company for analysis, should it not be returned to the patient?

DR. HEFFEZ: It is hospital protocol, if a foreign body or any metallic device is removed, and that is the reason why the patient presents them to the operating room, that it is sent to the Pathology Service of that hospital. It is from there that the company has to answer what happens.

MS. COWLEY: Right.

DR. CHRISTENSEN: I understand your concern, and from a company's point of view, and having been a surgeon for so many years, we want to see what is happening to the device and so that we can study it, and to my knowledge, I don't recall ever losing one or throwing one away or giving the wrong one back. I am not denying what you are saying. I don't know of that happening.

But we are there to help, come up with an answer to that, and then if it gets into a legal thing, I think we have to go to our attorneys, and so on.

DR. CURRY: But would you consider having some kind of consistent type of protocol for that, for the patients?

DR. CHRISTENSEN: I think in our physician booklet it says if it breaks or something happens to it, that it should be sent back to us. I think we can surely work out something.

MS. COWLEY: I understand. Dr. Christensen, if you don't mind, do you have a device tracking system in place as well as the patient registry, and if--well, answer that first.

DR. CHRISTENSEN: Yes, we do.

MS. COWLEY: Great. What is your attrition rate on the device tracking system?

MR. MORGAN: Device tracking is the registry. I am not quite sure, Ms. Cowley, what you mean by attrition rate.

MS. COWLEY: Well, your patient registry shows that you have lost an awful lot of patients, and I am looking at a patient registry for research purposes entirely different from the legislated device tracking system where you are supposed to find a patient within 10 working days in the event FDA deems there is a device failure.

MR. MORGAN: I can respond by saying that our device tracking system is in compliance with the regulation, and we do--I don't recall what the frequency

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of follow-up, what that requirement is--but we, on a regular basis, follow up to try and make sure that we have current information on the patients who have our devices.

Relative to attrition in a study, I think Mr. Albrecht can--

MS. COWLEY: No, I understand the attrition there, but I am more concerned about the device tracking system.

MR. ALBRECHT: May I just make a clarification?

MS. COWLEY: Sure.

MR. ALBRECHT: I would just like to make a clarification. The data that we presented from the registry was from the secondary part of the registry where we do try to collect information from the patients. That doesn't reflect that we are losing patients to tracking. The data presented was data we received back from patients on a voluntary basis. The tracking is up to date. On a monthly basis we do send out requests to patients to be sure that we still have their accurate address, phone number, all the demographic information, and then we update our files consistently, but every device that we do sell or distribute that is implanted, is in our device tracking registry.

MS. COWLEY: You communicate with the patient to keep that updated, right, not with the physician, the surgeon?

MR. ALBRECHT: I believe that is correct. If we cannot find the patient, then, we will go back to the physician and say do you know if this has moved, died, whatever, and can you give us the location of that patient.

MS. COWLEY: Great. Okay.

I don't know how should address this, perhaps Dr. Christensen. You have a prospective clinical study encompassing 10 centers. Does each center have IRB approval?

MR. ALBRECHT: Yes. We have conducted the study as close to an IDE study as possible even though it is not required as such, so for every center we have received IRB approval.

MS. COWLEY: Okay. However, you have an impressive disappearance rate of patients, and, as yesterday, I have to ask the question who is paying for this follow-up care, and is that a consideration when patients are having to travel as well as pay for doctors' services at the centers? Is this an impediment to

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compliance?

MR. ALBRECHT: It potentially can be. To answer the first part of your question, again, we cannot calculate the dropout rate yet because the study is not completed, but as the data suggested, the farther you go out, the less patients have gotten out that far, so they are not ready for that window yet.

To answer the second question with regard are patients charged for the follow-up visits, we have not stipulated that to the investigators that they should or should not charge, that is between them and their patient and their business. We can surely discuss that with them and come up with something, but that has not been done in the past.

MS. COWLEY: Finally, I would like to follow up on Dr. Altman's concerns about not being able to get--the patient not being able to get through to the company. As we discussed yesterday, one of the prime problems a TMJ patient has is they are stonewalled at the surgeon's door, and if there is a problem, they are at the mercy of the surgeon, they cannot get to the company to tell them, excuse me, my device is sticking out of my head, or anything else to that effect.

So, as they are being shuffled back, being told this is no problem, you have no problem, this isn't cracked, to find a year later at another doctor's office, yes, the device was broken, you know, you aren't going to hear this if you don't answer a telephone. I just want you to know that.

Thank you.

DR. JANOSKY: Dr. Burton.

DR. BURTON: This is for Dr. Curry. Who is providing the IRB approval for these? I believe, Dr. Curry, you said you were one of the centers involved in this, and I know you are in private practice, and I would assume--are these university-based centers, hospital-based, private practices, and, if so, who is providing the IRB approval in those settings?

DR. CURRY: I will speak for my IRB. It is through hospital.

MR. ALBRECHT: For all the other investigators, the majority of them are in private practice, and we have gone to their individual hospital IRB to receive IRB approval.

DR. JANOSKY: Dr. Heffez.

DR. HEFFEZ: Dr. Curry, can I ask you a question? You have stated in your presentation that

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there was no other device available that could be used for your intended purpose. What are the criteria of the other devices that are available, that have, in your mind, eliminated their possibilities for your patient?

DR. CURRY: I think I made that statement in reference to partial joint reconstruction only. I know that there are other devices available for total joint reconstruction.

DR. JANOSKY: Dr. Bertrand.

DR. BERTRAND: This is for Dr. Christensen, please, sir. You obviously probably have more experience than anybody else in this room placing implants, and I realize that you haven't seen that many failures.

How many implants have you placed, sir?

DR. CHRISTENSEN: To go back over all the years, I don't really know a number. It's in the hundreds, it is not as large as some of the people out there that have much bigger practices today than I had over many of those years.

DR. BERTRAND: What percent of those patients, do you have any idea, have you been able to do 10, 15, 10 year follow-up?

DR. CHRISTENSEN: At this time, I go back to only just a handful, a few, but I go back 39 years starting next month, so it is a pretty good length of time.

DR. BERTRAND: But just a few for a 10-year follow-up?

