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FOOD AND DRUG ADMINISTRATION

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

OFFICE OF DEVICE EVALUATION

MEETING OF THE DENTAL PRODUCTS PANEL

OPEN SESSION - VOLUME I

Monday, May 10, 1999

10:30 a.m.

Holiday Inn Gaithersburg
Walker Whetstone Room
Two Montgomery Village

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Gaithersburg, Maryland

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Pamela D. Scott, Executive Secretary

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Mark Patters, DDS, Ph.D.

CONSUMER REPRESENTATIVE

Donald S. Altman, DDS

INDUSTRY REPRESENTATIVE

Alton Floyd, Ph.D.

PATIENT REPRESENTATIVE

Theresa Cowley

TEMPORARY VOTING MEMBERS

Peter Bertrand, DDS
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Leslie Hefez, DMD, MS
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E. Diane Rekow, DDS
Willie Stephens, DDS

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Timothy Ulatowski
Dr. Susan Runner
Angela Blackwell
Dr. R. Murty Ponnappalli

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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 for May 10 and 11, 1999. My name is Pamela Scott. I serve as the Executive Secretary for the Dental Products Panel. At this time, I would like to read into the record several administrative items.

The first item is the 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.

At this time, I would just like to read 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 panel meeting on May 10 and 11, 1999; Dr. Leslie Heffez, Dr. Elizabeth D. 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.

The last administrative item is the appointment of temporary panel chairperson. I appoint Dr. Janine Janosky to act as temporary chairperson for the duration of the Dental Products Panel meeting on May 10 through 11, 1999. For the record, Dr. Janosky is a special government employee and is a voting member of the Dental Products Panel.

Dr. Janosky has undergone the customary conflict of interest review and has reviewed the issues to be considered at this meeting. Signed, Dr. Jacobson, Acting Director, Center for Devices and Radiological Health, May 6, 1999.

At this time, I would like to reintroduce our panel members for today. The panel members are listed in the back of the agenda.

As I stated previously, Dr. Janine Janosky is acting as our chair today. She is an assistant professor with the Department of Family Medicine and Clinical Epidemiology with the School of Medicine at the University of Pittsburgh. We also have with us Dr. Mark Patters who is the Chairman of the Department of Periodontology at the College of Dentistry at the University of Tennessee in Memphis, Tennessee. He is a voting member to our panel. Our consumer representative is Dr. Donald Altman who is the Chief of the Office of Oral Health with the Arizona Department of Health Services in Phoenix, Arizona. Dr. Alton Floyd is our industry representative. He is the President of Trigon Technology, Inc. in Edwardsburg, Michigan.

Our patient representative for today is Ms. Theresa Cowley who is the President of the TMJ Association in Milwaukee, Wisconsin. We also have with us today Dr. Peter Bertrand who is the Director of the Oral Facial Pain Clinic and a Specialty Advisor for Oral Facial Pain and TMD with the National Naval Medical Center in Bethesda, Maryland.

We have Dr. Richard Burton who is an assistant professor of oral and maxillofacial surgery with the Department of Hospital Dentistry at the University of Iowa Hospitals and Clinics in Iowa City, Iowa.

We have Gilbert Gonzales who is associate professor of neurology at the Memorial Sloan Kettering Cancer Center with Cornell University in New York, New York. We have Dr. Leslie Heffez who is the professor and Department Head of Oral and Maxillofacial surgery at the University of Illinois at Chicago in Chicago, Illinois.

We also have Dr. Stephen Li who is a senior scientist with the Department of Biomechanics and Biomaterials at the Hospital for Special Surgery in New

York. We have Dr. Diane Rekow who is the Chairperson of the Department of Orthodontics at the University of Medicine and Dentistry of New Jersey in Newark, New Jersey.

Dr. Harry Skinner will be with us tomorrow. He is professor and Chair of the Department of Orthopedic Surgery with the University of California at Irvine in Orange, California. And we have Dr. Willie Stephens who is an associate surgeon for the Division of Maxillofacial Surgery at Brigham and Women's Hospital in Boston, Massachusetts. He is also with the Harvard Oral and Maxillofacial Surgery Associates in Brookline, Massachusetts.

We would like to thank our panel for being present today with us. I would also like to state the FDA participants for today. We have Mr. Timothy Ulatowski who is the Director of the Division of Dental, Infection Control and General Hospital Devices with the Office of Device Evaluation, Center for Devices and Radiological Health, the Food and Drug Administration.

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, Office of Device Evaluation, Center for Devices and Radiological Health.

We have Ms. Angela Blackwell who is a biomedical engineer also with the Dental Devices Branch within the Division of Dental, Infection Control and General Hospital Devices. And we have Dr. Murty Ponnappalli who is a mathematical statistician with the Division of Biostatistics in the Office of Surveillance and Biometrics.

Thank you very much.

Also, I would like to remind all of the participants for today and all the people who are attending the meeting today that if you have not signed in, please do so at the table at the front. Also, if you would like summary minutes or a transcript from today's meeting, there is a sheet on the front table that gives you the address and the phone number that you can contact to receive that information.

Also, if you have not received an agenda or some of the handouts that we have today, those are also at the front sign-in table.

At this time, I will turn the meeting over to Dr. Janosky.

DR. JANOSKY: Good morning. At this time, we are going to have an update of FDA activities. There are two items on the agenda. One is a Y2K update by Mr. Neil Ogden followed by a postmarket surveillance presentation by Dr. Tom Gross.

Update of FDA Activities

MR. OGDEN: Good morning, panel members and Dr. Janosky. I am just going to briefly go over the FDA's and the Center's Y2K activities.

The Center and the FDA ask that--at least this presentation was given at once a year for the last two years at a panel meeting for each of the panels. You lucky folks get to hear it today.

Digital doomsday and medical-device problem, healthcare problem, millennium bug syndrome.

"Upwards of 80 percent of existing PCs are unreliable." This was an ad from 1996. Many medical devices utilize personal computers or PCs from operational control, pacemaker controllers, central monitoring stations and clinical lab instruments.

Other quotes from 1996 include, "The largest computer initiative in history needs to begin today," and,

"At one second after, more than 25,000 healthcare systems will not be working properly."

Medical devices are subject to Year 2000 problems. Microprocessor or PC-controlled products, software applications, device interfaces to databases and recording systems, embedded chips for date display or recording.

What is the Year 2000 problem? Failure of computer systems to properly process or display dates due to representing the year using only two digits or other date-related problems such as failure to recognize a leap year. Example; 00 leads to confusion between the Year 2000 and 1900.

Definition of Year 2000 compliance. For the purpose of the database, Year 2000 compliance means with respect to medical devices and scientific laboratory equipment that the product accurately processes and stores date-time data including, but not limited to, calculating, comparing, displaying, recording and sequencing operations regarding date-time data during, from, into and between the 20th and 21st Centuries and the Years 1999 and 2000 including correct processing of leap-year data.

Request of the panel: to provide advice regarding problematic devices from panel's domain of expertise; identify types of devices which, because of their use of dates could present risks to patients if not addressed; suggestions to the Center for Devices and Radiological Health regarding actions to reduce risks from the Year 2000 problems.

The FDA set up a database and there is the worldwide web address, www.fda.gov. Just select on the Year 2000 item under that address.

Other CDRH and FDA activities include letters to manufacturers, guidance to manufacturers, established

database of product information on Internet, monitoring and assessment activities, educational activities for manufacturers, clinicians and the public.

You can contact your panel executive secretary or you can contact Mr. Tom B. Shope at this address, phone number, e-mail address if you have further questions or issues or you know of devices that could be subject to this problem.

What has FDA done regarding Year 2000 date problem and medical devices? Internal assessment of potential impact and vulnerable devices. In June, 1997, a notification letter to manufacturers that advised of the problem, told how FDA will address this problem in premarket review. New submissions were not required for repairs which are only date-related. Repairs and updates before the impact would not be classified as recalls.

Participation in biomedical working group, federal users of devices and scientific equipment; a working group chaired by the Department of Health and Human Services; consolidated request for information in January, 1998; private and public healthcare organizations have the same information needs.

An FDA website was established in the spring of 1998 and guidance on FDA's expectations was issued in June, 1998.

Additional letters to manufacturers were sent out on June 29, 1998, September 2, 1998 and on September 21, 1998 a letter on manufacturing process concerns was issued. Additional communications planned included speaking with the manufacturers, healthcare facilities and clinicians and consumers.

The biomedical equipment database is an FDA-operated worldwide website and includes data provided by manufacturers, voluntary submission of data, certification by manufacturers, continually updated, is searchable by the manufacturers and is downloadable for people to use the information.

It also includes manufacturers lists of products which are impacted, noncompliant, so people can search to see if a device they have may be noncompliant. The manufacturer certifies that all products, both current and past production are complaint. Manufacturer certifies that none of their products use dates and the manufacturer provides a worldwide web link to their website where requested information is provided.

Contained in the January 21, 1998 letter to manufacturers, based on a definition in the Federal Acquisition Regulations, comprehensive product information and non-compliant does not mean a risk to the public health. What does the product database show? Many companies have not yet recorded assessments in progress. Most noncompliant products involved date

display or date recording--i.e., date stamping. A limited number of products with significant operational problems. PC-based products have PC-type problems. Manufacturers are providing solutions in a variety of approaches.

The FDA's role regarding recalls related to the Year 2000 problem. FDA can require recall of devices which present a significant risk to the public health. FDA will monitor reports of Y2K problems with emphasis on devices that could present significant risk to patients and investigate and take action where warranted.

CDRH and FDA future activities include establishment of a biomedical equipment clearing house and agreement with the Department of Veteran Affairs; expansion of the database; outreach communications with industry, clinicians and consumers; vigorous action on products which present significant risks; and increased inspection emphasis on Y2K problems.

Health-facilities issues; inventory and assess devices used; obtain information on device status; test devices for Y2K compliance; check interconnected or network devices; check device-information system connections; plan for or develop workarounds, upgrades or replacements; and develop contingency plans.

And that is the last slide. To conclude, I would just like to say that the FDA and the Center have taken the Y2K problem very seriously. We have been involved in a number of activities as you just heard about. We would like all of you to also take this issue quite seriously.

Thank you.

DR. JANOSKY: Thank you.

Are there any questions?

MR. ULATOWSKI: That slide for the panel, what the panel can do, is there a systematic means of interacting with the panel members? Who do they contact?

MR. OGDEN: They can contact the executive secretary, Pam Scott, or they can talk to Tom Shope at the numbers and information that was given there. Those are the two main people that we are supposed to focus the information through from the panel.

DR. JANOSKY: Any comments or questions from panel members?

Thank you.

The next is Dr. Tom Gross who is going to speak on postmarket surveillance.

DR. GROSS: I would like to take a few minutes today to talk to you about postmarket evaluation at CDRH. We in the Office of Surveillance and Biometrics believe that it is important that advisory panels are aware of postmarket programs because these activities may directly affect your deliberations about the product's safety and

effectiveness.

The objectives of this presentation are threefold; one, to describe a few of the key methods of device postmarket evaluation at CDRH; two, to present challenges in better accomplishing postmarket evaluation; and, three, to describe the pivotal role that advisory panels can play in this arena.

This slide entitled, "From Design to Obsolescence," makes three key points. One, it emphasizes the fact the medical devices have a definable life cycle from initial design to lab and bench testing, clinical testing, FDA review and, importantly, postmarket evaluation.

Two, that there are life cycles, that there are feedback loops throughout this life cycle leading to continuous product improvements. Postmarket evaluation and its related programs have an important part to play in this process.

The third point is that the clinical community, including the advisory panel, has a very important part to play in this process, not only on the premarket side but on the postmarket side as well.

As products move into the marketplace, questions of public-health interest may arise in the postmarket period. There may be questions about the long-term safety of a product, about the performance of a device in community practice as it moves out of the narrow confines of clinical trials.

There may be questions about the effects of change in user setting; for instance, moving devices from a professional setting to home-use settings. There may be questions about the effects of incremental changes in technology which may bring to question the performance of the device. Lastly, there may be unusual adverse events or patterns of adverse events which may present public-health questions.

Now, let's talk about some of these programs that are related to these public-health questions. The first program I would like to discuss is the medical-device reporting program. This is a nationwide surveillance system of voluntary or mandatory reports of adverse events related to device use.

Beginning in 1973, CDRH started receiving voluntary reports. In 1984, manufacturers were required to submit reports of death and serious injury if a medical device may have caused or contributed to that event to the FDA. They were also required to report malfunctions to the FDA as well.

Beginning in 1990, all user facilities, principally nursing homes and hospitals, had to report deaths to the FDA and serious injuries to the manufacturer.

All told, we have received about 1 million reports since its inception and, beginning in the early '90's, FDA continues to receive about 100,000 adverse-event reports per year. These are submitted on standardized forms and data are collected on device-specific event description, pertinent dates, and patient characteristics.

Unfortunately, many of the reports often have very limited information. Even basic demographic information such as age and gender is missing from the majority of reports. Nonetheless, they can provide FDA with critical signals about potential public-health problems.

There may be several actions that are prompted by the MDR program. When we investigate adverse events, this may lead to a directed inspection of a manufacturer facility. These investigations may ultimately lead to product injunction or seizures. It may lead to product recalls, as in the case of dental cements or endodontic probes.

It may also result in patient and physician notifications as in the '94 notification about Proplast.

And they may also prompt additional postmarket studies.

Now let's turn to the two postmarket authorities that we at CDRH have. One is entitled postmarket surveillance or section 522 and the other is the postapproval authority under the PMA regulation. Section 522 originally mandated in SMDA 1990 was changed in FDAMA 1997.

Now, in 1990 version, the statute had lists and categories of devices the manufacturers of which were required to do postmarket-surveillance studies on. In the '97 version, there are no longer those lists and categories. However, FDA has the discretionary authority to impose postmarket-surveillance studies on devices that have particular public-health questions.

Now, postapproval refers to class III PMA products. These studies are better known as "condition of approval" studies. Again, they are reserved strictly for PMS products. 522 extends its coverage to class II and III 510(k) products whose failure may present a public-health problem.

Now, both authorities are seen as a complement to the premarket process in continually assuring the safety and effectiveness of products in the marketplace.

In implementing the statute, the 522 provisions, we publish criteria in the form of guidance to help us in our considerations of when to impose postmarket surveillance on class-II or class-III products. The principal criteria is that we feel there should be a critical public-health question.

This may be driven by a for-cause event, an

adverse event that is worthy of further investigation. It may be linked to new or expanded conditions of use such as moving from professional to home use. It may be linked to the evolution of technology. There may be questions about the durability of the product as it changes in its technology.

The second criterion is that there should be consideration of other postmarket strategies, that imposing question 522 to address this particular public-health question may not be the most appropriate tool. Perhaps the question could be answered through the MDR program or through other mechanisms such as the quality-systems mechanism.

Thirdly, the study should be practical and feasible and a related question should be how will the data be used. This becomes particularly relevant when we deal with rapidly changing technology. By the time the studies are done, the data may be obsolete.

Lastly, what is the priority of this particular public-health question? What is the magnitude of the risk and the benefit, the extent of population exposure, the seriousness of the outcome at hand. This should all be taken into account to help us prioritize these studies.

Once we decide to impose postmarket surveillance under section 522, we should make sure that the study design is best matched to the public-health question. There are lots of study designs to choose from aside from going the route of clinically rigorous studies.

I have listed a few possible study designs. It may be as simple as doing a detailed review of the complaint history or literature, doing non-clinical testing of the device, using the existing databases, doing something simple such as telephone or post-care follow-up of patients, and then doing something more sophisticated such as use of project registries, case-control studies and, in rare events, turning to randomized trials to answer these questions.

These are some of the frustrations we have experienced in the postmarket period in terms of implementing postmarket surveillance under 522. These are challenges that face us today.

I mentioned previously the rapid evolution of technology can make studies obsolete. There may be lack of incentives for industry. Doing a postmarket study for industry, they may only see the downside of doing these studies because it may only bring bad news about their product. We have to change that paradigm and make it of interest to industry to participate in these postmarket studies.

There may be lack of interest in the clinical community. Clinicians may be more interested in studying

cutting-edge technology as opposed to addressing public-health issues related to mature technologies.

Lastly, there may be a lack of a clearly specified public-health question. We ran into this situation in the 1990 version of section 522 in studying standard vascular grafts. These are mature technologies.