DR. CHRISTENSEN: Well, there is a lot more than that now for 10-year follow-up because of the company, some of the people I have seen, some of the people I didn't see personally as a surgeon, but I was in surgery to watch the surgeries sort of thing.

DR. BERTRAND: But in your own private practice, there is no direct recall to bring these patients in yourself to see?

DR. CHRISTENSEN: I quit practice about 10 years ago, so it is a little hard to do that.

DR. BERTRAND: Thank you.

DR. JANOSKY: If we turn to panel questions, it should be toward the back of the agenda packet.

MR. MORGAN: Jim Morgan. Just for my sake, will there be opportunity for us to make a closing statement?

DR. JANOSKY: Yes, probably about a three-minute closing statement after we are done with the questions.

MR. MORGAN: Thank you.

DR. JANOSKY: I have listed three panel

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questions. I will read each of the questions and then we respond.

The first question. We are working on resolving fatigue-testing issues with the sponsor. What would be adequate fatigue and wear testing parameters for this device?

Responses from panel? Dr. Li.

DR. LI: It is a little tough to get at some of these answers without seeing more retrieved devices. Apparently, there is a number of them available somewhere, as the sponsors have seen, but as a panel member, I have seen very few of these. So, again, it is very difficult to judge the value or even set what laboratory tests you should do if it is unclear exactly what failure mode it is you are trying to duplicate.

So, basically, the data we have seen so far is entirely anecdotal in a sense that occasionally they were shown implant with broken screws, one with a broken plate, but we are looking at onesies and twosies out of tens of thousands of devices, so in that sense, I am not exactly sure how one creates a fatigue test that actually would be demonstrably transferable to the clinical situation.

In the absence of that information, then, you are going to just have to basically fatigue test these things in the most strenuous way you can, and just hope that testing has something to do with the clinical outcome.

In that regard, I would go with what Dr. Rekow suggested, if you want to do fatigue testing and then also failure, then, probably the most severe test would be to combine those two, which would be to fatigue it for a while, and then do a failure test, because unlikely they are going to fail as soon as you put them in for a failure test. If they are going to fail, it is going to be some long cycle of fatigue feature, and I think because of all your different sizes and the number of screw options, especially in the patient-specific one, the engineers are going to have to identify for each design option what the weakest point is, and then test that particular location on that device.

The best way, of course, is to know exactly where they break and how they break, and then you can set up a laboratory protocol to address that. In the absence of that, you are just going to have to do like any good engineer would, identify the weakest point and then accordingly test.

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DR. JANOSKY: Dr. Rekow.

DR. REKOW: I think that you could get a lot of that data actually if you knew the degradation mechanics of your material with time and loading, and then have some experimental data to confirm that your finite element model is a good predictor.

I think that you could accelerate a lot of your testing by using your finite element model, but I think you need to be able to show that there is a very high correlation between your predictive values and your experimental values, and then you can take care of a lot of the geometry questions, as well, in terms of the different devices that you have the sizes, and all of that sort of stuff.

DR. LI: Let me add to that. My previous comments were to the metal components of your system. I think my testing would be more rigorous on the methacrylate option that you offer, which not that I don't believe the results, but the performance is nothing short of miraculous based on the material properties of that device and the design as I saw as I passed it around. It almost goes against every--if I was a betting man, I would have lost my house that the thing performs the way it does.

So, either you have got some miraculous performing methacrylate combination design, but if that is the case, you ought to be able to actually prove that in the laboratory, but designing an appropriate fatigue or failure test aimed at again isolating the weakest component of that structure, and the directly testing it.

So, I don't think any of the tests you do actually are rigorous or are worst case scenarios, because you have not identified and tested specifically the weakest point or points in that structure.

DR. JANOSKY: Dr. Heffez.

DR. HEFFEZ: Just to follow through, I believe also we have to look at the loading forces. They should be increased and they should be applied in a consistent manner, not in an intermittent or sinusoidal fashion.

DR. JANOSKY: Dr. Skinner.

DR. SKINNER: Regarding the wear testing, I think that the orthopedic history suggests that for total hips, the criss-cross wear is more useful in sorting out wear patterns than a wear that is back and forth like a reversing pin on disk type of thing. So, I would suggest something along that line.

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DR. JANOSKY: Additional comments or responses?
Moving on to Question 2. Wear particles generated from previous implants have proven to be problematic. Does the wear testing demonstrate that this device has adequate safety in terms of wear?

DR. LI: I guess I have three points. One is, just to shorten, a brief comment. The lack of being able to just find any particles in histology from patients is bothersome, and it has got to be technique oriented, so I think as a follow-up to a retrieval program or any kind of explantation, I think there are techniques around where, if you are looking for methylmethacrylate, that you can isolate those tissues and find them. So, I believe that is basically a protocol deficiency to date.

As far as the wear test goes, neither wear test, the pin-on-disk or the more anatomic one done at Rose Medical have been validated from two centers. Again, we don't have, or at least I have not seen very many retrieved devices, so I don't know what wear pattern I am supposed to get in my wear test.

So, without that again, there is no way to validate if I am wearing appropriately or not appropriately, and I like Dr. Skinner's thing about the emotion of the wear test. The third validation is the size and shape of particles. It could be that even if the surface looks the same, the test is still invalid in the sense that the size and the shape of the wear particles you are generating are not those ones that you generate clinically.

So, I think you have to validate the test and basically those three conditions, otherwise, you might as well just take sandpaper and rub them and see how they do, because otherwise there is no connection again with the clinical outcome.

As far as the challenge of the wear particles in our rabbit study, it is quite often the case, even if you are using submicron polyethylene particles, which we know are highly reactive, that you do it that particular model and don't get a response.

So, your animal model for tissue response is not a particularly severe one, and there are other more severe tests--you have got to use a test at least for polyethylene more often than not elicits a response as opposed to a test where often polyethylene doesn't even elicit a response.

So, your rabbit test was okay, but it certainly was nowhere near a severe test. This is a final note.

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Although the word we have on metal-on-metal implants--and I don't know if Dr. Skinner wants to add something on that--is that there is no question that metal-on-metal implants have lower wear than metal-on-polyethylene, but it is also relatively agreed that at least in tissue culture, size for size metal particles are listed as stronger cytokine reaction than polyethylene.

So, history is kind of on your side that you don't get as much osteolysis in metal-on-metal hips as you do on metal-on-polyethylene, but the potential is still there.

DR. JANOSKY: Additional responses, comments?

Moving on to Question 3. Do the data demonstrate reasonable safety and effectiveness when taking into account possible risks and benefits to the patient? Please state the basis for your answer.

Dr. Patters.

DR. PATTERS: As I was concerned yesterday about the high number of dropouts and feeling that the cohort, which was usually less than 20 percent of the cases started, may be a biased cohort in that the patients who didn't continue, and data was not gathered from them, may be either those that were extremely happy and extremely successful, or, on the contrary, those who were total failures, and that the cohort that you test may be a biased one.

It is particularly of concern, I think, for a company that has been selling TMJ implants for more than 30 years, that they have yet to conduct a rigorous scientific test, but rather have tried to gather data from the selling of their implants to private practitioners and try to gather anecdotal data as to how these implants fared.

I really think it is time that you sit down and support, not just sell, but support a study to answer the question of whether your implants are safe and effective long term. The data is not available to this panel at this time in my opinion.

DR. JANOSKY: Dr. Gonzales.

DR. GONZALES: I do not feel that the efficacy regarding pain has been adequately evaluated due to the single-point average visual analog scale in a very complex situation. I think that there is a lack of information regarding pain type, and I feel that the benefits for pain relief have not been addressed, and that the risk of worsening pain in some small subgroup still needs to be investigated.

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That is to say, there is still the possibility that a small subgroup of patients can be worsened and potentially identified before an implant is performed, and the only way to get to the small subgroup is to do a study regarding pain, addressing the issues of pain type, as well as other characteristics of the patients that are undergoing these implants.

DR. JANOSKY: Dr. Heffez.

DR. HEFFEZ: I think given the multi-indication for the multiple devices, I do not feel that they demonstrate reasonable safety and effectiveness. If we want to look at utilization of some of the devices for salvage procedures or mutilated joints, then, I have to state that the risk versus the benefits of using some of the devices may lean to replacing the devices.

As far as effectiveness, I don't believe that the data has been adequately collected in order to demonstrate effectiveness.

DR. JANOSKY: Dr. Skinner.

DR. SKINNER: I am surprised to hear you say that, Dr. Heffez, because you were the one that convinced me that it was probably safe and efficacious. You made the comment that this device has been around for a long time, and I think it is pretty obvious that this is far from being a Proplast type safety device. I think it is much safer than that. It may not be a perfect device, but I think that it falls into the range of being safe and effective.

I think that there are problems, and I think it would be good if the indications were limited to salvage procedures, but I think that that is getting into the range of regulating medical practice even though the FDA is charged with indications and labeling.

I would say that, yes, it demonstrates reasonable safety and effectiveness when you consider the risks and benefits to the patient.

DR. JANOSKY: Dr. Stephens.

DR. STEPHENS: I think that clearly, the devices require additional studies, and that the studies in particular need to break out the partial joint reconstruction from the total joint reconstruction, and it would also be helpful to look at the all-metal joint separate from the PMMA joint.

I think that in looking at safety and efficacy of the device, it is somewhat difficult with the data that has been presented, but I think that some leverage has to be given to the longevity of the device, and I am

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not sure that I have seen indications of safety problems over the length of time that the device has been in use, and I think that the effectiveness of the device is reasonably well shown within the longevity of the device, the time that it has been around.

But clearly, I believe that additional studies with each of the three devices, the PMMA device, the all-metal device, and the partial joint reconstruction device need to be separated out and looked at separately.

DR. JANOSKY: Dr. Bertrand.

DR. BERTRAND: I am very concerned about the prospective study as giving us any future data that is going to help us understand what is happening in that the opening measurements, opening measurements of this group indicate that those patients already have some degree of translation, otherwise, they wouldn't be opening 31.5 mm.

From clinical experience, we are talking about a great deal here today. A large percentage of those patients may well have primary muscle problems with a perception of a joint problem irregardless of what imaging shows.

So, my concern that this prospective study, because there is nothing about lateral movements that I have read either, I don't really know if we have a primary joint problem for which a surgical fossa or a subsequent condylar implant would be provide any benefit other than maybe contributing to future problems.

DR. JANOSKY: Dr. Burton.

DR. BURTON: I think you obviously have to separate the safety and effectiveness issues. I think it has been shown that the data that they presented really does not show good clinical effectiveness. I think it's a safety issue probably best answered by the longitudinal amount of time that it has been on the market, however, I think that the panel and all the different people on the panel and engineering support that we have received have raised some serious questions regarding the PMMA version of that in terms of both wear debris and in potentials for failure within that.

So, I think again when you talk about safety, it also depends very much on which one of the devices. We have a number that are actually being considered here.

DR. JANOSKY: Dr. Heffez.

DR. HEFFEZ: Just a point of clarification for Dr. Skinner. I felt that the way the data was presented did not demonstrate the safety and effectiveness, but the longevity is clearly the hallmark for this company.

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DR. JANOSKY: Dr. Stephens.

DR. STEPHENS: I think the problem with the opening data in the prospective study is the fact that the indications for the partial joint reconstruction, I think is an entirely different animal from the total joint reconstruction.

When you are talking about patients with internal derangement, those patients' opening can be anywhere from very restricted or close locked of less than 10 mm to greater than 40 mm, and still require some sort of intervention at some point.

I think that that is a great problem. Those patients have to be taken out, because it really tells us nothing about that group that requires total joint reconstruction. I think that that is a major problem with the prospective study.

DR. JANOSKY: Additional comments or responses?

Dr. Runner, have we answered all the questions that you wanted us to consider here today? Yes. Okay.

At this point we are going to take a very, very short break, five minutes, and when we return we will have a three-minute wrap-up from industry followed by a motion and a vote.

MR. MORGAN: Could I make a plea for 10 minutes, please?

DR. JANOSKY: Why don't we compromise and say 7?

MR. MORGAN: Seven and a half?

DR. JANOSKY: I will keep the watch. We will say 7 1/2.

MR. MORGAN: Thank you.

[Recess.]