Industry and ourselves felt that many of the questions had already been addressed. So, in that particular instance, it was a device looking for a public-health question.

What is the challenge to the advisory panel? It is really a challenge to us all. That is when considering postmarket studies, whether postapproval or 522, we need to make sure that this is of primary importance. We can envision, in the future, coming to you, the advisory panel, for your input on potential 522 studies.

We need to clearly specify the public-health question and we need to note the clinical and regulatory relevance of answering the question. In other words, what will we do with that data? Are the data there to reassure us that the postmarket experience is similar to the premarket experience?

Is it there to address residual questions? Can it be done in a timely fashion?

Lastly, what is the future of MDR and postmarket surveillance? Well, with regard to medical-device reporting, we are moving more towards summary reporting and away from individual reporting for efficiency sake. We are exploring the opportunities of using a sentinel reporting system using a subset of user facilities to report to us rather than the universe in an attempt to get high-quality reports.

We are moving into the electronic age and we hope that reports could be submitted electronically as opposed to hard copy. We hope to integrate more with the quality-systems regulation especially in trending requirements of adverse-event reports. And we are beginning a process of exchanging adverse-event reports internationally.

What is on the front for postmarket surveillance? As I have alluded to previously, we need to have at our disposal a wider variety of design approaches. There needs to be more collaboration with industry and the clinical community, and we need to have expanded access to different data sources to help address these important public-health questions.

Thank you.

DR. JANOSKY: Thank you.

Are there any comments or questions from the panel? Again, thank you.

At this time, we will move into the open public

hearing. At issue today is a review of a premarket approval application by the sponsor TMJ Concepts.

For the open public hearing, we have five presentations. The order in which we will go through these presentations is as follows: the first will be by Ms. Lisa Brown from the TMJ Association. The second will be by Mr. Kevin Clark from the TMJ Association. The third will be by Diana Zuckerman from the National Women's Health Network followed by two letters which will be read into the record by Ms. Pamela Scott.

Each of the presenters are given ten minutes and I ask the speakers to state whether or not they have any involvement included, but not limiting to, financial involvement with manufacturers of the products being discussed today or with their competitors.

Before we hear from Ms. Lisa Brown from the TMJ Association, Dr. Susan Runner has some comments for us.

DR. RUNNER: Just briefly, it was brought to our attention that the terminology for these different devices today can be confusing because of the use of the word TMJ implants, et cetera, in many of these devices.

So, for the purposes of this meeting, when we refer to TMJ implants, we are talking about the generic device type. When we are referring to the TMJ Concepts device, we will refer to it as the TMJ Concepts device. When we are referring to the TMJ Implants Inc. device, we will refer to that as the Christensen device.

I have checked this with the sponsors and they are all in agreement with that. So we have TMJ implants is the generic device type, TMJ Concepts is the device we are considering today. And the Christensen device is the third device type.

Thank you.

DR. JANOSKY: Thank you.

Ms. Lisa Brown from the TMJ Association.

Open Public Hearing

MS. BROWN: Good morning. My name is Lisa Brown. I am a TMJ patient and board member of the TMJ Association. I have no involvement with manufacturers or products being discussed today, financially or otherwise, or with their competitors.

I would like to thank the FDA for the opportunity to testify before you today. The TMJ Association was founded by two women who were experiencing problems with their TMJ implants. In the thirteen years of its existence, the Association has grown from a local to a national organization in touch with thousands of TMJ patients.

With the advent of our website, newsletters, e-mail and other contacts, we have heard from many thousands more nationally and internationally. We are here today to speak for over 10 million people in

America, the majority women, who suffer pain and dysfunction in and around the temporomandibular joint.

Not all of these women need implants. But for those who do, it is the responsibility of the FDA and the panel to assure them that safe, reliable and effective devices are available, ones that will give them back the proper use of their jaws, ideally allowing them to bite, chew and swallow food, to smile and kiss, to laugh, talk and sing and to do so without pain or discomfort.

I have with me samples of letters and comments we have received from people within the last several years describing their experiences with TMJ implants. We feel there is no better way of communicating these patients' perspectives than to let you hear them in their own words.

I will start by quoting a woman who called the Association. The bilateral devices she received were her first implants. She said, "The implants hurt so bad I cry all of the time. My surgeon told me these implants work 97 percent of the time."

Like so many others, this lady thought she would be rid of TMJ problems after she received these devices, cured so to speak. She had the devices implanted in order to regain her quality of life and thought that a 97 percent chance of being cured was almost a guarantee of success. In reality, what she received was increased destruction of her jaw joints and her life. She wanted to know if she was the only one.

What is sad about this is the only comfort we could offer her was that she is not alone and that there are many others. We desperately need safe and effective devices and we desperately need a solid scientific base that goes at the heart of the problem of what cause TMJ diseases and disorders and how best we can treat them.

Now let me turn to the letters. From Missouri: "I have piercing pains in my jaw joints since the most recent implants were put in. I called the implant manufacturer and they won't send me anything. I have also called the FDA. I hear the implants cracking."

From Pennsylvania: "I continue to work because I don't want this to conquer me. I am in very bad physical condition since my implants and my coworkers see it. My eyes are black and blue and I have lymphoma. When I see a doctor or surgeon now or go to the pain clinic, they tell me it is all in my head. If I add up what I have spent on treatments, it is over a million dollars."

From South Carolina: "I developed a massive lump when my first implants were put in. When I called the surgeon, he blamed me for flying in an airplane and then abandoned me. I have had to have my parotid gland removed and my eyes sown shut for a year. My most recent implant failed, had to be removed and they left my jaw

with nothing for more than a year. I now have a rib graft and I am going to a pain clinic."

From Mississippi: "My doctor now has me on shark cartilage and magnets for pain. Is that a good idea around my implants? I have severe pain 24 hours a day and I can't hold my head still. It bobs up and down from spasms."

From Delaware: "I am now on two seizure medicines. I had to have the implants removed because the screws came out. The hip cartilage didn't work at all and now I have a new set of the same implants again.

I am now having problems with the hip that they took the cartilage from."

From West Virginia: "I have excess bone growth and scar tissue after my implant. The surgeon placed a bite block in my mouth during surgery and I woke up screaming. The surgeon said it was the drugs and put me in detox the day after surgery. Now no one will listen."

From Michigan: "My vision is blurred terribly, but the surgeon told me there is nothing wrong, the implants look fine. The implants I have now are loose. They are not holding so I can't eat anymore. Physical therapy just makes things worse."

From California: "I am not doing good after these implants. Doctors and surgeons want nothing to do with me now. I need a competent physician. I want to know how victims of the lack of standard of care can protect themselves. How am I supposed to get insurance coverage now?"

From Florida: "Since I had these implants put in, I am still having four more seizures per day and terrible double vision even though I am taking dilantin. Now, I have no money for the doctor and don't know what to do."

From Hawaii: "My surgeon tells me that the Vitek implants I had are eating away at my current implants. I am getting a lot of adhesions. My ears burn and ring and I am constantly tired. I have no energy."

From Ohio: "I keep getting a spiel about the false-positive/false-negative results on my test. Since my implant is failing, my oral surgeon thinks I need a new condyle part of the same implant. My neurologist says not to have any more surgeries because of the neurological damage that already exists. Then my oral surgeon says, 'You need surgery.' What do I do?"

From Georgia: "My surgeon told me, 'You all have this disease. It is not the device. It is the disease. Then he told me that there is wear on my current implants, but he only puts them in; he doesn't take them out.'"

From Canada: "Since these implants, I am unable to work and have a constant fever. I have to take

Demoral for pain. Now my joints are coming out through my skin and I am not sure what to do."

The TMJ Association was begun when problems were occurring from Vitek and Silastic TMJ implants. To quote the late Congressman, Ted Weiss, "These devices fail 100 percent of the time." When Vitek implants were finally recalled by the FDA in December, 1990, the disaster for patients was swept under a rug, a rug of denial, abandonment, mistrust and abuse.

The recall was not the end of the disaster, however, as Silastic became a big seller along with a dozen other devices. Many of these devices slipped through the FDA approval process by being called "custom devices," or qualified as being substantially equivalent to the devices already on the market.

The TMJ Association has been asking for valid clinical data for years now. We, the patients, need hope and reassurance that there are safe and effective devices to restore jaw function, but we have been burned before and we are twice shy. We do not know whether the devices under consideration today are safer or more effective than the Vitek or Silastic devices.

No one can even tell us how many of these devices have been implanted. No one can tell us why we have received hundreds of calls from patients who say they are failing. The problem is especially tragic for people originally injured by Vitek and Silastic devices.

Their lives are a constant torment. They need replacement devices, but continue to experience implant failure after failure in a pattern that increases complications and diminishes the quality of their lives.

For the patients who have had no prior implants, and who need devices, a potential for disaster exists. Members of the panel, it is no exaggeration to say that lives are at stake. We respect the science and clinical experience you bring to the issues before you. The decisions you make in the course of the meeting are critical to us and to the millions of TMJ patients we represent.

Thank you.

DR. JANOSKY: Thank you.

Mr. Kevin Clark representing TMJ Association.

MR. CLARK: Good morning. My name is Kevin Clark. I have no involvement, financial or otherwise, with the companies here today and tomorrow or any of their competitors.

By profession, I am a stock trader and a partner in Hartland Advisors, a Milwaukee-based money-management firm. By marriage, I am Heidi Clark's husband. Heidi is a beautiful 35-year-old woman who had a promising career which was nipped in the bud by multiple surgical procedures involving multiple types of implants.

Heidi, as many TMJ patients, is in desperate need of her fourth and fifth surgical implants, total joints, because the last three have failed. Perhaps it was the many evenings when I returned from work to find Heidi writhing in pain, begging me to help her take her life or when I visited her in locked word after the total joints were implanted, but, at some time, I knew something needed to be done to change the TMJ system.

Two years ago, I became a member of the board of the TMJ Association. I joined this patient-advocacy organization because it is fighting valiantly and against incredible forces to change the face of TMJ by demanding the science to explain the etiology and pathogenesis of this disease as well as the science underlying the many treatments being recommended to the patients.

In short, our motto is, "Show us the science." This philosophy has evolved from being sold hope along with the treatment only to have it shattered time and again with the lives of the patients and we who love them.

Lisa Brown has given you a picture of what life can be like as a result of implantation of a TMJ device.

Needless to say, we believe there are some patients which these devices have helped and improved their life, but we have heard from only a few or a handful of them.

The ones we have heard from are those whose lives and health have been increasingly compromised, worsened, or, in some cases, even resulted in death. This panel meeting is a monumental event in the lives of TMJ patients. TMJ devices, some on the market since the early 60's, are being implanted a fourth of an inch from one's brain, fell through the cracks of the FDA classification process.

It was only in 1992, during the Congressional hearing entitled, "Are FDA and NIH Ignoring the Dangers of Jaw Implants?" that the late Congressman, Ted Weiss, relentlessly asked the FDA, "When will you classify these devices?"

Upon the third time, Mr. Benson responded, "This month." A month short of seven years, and ten years after the Vitek class I recall, TMJ will finally learn how safe and effective TMJ Concepts and TMJ Implants, Inc., devices are.

The panel meeting is monumental in another aspect. It is the first time that a TMJ patient will voice the concerns of all of us. In 1993, the Human Development Report of the United Nations stated, "People today have an urge, an impatient urge, to participate in the events and processes that shape their lives. Properly harnessed, this resource can become a source of tremendous vitality and innovation."

We thank the FDA for recognizing the importance

of letting someone speak for the many who can't. The TMJ patients issue a challenge to this panel and, ultimately, to the FDA. The challenge is to simply critically evaluate the scientific information that these two manufacturers have submitted to you.

We ask nothing more from you than to evaluate submitted studies and determine whether these products are so safe that you would have them put into your child, your spouse, or even yourself.

Thank you very much.

DR. JANOSKY: Thank you, Mr. Clark.

The next speaker is Dr. Diana Zuckerman from the National Women's Health Network.

DR. ZUCKERMAN: I am Dr. Diana Zuckerman. I am on the board of the National Women's Health Network which is a private, non-profit, consumer organization that has no financial ties to the TMJ issue. The Network is dedicated to improving healthcare for women and is especially interested in making sure that medical products are appropriately regulated and that women have accurate information about medical products and procedures.

I am here to urge you to carefully consider whether the studies submitted for the PMA today and tomorrow prove that these products are safe and effective for long-term use. As you all know, TMJ implants are intended for long-term use and the history of jaw implants is that some implants have provided temporary relief in the short term and tragic consequences in the long term, as you have heard earlier today.

I have no experience with TMJ implants as a patient, but I have personally had a great deal of experience regarding FDA's role in the regulation of TMJ implants. For eight years, I worked as a Congressional investigator for the House subcommittee that has jurisdiction over all of the federal health programs.

In 1992, I urged the Chairman of that subcommittee, the late Representative Ted Weiss, to hold hearings on the inadequacy of FDA oversight of TMJ implants and I conducted the investigation for the subcommittee.

During our investigation, we were shocked that the FDA had allowed TMJ implants to be sold and continued to allow them to be sold despite very clear evidence of very serious, irreversible damage in many patients. At our hearing, which was held in June of 1992, James Benson, who was Head of the Center for Devices at FDA, promised--promised--the Congress that FDA would require the manufacturers to submit safety data through the premarket-approval process, "As swiftly as we can."

It was not long after that hearing that Mr. Benson left the FDA and went on to a leadership position

at HIMA, which is the Association for Medical Device Manufacturers. HIMA, of course, works very hard to keep devices on the market. Congressman Ted Weiss died a few months after the hearing on the TMJ implants and, as a result of his death, I also left the subcommittee.

It has taken seven years now, seven years, for FDA to finally hold these hearings on TMJ implants. I would have to say the system, so far, has failed that patients. These hearings are long overdue and it is now up to you to make sure that FDA finally gives these devices the scrutiny that they deserve.

I am a researcher by training and I realize it is very difficult, very, very difficult, to evaluate the effectiveness of these kinds of devices, particularly for long-term use. One particular problem is that so many of the patients have had other devices previously put in that have failed and yet you are supposed to evaluate these devices which are maybe different from the devices that these patients have had before.

But that is the real world. Those are the patients that are using these implants. That is the population that really does need to be carefully studied.

The damage caused by unsafe TMJ implants, as you have heard, can be serious, debilitating and irreversible.

I have spoken to patients whose lives have truly been ruined by the pain and serious health problems cause by their implants. As you have heard, these are patients who cannot eat regular food. They cannot speak or kiss without pain and there are those who can barely think or function because of the pain and the debilitating effects of pain medication.

It is unfortunate that, because of that very serious damage, that there are not more people who were able to come and speak to you today. They are not in a position to do that and so those of us who can come, it is our responsibility to tell you what it is all about.

When FDA determines that a medical device is safe and effective, patients are, of course, much more likely to use it. Since these TMJ implants have already been available for many years due to grandfathering and due to the lax regulation, the standard for approval should be even higher than is usually the case in a PMA.

If FDA gives approval to implants that are not really proven safe or effective, obviously, it undermines FDA as an agency and the trust that Americans have in FDA, in particular, and in their government more generally. So, in reviewing these PMA applications, the National Women's Health Network asks you to consider the following three issues.

Number one; is there clear evidence that the product is safe for long-term use, by which we mean more

than five to ten years, for patients who have not previously had any implants? How does the implant patients fare compared to patients who have not had any implants?

Number two; is there clear evidence that the product is safe for long-term use, again more than five to ten years, for patients who previously have had other kinds of implants? What is going to happen to those patients and how do those implant patients fare compared to other important patients who have previously had those kinds of implants but those implants were removed?

Three; if a patient has problems with one of these implants, do the problems persist after the implant is removed? What happens if an implant has to be removed? What happens to that patient? Can the implant cause irreversible damage even after the implant is removed?

Of course, I haven't seen the studies that you are going to be looking at this morning and reviewing. That is not what I am used to. I am used to having seen them before anybody else. But I can't, therefore, comment on the study design or the quality of the research. Based on my previous experience, I am concerned that they may not include a large random sample of patients who were followed for a substantial period of time, that they may not be evaluated as objectively as possible by individuals who do not have a financial interest in the outcome of the study.

Studies of selected patients or patients who have been studied for short periods of time, or samples were a large percentage of the patients have dropped out, will not provide the kind of information that you need to determine whether these implants are safe and effective.