DR. JANOSKY: At this time, we will have a 7 1/2 minute presentation from the sponsor followed by a few comments from Dr. Floyd, who is the Industry Representative.

MR. MORGAN: We are grateful that we have had the opportunity to present our products to you today. We recognize that there are differences in the approach, our approach and FDA's approach regarding the data, and we have tried today to clearly delineate what we did and why we did it.

I would like to emphasize that in over 35 years of use, the objective has always been on the part of Dr. Christensen, and then later, on the part of TMJ Implants, Inc., to keep the patients' interest first and then also the safety of the patient.

Second, we provide systems that we believe are

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not otherwise available, and it is essential, we believe, to keep these devices available and in commercial distribution for use.

In this regard, we would welcome any guidance the panel would care to provide on labeling conditions it believes are appropriate.

Third, we are conducting additional confirmatory tests that we will supply to FDA, and we plan to continue postmarket studies to provide further support for the safety and efficacy of our devices.

There are just a few specific issues I would like to address.

One, in the clinical area, the statistical analysis indicated that a case for effectiveness had been made, but the panel seems to feel that that has not been done. We would be grateful if the panel could expound on the issue, particularly in light of yesterday's presentations where effectiveness was considered proved.

Secondly, in terms of the expectation of the, for example, 25 years of data, while the device has been in use for 35 years, over 35 years, the company itself is 10 years old, so we would not be able to have or provide 25 years of data.

Also, relative to PMMA, we certainly have heard your concerns in the discussions. We do want to note that there has been no clinically confirmed reaction to PMMA from our devices.

It also seems that there might be some concern relative to MDRs, and we would like to clarify that we take an approach towards the MDR regulation that results in our filing MDRs if even there is some question as to whether or not it might be filed. Well, that is what we would consider a conservative approach in terms of filing as opposed to not filing.

Secondly, we are a major supplier and have been a major supplier of these devices through the period considered for MDRs. It is not unexpected, then, that we would have a large number of MDRs reported to the FDA as a percentage of total reported to the FDA.

However, when you look at the number of MDRs reported as a percentage of our devices in the marketplace, the percentage, as Mr. Albrecht pointed out, is very small, less than or about 1 percent total.

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Finally, relative to indications, currently, our labeling for the fossa-eminence prosthesis, and you can see it on the overhead, we state where conservative

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therapies and treatment plans are not or are no longer indicated.

If the panel feels that there should be some expansion of that, certainly, we would consider it, but we do believe that, for the clinician, that captures the essence of the indications for use for the fossa-eminence.

Once again, thank you very much for your time.

DR. JANOSKY: Dr. Floyd, as the Industry Representative, do you have some comments for us?

DR. FLOYD: This has been a very interesting presentation. There are a couple of comments I would like to make.

Firstoff, having been associated with device companies for some time, we have to be aware that device companies and the medical device industry do not general market directly to the consumer, i.e., the patient. The consumer in this case is the medical professional, practitioners of medicine, and in many cases, companies cannot really control the way a device is used.

They certainly have the labeling, and that is prescribed by the regulations and the approval of the device, and if those regulations aren't obeyed, the FDA does have something to say about that.

On the other hand, we all know that we have colleagues who may or may not use a device as prescribed in the labeling of that device. So, that is something we all have to be concerned about at all times.

The other issues that come about and that are going to become increasingly important, and it is not a matter to be addressed by this panel today, but I think it is something we all have to put in the back of our minds and start considering, is that the amount of information that is available to the consuming public, the potential patient population these days is increasing at a rapid rate.

The access to information is now worldwide and instantaneous. All of the information that is available is not necessarily accurate in all cases, and how we address that and how both manufacturers and regulatory bodies and scientific bodies and advocate groups, how we all address those issues and work together to ensure that the information flow is as accurate as possible and is directed as possible to the real issues is certainly a matter of concern.

Thank you.

DR. JANOSKY: Before calling for a motion, Ms.

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Scott has some guidelines that she would like to read to the panel.

MS. SCOTT: Before the vote I would like to remind the panel of the options that they have. If you would like for me to read through the whole option document again I can or I can just briefly read through it. Okay.

As you know, a PMA must stand on its own merits and your recommendation must be supported safety and effectiveness data in the application or by applicable publicly available information.

I will reiterate the definition of safety provided in the Act, which is the reasonable assurance based on valid scientific evidence that the probable benefits to health under conditions of use outweigh any probable risk.

Effectiveness is defined as reasonable assurance that in a significant portion of the population, the use of the device for its intended uses and conditions of use, where labeled, will provide clinically significant results.

Your recommendation options for the vote are as follows:

1. Approval with no conditions attached.
2. Approvable with conditions.
3. Not approvable.

Of the five reasons that the Act specifies for denial of approval, the following three reasons are applicable to panel deliberations: (a) the data do not provide reasonable assurance that the device is safe under the conditions of use prescribed, recommended, or suggested in the proposed labeling; (b) reasonable assurance has not been given that the device is effective under the conditions of use prescribed, recommended, or suggested in the labeling; and (c) based on a fair evaluation of all the material facts and your discussions you believe the proposed the proposed labeling to be false or misleading.

We also ask that if you recommend the application not approvable for any other above stated reasons, that you identify the measures that you think are necessary for the application to be placed in an approvable form.

Lastly, in rare instances, the panel has decided to table an application, although we request that the panel not take this option if possible.

One other thing that I just wanted to clarify,

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there was discussion as it relates to the fact that there are several different prosthetic options contained within this PMA, but as submitted, the PMA needs to be voted on as submitted, it needs to be voted on as a whole, as a submission, as an application. So, the vote has to be on the PMA.

Now, if you have specific recommendations to the agency regarding any specific portions or any specific prosthetic options or devices included within the PMA, you may provide those recommendations or statements to the agency after the vote.

DR. JANOSKY: At this time I would like to call for a motion.

DR. BERTRAND: I need a clarification. We are voting on all of the aspects of the PMA and all their indications as one unit?

MS. SCOTT: Yes.

DR. HEFFEZ: One further clarification. We are voting the PMA as a unit, but not the indications, is that correct? The indications can be modified with conditions, is that correct?

MS. SCOTT: Yes. I believe that the panel can state the specific indications for which you make your final recommendation regarding.

DR. JANOSKY: Dr. Skinner.

DR. SKINNER: You want a motion I assume.

DR. JANOSKY: Yes.

DR. SKINNER: I move that the PMA be approved with the condition that a controlled clinical study be performed and the indications be modified as will come out in the discussion.

DR. BURTON: Second.

DR. JANOSKY: We have a motion and a second. Discussion of the motion?

DR. LI: Excuse me. Can we amend by adding conditions at this point?

DR. SKINNER: That was the intention.

DR. LI: I would like to see justification of the continued use of the PMMA version of the device given that there is a metal-on-metal alternative and their own data also see that the methylmethacrylate wear is higher and then the backup fail/safe of the methylmethacrylate, if the methylmethacrylate fails, they end up with the metal-on-metal. With all that together, it is unclear, at least I believe the sponsor should justify why the PMMA option should be continued other than that somebody wants to buy that version.

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DR. JANOSKY: Can I get a clarification? Are you asking for a justification in terms of providing safety and effectiveness data or a --

DR. LI: I would like them to provide some data to justify the continued use of the PMMA version.

DR. JANOSKY: And what form would that data take?

DR. LI: I would like that form to take clinical trials as a specific option and Dr. Skinner's, and I would like to see the appropriate laboratory tests accompany that, specifically, basic property data on the PMMA including fracture toughness data.

I would like to see fatigue testing aimed at the known weakest engineering points of that device. I would like to see the appropriate wear test, a validated wear test and that it generates the appropriate size wear particles for that device, and I would like to see a collection of retrieved devices, however they get them, for whatever reason they were retrieved to serve as a further validation of the laboratory tests.

DR. HEFFEZ: For point of discussion, it would be very difficult to develop a controlled study on these patients because the population is so heterogeneous, the reasons for performing the procedure are so heterogeneous that even the same particular patient, a patient who has had a mutilated joint from Proplast Teflon implant, the goals for each individual patient are different. I think it would be difficult to develop a controlled study.

DR. SKINNER: Dr. Heffez, are you saying that a physician or surgeon couldn't ethically use another treatment for such a patient, because if there is another treatment, they could ethically be used in a controlled study.

DR. HEFFEZ: I am saying that the numbers of patients that would fall in specific categories to make that a statistically valid study would be small. I am not saying that a control can't be found. I am saying that the population breaks into such small groups that you won't have enough cases to make it statistically valid.

DR. SKINNER: I think that a good statistician could take care of that problem. I have one in mind actually, not me, but I think a good statistician could take care of small numbers in a heterogeneous group, having served on other panels with a statistician, but I see what you mean.

I think, though, that if there is an ethically valid treatment, no matter how small the numbers are, you could

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form a controlled study. If there is no treatment that is ethically an alternative, then, I think that the prospective study as they have planned with appropriate means of evaluating the patient, which I think are marginal in the present study that is ongoing, things like the SF36, for instance, would be a reasonable alternative.

DR. JANOSKY: Dr. Patters.

DR. PATTERS: I believe that a controlled study can be done in this situation. Many patients are unable to accept treatment, and it is not unethical to continue to monitor those patients who, given the treatment option, could not accept it and are accepting another treatment. What I am most concerned about is that I think the onus is on the sponsors to assure that long-term data is gathered by supporting the patient, and obviously, an 80 percent dropout rate suggests that the patient was not supported and the patient may not have returned for future data collection because the costs were too high for the patient to bear, et cetera.

So, I think that gathering the long-term data to me is a critical issue, and that has to be designed in the protocol to begin with.

I also would like to see--as I understand it, they did break out some of the data into the different implant types as they presented it today, but the PMA really needs to be rewritten to have that data available for scrutiny by the FDA staff. So, I would recommend that as a condition, as well, that that data be provided to FDA in writing, so it can be investigated.

DR. BURTON: I also think it needs to maintain the patient registry and also that we should have some specific engineering studies that deal at least in the lab bench model with the patient-specific model. It didn't appear that there was much discussion on that, but from what I could see in looking through the materials, there didn't seem to be much of an engineering validation to that. You admit that it is a different design, but there is not much other than the fact that it is different.

DR. JANOSKY: Dr. Bertrand.

DR. BERTRAND: I do not think that these implants should be approved as a primary surgical intervention for internal derangements. I am suspicious of whether they should be approved as a primary intervention for meniscal tears or perforations and also adhesions, and I have real concerns about approving the delivery of these implants

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unless those things are excluded from primary interventions.

DR. JANOSKY: Are you proposing a limit to the indication for use?

DR. BERTRAND: Yes.

MR. ULATOWSKI: One comment concerning the recommendation. I am detecting a little bit of difference perhaps, and maybe you can clarify this for me.

When one makes a recommendation for approval or approval with conditions, one is saying that given the data in hand that has been presented to you, you made a baseline, a fundamental decision that you have sufficient data, sufficient valid scientific evidence upon which to make a recommendation to FDA that the product should be approved irregardless of the conditions for the moment.

So, we have data which supports the safety and effectiveness, but we have some concerns now, you should do this, you should do that, to support that fundamental decision.

So, when you make recommendations, and I hear, well, we need a prospective study to evaluate safety and effectiveness, there is a disconnect there.

So, I am asking the panel in your discussion here, have you made that baseline decision individually that you have seen sufficient data to get over the initial threshold, and the follow-up and the additional data is supporting data in terms of longer term follow-up or some aspect of patients or subpopulations that were inadequately studied to support that baseline recommendation.

DR. SKINNER: Can I address that?

DR. JANOSKY: Yes, you may address it. Refresh my memory, was it Dr. Heffez who put forth the motion?

DR. SKINNER: No, I did.

DR. JANOSKY: Thank you. There, you go.

DR. SKINNER: The normal situation from the time I have served on panels in the past is that the company presents with a PMA that has had 100 patients in the control group and 100 patients in the study group or some number that appears to be the appropriate number to provide a statistically significant result that there is safety and efficacy.

Frequently, those studies were designed without the aid of the FDA, and there are flaws in the study which raise questions. In that situation, the panel frequently recommended a postmarket surveillance, but the data that

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have been provided was data that was much cleaner than the data here.