So, based on the experience of many TMJ implants, it appears that, to paraphrase an old advertisement, "Implants are forever." Unlike most drugs, the detrimental effect of unsafe implants may be and can be and has sometimes been irreversible. So, any short-term safety data doesn't tell us what we need to know.

In order for you to do your job to make sure that TMJ patients are protected, it is essential that a substantial number of patients be studied for a long period of time and that patients not disappear during follow up. Please keep that in mind as you review these studies. The lives and the quality of lives of many thousands of patients depend on it.

Thank you.

DR. JANOSKY: Thank you.

The two letters that I had alluded to earlier are concerning the Christensen device so we will hear those letters tomorrow during the open public forum.

Any questions or comments from panel members?

DR PATTERS: I would like to ask spokespersons from TMJ Association as well as Dr. Zuckerman that, hypothetically, if this panel found that, indeed, clear evidence of long-term safety and efficacy did not exist, what do you believe this panel should recommend to FDA?

DR. JANOSKY: Would one of the three presenters like to comment, Ms. Brown, Mr. Clark or Dr. Zuckerman?

DR. ZUCKERMAN: Given the history of TMJ implants, I would have to say that if there are no long-term safety data, that it doesn't prove that they are safe long-term, they shouldn't be approved for sale.

DR. JANOSKY: Additional comments or questions? If not, then, at this time we would like to move into the presentation by industry. The presentation will be done by TMJ Concepts. You have one hour for the presentation.

Industry Presentation

TMJ Concepts Patient-Fitted TMJ Reconstruction Prosthesis

MR. ROSE: Good morning. My name is Greg Rose.

I am the Director of Regulatory Affairs and Quality Assurance at TMJ Concepts. I am a mechanical engineer with twelve years of experience in the design and development of medical products with an emphasis on orthopedic implants and instrumentation.

This morning I will be presenting a description of our device and a summary of the preclinical studies that were performed. Following my presentation, Dr. Louis Mercuri will be discussing the clinical aspects of this implant and the summaries of the clinical studies.

This patient-fitted TMJ reconstruction prosthesis is comprised of a mandibular and a glenoid-fossa component that have been manufactured specifically for a particular patient. An anatomical bone model is produced from a CT scan of the patient's mandible and maxilla. This model is used to design and manufacture these implants to accommodate the patient's unique anatomy and the implanting surgeon's preoperative plans.

I have several slides to show, and I also have some samples that you are welcome to look at during the break.

This demonstrates the unique nature of each set of implants.

The mandibular component is composed of a condylar head fabricated from raw cobalt-chromium-molybdenum alloy in a mandibular body that is fabricated from titanium alloy. The glenoid-fossa component is comprised of a fossa bearing fabricated from ultra-high-molecular-weight polyethylene in a mesh backing which is fabricated from unalloyed titanium, as shown in this slide.

The implant fixation of both the mandibular and glenoid-fossa components is achieved using small bone screws, 2.0 millimeter diameter. 2.3 millimeter diameter screws are also provided as a safety screw.

The materials that are used to make these implants comply with various ASTM standards which are currently accepted by the Dental and Orthopedic Branches within ODE. They are also state-of-the-art materials that are used for orthopedic implants such as hips and knees.

We also provide an instrument set that is used to replace the implant for anchoring the bone screws.

Both the fatigue and the static-strength testing that were performed were done using a similar setup. Implants were held in an anatomic position. They were angled at 23 degrees in the anterior-posterior plane and 10 degrees in the medial-lateral plane.

This shows the setup that was used to perform the static-strength testing.

The fatigue testing was done on six specimens that were manufactured to the worst-case conditions being the narrowest and thinnest implants. The loading was sinusoidal. It was done from 150 pounds maximum to 75 pounds minimum at 12 Hertz. Testing was performed over 10 million cycles. The failure criteria was for looking for gross fracture of the part or a crack present under zygopenetrant inspection. No failures were observed.

The static-strength testing that was performed was on six specimens, also. The specimens were loaded until yielding a fracture and the peak load was recorded.

The average failure was identified as 790 pounds.

Bond testing was performed to ascertain if the implant could withstand possible separation forces on the fossa component. Failure criteria was established at 75 pounds force and shear. The normal implant loading is in compression and doesn't actually create any separation forces. This was established as a proposed impact load that the device may receive.

The results of this test was that there is no specimen failure and the average shear strengths were reported below. Low and high parameters were evaluated in the bonding process. Average shear strength at the low process parameters was 368 pounds and 322 pounds at the high parameters.

The wear testing that was performed was done on a special mechanism which was developed that articulated the device over 25 degrees of rotation. This provided about 8.3 millimeters of translation and it was done under a 9 kilogram constant load through the entire cycle. This was considered worst-case as, during the normal chewing cycle, the joint is actually only loaded temporarily.

There were six specimens tested over 5 million cycles under this constant load. The frequency rate was approximately 54 cycles per minute. The environment used was bovine serum at room temperature. The setup is shown here in this slide.

The depth of the wear track that was created in the fossa component was then directly measured. This was plotted against the number of cycles that implant had been exposed to.

A linear regression was then performed to estimate the wear rate that was occurring on each of the implants tested. You can see here the linear regressions and the slopes of the lines were determined.

The wear test results were then evaluated and we established a penetrative wear rate for the implant. We have a 3 millimeter minimum polyethylene thickness. The average penetrative wear rate was 0.0097 millimeters per million cycles shown in the bottom right-hand corner.

The worst case of all of these wears that were seen was looking at the worst one of these specimens. The wear life was estimated at 173 million cycles, looking at the worst case of these specimens. There are different models for the number of cycles a patient may see, but a commonly accepted one in the literature has been a million cycles per year and, with this testing, the device should withstand more than a lifetime for any given patient.

That concludes the preclinical testing that was done. Thank you.

DR. MERCURI: Thank you to the panel for allowing us to present this material today. My name is Louis Mercuri. I am a professor of surgery at the Loyola University School of Medicine, Department of Oral and Maxillofacial Surgery.

I have been involved with temporomandibular-joint problems for over thirty years in my clinical career and I have been involved with the temporomandibular-joint concepts in Techmedica prosthesis since its inception. I have no financial involvement with the company as of the present date. I have received some computer support and a minimal consultant's fee for the work that I have done over these ten years.

Since we have such a diverse and varied group here, I don't want to be pedantic, but I think we should all be sure that we understand the problem that we are dealing with. I would like to start out by saying that we are dealing with temporomandibular-joint disorders here and it is a spectrum of problems that we deal with.

Today we are going to basically focus on the problems that affect the temporomandibular joint, itself.

Not only is there a spectrum of this disorder but there is also a spectrum of the management for this

disorder. This is my own classification of the modalities that have been used in the past. It is certainly not all-inclusive, but, for today's discussion, I would like to focus, again, down on the invasive modalities. We are specifically going to be talking about total temporomandibular-joint reconstruction.

I bring this slide to your attention because I would like you all to understand that my own philosophy is that the vast majority of patients with temporomandibular-joint dysfunction can be treated in a non-invasive manner, so I do not like the panel to feel that my thoughts on the clinical aspects of temporomandibular-joint management are only focussed on total joint replacement.

I firmly believe that the vast majority of patients, as we stand here today, can be treated in a noninvasive manner for generalized temporomandibular-joint dysfunction. But, for the sake of today's discussion, we will focus only on total joint reconstruction.

The reason I got involved in this was this is the profile of patients that I was starting to see in 1989. As I said, I have had ten years of involvement with this. They presented me with a significant problem. The patients that were discussed in the patient advocacy part of this presentation were basically these types of patients.

I was presented with the clinical dilemma of how to deal with the functional problems that these patients had. In 1989, the available prostheses, the stock prostheses, that were available, the TMJ implants that were available, could not handle the mutilated joints that we were seeing in these patients.

Therefore, we started looking at what should be the goal in treating this type of patient. We are now focussing in a very specific type of patient that I think you have gotten the flavor for. What should be the goal in reconstructing these types of patients?

I went back into the orthopedic literature and Dr. Petty's book talks about what the orthopedic surgeon would do to manage this type of problem because I firmly believe that this problem is an orthopedic problem.

These are the goals that have been developed for the management of this particular focussed group of patients. We would like to improve their function and form. We would like to reduce their suffering. We would like to contain excessive treatment--in other words, stop any further treatment that they would have to have, contain further costs to the system, and prevent further morbidity.

When I looked into the goals for temporomandibular-joint reconstruction that were proposed

by the American Association of Oral and Maxillofacial Surgeons, those goals do not address the problems of this particular type of patient. Expecting pain relief that is 100 percent is not possible in this particular type of patient.

So the criteria that was established by AAOMS and was published by AAOMS is really not applicable to this particular group of patients.

I then realized that I could not deal with treating these patients, or managing these patients, with autogenous tissue. Autogenous tissue failed routinely. In other words, we are talking now about rib grafts, bone grafts, these kinds of things, because these patients were so multiply operated that the vascular bed that is required for a free bone graft to exist and to head was not there.

So, again, borrowing from my experience in the orthopedic literature, this is basically a quote borrowed from Dr. Harris at Harvard, that, we saw an alloplastic temporomandibular-joint reconstruction--in other words, a temporomandibular-joint implant--as the only possible way to deal with these particular focussed groups of patients.

We must understand that an alloplastic temporomandibular-joint reconstruction is a biomechanical solution to severe debilitating anatomical joint disease.

It is not a primary device. These devices are used to salvage patients who have an end-stage disease because they have pathologically mutilated joints.

We then looked at what types of materials have orthopedic surgeons used successfully over the years. If we can again go back to the work of Sir John Charnley, back in the 1960s, he found that having a stable part or a non-moveable part, being a metal-backed, ultra-high-molecular-weight-polyethylene fossa operating against a moveable metal condyle had the best potential for wear.

It also had the best potential for the device having long-term success. So, orthopedic surgery, the benchmark for devices was an ultra-high-molecular-weight metal-backed fossa with a chrome-cobalt-molybdenum mobile element or condyle. Therefore, the decision was made to develop a device that mimicked the success that was seen in orthopedic surgery with these benchmark materials.

As you have read in the PMA, these are the indications that have been proposed in the PMA for the use of the TMJ Concepts device.

What I would like to do now is go through some clinical slides to give you the flavor of the types of patients that we are dealing with.

The indications I want to talk about is, number one, ankylosis. For the non-clinicians in the group,

this is a CT scan in a sagittal view. The temporomandibular joints are these areas right here, so we are looking at the right and the left temporomandibular joint. Normally, the joint should look like a drumstick, the end of a drumstick, like a chicken leg.

You can see, obviously, that these joints are mutilated by the disease process and there is, to my estimation, and the estimation of many of my colleagues, there is no way that a stock device can be made stable to fit this situation.

As Mr. Rose has shown you, this is a model made from the CT scan of that particular patient's problem. There is no joint anatomy in this situation. Failed otogenous bone or soft-tissue grafts. These are rib grafts that were placed in a patient who had had Proplast/Teflon implants. You can see the penetration into the medial cranial fossa here.

Once again, these joints should look like drumsticks on a chicken leg and you can see you have a very mottled appearance here. These are failed rib grafts. The work of Wolford and his colleague have shown that the placement of autogenous tissue into a joint that has previously experienced Proplast/Teflon is doomed to failure.

This is a typical patient who has had a rib graft that has failed after Proplast/Teflon. Once again, you can see that there is no anatomy here. This is the fossa. There is no way a non-patient-fitted device or a stock device would be able to fit in this particular situation.

Destruction of autogenous graft due to pathology. This is an auricular cartilage graft that has failed in a patient who had Proplast/Teflon in place prior to that. You can see again, in a sagittal view, that the joint, the fossa, has been completely destroyed as well as condyle. The patient has lost vertical dimension because of that.

Here is the model that demonstrates the mutilated anatomy associated with this particular problem.

Failed Proplast/Teflon interpositional implants; here, again, is a sagittal view of the patient. This is posterior-anterior. This is left of the condyle. You can see the implant in place and the destruction that it has caused not only to the fossa but the to articular eminence as well.

Here is a model of that particular patient with the mutilated anatomy.

This is another patient who had Silastic in place for about seven years and the destruction that that had created, again creating a mutilated anatomy which is

very difficult to deal with with a stock prosthesis. I must remind you that the principle in the alloplastic management of joint replacement is that the device must be stable in situ in order for it to have any sort of lifespan.

Failed total-joint prostheses, not only the Vitek. This happened to be a Vitek that is eroded into the articular eminence. But we have also seen failure of other alloplastic implants. This is a device that fractured after one year because the stem was too narrow.

Here is another device that was used to reconstruct the temporomandibular joint that failed. Interestingly enough, we see, from the literature again, in Fontino's work, that typically temporomandibular-joint implants have a tendency to show failure within the first three or four years, if they are going to fail.

Most of these patients have these failures in that period of time. Here is another one, a fracture in the implant. Here is another implant; the screws are fractured as a result of the fact that it is much too thin.

This is a fossa that was grouted in place using polymethylmethacrylate. Someone determined that since orthopedic surgeons use polymethylmethacrylate, maybe we can grout these things into place. The problem with this in the temporomandibular joint is that we see fractures of the mantle of polymethylmethacrylate. This creates a foreign-body giant-cell reaction and causes these implants to fail.

So grouting implants in is not a reasonable approach.

Here is another failed implant, fracture of the implant, also loss of the polymethylmethacrylate, the head. When we look at the tissue, we can see particulation of the polymethylmethacrylate, not a tremendous reaction. Certainly nothing like we saw with Proplast/Teflon, but there is still particulation in the tissue.

Something we are seeing now are failures of the metallic fossa where the fossa is fracturing and creating particulation with the process of metallosis and a little bit more of a reaction to this type. So we are now seeing patients where we are removing these prostheses and, again, developing this mutilated anatomy that can only be dealt with with a--

Here is another one. This will give you the flavor for this. This is a patient with rheumatoid on the model. You can see there are no condyles in this patient, so it is a significant deformity for these folks.

If I could go to the overheads.

I just want to have one more--this is some data that we looked at in patients with failed devices. I am

sorry that this doesn't project well but maybe you can see it. It was 162 patients with failed devices or failed grafts. This sort of gives you the distribution of the failed grafts. 33 percent of the patients had failed previous grafts; reported with failed devices, 48 percent with failed devices.

Obviously, the vast majority of those, 22.8 percent of those, were Vitek devices but there are other devices associated with failure in here as well. So I just want to give you a flavor for the devices that we have seen in the patient cohort that I am going to present to you now.

I am going to go into the clinical studies now.

This data was collected from eight different surgeons in five different states using established inclusion and exclusion criteria with a protocol that was published in the 1995 Journal of Oral Maxillofacial Surgery article that I authored along with three other surgeons and a biostatistician which formed that basis for the 510(k) application that was made and approved.

I am going to present three studies today. The first one is a review of this study, but all of these studies were based on the use, for subjective criteria, of the visual-analogue scale. Again, not to be pedantic but so that, again, we are all on the same wavelength, I would like to discuss the visual-analogue scale that was used in these studies.

The visual-analogue scale is a way for the patient to be able to objectify a subjective response. I think all of us will agree that pain, jaw function and a patient's ability to eat is a subjective response. In order to quantify that response, we have asked patients to make a mark along this 55-millimeter line as to where they consider their pain level to be, their jaw function to be and their diet to be.

The left-hand anchor is the lowest possible response so the mark is 0. The right-hand anchor is the severest response or the worst-case scenario and that would be the highest level of pain. So a patient that would mark at this level would be a 55 and a patient who would mark at this level would be a zero.

This is from that article. It is a table that shows the changes in subjective and objective measures. When we address the subjective measures, what we are talking about here are the time elements, the time scale. We looked at the preoperative level of 215 patients with the mean score and their subjective responses for pain at 42.

Their mean, on a subjective response for function, was 39.5 and their mean diet score was 37.3. As we follow these patients along with an average of a 13-month follow up, we can see that these numbers drop

significantly in the area of pain. 42.2 became 19.5.

Obviously, the higher score in these measurements reflects more dysfunction and all three measurements improve significantly over time. Paired T-tests showed that all improvements were significant at the p less than 0.0001 level. Therefore, the improvements created by the prosthesis in this particular study appeared in the second month postoperatively and continued throughout the four-year follow-up period.