This is a much different situation with a prosthesis that has been on the market for a number of years, has demonstrated by its mere repetitive use by surgeons like Dr. Curry that it has some efficacy and safety, but it doesn't have all the i's dotted and the t's crossed that would normally be found in a PMA.

I think that is what I, as the maker of the motion, and I think the rest of the panel, feels would be appropriate to cover the bases.

DR. JANOSKY: Dr. Stephens.

DR. STEPHENS: I have a question to Dr. Bertrand about your motion. Is your concern that the device doesn't work for this indication or is your concern regarding the patient indications for which it has been used in the past? I will tell you the reason that I ask.

This particular device, as someone who does a lot of temporomandibular joint surgery, I don't do this procedure, however, I know that the re-op rate for every other procedure that is used for that indication is very high, and my question is would you consider some study mechanism to look at the device.

DR. BERTRAND: What I base what I said on is that there is 30-year follow-up on people with internal derangements in Holland who had nothing done and did very well after a couple of years. It seems to me that with people who have primary internal derangements, to place something as an alloplast in, when we have that longitudinal data on patients, I think it is a first surgery and a step that might otherwise be avoided.

Now, if there is a way that you are going to divide those groups of patients into two groups of 100, and one is going to get a fossa implant, and the other group is going to be followed, I might be convinced otherwise.

DR. STEPHENS: I think the question is whether those patients are going to get this treatment or some other surgery is probably the fairer question.

DR. BERTRAND: Or is surgery even necessarily indicated and maybe just other treatments to support them.

DR. STEPHENS: The trouble I have is that it seems like we are making treatment decisions rather than decisions about the device, and it is hard to read the surgeons' minds in decisionmaking process to go forward with any type of surgical procedure. I understand your concern, but I also wonder if we are making treatment decisions rather than decisions related to the device.

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DR. BERTRAND: Well, as Dr. Skinner said, an ethical treatment doesn't necessarily mean another surgical treatment. In the time course of this supposed disease, it seems to burn out in most of the population epidemiologically at age 45 or 50, whether treatment is done or not.

DR. HEFFEZ: I believe the difficulty we are all having is that the implants have been around for many years, so the longevity is again their strongest suit. The problem is that the data is muddled because it involves patients who seem to have had a more aggressive approach using -- I take that back -- patients have had a device placed when, in the minds of many clinicians, other alternative treatments could have been performed, and therefore it is hard to interpret the data as presented. That is the difficulty, and I am just airing it.

DR. JANOSKY: Dr. Patters.

DR. PATTERS: Getting back to the issue that Mr. Ulatowski raised, I personally am convinced that the data presented by the sponsor shows safety and efficacy short term, but there were enough patients in my mind to validate the data at the six-month interval and perhaps at the one-year interval, but beyond that the dropout rate was so high, I feel now that to answer the question is this device safe and effective long term, which I believe is what the public wants to know, is it safe for long-term use, I believe that additional, well-designed, prospective studies need to be done, but I am quite happy that the data, as presented, makes the device approvable for at least the short-term use that the data support.

DR. JANOSKY: Dr. Gonzales.

DR. GONZALES: I have one other difficulty, and that is that others have tried to express or add to those other difficulties, and that is, the indications that are listed by the manufacturer are not the indications necessarily of the surgeon. Dr. Curry, has indicated that, in fact, one of his goals, the first goal listed on his slide, in his summary, of pain reduction.

We have also heard that from the patient advocates and others, that it keeps coming back to this issue that pain is one of the indications, whether it is indicated or not by the company, that is being used for the placement of this device.

So, I think that a condition on the motion or a couple of conditions on the motion would potentially expand the indications of the company, first, that a prospective study, that they are doing, be expanded and improved to

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include measures of pain type at one point in time, that is measurable, that is fixed, such as postprandial, for instance, as well as pain relief, and the medications used to modify pain, because this is not in a vacuum, these patients are undergoing other treatments for their pain.

So, in addition to the pain studies that you are doing presently, that this be expanded and improved. The second is that the patients should be told that the studies do not yet reveal that pain is significantly modified by the device, until these studies show that, if, in fact, they show that.

So, that would also modify the indication that the company presently places on the device potentially. So, that is a modification or a condition to the motion, the two that I have just stated.

DR. LI: If the notion is that you need a prospective clinical trial, if that is what you want, are you saying that you should vote not approved?

MR. ULATOWSKI: I think Dr. Patters put it very well, that in his instance, he has made a determination based upon the data in front of him that he is comfortable with the determination of safety and effectiveness, that there is sufficient valid scientific evidence for the indications for use albeit all the data is not there, but there is sufficient information for him to base a clearance decision.

If you don't believe that to be the case, if you believe that the data fundamentally are insufficient upon which to render a decision that it is safe and effective, that is quite another thing.

The conditions of approval in terms of clinical data usually follow the path of we need longer term data on a certain set of patients, we need certain data on types of patients or types of indications that weren't studied sufficiently perhaps, so those are the sorts of conditions that come into play with clinical data.

DR. LI: So, those would be approval with conditions.

MR. ULATOWSKI: That would be the typical form of conditions for clinical studies, but let me also, if I may just for a moment, I think the point is well taken by Dr. Skinner that--and Dr. Skinner I think missed my presentation the first day, early in the morning, where I spoke about the devices that come forward in 515(b) applications and that they typically are the longer, the older devices that have been around for quite some time, and the data is a mixed set of data, and it is more

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difficult for the panel often to come to grips with that information, but again, threshold is not an absolute threshold on safety and effectiveness. It is a reasonable assurance, not an absolute assurance, of safety and effectiveness which gives you a lot of leeway as a panel to consider within that context the sufficiency of the data.

DR. JANOSKY: Dr. Heffez.

DR. HEFFEZ: I believe any studies that are undertaken have to actually break up the population into specific rubrics, and the rubrics have to be indication/diagnostic categories, not categories such as persistent pain or failed prosthesis.

I think that in order to really understand if these devices are effective, we have to more accurately look at the indications/diagnosis.

DR. JANOSKY: As I understand the motion presented from Dr. Skinner and seconded, is that the motion is for approvable with conditions, and the conditions that were outlined by the panel. Is it my understanding, Dr. Runner, that you were able to keep track of them a little better than I was?