We did the same thing with the objective scores.

Objectively, we measured the interincisal opening of the patients using a bolley gauge. These measurements are recorded as shown here, that the mean preoperative opening was 24.2 and that increased as the study progressed over four years.

We also measured left and right lateral excursions, again because these could be measured objectively, easily. If we look at the statistics behind this again, it showed, using the paired-T-test that the improvement found in the objective results were statistically significant at the p equals 0.0001 level.

When we go to lateral excursions, we find that there is no significant change. In fact, the patients actually look like they got worse. The reason for that is that lateral excursions are controlled by the lateral pterygoid muscle which is attached to the condyle and, in the process of placing any reconstructive prosthesis, the lateral pterygoid is sacrificed and, therefore, lateral excursions do not change. In fact, they almost are completely eliminated.

In order to look at the closest follow-up patients in the study, we looked at 111 patients. These were basically my patients and Dr. Wolford's patients since they seemed to have the closest follow up. We then did the same analyses using the subjective variables that I mentioned before using the visual-analogue scale. Then I will show you the objective variables in a moment.

This 111 patients were subjected--these were the 111 patients that came out of the 215 that were mentioned in the 1995 study. You can see, again, a statistically significant decrease over the first six months in pain, function and diet scores which, as you follow these all the way through, seem to be consistent.

If you look at the raw data for this, you will see that, as we get down to here, there are small numbers of patients who have entered the study period. I will address that issue when I get to the life-table analysis towards the end of my presentation. But just to give you a flavor for that, there are about three patients here at 96 months. There are 13 patients at 84 months, 21 patients at 72 months. And there are 41 patients at 60 months and then the number drops up into about 60-some

patients at 48 months.

There has been a question raised about the gaps or the dropout rate that has been seen. There are a couple of issues here and I will address the statistical issue first. This is the objective results which pretty much follows the other--we can see that the patients started at about 24.something and gradually increased their opening. Again, remember, we are talking about three patients here so these numbers, as we come out here, may not be quite as significant.

I would like to address this dropout issue. Based on the 111-patient study which we are calling study 2, the gaps in the follow-up measurements appear to be random and unrelated to the values of the measurements. These patients with a one-year follow up are similar to those without, in fact. None of the baseline variables are different between the two groups.

This is an analysis that was done by the biostatistician and submitted on page 0900 of the PMA. Comparable analysis between the baseline variables of those patients with and without two-year follow up show that the two sets of patients are statistically similar.

So we are dealing with a subgroup of the large group. And when we look at them, they are statistically similar based on the statistical study that the groups were subjected to. You must understand that I am not a statistician. I am a clinician. I am presenting the data from that standpoint.

I would also like to read a quote from the review, Dr. Runner's report in the review, which you have in your presence. She states that, "Patients with one-year follow up are very similar to those patients without follow up with no statistically different variables between the two groups." So this has been subjected to statistical analysis as well as the FDA's analysis as well.

The question also was raised as to, "Can we be sure that this is a sustained change?" So a biostatistician, Ms. Hurder, did a Wilcoxon Signed Rank Test which was performed on the dataset of this 111 patients for which she was able to subset out 69 patients to see if there were any significant changes between the baseline and twelve months.

She found, again, if we look at the p-values here, highly significant p-values which indicate that change in pain level between baseline and one year was there. For the mean change data, it appears that the pain levels declined significantly during the one-year post-operative period.

The average change data shown showed significant decreases in function and diet scores during the first year of follow up. The maximum incisal-opening scores

increased significantly during the same time interval. In other words, if we look at the means here, a negative mean will mean improvement towards the positive side.

A positive down here in maximum incisal opening means that the patient has opened wider. Over the first year, using the Wilcoxon Signed Rank Test, it showed, at a very significant level, that there were changes.

What we also, then, wanted to look at is this change sustained over the 12, 24 and 36-month interval. And so a repeated measure ANOVA-F test was done to prove statistically that there were changes that occurred.

Stabilization is interpreted to mean that the slope over the interval is zero. In other words, it doesn't change. The slope of the regression line doesn't change and if we come up with a p-value of less than 5.0, then we have no change there.

The accompany table shows--I am looking at this table, now--the estimated coefficient of regression of the slope, standard error of the estimate of the coefficient, the degrees of freedom for the test and the f-value statistic and the p-value for each of the measurements.

Nonsignificant p-values for both pain and function would indicate that the slope of the regression line is not statistically different from zero; in other words, that there is a sustained change. Both of these measurements appear to show stability between 12 and 36 months. So, for pain and function, we have a significant change that is stable from 12 to 36 months.

The slope of the regression line for diet was significantly different from zero; therefore, there was a change. But when we look at the change that occurred, the change was 1.8 millimeters on the visual analogue scale per year over the study period.

Also, the rate of change from the maximal incisal opening showed an improvement of 0.8 millimeters per year. Again, it wouldn't be reflected in the p-value because it is not a statistically significant number.

I would also like to comment from Dr. Runner's review. "A preliminary evaluation of the prospected postmarket surveillance study was also presented," which is what I am going to present at this time. "The results are consistent in the trends for decreased pain, increased function and increased interincisal opening."

What you have before you now is the initial data from the postmarket surveillance study that has been done on the patients that have been implanted since 1998. So we have basically a one-year follow up on these patients.

I realize that one-year follow up is not something that we can actually base our presentation on but what I would like to be able to show you is that we can now reproduce the data that was shown in study 1 which was the report

in the Journal of Oral and Maxillofacial Surgery and study 2 which was the subset, which, by the way, that study has been accepted for publication in the peer-reviewed Journal of Oral and Maxillofacial Surgery.

So we are now talking about 128 patients that have been implanted and ten of those patients have come to one year at this point. So this slope of this line is in agreement with the slope of the lines of the other two presentations showing reproducibility of the data.

This is, again, the objective results of that same group of 128 patients. Again, to give you a flavor of the numbers of patients we are dealing with, this is 128 patients at time 0. At two months, there were 80 patients. At six months, there were 52 patients and at one year, there were ten patients.

Again, I want to stress the reproducibility of this data.

I think it is important that we talk about adverse events that have been reported. These adverse events with the TMJ Concepts device only involved the removal of nine devices--I'm sorry; thirteen devices in nine patients. If you look closely at the categories, device removal due to failure or complication, there are five. These occurred early in the use of the device and were basically design issues.

The design, as Mr. Rose showed you and that I showed you, has changed to the point where we use more screws than were used before. Interestingly enough, even though we have gone to more screws, these all occurred early on. As I mentioned before, Fontino's report showed that alloplastic devices typically will show failure in the first three to four years.

We also had devices removed not due to failure or complication. These were eight devices that were removed in four patients because the patients wanted them removed. I don't like to give you anecdotal data but one of the patients decided that she was receiving radio signals through it and decided she wanted it removed for that purpose.

Another patient had hers removed because she decided she didn't want to have metallic devices in place. We were able to retrieve the histology from the surgeons who removes these devices--I did not remove these devices--and found no clinical evidence of any failure of either bone or soft tissue associated with these devices.

So these devices were removed because the patients wanted them removed not because of a clinical reason to have them removed. So we only have thirteen devices that were removed. There was improper fit and dislocation involved early on. Again, we are talking about the patient-fitted device that involves a CT scan

and it involves a new technology.

As with any new technology, the initial placement of these can result in learning-curve failures.

The dislocation led to a change in the fossa, putting a lip on the anterior and a larger lip on the posterior. Since that has been done, there has not been another dislocation that has been reported.

Postoperative infection was only seen in three devices and three patients all of which resolved easily.

The largest adverse effect, again which didn't result in removal of the device, was the development of hypertrophic bone. When we did an analysis of these patients, we found out that all of these patients, the hypertrophic bone developed within the first thirteen months.

All of these patients had had ten or more prior procedures, so we feel that there is an important issue there that should be addressed. And there were others.

I would like to take you through the life-table analysis now. The feeling of a life-table analysis is that, since patients are not all entering the same interval at the same time, there should be a statistical way to find out how long a device that was implanted at time zero will last, what is the likelihood of that device lasting all the way through the period.

The life-table analysis was developed in two ways. The first one that you have before you is the life-table analysis, patients having devices explanted with or without indication. So that is both groups that I talked about in the previous slide; the patients who had an indication for removal of the device and those patients who did not have an indication for the removal of the device.

This is in our dataset with the closest follow up of 11 patients. The key to this is if you look at the seventh column over, these are the patients that have not yet entered the period. We can see that there are a large number of patients who have not entered certain periods. One of the reasons that it appears that the data has a lot of holes in it is the fact that we have a large number of patients who have not even entered the period in order to collect the data.

The other one I would like you to look at is the fifth column across, this column right here, the total patients having patients having devices explanted. If we go down here and we find the fourth and fifth year, all of the explantations have occurred up in here which basically agrees with Fontino's study that I mentioned twice already.

But now, if we go back down to the fifth year all the way through the tenth year, granted that the numbers are small, we still should be seeing some devices

that are failing if this is a bad device. We have no devices that have failed requiring explantation from the fifth year to the tenth year.

So this life table includes both implants that are explanted with or without indication and we can see that the 95 percent confidence for the cumulative probability that these devices will last to the ten-year mark, which is the orthopedic standard is about 85 percent.

The next slide is the same life-table analysis that was done only with those devices removed for an indication. In other words, we have now eliminated the patients who requested the device with no clinical reason to have them removed from the study.

We can see, again, basically, that this column stays the same. There are none here. We have these patients entered at the interval here. Now, with the 95 percent confidence interval for cumulative probability, the likelihood of an implant placed in day 1 surviving ten years is 90 percent.

So I think it is important that the panel and the audience understand that aspect.

I have a few more minutes. I would like to show the next series of slides. I think it is important for the panel and the audience to maybe see what a case looks like from the beginning to the end. I don't want to give you all the details on this case, but this is obviously a patient who has had multiple temporomandibular-joint procedures with a mutilated anatomy of the joint here.

She has an open-bite deformity. Her mandible is deviated to the right. She is in significant discomfort, not only from the fact that she can't open and close her mouth but the fact that she has tremendous muscle spasms not only on this side but also on the opposite side because of the shift of the mandible.

This is the model of that particular patient and I think it is pretty evident, the shift in her jaw. You see her teeth don't come together on this side.

This shows the normal anatomy on the patient's left side and this is the mutilated anatomy on the right side. This patient had five prior temporomandibular-joint operations.

The model can then be adjusted to the patient's occlusion so that their bite can be placed appropriately.

A wax-up of the device is done. Because there is a wax-up here and, for the people with dental training in the audience, does not mean that the device is cast. This is just merely a design. The device is actually milled so that there is no casting involved in this.

Casting can instill crystalline defects so milling the device is an appropriate way to deal with this. This just merely shows what the device would look

like.

The device is placed through two incisions here.

This was the lower device and, again, you can see, from Mr. Rose's presentation and my presentation, that all of these devices are completely different. They don't look the same at all.

This is the device in place before the screws have been placed in the fossa component as it is attached to the zygomatic arch. You can see that the ball which has a geometry which is perfectly mated to the geometry of the ultra-high molecular-weight polyethylene, again stressing the fact that this is the benchmark materials that have been used in orthopedic surgery for over thirty years. This shows that relationship.

This is the patient's panoramic radiograph that shows the device in place. The fossa liner of the titanium mesh shows up on the radiograph. Obviously, the ultra-high molecular-weight polyethylene, since it is not radiodense, does not show up.

And then, in an anterior-posterior view, we can see how nicely the titanium mesh conforms to the remnant of the fossa, how centered the condyle is in the fossa and the bicortical nature of the screws as they pass through the implant and through the remnant of the ramus.

It also shows now that the patient's jaw is symmetrical and this patient has gone on to do very well.

That is the end of the slides.

I would like to close with a statement read directly from the report of the FDA, that "The TMJ Concepts Inc. documentation answers most of the essential questions that should be asked in relation to total temporomandibular-joint reconstruction. They have presented evidence that the characteristics of the patients that did complete the extended period of follow up are very similar to those who were lost. The company has also started a postmarket study to prospectively follow additional patients.

"In addition, the engineering review of this implant has demonstrated that its principles of action are very similar to other, more fully characterized, joint reconstruction--i.e., total hips--in terms of the materials and the mechanical characteristics."

Thank you very much and I look forward to any questions that you may have.

DR. JANOSKY: At this time, we can have a few questions from the panel members for TMJ Concepts.

DR. PATTERS: Dr. Mercuri, can you estimate the percentage of adverse reactions?

DR. MERCURI: It is about 8 percent.

DR. PATTERS: And the percentage of implants removed was 13 percent in study 2?

DR. MERCURI: It was not 13 percent. It was 13.

DR. PATTERS: Out of 113 patients?

DR. MERCURI: Right; 113 patients.

DR. PATTERS: And 13 patients had them removed?

DR. MERCURI: Right.

DR. PATTERS: 12 percent?

DR. MERCURI: Right.

DR. PATTERS: What percentage of patients were not improved or their symptomatology was not improved, or was made worse?

DR. MERCURI: I didn't include that in my presentation. That depends on the number of prior operations that the patient had. We had that data in the PMA. It shows you that if a patient has had zero to four prior surgeries that the likelihood of them not improving is very low whereas if a patient has had five to nine, or nine or more, prior operations, that their improvement is much less.

So I would direct you to that data as a response to that particular question. That has also been reproduced in other studies that have been done in the literature. The more surgery that is done, the less likely the parameters that we looked at would improve other than for function.

DR. PATTERS: Lastly, then, if I understand your dataset, you show that the preoperative conditions of the patients that return for follow up did not significantly differ from the preoperative conditions of those who did not return. How can we be sure that the result of treatment wasn't different between those two groups?

DR. MERCURI: I think the reproducibility of the data in basically three different studies which shows statistically significant improvement over the time period of the studies is a significant response to the device.

DR. PATTERS: Could it be argued that those patients who did not feel they were helped did not come back?

DR. MERCURI: That could be argued. It could also be argued that we are dealing with eight different surgeons over five different states and even in study 2, when it was just Dr. Wolford and my patients that we were looking at, because this was a limited clinical trial and there were a limited number of people doing these procedures, patients traveled a significant distance in order to receive treatment.

In many cases, the evaluation of these patients was left to the referring surgeon. In many cases, despite repeated attempts to have the referring surgeon or the patient respond to the data questions, it was impossible to receive that data.

DR. PATTERS: Thank you.

DR. BERTRAND: Peter Bertrand for Dr. Mercuri. On this gap of patients follow-up-wise, when you initially assessed the patients, was there any type of psychometric inventory to measure the impact of what has already happened to that patient in the past, or what kind of life challenges they may have faced apart from the surgical procedures that had confronted them in order to more adequately characterize what kind of patient you were dealing with from the beginning?

DR. MERCURI: To answer your question quickly, in a majority of the cases, no. To expand upon that, the issue with these patients was, as I stated from the beginning, a functional issue and in hopes to try to allow them to regain some function and be able to eat, I think it was addressed in the patient advocacy group that these were patients whose lives had changed dramatically in terms of their ability to eat, their ability to gain weight because they were losing weight because they were not able to eat, it was important that they get their function back.

I also addressed, in one of the goals, the fact that these patients were suffering. When you are looking at the chronic-pain, the component of suffering increases rather dramatically in those patients. Part of the suffering that these patients have, as a clinician who sees these patients all the time, is the fact that, number one, they can't open and close their mouths and, number two, they don't look very good because their jaws are deviated from one side to the other.

I have found in my experience of over thirty years in dealing with these types of patients that as soon as we send them off for psychometrics, and I understand that psychometrics is very important in dealing with these patients and I have a whole dataset on the psychometric component of this, but as soon as we start sending them off for psychiatric evaluation, or psychological evaluation, we immediately turn them off and they immediately leave.

The concern, at that point, is that they become, again as the patient-advocacy group spoke, "It is all in my head." That is a point that I, as a clinician and as a surgeon, have no expertise in that area.

We have referred some of the significant patients with significant psychometric problems to the clinical psychologist. But I cannot, as I sit here today, give you the exact number of those patients. It is a long answer to your question, but I think it is germane.

DR. BERTRAND: The literature on chronic-pain patients is showing that upwards of 50, 60 percent of them may have some type of history of abuse in their past. So, in this particular group of patients, we have

no way of assessing whether that was ever an issue for these particular patients.