MR. ULATOWSKI: Madam Chairman, may I make a comment?

DR. JANOSKY: Yes.

MR. ULATOWSKI: I think one condition that was discussed yesterday and today in regard to this compensation of patients--support for patients in some way, shape, or form, I think there is no question it is well taken to encourage follow-up and motivate subjects in a study to return for follow-up is certainly laudable. As far as FDA's ability to mandate certain requirements of that sort of thing is extremely limited, but it is certainly appropriate for the panel to make recommendations of that sort for the benefit of the sponsors, so that they can build in these sorts of concerns into their studies and perhaps get the sort of follow-up that is necessary because even though we are not mandating certain compensations or whatnot to subjects, we have a high expectation for follow-up, which goes for every study, that is an aid to us, and when you have a lot of dropouts, and you have the sorts of concerns expressed here the last couple of days, so whatever the sponsors can do to improve follow-up, these points are well taken.

DR. JANOSKY: So, the motion outlined is approvable with conditions was presented by Dr. Skinner, seconded by Dr. Burton, and the conditions are --

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DR. RUNNER: That there will be a patient registry, that there be a prospective study for safety and effectiveness, that engineering and materials property data be presented -- I have on the patient-specific implant, on other implants, as well, is that correct?

DR. LI: In particular, the polymethylmethacrylate.

DR. RUNNER: And the PMMA -- that it have limited indications specifically the fossa-alone element should be removed, is that correct?

DR. BERTRAND: As a primary measure for first-time surgery for internal derangements.

DR. RUNNER: -- that measures of pain should be made at one point in time, and the study should include pain medications and other factors that are entering into the pain management of the patient; that the use of the PMMA device itself should be justified by the sponsor, and that in any study, the population should be broken up such that indications and diagnosis of the patient groups are clearly specified.

DR. JANOSKY: Dr. Runner, I also have long-term follow-up data.

DR. RUNNER: Could you be more specific as to what long term is?

DR. JANOSKY: I thought I had heard three years or longer -- three to five years.

DR. HEFFEZ: I would like to add one condition which was raised by some of the patient advocate groups, that a consumer hot line be available to answer questions, and then I have one question, is that the PMA presented, as the PMA stands, the eminence-fossa prosthesis was utilized, the indications were as stated by the sponsor.

Can we indicate that as a labeling issue that we are, as Dr. Bertrand brought up, that it wouldn't be used as a primary surgical procedure? Are we permitted to do that or is that splitting up the PMA as it was presented?

MR. ULATOWSKI: I think labeling recommendations are appropriate.

DR. RUNNER: So, you are saying that the fossa-alone would not be used as a primary surgical intervention?

DR. HEFFEZ: That is what Dr. Bertrand -- specifically for internal derangements. I concur, that is what Dr. Bertrand said.

DR. BERTRAND: What about meniscal perforations?

DR. HEFFEZ: I consider that internal derangement.

DR. PATTERS: I think there was another condition, that the data be broken up into the various implant types and resubmitted to FDA for their evaluation, because the data

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in the PMA was presented as group data, and that was in the staff's recommendation.

DR. REKOW: I think there needs to be heavier loads in the fatigue and wear, the recommendations that were made before, and the wear debris reanalyzed.

DR. LI: To add the presentation of the analysis of all retrieved devices that are available.

DR. REKOW: And confirmation that the wear data from the laboratory reproduces the retrieved wear patterns, wear patterns on the retrieved devices.

MR. ULATOWSKI: Just to bring the point back again, there is two conditions here concerning clinical studies. One states a prospective study to evaluate safety and effectiveness. The other condition is longer term follow-up. If you could fold those into something and restate it in the context that Dr. Patters characterized it, I think that would be more appealing as a condition to FDA.

DR. PATTERS: I didn't intend to make a separate recommendation for a separate study.

MR. ULATOWSKI: So, the two in fact are one?

DR. PATTERS: Indeed.

DR. RUNNER: Could I also ask for a clarification? There was the recommendation to justify the use of the PMMA. What would you consider as a justification process for using the PMMA device?

DR. LI: I am not quite sure how to put it in terms of the FDA, but it seems to me the PMMA product is one that demonstrably has higher wear, and demonstrably has more engineering structural weaknesses than the metal-on-metal.

So, given the fact that the metal-on-metal is available, and they don't seem to be able to present a clinical reason why you would pick one over the other, my question is why would you offer a device that is weaker and has higher wear.

So, the question is how would you justify, why, in a justification selling a higher wear product? I am not sure I put that in terms of a condition.

DR. RUNNER: Do you feel that the company should offer a justification if they continue to offer this portion of their line?

DR. LI: I would say absolutely.

DR. BURTON: I would agree with that. I think that if they want to continue to offer that particular product, I think they have to justify the fact that it continues to be offered in light of some of the engineering things,

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and the fact that it may wear through the material, obviously, then, you have something. We keep saying that these don't have a life span. The point at which it wears through the PMMA, you have altered the product to the point that I think that it does have a life span, and then if it continues to be offered, then, the patient needs to be informed that that particular version has a life span of whatever, which can be determined from adequate wear studies.

DR. HEFFEZ: I believe that if a prospective study is done where the proper diagnostic categories are developed, it is possible to address something that Dr. Skinner brought up, it is possible that the numbers may reflect an ability to establish a control.

So, I would prefer to say that is my preference, I ask for the panel's input, prospective studies with clinical controls where possible, and I would suggest amending the original proposal to remove the word "controls" and place the control into the condition.

DR. REKOW: Tim, can I ask you a practical question? We have come up with a pretty long list. Are we talking ourselves into a different recommendation?

MR. ULATOWSKI: I have seen some long lists in terms of conditions in the past. I think when we look at it, we will try and make some sense out of it, what is appropriate to do before we clear it if we can't see our way through to a clearance without certain data, but I have seen a mix of information from engineering to clinical under conditions. So, I don't think you have changed the scenario yet, in my mind. I had the fundamental, to me a pivotal point, which was answered by Dr. Patters and others, so that was my primary concern.

DR. JANOSKY: As I understand the motion, it is approvable with conditions, and the conditions that were just outlined--shall we redo those conditions again or are they clear in everyone's mind--read the conditions is necessary? Dr. Runner, please.