DR. MERCURI: That's correct. It is uncommon for a patient to volunteer that information even when asked directly. I read the same literature you have talked about and I have tried to address that issue as a clinician with these patients, but, in most of the evaluations that I do of these patients clinically, the significant other, the spouse, is typically in the room and it is very difficult to get these patients to give that response.

But I agree with you.

DR. BERTRAND: Thank you.

DR. HEFFEZ: I have a question for the engineering department. I'm sorry; I didn't catch your name. My name is Leslie Heffez, by the way.

MR. ROSE: Greg Rose.

DR. HEFFEZ: And then I would like to ask Dr. Mercuri two questions.

You tested in vitro the mechanics of the joint in worst-case scenarios. You also tested it with translation of the components; is that correct?

MR. ROSE: That's correct.

DR. HEFFEZ: I would like to know, from an engineering point of view, do you feel that the worst-case scenario would be one in which there was no translation versus one that there is translation?

MR. ROSE: Are you referring specifically to the wear study?

DR. HEFFEZ: Wear study and--I don't have the names of the studies.

MR. ROSE: The fatigue strength and the static strength were done without any translation to assess the likelihood of the mandibular component to withstand fracture. And that was done with compressive loads. There was no translation in that test.

In the wear study, we created translation and we loaded it throughout the cycle and that was considered worst-case since those loads would not normally be seen by the implant throughout the chewing cycle.

DR. HEFFEZ: Did you test it at all for pure rotation? Did you test the wear under pure rotation?

MR. ROSE: No; the wear was tested with translation.

DR. HEFFEZ: I have a question for Dr. Mercuri.

Typically, these patients are a heterogeneous population with heterogeneous symptoms. One of the problems is that you identify indications for doing the procedure but there are, within those indications, one particular subset which is particularly difficult to reconstruct, and that is the Proplast/Teflon patient, we will call it.

When you mix the data between the different

types of populations, sometimes it is hard to interpret the data. Did you make any effort to identify simply that patients who have been implanted with Proplast/Teflon and their outcomes?

DR. MERCURI: That data was looked at. It was done a while ago. I don't believe there was any difference in the ultimate end result. That has not been published and I don't think that is part of your report.

Dr. Wolford presented a paper where he looked at the Proplast/Teflon patients and compared autogenous grafting to alloplastic reconstruction and found a statistically significant improvement using an alloplastic over autogenous tissue.

That is not the same study that you are talking about but it is an analogous study.

DR. HEFFEZ: One of the problems is that, as a clinician, one can see the results of treating patients with inflammatory disease and patients being treated for bony ankylosis. Those patients typically do better than the other type of patient which is one who has had a failed prosthesis.

It would be interesting to know how your data plays out simply looking at that data rather than those other patients which typically do better postoperatively, or medically.

DR. MERCURI: I would suspect that they would do better. I think we have the data that would show that. I just don't have it available.

DR. HEFFEZ: I have one last question. Is there any disadvantage to not having the ultra-molecular-weight material radiopaque and monitoring the device as far as fracturing of the material, or significant wear of that material?

DR. MERCURI: I think from the wear data that Mr. Rose has presented, it is so minor and minimal that it would be not measurable on a radiograph. In my 1995 paper, I present two- and three-year histology taken from patients who have been implanted for two and three years of the soft tissue between the ultra-high molecular-weight polyethylene and the chrome-cobalt-molybdenum head.

In fact, I have those slides if anybody is interesting in seeing them. The histology shows no particulation. We are seeing just dense fibrous connective tissue. So, again, in two to three years, follow up on those patients, we don't see that.

DR. HEFFEZ: Early in the device fabrication, there was some separation of the ultra-molecular-weight from the backing.

DR. MERCURI: There was one case; yes.

DR. HEFFEZ: That has not occurred since?

DR. MERCURI: That has not.

DR. BURTON: Richard Burton for Dr. Mercuri. I have three short questions for Dr. Mercuri. The first one is have you made any kind of judgment--you said that the orthopedic standard is approximately ten years on what is the potential life span. Most of these people, looking at your demographic data, are still relatively young and looking at life spans, whether or not this device should have at least some type of life span associated with it?

DR. MERCURI: We have given you the life-table analysis for ten years. I think that, since the device has only been used for ten years, we have to say that following the benchmark of orthopedics that we are talking about ten years. But I will amend that by saying that we know that patient-fitted devices--in other words, devices that are made specifically for the anatomical problem that is associated with these patients--since they fit so well and that the failure of devices is typically when these devices do not fit well and that they start to move, the analogy for the dental group here is dental implants, that if we place a dental implant that is not completely solid in bone and it rocks or it moves, it is going to fail, whereas if you have an implant that fits perfectly or fits as close to perfect as we can humanly make it, that the implant will stay for a long period of time.

So my feeling is that because these are patient-fitted devices, or fit so well to the patient, that they should last longer. But I have no data that will prove that.

DR. BURTON: This may be for either one of you, but why did you develop a subset of your original data and present it sort of as a secondary study when, really, my reading of it is it is an extension of the one grouping of patients, in terms of just involving two surgeons by the total eight?

DR. MERCURI: As I stated in my presentation, we felt that we wanted to look at the patients that were the closest followed of that large group; in other words, where the data was the most complete and, for the reasons I mentioned before for Dr. Patters, the fact that we have eight different surgeons, five different states, in the original study.

The dropout rate, trying to get the data, was large so we wanted to narrow it down so that we were only looking at the patient that had the best follow up. Again, even with two surgeons, because we are dealing with patients coming from different parts of the country, different countries, we still were not able to get the data as closely as we would like to.

So that is the reason for the 111.

DR. BURTON: One last point. You mentioned, in

your presentation--you showed, in fact, one set of radiographs in a rheumatoid arthritis patient. How many of these have been used in rheumatoid reconstruction as opposed to patients with other types of surgery. Dr. Hefez mentioned Proplast. Do you have any idea what that might be?

DR. MERCURI: It is a smaller number. Again, I have that data someplace. I just don't have it with me now, but I can tell you percentagewise, it is a smaller number than Proplast/Teflon patients. It is a smaller number than the multiply operated patients.

I can all tell you, as, again, I responded to Dr. Patters' question before, these are the patients that represent the zero prior operations. I will tell you that those patients do remarkably well compared to--if we broke out just those patients and showed you that particular data, it would be remarkably different.

DR. BURTON: Thank you.

DR. JANOSKY: Dr. Rekow, just one last question and then we will resume later.

DR. REKOW: Can I make it two short ones?

DR. JANOSKY: Okay; two short questions.

DR. REKOW: This is Diane Rekow. Dr. Mercuri, you had a few patients that you ended with failures from your device. I assume that they were explanted, at least a few of them. I don't remember the number.

DR. MERCURI: Yes.

DR. REKOW: What happened to those patients?

DR. MERCURI: I can only tell you about two of those patients. I received information from my colleagues in other cities where these patients had these devices explanted--are you talking about the patients that had them explanted for no reason?

DR. REKOW: No, no, no. The ones--

DR. MERCURI: You are talking about the failures.

DR. REKOW: Yes.

DR. MERCURI: Those patients ended up with either rib grafts or the Christensen prosthesis. I don't know how those patients did. Of the patients that had them removed for no clinical reason, there were two patients that I was able to follow up on and do the histology from. As I mentioned in my talk, one of those patients ended up having nothing done.

The other patient ended up having a rib graft placed that failed and then she had a Christensen prosthesis placed that she then also had removed. And she is now left with nothing.

DR. REKOW: The other question I have is for Mr. Rose. Could you tell us a little bit more about what wear degree you did see when you were doing your tests, what size particles? You had some wear, so I assume that

there was some debris of some sort. What size was it? How much of it was there and what shape and what were some of the mechanisms you suspect were the cause of the wear?

MR. ROSE: The wear that we saw was just caused by the translation. We approximated the volumetric wear by calculating the area of the wear tract that we saw. We did not do any analysis of the particulates.

DR. REKOW: Did you collect any of them?

MR. ROSE: No; we did not collect any of them.

DR. JANOSKY: You will be available this afternoon for additional questions by panel members; is that correct?

MR. ROSE: Yes.

DR. JANOSKY: I am pretty sure panel members do have some questions. We will let those go until after lunch and after the FDA presentations.

MR. ROSE: Can I point out that we have some implants that we are going to leave on the table if people would like to look at them during the break.

DR. JANOSKY: Is it my understanding that they need to be described for the record, what those implants are? Is that true? Okay; that's fine.

At this time, let's break for lunch. My watch says that it is 12:50. We will return at 1:50 which is one hour. We will resume at 1:50.

[Whereupon, at 12:50 p.m., the proceedings were recessed to be resumed at 1:50 p.m.]

A F T E R N O O N P R O C E E D I N G S

[2 o'clock p.m.]

DR. JANOSKY: We will continue the afternoon session. At issue is a review of the premarket approval application by TMJ Concepts. This afternoon's session will start with an FDA presentation.

The order of the presentation for the FDA will be Dr. Susan Runner, Ms. Angela Blackwell followed by Dr. Murti Pannapolli.

FDA Presentations

DR. RUNNER: Good afternoon. I hope you all had a good lunch.

Over the next two days, this panel will consider premarket approval applications for devices intended for the prosthetic reconstruction of the temporomandibular joint. These devices have a very long history with the agency, with the patient population, researchers and with surgeons.

I would like to begin with a little bit of a history of these devices, then give you some of the agency concerns and then give some specific information on the clinical review of the PMA that is the subject of today's deliberation.

The final rule that classified TMJ implants into class III included the total temporomandibular-joint implant, the mandibular-condyle prosthesis, the glenoid-fossa prosthesis, the intraarticular-joint prosthesis. This occurred on December 20 of 1994.

The panel believed that these devices presented a potential unreasonable risk to health and that insufficient data and information existed to determine that general controls were adequate to provide safety and effectiveness information for these devices. This classification, as you all know, came after several very well-known implant disasters related to TMJ implants.

The earliest day by which PMAs could be called for was June 30, 1997, thirty months after the original classification. The FDA subsequently issued a proposed and final rule to require the filing under Section 515(b) of premarket approval applications. The actual call for PMAs then occurred last December 30, 1998.

The FDA did receive a reclassification petition on April 30 of 1996. This requested that the agency reclassify from class III to class II the mandibular-condyle implant that is meant for temporary reconstruction in tumor-resection patients. Based on panel recommendations and data, the panel recommended that class II with special controls was reasonable for this type of device.

This reclassification does not encompass all of the indications for the mandibular-condyle implant. This is limited to the intended use for implantation in the

human jaw for temporary reconstruction of tumor-resection patients. The agency intends to grant this reclassification but it has not become finalized yet.

The term "temporomandibular-joint disorders," as you have heard a lot about today, is a collective term and it may include a variety of different diseases of the masticatory muscle system and the associated joint. The mechanics of this joint allow insight into its function and its dysfunction.

The temporomandibular joint, like other joints in the body, is subjected to intrinsic and extrinsic stresses and the normal process of aging. The TMJ, itself, is a very complex joint and it is intimately related to the muscles of mastication, the teeth, the nervous system and other cranial-facial musculature.

A fibrous disc divides the joint compartment into two cavities and provides a moveable articular surface. The nervous system provides joint and the associated muscles with important information on pain, touch and movement.

The terminology involved with temporomandibular joint has also had a complex history. We have heard it called TMJ, craniomandibular dysfunction, occlusal-mandibular dysfunction, temporomandibular-joint dysfunction, et cetera, et cetera.

The original symptoms and signs of the varying disorders do include pain, joint sounds and limited mandibular movement and range of motion. Disorders of this joint are an extremely important source of oral-facial pain, especially in women. Treatment strategies range from reversible recommendations for reversible therapies such as mandibular splints and two more non-reversible therapies such as occlusal adjustments and invasive surgical procedures.

Most recent recommendations suggest that conservative approaches to therapy should be initiated before non-reversible therapies are tried. There is, however, a patient population for whom nonsurgical treatment is not an option. This subset of patients has had a variety of previous non-surgical treatments and has also had at least one previous surgical procedure.

These surgical procedures could include failed Proplast/Teflon implants or other types of alloplastic-joint reconstruction or failed autogenous grafts. Often, these patients have experienced numerous surgeries to one or both joints. The original presenting complaint is often clouded because numerous surgical procedures have complicated the diagnostic picture.

Inflammatory and/or immunologic responses in some of these patients may preclude further autogenous reconstruction. These patients present with severe pain, as you have heard, and extremely limited function.

The population in need of surgical reconstruction may also include patients with severe trauma, neoplasms, arthritis to the joint, that render it dysfunctional. There is a significant need in the clinical community for devices to reconstruct this joint.

Success of the surgical results from these reconstructions has to be tempered with the realization that the reduction in painful symptoms and the increase in function may be limited at best for many of the patients.

Total joint replacement in the temporomandibular joints have had a mixed history as well. Surgeries to address the lack of function and chronic pain have been overutilized. This overutilization of irreversible procedures was well-documented at the National Institutes of Health Technology Assessment Conference in 1996.

The overutilization of procedures has resulted in use of some materials that have been inadequately characterized prior to implantation. The result of this is a cohort of patients who have significant chronic pain and dysfunction with few alternatives except for total-joint reconstruction.

Adequate examination of the mechanical and structural characteristics as well as biocompatibility characteristics of the materials used in prosthesis joints is essential to successful reconstruction.

Perfect biological substitutes, of course, have not been developed but we do know that the characteristics of successful reconstruction include biocompatibility of materials, devices that are designed to withstand applied loads, and stability. It is important, from the agency's point of view, that devices that are intended to reconstruct this joint have a complete characterization and include as much patient information and preclinical testing as is reasonable.

In addition, adequate follow up of the patients receiving reconstruction is essential to interrupt any potential problems that may occur. With this information in mind, I would like to present my clinical review of the PMA that we are considering today.

TMJ Concepts has presented clinical data to support their premarket approval application for their total joint. This study was initiated to evaluate the outcome on 215 patients which included 363 joints. They were treated with the same protocol by eight different oral and maxillofacial surgeons, as you have heard before.

Endpoints in the study were pain, function and interincisal opening. All patients were fully informed as to the nature of their prosthesis and the nature of their diagnosed condition.

The CAD/CAM TMJ reconstruction device was placed.

This dataset, on initial analysis, suffered from a significant loss-to-follow-up. Approximately 35 percent of the initial group was lost to follow up. A second analysis was performed that analyzed a subset of these patients which you heard before, another 11 patients, that were primarily seen by two surgeons, who were implanted with 195 joints.

Overall results, as you have also heard in terms of their statistical analysis, was remarkably similar to the characteristics of the total group.

At issue is are the characteristics of these patients any different from the patients in the larger group and are these characteristics different from patients that were lost to follow up. We have heard some of the explanations for these kinds of missing points of data.

In addition to the data from this previous study, the company, after receiving their 510(k) clearance, did initiate a required postmarket surveillance study. This study, as you have also heard in their very early preliminary data, also correlates well with the data from their previous studies. This study was prospectively designed and approved by the agency and, to date, over 100 patients have been enrolled.

The TMJ Concepts documentation answers, as you have heard my words come back to me, most of the essential preclinical questions that should be asked in relationship to the total temporomandibular-joint reconstruction. Follow up is not ideal. They had many patients that were lost to follow up.

The sponsor has provided some explanation for this loss to follow up but they also have provided preclinical data that indicates that the characteristics of this joint are similar to other successful joints that are reconstructed in other parts of the body; i.e., total hips.

We are going to go on with our evaluation here and Ms. Angela Blackwell will give her engineering review.

DR. HEFFEZ: Dr. Runner, can I ask you a question.

DR. RUNNER: Yes.

DR. HEFFEZ: The approval of the prospective study; what was, exactly, approved, the methodology or--

DR. RUNNER: The company, after they received their 510(k) clearance, because they received clearance to market the device before PMAs were called for, and because this was a device that has a required postmarket study, the company came to the agency with a prospective protocol which included numbers of patient, endpoints, follow up, all the forms that you would in a prospective

study.

We went back and forth a few times and then it was cleared for them to begin this study.

DR. HEFFEZ: So this is essentially--it is not similar to an IRB institutional review; is that right?

DR. RUNNER: It is more similar to an IDE-type of review, if you had to compare it, because we had to approve the protocol before they could begin the study.

DR. BERTRAND: This study is ongoing; correct?

DR. RUNNER: This study is ongoing.

DR. BERTRAND: For how long?

DR. RUNNER: It is a required three-year follow up of the patients that are enrolled. So, once they reach their--I don't remember how many patients. It is 100 percent of all patients that received the joint for the first two years it is on the market. So that is the requirement. And they will be followed for three years.

DR. BERTRAND: Thank you.

MS. BLACKWELL: I am the lead reviewer for the PMA for TMJ Concepts. I also performed the engineering review of this PMA.

The sponsor has conducted appropriate fatigue and wear testing. In my presentation, I will outline the summary of the data that was presented.

Testing was reviewed under the 510(k) K954224 except for the bond-strength validation. So, in other words, all of the engineering testing that appeared on the PMA was present when we reviewed the 510(k) in 1995.

The materials and designs for this implant are similar to successful orthopedic implants.

One of the types of testing they performed was dynamic-fatigue testing. The parameters of the test, I believe most of these were stated earlier in the company's presentation, but it was 12 Hertz assessed in air for 10 million cycles. They used six samples and their sinusoidal load was between 7 and 150 pounds.

They had no failures and there were no cracks detected when they used a dye-penetration test. No S/N curve was generated because there were no failures. Normally, an S/N curve is the type of data that you would generate from a fatigue test, but you have to have at least one failure to get your endpoint for the curve. So if you have no failures, it is not really useful.

Literature references show that the maximum bite force is in the range of 300 pounds. If you look back, we will see, on the testing parameters, there load went up to 150 pounds. So that is why this is of importance.

The TMJ surgical patient would have a decreased bite force secondary to a loss of muscle attachment. So, the 150 pounds is reasonable for a maximum considering that your patient is going to have some of their muscles

missing.

The average yield strength for the device was 790 pounds. So that is much higher than the average bite force referenced in the literature.

Another type of testing performed was wear testing. This was for 5 million cycles in bovine serum.

It was 55 cycles per minute with a load of 9 kilograms or 19.8 pounds, approximately.

There were two types of wear data reported. One is penetrative wear which means that distance that condyle head wears into the fossa. That was given as 0.01 millimeters per million cycles.

Volumetric wear, that is the volume of material worn away by the fossa. That was reported as 0.39 cubic millimeters per million cycles. Both of these numbers are very small compared to the volume or the size of the implants in question.

The company calculated that, for a 3-millimeter-thick fossa, the average wear life was 309 million cycles. That was a maximum. I think one of the other numbers they came up with was 173 million. The general assumption that we make when asking for testing, for TMJ implants and other types of dental implants as well, is that the average patient has 1 to 2 million cycles of chewing per year.

If you assume that that is, indeed, the case, then the data indicates the device should have sufficient wear characteristics over the life of the implant.

Thermal-bond testing was used to determine the mechanical bond between the titanium mesh backing and the ultra-high molecular-weight polyethylene which is the fossa component. These two components are essentially compressed together while the ultra-high molecular-weight polyethylene is in a heated state. So there are no screws or anything else to disturb the articulating safety of the fossa.

Under mechanical compression, all the samples had a shear strength greater than 75 pounds.

The company used a literature model for loading on the TMJ to determine that the worst-case scenario would be a side-impact load of about 25 pounds and that would be right at the juncture of the polyethylene and the backing which, you would think, would be the most serious thing that could occur.

Probably, in a patient, it would be from trauma, a car accident or something, could cause it to separate.

So, using that 25-pound load that they calculated with their model and using a three-times safety factor, they came up with the 75 pounds. So if their testing showed that everything had greater than 75 pounds shear strength, that should be sufficient.

Are there any questions?

DR. LI: Ms. Blackwell, did you see any retrieved devices that were submitted to you as examples of how a device would look after it was used for some period of time?

MS. BLACKWELL: I don't know that they have any retrieved ones that are recent. The only failures are early in their study and that was six years ago.

DR. LI: So there is no way for you to compare whether or not the wear area or wear type of damage that occurs in their force simulator is similar to what they might find clinically.

MS. BLACKWELL: No. Unfortunately, that is not the case. But even in cases in orthopedics, I don't think the lab's correlation is very close. Even for well-characterized hips and knees, they don't have a real good way to generate the same type of particles in the lab. So that is not really expected for preclinical testing.

DR. HEFFEZ: The maximum bite force you indicated was 300 pounds but 150 pounds would be reasonable. Was there any study indicating that, in these types of patients or in different types of subsets of patients, that they do generated only maximally 150 pounds?

MS. BLACKWELL: There is a model that is in the literature that shows the different contributions of the different muscles for how much force for each muscle. So if you take the muscles out of the model that are missing in the TMJ device patient, then you get an estimate that is about 50 percent.

DR. HEFFEZ: Which muscles were eliminated to make that model?

DR. RUNNER: Lateral pterygoids.

DR. HEFFEZ: So the later pterygoid muscle contributes 150 percent of the biting force?

DR. RUNNER: And the temporalis.

MS. BLACKWELL: And the temporalis.

DR. HEFFEZ: So the temporalis plus the lateral pterygoid contributes 50 percent of the biting force. Is that the assumption?

DR. RUNNER: That was the estimation; yes.

DR. JANOSKY: Is there anyone from the sponsor that would like to respond to the question that was presented to Ms. Blackwell concerning retrieved devices?

It is an invitation to respond. It is not a requirement.

Is it fair to assume there is no response from the sponsor?

MR. ROSE: The early failures that we saw were with loosening on the mandibular component. Many of those devices were replaced with well-fixed components of the new design.

DR. JANOSKY: Would you please state your name?

MR. ROSE: I'm sorry; Greg Rose. So there were no fossa components to examine that were removed from patients where we could examine wear patterns. It was due to the nature--those failures were not to remove the entire device.

DR. LI: May I follow up on that?

DR. JANOSKY: Yes.

DR. LI: Steve Li, just to follow up on that question. For those patients, for instance the ones that requested removal of their device, obviously the component was removed in those cases. Did no one look at the devices to get an idea of what those things would look like?

DR. MERCURI: Louis Mercuri responding to the question about the wear pattern. Yes, to answer question, Dr. Li, those devices were looked at and the wear pattern was what was to be expected in a patient who had this device. It was a short, transitory wear pattern with a rotational component to it.

DR. LI: How close was that wear pattern to the posterior flange?

DR. MERCURI: At but not beyond.

DR. LI: So, was there wear against the posterior flange I guess is my real concern.

DR. MERCURI: Not as much as would be seen in the fossa component. Not significant. And, as I stated before, in the 1995 paper, we have two-year and three-year histology of this device in patients with no evidence of particulation.

DR. LI: Could I follow up on that? Steve Li, again. Polyethylene, especially submicron particles, are notoriously hard to see in histological sections. Did you use any staining techniques such as oil red O at high magnification because often submicron particles, for instance in your repetitive kind of reference back to orthopedics, total hips and total knees, the most biologically active particles are virtually invisible to the eye unless you stain them and use very high-power microscopy.

So typical histology often does not yield polyethylene particles where a closer examination might.

DR. MERCURI: Polarized light was used but not the stain that you alluded to.

DR. HEFFEZ: I would like to return to the question about maximal bite force. Was there any effort--I will direct this to the company. Was there any effort in studying the maximum bite force in those patients prior to placement of the implants?

DR. MERCURI: To directly answer the question, no. And one of the reasons for that is that many of these patients were not able to function at all and so it

was felt that it was impossible to develop any kind of significant data, number one. Number two, we looked into the mechanism to do that. All the mechanisms that appeared to be available were too crude to measure the amount of preoperative bite force that these patients would be able to generate.

DR. HEFFEZ: How did they study it in the model in which they attributed certain percentages to different muscles?

DR. MERCURI: The 50 percent figure was generated from some literature. It was a citation to the literature. It talks about the percentage of force that is lost by muscle, by not having certain muscles. The other problem that has become quite evident, as I have proceeded through this, is that, unlike orthopedic surgery where anatomical, mechanical and mathematical models have been developed for force, unfortunately, due to the complex mechanism associated with the temporomandibular joint, no adequate anatomical, mathematical or mechanical model has been developed.

That is something that the NIH is well aware of and is presently looking for RFPs to look at a solid model for the temporomandibular joint, taking into consideration all of the muscular forces that are placed on the mandible that vary, unlike the hip and the knee, with head posture. Through some research that I did as a resident, I found out that variations in head posture will change the forces that are placed upon the mandible by the muscles.

DR. HEFFEZ: If no mathematical model exists, are we relying on data that is generated from a model to indicate 300 pounds based on such a mathematical model?

DR. MERCURI: That is presently in the literature. That is the only number that has been able to be dug out of the literature to use as a standard.

DR. HEFFEZ: I understand it is present in the literature. I just wonder of its validity and then relying on a percentage of that number that is calculated, perhaps on a number that is maybe not very valid.

DR. REKOW: This is Diane Rekow. Leslie, the 300 pounds, I think, is from Charlie Gibbs' article and he did a measurement with transducers for it. But then the distribution of muscles, as I understand it, was based on this Costra article with a finite-element analysis based on muscle mass and direction.

Is that accurate?

DR. MERCURI: Yes.

DR. HEFFEZ: I just wonder about the accuracy of that study and then to rely on 50 percent of the number.

DR. LI: I have one question either for the FDA presenters or the company. In the earlier clinical trial

with the 363 TMJs and the 215 patients, I couldn't quite tell from the documentation, but were all the implants, in any clinical series, ethylene-oxide sterilized polyethylene or, historically, did they change from one--were they gamma at some time and then switches to ETO or were they always ETO?

MR. ROSE: Greg Rose. All these implants were shipped in the non-sterile condition and recommended for ETO sterilization at the hospitals. To our knowledge, that has been the only technique that has been used.

DR. JANOSKY: We are going to continue with the FDA presentations. Dr. Pannapolli.

DR. PANNAPOLLI: My name is Murty Pannapolli. I am going to give you a review of the statistical aspects of this study. As you know by now, there are two clinical studies here or, more appropriately, two analyses of a clinical study.

In the first one, there are 215 patients with 363 temporomandibular joints. The study was made by eight different surgeons. The data on efficacy variables and safety were collected up to 48 months.

In clinical study No. 2, the number of joints is 195 and the number of patients is 111. The data on efficacy variables were collected up to 96 months so there is more follow up in study No. 2. The primary efficacy parameters are reduction in pain measured in 55 millimeter VAS and maximal incisal opening in millimeters. The secondary efficacy parameters are jaw function in 55 millimeter VAS and diet restriction in 55 millimeter VAS.

The first study No. 1 reveals the following results. To start, preop, there were 205 patients. The mean pain level turned out to be 42.2 with a standard deviation of 11.6. This is for pain. For opening, there were 198 patients with a mean opening of 24.2 and an standard deviation of 10.6. And so on.

It goes up to four years. An important point to note here is the following. In the second row, for example, the 104 patients in the second row does not contain the number of patients in the third row, 70 patients in the third row. Some patients in the third row are in the second row. Some patients in the second row are in the third row.

In other words, we don't have a single cohort of patients observed over time. What we would like to know is whether the pain is decreasing, say up to a certain point, to one year or two years. It is not comparing preop with four years, comparing preop, for example, with one year. It is only pairwise comparisons, what we are interested in.

One more point I would like to make at this point is even for pairwise comparisons, for subjective

measurements, non-parametric tests are better than the T-test because subjective measurements are relative. If a patient says at 12 months that he does not have pain is, like I say, 20 and, at four months, 30, it is only relative. Time levels, taken by themselves, are not very accurate. All we can say is at 12 months, it is less than at four months.

In study No. 2, there are similar observations for pain and opening. We have, again, the same problem. The cohort for patients is not observed over time. But at my suggestion, what the sponsors did was, one year is a typical level time point to observe. At 12 months, the pain level, for example, is 69, 18.5. And these observe the pain level of the very same 69 patients at preop. I found, in the Wilcoxon Signed Rank test, to see if there is a direction of pain at 12 months.

It turned out when we performed this test, the p-value turned out to be less than 0.0001 which indicates that the pain level went down, really, at 12 months compared to preop. A similar thing holds for opening. At this time, the opening has increased rather than decreased.

Next is the question of survival probabilities, how long does the device last, roughly speaking. It depends on the definition of failure. Originally, the sponsors did came up with an acceptable definition of failure, but later revised the definition.

According to the first definition of failure, the last two columns in this table are the most important. At 1 year, the cumulative probability of survival--which is to say the probability of survival to 1 year--is 0.90. It is an estimate from the so-called Kaplan-Meier estimate which is a very good way of estimating with confidence intervals of 0.84 and 0.96.

The confidence interval involves the variance of the estimate. And that is obtained by the so-called Greenwood formula. At two years, the probability of survival to two years turned out to be 0.75 with the confidence intervals of 0.67 and 0.84. At four years, it was 0.75 with confidence intervals of 0.67 and 0.84.

According to the data updated, as of 4-1-99, the estimate for the cumulative probability revised, as I already pointed out, the failures have changed. It is very different as one might expect. What do we mean by failure, which is, what do mean by survival?

According to the new definition, according to the updated data, those three values of survival probabilities at one, two and four years turn out to be 0.99, 0.9723 and 0.9723 with the corresponding intervals as 0.97, 1.0, 0.94, 1.0 and 0.940, 1.0.

The survival probabilities I just mentioned were in study No. 2. The corresponding properties in Study

No. 1 at one, two and four turn out to be 0.9229, 0.9229 and 0.8730. The corresponding intervals are corresponding to one, two and four. Notice that, at four years, the number of patients I would say the last interval, the last point estimate, is not as reliable because that number is very small.

Are there any covariates that influence the postoperative scores of pain function in the opening? A multiple regression analysis was done to study this and the covariates studied were age, TMJ duration, prior surgeries, sex, trauma, left prosthesis, right prosthesis, baseline values.

It turns out pain--I will go through them one-by-one. The covariates that influence the outcome of pain were prior surgeries and trauma, trauma yes or no. There are only two values. The covariates that influence functioning are the number of prior surgeries. That is the only one. The covariate that influenced the opening--there are two of them, again--are number of prior surgeries and the baseline opening. This is from study No. 1.

For study No. 2, the same type of multiple regression analysis was made and it turns out there are no covariates that influence the pain but, for function, it is trauma and baseline. For opening, it is just the baseline value.

I thought I would give the details of this Wilcoxon Signed Rank Test which is the nonparametric test I referred to since the above test compares the two variables on the same 66 patients. A reasonable conclusion from both p-values is that pain and function decreased and the opening increases from preop to one year.

The type of pairwise test that Dr. Mercuri referred to are from a T-test. By the time it was to four years, I think it is, the number dropped down to six in study No. 1. That means that the pairwise T-test compared only six pairs. They took the preop values of these six people and that means there are only six pairs. So the paired T-test, for one thing, we only have values, a subjective parameter.

And there are too many tests. This is so-called multiplicity of tests which is a statistical problem.

My final comment. The data to compare the outcome variables simultaneously at several time points are not available in this submission. A way to do this is to observe the variables in a cohort of patients and use either repeated measures ANOVA F-test or a nonparametric test. Pairwise comparisons at different time points, as I already mentioned, lead to multiplicity of tests.

Two, as I already mentioned, pairwise T-tests

are less reliable than nonparametric tests, particularly for pain and function, since the preop and postop levels are only relative.

Three, of patients who are better off or worse off have a tendency not to return for follow up, this introduces bias in the comparisons of outcome variables on different sets of patients.

Thank you.

DR. JANOSKY: Questions from panel members for Dr. Pannapolli or Dr. Runner or Ms. Blackwell?

DR. PATTERS: Dr. Pannapolli, it would seem to me that the key issue here is the high number of patient losses and whether or not the existing patient data can be extrapolated to all patients that were treated or not.

Is there any way to get a better handle on that because I think it is a critical determination as to whether the 69 patients that all data are available on are actually a biased subset or, alternatively, clearly reflect the population.

Any way to get a better handle on this?

DR. PANNAPOLLI: As you can see, the only way--if we have the pain levels of all the patients at 12 months, pain levels of all the patients, preop, if I understand correctly, we don't have that data. Some are missing. If there are too many are missing at any particular level, that is bad. We cannot perform a statistical test. It is difficult. What we would be essentially testing is the mean of the subset is equal to the mean of the whole population. That is difficult.