DR. RUNNER: I think I have separated them up into three sections. One is the prospective study with controls where possible, to gather long-term data, i.e., three to five years, with the measurement of pain at one point in time with an indication of the pain medications and other interventions that are associated with this patient population. The study should also break up the population into indication and diagnosis for use, and should also have the data broken off into separate implant types.

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The company should also resubmit the data in the present PMA, separating the data out into separate implant types.

The sponsor should also justify the use of the PMMA data with either literature or engineering testing to indicate why this device with its increased wear should continue to be marketed.

Labeling should indicate that a decrease in pain has not been found in long-term studies with this device.

Engineering data should include more testing on materials property and specifically on the PMMA device, the patient-specific device, and the fossa-alone.

There should be a consumer hot line set up, and in the engineering data, heavier loads should be used in the fatigue and wear data with debris analysis, and there should be an analysis of any and all retrievals with wear data correlated with lab data.

DR. HEFFEZ: I would clarify the consumer hot line so that the patient actually has their questions answered. It is easy to say a hot line is established. So, I would say a consumer hot line should be established in order to respond directly to patients' concerns and offer avenues for resolution of their complaints.

DR. JANOSKY: Dr. Runner, did you have the item of patient registry? I might have just missed it when you read it.

DR. RUNNER: I may have missed it. There was a patient registry.

DR. GONZALES: Can I add one other thing? Where you stated that patients should be told that studies do not reveal that pain is significantly modified, that really should read patients should be told that the studies do not yet reveal that pain is significantly modified. I don't think that the studies disprove or prove the impact on pain, and I wouldn't want the other condition that patients get the impression that this device will not help their pain, because the studies have not been done, so I would add the "do not yet reveal."

DR. JANOSKY: So, the motion is for approvable with the conditions, the conditions outlined as read to us by Dr. Runner.

At this time I would like to call for a vote. I will start with Dr. Patters.

DR. PATTERS: I vote in favor of the motion because I believe that the company presented sufficient data to determine safety and effectiveness of their device short term.

DR. JANOSKY: Dr. Li.

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DR. LI: I vote to approve with the conditions read. I think the thing that saves the device is that it has been out for 30 years. I think it is unfortunate that after 30 years, the data isn't tight enough to demonstrate everything that it ought to demonstrate, and the performance is in some ways a mismatch with other laboratory data, and I think that gap needs to be closed.

DR. JANOSKY: Dr. Gonzales.

DR. GONZALES: I vote for approval of the device with the conditions that have been stated. I think that the indications, that there is a mismatch between the indications as stated by the manufacturer and the way the device may be used in a lot of cases, and I hope that these studies will help to clarify that.

DR. JANOSKY: Dr. Rekow.

DR. REKOW: I vote to approve it as stated with the conditions and the justification is essentially a repeat of what Dr. Li has said.

DR. JANOSKY: Dr. Burton.

DR. BURTON: I vote for approval with conditions as read. I concur with the fact that the longevity of the device as shown safety and efficacy within the standards that are necessary, however, its laboratory data and its long term data collection is insufficient to promote long term support.

DR. JANOSKY: Dr. Hefez.

DR. HEFFEZ: I vote in favor, and to reiterate, the longevity of the data is the strongest suit for the sponsor. I feel that the conditions that have been outlined will greatly improve consumer awareness and lend greater confidence to the data presented.

DR. JANOSKY: Dr. Skinner.

DR. SKINNER: I vote for approval with the conditions as read.

DR. JANOSKY: Dr. Stephens.

DR. STEPHENS: I vote for approval with conditions, and would hope that the conditions will help to improve the confidence in this device, which is without question very much needed in the clinical community.

DR. JANOSKY: Dr. Bertrand.

DR. BERTRAND: I vote for approval with conditions, since the conditions will help us understand the restrictions by which these implants should be used, and will help collect data that will better define the long term effectiveness or lack of effectiveness in specific situations.

DR. JANOSKY: So, the motion carries.

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The rationale for the votes. Dr. Skinner, did you provide a rationale for your vote?

DR. SKINNER: I agree with Dr. Patters. I think that the short term efficacy is demonstrated, and the long term efficacy needs to be demonstrated through further investigations.

Am I correct that everyone else provided a rationale for their vote? Yes. Okay.

One more item of business in terms of the motion. The conditions, to see whether they are met or not, would you want it to come back to panel or to go back to FDA?

I hear a panel response. Dr. Patters, you are saying panel? Any dissenting? Dr. Heffez?

DR. HEFFEZ: I agree.

DR. JANOSKY: Dr. Bertrand?

DR. BERTRAND: Panel.

DR. JANOSKY: I see a lot of head nods. It is unanimous in terms of coming back to panel.

We have some closing comments from Ms. Scott.

MS. SCOTT: I just would like to remind all of the attendees to the meeting today that if you would like transcripts or summary minutes from the meeting, there is a small sheet of paper on the registration table indicating the numbers that you can call or the addresses that you can write to, to request that information.

Also, I would just like to remind all the attendees that you may call the FDA Advisory Committee Information Line for future information regarding upcoming Dental Products Panel meetings as the information becomes available. For long-distance callers, you may call 1-800-741-8138, and for local callers, you may call 301-443-0572. The code number for the Dental Products Panel is 12518. There is also a sheet of paper on the registration table that has this information on it, also.

Lastly, we have one of our former panel members--and when I say panel members, meaning a voting member to the panel--who recently came off as a voting member, but has continued on as a consultant to the panel, and that is Dr. Willie Stephens. We have a plaque of appreciation to present to him at this time.

[Applause.]

This plaque is from the Center for Devices and Radiological Health, U.S. Food and Drug Administration. Certificate of Appreciation presented to Dr. Willie Stephens in recognition of distinguished service for the Dental Products Panel of the Medical Devices Advisory Committee, term from February 24th, 1995, to October

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31st, 1998.

Signed by Dr. Burlington, our former Center Director, and also our former Acting Commissioner, Dr. Friedman.

[Applause.]

DR. JANOSKY: The meeting is ended.

[Whereupon, at 3:40 p.m., the meeting was adjourned.]

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