But we can examine if they are close to the mean of the whole population values, as many of the population values as we can get.

DR. PATTERS: Would you agree that that is critical in interpreting the data?

DR. PANNAPOLLI: If you pretend that that the experiment was done only on 69 patients, which is a small number, it is not too bad. What can we do if the data are not available?

DR. ALTMAN: I am just a little bit confused--well, probably a lot confused, but the question on the third-to-the-last page of your handout, at the very bottom where you said the prior surgeries and site of the prosthesis are not important predictors? Didn't we hear earlier that that was a predictor?

DR. PANNAPOLLI: Are you referring to the last-but-one page?

DR. ALTMAN: Third-to-the-last page, at the very bottom, your comment on there on study 2. Is that not contradiction from what we--

DR. PANNAPOLLI: It is. It seemed to me I did not have all the data. It does contradict. It is puzzling. I might call it one of the vagaries of

statistics because I don't have all the data to examine that and I cannot think of any possible explanation of this discrepancy.

DR. LI: Did you look for any correlations with device performance, for instance, with physician? In other words, you only had a relatively few number of physicians here. Was the data biased to any one particular physician and, as a follow-up question, did you also look at the performance of the device, as a function of some device features. For instance, did those devices that use more screws have more pain or did those devices that had thinner polyethylene than thicker have more pain?

DR. PANNAPOLLI: The answer to the second question is no. What was your first question?

DR. LI: Was there a surgeon dependence on the outcome?

DR. PANNAPOLLI: I have reason to believe, although I have not examined it thoroughly, that, for a couple of physicians, the way their patients scored the pain levels seemed to be different. You see, it is subjective. If you and I have pain, you may score it as 40 and I may score it as 20. That is possible.

So I have reason to believe that for a couple of physicians the patients scored the pain consistently higher.

DR. LI: My question was more aimed at Dr. Mercuri's earlier comment that there was a learning curve that they went up early on in this device. I guess my question is did some surgeons never go up that learning curve?

MS. BLACKWELL: This is Angela Blackwell to comment on the learning-curve thing. I believe most of the learning curve was with the company and not with the physician. It was a manufacturing learning curve as opposed to a clinical.

DR. LI: Did you look for a surgeon factor in the outcomes? Have you looked at the data?

MS. BLACKWELL: The reason the dataset for clinical study 2 was done was because those two physicians had more follow up. We actually requested that in the 510(k) because when we looked at the whole subset, originally, we saw just clinical study 1. When we looked at that, there was a trend that two of the clinicians had more datapoints than the other six. And that is why they were pulled into a subset.

DR. LI: I understand that. I guess I am trying to figure out if those two surgeons had a difference in performance of the device than the other six?

MS. BLACKWELL: There didn't appear to be a difference in the data, no--just in missing data, not in the data--

DR. LI: But you did look for that, though, a surgeon dependence?

DR. JANOSKY: Would someone from TMJ Concepts like to respond?

DR. MERCURI: Louis Mercuri. I actually did look at the difference between Dr. Wolford's patients and my patients and compared them and there was no difference in them. This was a homogenous cohort.

DR. JANOSKY: Any additional questions for the FDA presenters?

DR. PATTERS: To go back to Dr. Altman's question again, the fact that study 1 shows that number of prior surgeries has a very strong agreement with the amount of pain reduction, inverse agreement with the amount of pain reduction, and the subset of that data, study 2, says that it doesn't, does that suggest that study 2 is a biased subset of the total population?

Did you want me to repeat that? Study 1, as I understand it, shows that there are a number of prior surgeries where there is a very strong inverse correlation.

DR. PANNAPOLLI: Right.

DR. PATTERS: Study 2, which is a subset of study 1, does not show that. Does that suggest, then, that the subset which comprises study 2 is a biased subset of the total population?

DR. PANNAPOLLI: Yes. This ends up a bias with this respect, with respect to number of prior surgeries. Yes.

DR. PATTERS: I think that was a yes. Thank you.

DR. JANOSKY: I actually have a follow-up question concerning Dr. Patters' question, Dr. Pannapolli. Is that an issue of bias or is that an issue of power? Was the power tested for that linear regression model for the second presentation?

DR. PANNAPOLLI: Yes, but you can't predict it so much if it is a question of power. It is in total contradiction.

DR. JANOSKY: Exactly, the directionality is. But one of my concerns, and I will touch on this a little later, is that once you take that subset down, you are still only dealing with essentially 66 subjects, or 66 patients.

DR. PANNAPOLLI: That is a possibility; yes. You cannot conclude--the term "bias" is very vague. I agree with you. It could be due to lack of power. You could say due to lack of power, we got a bias.

DR. JANOSKY: There you go. You sort of marriage the two concepts.

DR. PATTERS: Dr. Janosky, if you could maybe help me a little bit. If it were a lack of power, would

one expect the p-value to go from 0.002 to 0.83? Could that be explained by power alone?

DR. JANOSKY: Let me take a look at what you are looking at. Just pull it up here in front of me.

DR. PANNAPOLLI: That is what it is, a total contradiction.

DR. JANOSKY: I don't think that could be accounted for by power alone, but one of the issues that I see creeping in there that, hopefully, later I will have a chance to address some of these issues, is what happens when you chop, chop, chop this group to essentially a very small group? So, no; I agree that it is not most likely power alone but I think that power is part of it, power and bias together.

DR. PANNAPOLLI: Right. It could be both, due to power and bias.

DR. JANOSKY: Just sort of for my own mind, what we are essentially talking about when we get to that second dataset is relatively complete data on 66 patients for one year of follow up, end of story; is that correct?

DR. PANNAPOLLI: Correct.

DR. JANOSKY: So anything past that gets to be on very uncertain grounds, anything past 12 months.

DR. PANNAPOLLI: But you should remember, the patients say at two months and four months.

DR. JANOSKY: Right.

DR. PANNAPOLLI: They do not contain all these 66. They are different. At any time point, the set of patients is different from set of patients at any other time point.

DR. JANOSKY: So we are essentially looking at different groups of patients even at different time points with a fair amount of missing data.

DR. PANNAPOLLI: Exactly.

DR. JANOSKY: Thank you.

Would you like to reply to that discussion?

DR. MERCURI: Yes. There are two issues I would like to respond to. Number one is the issue of a different dataset. The reason that the ANOVA with repeated measures was done was to see if there was a repeatability or a sustainability of effect in study 2 over the study period. I believe I presented that data that showed that, according to the regression lines, that there was a sustainable effect in pain and function. So I think that may respond to that question.

The second question I would like to respond to was the issue of the number of surgeries that were done.

If the panel, and I'm sorry I don't have an overhead for this one but I do have an overhead for study 2--but in study 1, on page 0865, we have graphs showing 0 to 4 surgeries, 5 to 9, and 10 or more surgeries.

And then I have an overhead of study 2. I would

like to address the issue of bias in this. I think there is a power effect here. For the sake of time and complexity, can we just look at figure No. 10 in study 1 and this figure. Again, I am sorry that we don't have an overhead for this, but this shows what I was talking about before, the problem with the number of prior surgeries that a patient has.

The closed diamonds represents 0 to 4 surgeries. You can see that those patients did very well. I would like you to forget the 84 here. This is a small number of patients but let's track it to 72 months. The filled square is 5 to 9 surgeries. You can see that those patients did not do nearly as well.

And then when we take the open triangle, which is 10 or more surgeries, we can see, as they track along, they did not do nearly as well. So it is dependent on the number of surgeries. It may not be as statistically significant as it was in study 1 which is in figure 10, but the reproducibility of this data, based on this subset which we have already agreed was a subset of the total cohort and had some reproducibility, I think shows what we were talking about here.

Again, I am not a statistician. I apologize for my inability to articulate that, but, as a clinician, looking at these data in this manner, I think it shows reproducibility.

DR. JANOSKY: One of the issues, just to address your first comment, if we think about--you made the statement a couple of times in your presentation and here also that past 12 months, you don't see a change, where there was no significant difference across time in terms of pain, in terms of--what was the other concept that you were talking about?

DR. MERCURI: Function.

DR. JANOSKY: Jaw function. And that gets back to the issue I had just asked previously is was it a power issue, though, because even once you get past the 12 months, the number of patients that you have data on is quite small. So, if we say we have no significant differences, one of the conclusions I could possibly make is you just didn't have enough power to pick something up.

So, can you differentiate between those two possible conclusions?

DR. MERCURI: I have another set of data.

DR. JANOSKY: If it is very short presentation. Is it going to be something we had seen before?

MS. BLACKWELL: Dr. Pannapolli's suggestion on his last page.

DR. JANOSKY: Ms. Blackwell, you are talking about this, the recommendations?

MS. BLACKWELL: Yes. I am a little bit ahead.

DR. JANOSKY: That actually is the issue that I am trying to address.

MS. BLACKWELL: Yes; they have some of that.

DR. MERCURI: These data represent 34 of the patients that had a complete dataset in study 2. This slide was prepared in response to the review by the statistician, Dr. Pannapolli. We have now taken the 34 patients, of the 69 patients from study 2, that had the best follow up. We now have datapoints at each one of the intervals up to 36 months.

Again, we are seeing the same reproducible graph over the time period of three years. And the same thing happens with the objective data.

DR. JANOSKY: Do you happen to have that graph with error bars on it? Do you have a version of that graph that would show error bars around each of those time--

DR. MERCURI: We have the standard deviations.

DR. JANOSKY: Again, those are not the same patients, necessarily, at each of those time points; is that correct?

DR. MERCURI: That is the same patients.

DR. JANOSKY: But you have dropout; is that true?

DR. MERCURI: Here are the numbers.

DR. JANOSKY: Is that the entire 69, all the way to the end?

DR. MERCURI: It is 34 from beginning to end.

DR. JANOSKY: So you are taking the number of 200 or something and we are all the way down to 34 with complete data; is that correct?

DR. MERCURI: Yes. I have mentioned why the dropout rate is as it is, and I will not reiterate.

DR. JANOSKY: So that goes back to the issue I was raising about do you now have enough power. Was there a power analysis done to see whether you are really finding no change in pain, no change in jaw function, due to lack of power or due to truly no change?

DR. MERCURI: To answer your question; no.

DR. JANOSKY: You just haven't done that analysis.

DR. MERCURI: That's correct.

DR. JANOSKY: Okay.

DR. HEFFEZ: What was the repeat-surgery distribution in that group of 34 patients, Dr. Mercuri?

DR. MERCURI: I can't tell you that.

DR. JANOSKY: Any additional panel questions for FDA at this point?

Open Committee Discussion

Presentations by Panel Members

At this point, I would like to move into the open committee discussion. Within the open committee

discussion, we are going to hear from two panel members.

The first is Dr. Diane Rekow and the second one will be Dr. Leslie Heffez--Dr. Richard Burton; excuse me. We have been going back and forth on this.

Let me repeat myself. In the open committee discussion, we will hear first from two panel members, the first being Dr. Diane Rekow, the second one being Dr. Richard Burton. After that time, then I would like to around the panel and address particular questions that each of the panel members might have.

DR. REKOW: This is Diane Rekow. The company was asked, as I read this information, in 1995 to respond to a number of questions. Most of them were addressed quite adequately but there are some that I still have a little trouble with and I want to address three of those questions specifically, and then I have a couple of other general comments.

In question 7(d), an explanation was requested for why the fatigue testing was performed in air and at room temperature with an angulation and a load of 150 pounds. The angulation and the load, I think, was adequately described but the response regarding the environment was, as I quote, "We don't believe that performing the test in an aqueous environment at body temperature would affect the results in any way."

There was no rationale or explanation or references provided. I have a suspicion, and Dr. Li probably knows the literature better than I, but there may be some--and at least a reference in the literature that would support that belief would have been helpful.

My biggest concern is really relating to the wear test. A finite-element model was used and calculated a load of 16.82 kilograms. Literature suggests that loads could be much higher and the tests were done at 9 kilograms. A request was made to justify the load based on information in the literature. The response was that the joints are not anatomically normal and the forces were reduced because of scarring and previous surgeries, which is certainly the case.

The load chosen is based on "a thorough review of the literature and, to the best of our knowledge, approximates the in vivo loading of the prosthesis." And they reference the Gibbs article which has a maximum force of 8.3 kilograms arguing, also, further, that the forces will be reduced by 63 percent and 33 percent of that figure depending on molar position and the model used, although I didn't find justification for how you got the 63 percent and the 33 percent.

And then removing the temporalis and lateral pterygoid will further reduce that. It's true that certainly these are compromised joints. There is no question about it. And then there is some reference to

the track record of the material.

But what I found perplexing was why you would bother to do the finite-element model and then only use 50 percent of the value that you predicted in your own model. So that, in my mind, is still a confusing issue.

In the 1995 information, you were directed to either repeat the joint-simulation wear test at a greater load or to provide results using another test method, for instance, a pin-on-disc, at a higher load. Neither of them were done. And this is of particular interest relating to the wear debris that could accumulate and the pathologic reactions, which has come up before.

In question 7(h), you were requested to provide a detailed explanation of how an in vivo maximum shear load of 25 pounds was established and your response argues that the maximum load can be estimated as roughly equal to the maximum force generated by the muscles that generate or resist forces along the vectors that you show.

The forces are based on the predicted values on cross-sectional area and you reference the Costra article. Solving for those gives you a joint axis. And you go along, but you never get to why you use 25 pounds and a safety factor of 3. So I got confused with some of that logic and never could find an answer in the read that I did.

The static-strength tests are a little bit of a concern to me. There wasn't any information provided about the number of specimens tested and the raw data, apparently, is no longer available. So we don't know anything about the range and standard deviation for the tests, only the average values. That would have been less of a concern except for when the--no; this is probably not a large issue since the averages that you have greatly exceed any values that we will see as probable loads.

But it is a little bit of a concern that there may have been one value that was extremely low or there was something that fractured at a very low value that could be important but would fall out in average data. Again, that is not a big deal, but it is perplexing when the raw data isn't available.

I also think that the surfaces and subsurfaces need to be looked at for cracks. I know that you looked at the surfaces, but I think that there is some concern in damage mechanisms that it may occur beneath the surface, especially in the polyethylene and especially under load in a water environment. And that is a concern that still remains.

Those are the issues that I have. Thanks.

DR. BURTON: Dr. Richard Burton. In my review, there were some things I am going to cover, since we are

behind schedule, reasonably quickly. Some of these have already been addressed. I think the first one is the loss of power in the dataset and the fact that you have gone to smaller and smaller, increasingly smaller, subsets which, when I look at the statistics, lead me to come concern about whether we do see changes or we do see differences between various groups that are not addressed because of the small number included within that.

I am not sure that the company has adequately addressed why so many of these patients have been lost to follow up. I do clinical trials myself. I know how difficult it is to follow those. However, in this type of study with the type of patient population, it is relatively imperative to try to keep those.

It appears, though, that they are trying to address that in their ongoing study now.

The second one comes out of the package insert from a clinical standpoint. It talks about the various indications and contraindications for the use of the implant. My question is certainly I think most of the patients met the indications for their use but, again, when we are looking at this type of patient population, whether some of those patients maybe had contraindications to their use and how that can be monitored because two of the contraindications include uncontrollable masticatory muscle hyperfunction, clenching/grinding, which may lead to overload or loosening of the screws and, two, any disorder mental or neuromuscular that may cause the patient to ignore the limitations and precautions in the use and function of the implant.

Again, concerning the fact that we have spoken earlier about, the fact that this is certainly a multifactorial type of problem which has a neuromuscular component, again, how that is a contraindication and how that is addressed in the selection of patients for that I think needs to be looked at as we evaluate the product.

Also, in the area of failure. Again, you have given some information regarding implant loosening and the loss of those. The question is, again, is that a contraindication and, in fact, is that due to muscular or neuromuscular activity as a component in those patients in which the implant was lost.

Secondly, along the failure line, there was a question of is there any stress shielding in the bone surrounding the base of the condylar portion of the implant, whether that may affect its long-term survivability. Again, in those where it has been lost, was there anything done clinically or otherwise looking at the bone underneath the implant when it was removed.

You also addressed the fact that there was a learning curve, that early on there were a number of

these less--in looking back through and reviewing material, there are obviously some design changes. The question is, at this point in time, do you feel that this is a stable finished product or is it still in an evolutionary stage.

I know that both the shape and size of the attachment point to the mandible, the number of screws that are placed, has changed in this evolution and how that has affected, again--obviously, your losses were more in the early group as opposed to the later group.

Also, it would be the questions of clinical efficacy I think that would should consider. Again, whether there are functional issues, number one, which were addressed somewhat, I think, adequately in your statistics in terms of range of motion and masticatory function. However, how that relates back to the questions that came from Dr. Altman and Ms. Cowley regarding the clinical efficacy of in terms of pain patients, the suffering aspects, whether the pain complaint was adequately evaluated in these patients postoperatively.

Then the last one, your follow up--I know you are looking at 100 percent two-year follow up when, again, you also stated that most of the failures in this seem to be in the three-to-four-year point and how long this dataset would be followed out until completion and, again, the comparison to--I know we have a person on the panel from orthopedics, but how this compares to the long-term studies in orthopedics in terms of length of study to failure.

DR. JANOSKY: Would the sponsor like to reply to either of the comments by Dr. Rekow or Dr. Burton?

MR. ROSE: Greg Rose to respond to the concerns on the testing. It was regrettable that the raw data was lost from this first test for the wear strength and static strength, but clinically that has not proved to be a problem with these implants so we really haven't looked at repeating any of that type of testing.

The same pretty much goes for the wear-test values in that we haven't seen any evidence, clinically, of wear-related problems with particulate matter and many of the analyses that presented the information were done in response to FDA questions for the 510(k) clearances. But most of those things have not been problematic, clinically.

DR. REKOW: This is Diane Rekow. I was just a little surprised with the Proplast problem that was really obviously related to wear debris, that you didn't do that. You don't need to justify it.

MR. ROSE: But this material has been well-characterized and in use for orthopedics. It was when the device was initially made, the concern wasn't of

characterizing a new material. This was considered to be a proved material that had been used, studied out for orthopedic implants, and that was not as much of a focus initially.

Also the early comment regarding some of the early failures. This is definitely a stable design. The evolution was to put smaller and a greater number of screw holes in. I believe it is five failures that we have recorded that were involved with implant loosening.

We actually do not expect to be repeated. That was five cases out of 111 patients.

In the life-table analysis, we saw, that, in recent years, there have been no failures and we actually don't attribute that as an expected failure mechanism to be seen. For example, in the postmarket surveillance study that we are doing, we don't expect to see those percentages recur because that was really attributed to early design evolution.

Also, the one dislocation, failure or adverse event that we reported, we modified and added the posterior lift and anterior lift onto the prosthesis and that has prevented recurrences of that adverse event.

Thank you.

DR. MERCURI: Louis Mercuri to address the clinical questions of Dr. Burton's. Number one, I would like to address the issue of the dropout, maybe from a different angle. Number one, I believe we were too aggressive with a number of data time points that we looked at.

As I mentioned before, we were dealing with multiple surgeons, multiple states, patients moving around in multiple states. It is very difficult with the data points at two months, four months, six months, to get those patients to get on an airplane and come back, number one. So I think we were a little too aggressive with that.

Secondly, I think a big component of the dropout here is the fact that Sulzer, who was the parent company of Techmedica, decided, for business reasons, to close Techmedica. It had nothing to do with the temporomandibular-joint issue. It was just a business decision on their part. They are from Switzerland.

At that point, the study lost its sponsorship and it was very difficult to have these surgeons, including myself and Dr. Wolford, to be able to follow all these patients as closely as if we had a study going that was sponsored. So I think that has to be taken into consideration as well.

The other issue that I would like to address is the fact that Dr. Patters asked this morning about the percentage of failures, and I gave a number of 8 percent.

When I gave that number of 8 percent, I was talking

about the big study, the 215 patients, 363 joints.

I would like to characterize the study 2 numbers which show there were five patients that had the device removed, again early on in the study, which is five of 111 which comes out to 5.5 percent. If we look at joints, it was five joints out of 198 joints which, when calculated out, is a 2.5 percent for study 2 which was the closer follow-up study.

The fourth thing that I would like to address is the issue that Dr. Pannapolli brought up of failure. What we were considering as failures in the first study.

Again, I think from a clinician's standpoint, we were maybe too hard on ourselves and, in the life-table analysis, we included patients, as I alluded to, that we would normally not consider failures.

In an orthopedic surgery, a device is not considered failed when the patient asks that it be removed. It was not a problem with the device. It was a problem with the patient. Therefore, I think the definition of failure for study 1 was much different than the definition for failure for study 2.

For study 2, we used the orthopedic adverse events definition rather than the definition of failure used in study 1. So I would like to clear that up.

Lastly, I would like to say that, again going back to the life-table analysis, that the failures that we showed occurred in the initial stages of the device. I think the question was raised about the surgeons involved. There was a protocol that was developed. All the surgeons were initiated on that protocol so that the variation in surgeons, I don't think, is an issue here.

The fact that there were no failures or MDRs that were reported in the past five years indicates that the device has performed satisfactorily.

Thank you.

DR. JANOSKY: Continuing with the open committee discussion, are there any questions for FDA, for the sponsor, for other panel members?

MS. COWLEY: I'm Terry Cowley. I have a question for the company. High-end particulate load from the first bite takes place and, like the first step, it produces a large or small number of particles. In the hip, apparently, they are fairly well contained in the cup portion where isn't the nerve and blood supply as in the TMJ.

Do you all know where this stuff is going in the patients? And, to add to that, are you seeing any difference in the patients who have had devices implanted previously and in those in whom this would be their first device, by way of reaction to materials?

DR. MERCURI: The first question was do we know what is happening to any articulation. In deference to

Dr. Li's response and my response to Dr. Li, as I have shown in our paper, we have not seen particulation. So I can't answer that question.

The second question was is do we see a difference in the patients that have never had Proplast/Teflon in place or any other device in place in the rheumatoid patients, which I would have to characterize as the zero prior surgeries. Yes; there is a difference. The rheumatoid patients, as I testified to before, do much, much better than patients who have had previous material failures.

MS. COWLEY: Has the company considered using commercially pure titanium instead of the one which includes vanadium and aluminum?

MR. ROSE: We do use commercially pure titanium as the backing for the fossa component. The alloy which you refer to is made for the bone screws. They are made out of the vanadium-aluminum alloy. And the mandibular body, itself. That is a much stronger material. Of course, the pure titanium would not exhibit the same strength that we would require in a device like this.

MS. COWLEY: I have just heard of the first patient who called us and said she had an allergic reaction to the vanadium and that is why I am asking if there is a problem.

May I respond to things said this morning? I would like to address Dr. Bertram's concern about the abuse as a cause of chronic-pain patients and we do not have any data on how many TMJ patients were abused and that they now have this problem as a result of it.

However, these patients have suffered an incredible amount of physical and psychological abuse by the dental and bioengineering communities. At this point in time, the psychiatric community really does not deal very well with iatrogenic damage.

So I would just like to make that point. The extreme of this damage is--two examples that I will give you. That is the patient in New Jersey whose husband called to tell me she had twelve surgeries, three different devices. They went to the surgeon. He told them that there is absolutely no reason for her pain, she needed a psychiatrist. They went home. The husband asked who should he believe, the surgeon or her; he was the expert. And she promptly went in the bedroom and blew her head off.

And another woman who the doctor refused to take her implants out and the pain was so incredibly excruciating that she took all of her pain medication, shot her two children and killed herself.

So you better believe we have some psychological trauma going on, but it isn't all from abuse when we were-- before we could remember.

The problem with follow up, Dr. Mercuri--you know that we hear from an awful lot of patients. You are right. People don't ask us anymore for a "doctor in my city." They say, "Where in the world can we go?" So they do travel. These surgical procedures are costing anywhere from \$30,000, and I have an estimate here for \$101,000.

They are terribly expensive and, by the fifth surgery, most patients are bankrupt. Who pays for the patients follow-up treatments? I happen to know your doctors do not--they do charge for these visits. And I happen to know that your other partner in this will not see patients if they actually have a balance on their account.

Obviously, the financial status of the patients is to be considered here. If this a "study," isn't there some accommodation that the company is able to make or the surgeons see these patients free of charge. That is one question.

I think any patient who is doing poorly, and certainly we know them. They live with emotional blackmail. They don't want the surgeon to know that they have that device out and were lucky enough to get another surgeon to see them and explant that broken device. So I think this is a major issue.

I happen to know that one of the patients who had had a Techmedica device, the previous company, she had it explanted, another implant, and she died shortly thereafter. Did she die from your device? Do we say that? Of course not. Was it a progression of this disease? Was it the 26th surgical procedure? We don't know this, but I think these are issues that really need to be looked at.

And then let's try to throw a positive on this.

How can we change the system that you are in at this point to make it better? And how can all of us work on this?

DR. MERCURI: I would like to address these three issues. Let me get them clear. The first issue was the financial aspects of follow up. I cannot speak to the financial arrangements that patients make with other surgeons or who you characterize as a partner. That is their issue. I cannot deal with that.

I can tell you that, typically, with surgery there is a global fee involved, and that surgery involves the fee for the surgical procedure, itself, and the follow-up appointments up to a certain period of time. Typically, it is about 90 days. After 90 days, a fee can be charged for follow-up visits. I can't answer more than that on that issue.

The second issue was--

MS. COWLEY: The patients that are doing poorly.

They don't go back to their surgeons for follow up. They just drop off and end up finding another doctor to explant that device and do another.

DR. MERCURI: I think, as I brought up in the beginning of my presentation, the profile of this particular group of patients is so completely different from the profile of the average patient that we see for any form of reconstructive procedure.

It is an anatomical profile that is completely different. It is a psychological profile that is completely different. I don't know that we have our arms around this problem. And, as I said, in dealing with this thing for ten years, I don't really have my arms around that particular component of this problem.

I will tell you, though, that unless patients that fit this profile, that are in this group, understand that the surgeons, the companies who make these devices that these patients desperately need in order to function, will work with us in trying to solve this problem. I don't know that we are ever going to come to a solution with it.

And then I would like to use that as a segue into your third question about reimbursement and who is going to pay for this. I think the third leg of that triangle that has to work together on this is our insurance companies. We are talking now about patients who had significant problems that require significant surgical procedures with very technically difficult devices to manufacture and to implant.

The insurance industry has to understand that this problem exists, that it is not just a problem that the surgeons have to deal with. It is not just a problem that the patients have to deal with. It is a problem that we all have to deal with.

My biggest hope is that somehow we can bring these three groups together and develop an understanding of the problem and the way we can solve it because I think what is going to happen here, the future of this, is the fact that we are going to get over a big curve here and these patients will be able to be treated or managed. I think the better term is managed than treated.

And then we are not going to see many of these patients for a period of time. So that is what I hope. I hope that addresses your question.

MS. COWLEY: You missed probably the most important component of this picture. You mentioned surgeons, manufacturers and insurance companies. I think you better include the patients in that group, too, to make this change.

DR. MERCURI: No; I said the patients.

MS. COWLEY: You said three.

DR. MERCURI: No; I said the patients, the surgeons and manufacturers and the insurance.

MS. COWLEY: Another question on the design failure. I have to comment on this because I understand the trauma a patient goes through just trying to sign a consent form. I just have to find out what you all did for those people who woke up from surgery thinking they were going to have a new TMJ Concepts device and were told they don't have it because the device did not fit, and what did you give them to control outrage?

DR. MERCURI: I would like to characterize the reasons that the device didn't fit. All of those cases were my cases, so I can tell you about them. The very first patient that ever was implanted with this device, the device did not fit. And the reason the device did not fit is that Techmedica was an orthopedic company and they felt that the device had to be 8 millimeters thick, the fossa component.

An 8 millimeter fossa will not fit into the temporomandibular joint both in a superior-inferior direction and 17-18 millimeters medial-lateral will not fit. Again, it just didn't work. So the patient was awakened and told the device didn't fit. She understood and went--the second one was a patient who moved in the CT scanner. As you saw from the presentation, the model is an extremely important component of this.

Two implants did not fit because she moved in the CT scanner. Therefore, of this developed the fact that a graphite rod is now used to assure that if there is movement in the CT scanner that this won't happen again. And that has never happened again.

The other one was a patient who--

MS. COWLEY: You don't have to go on. It was the emotion of that question.

DR. ALTMAN: What sort of training is provided to surgeons on using the TMJ Concepts. The second part of that is how does a patient know that, in fact, the surgeon they are going to has actually been trained, if, in fact, there is training?

DR. MERCURI: I would like to be sure I completely understand the question. You are now restricting the question to the TMJ Concepts device and you are no longer talking about Techmedica device.

DR. ALTMAN: Correct.

DR. MERCURI: Using the PMS study that we are doing now, we have given courses to surgeons and I have personally, in order to be sure that the surgeons know how to put this device and they are putting it in correctly, I have personally gone and proctored surgeons in a number of different places around the United States, obtained privileges to operate with them at surgery, gone into the operating room and actually proctored them

placing the devices.

DR. ALTMAN: That's great. TMJ Concepts will sell the product to any surgeon that wants to purchase it regardless of whether or not they have received some sort of training? Do you know that?

DR. MERCURI: The 510(k) certification allows them to market the device. There are a number of surgeons around the country who are very versed in temporomandibular-joint surgery. There are a number of surgeons around the country who have used what we are calling the Christensen device in the past. It is a very similar installation process in order to place these devices in as the Christensen device.

Therefore, not every surgeon needs to be proctored by those surgeons where we know that they have done few temporomandibular-joint reconstructive procedures, those are the ones where I make it a point of going and proctoring.

DR. ALTMAN: The second part to that question; how would a patient know whether how to choose--say, they have read about TMJ Concepts and wanted to use that product. How would they find a surgeon who was skilled in using that project?

DR. MERCURI: There has been no marketing of this device. This has been a device that has gone by word of mouth. Typically, patients will call TMJ Concepts and speak to either Mr. Sampson or Mr. Rose or other of the engineers, and they will give them the names of the surgeons in their particular area.

Or many of the patients will ask, "Who are the surgeons who have performed the most of these surgeries?" and they will be given the names of those surgeons.

DR. ALTMAN: Does TMJ Concepts not have--but they do have information to patients on the product and what is to be expected?

DR. MERCURI: Yes; there is a brochure, a patient information brochure, that has been developed that talks about what temporomandibular-joint reconstruction involves. It may be part of your--

DR. ALTMAN: It was.

DR. MERCURI: It is a brochure which I wrote so I know what is in it. It says, "Considering total temporomandibular-joint construction." It talks about the reasons for temporomandibular-joint reconstruction. It talks about what are the causes of the temporomandibular-joint breaking down. It talks about how the surgery is performed, what are some of the possible complications, what can I expect following surgery, how much will my pain be reduced.

That is based on the data of 0 to 4, 5 to 9, 10 or more surgeries, how long will this reconstruction last. And we discussed the issue of the orthopedic

ten-year business. What can I do to enhance the success of this reconstruction, explaining to them--I think an issue that was brought up was that, in the contraindications, we have talked about the fact that there are patients with continuing aggressive muscular activity.

We explain that in here to these patients. That is a surgeon-patient determination as to has a lot of excess muscle activity. Then it goes on to discuss alternatives to temporomandibular-joint reconstruction. Then it goes through the whole--what are the steps involved in the preparation to receive this device. It goes through the whole protocol of how this device is manufactured.

And then, what are my responsibilities should I choose to have this device implanted. In those responsibilities are included, "I must see my surgeon for follow-up appointments. I must immediately report to my surgeon any problems. I must take care of my implants. I must request that my implants be returned to TMJ for analysis should they be removed. I must keep TMJ Concepts informed of my current address so that we can follow these patients."

When they sign their consent, part of the consent is what I just read. So we are making every possible way of keeping track of these patients.

DR. GONZALES: Gilbert Gonzales. I have a clinical question for Dr. Mercuri regarding the visual-analogue scales and the clinical studies measuring pain, function and diet. When I looked through the paperwork that was given to us, and the studies, the data collection was stated to be in a standardized manner.

It seems that, in the first study and second study, pain and opening, that the numbers of patients throughout 2 through 72 months varied. If the data collection was in a standardized fashion where I am supposing, and the question is really how this was standardized; that is to say, the visual-analogue scale was given before and after surgery at set times.

Pain is rarely a constant phenomenon. Oftentimes, especially in TMJ patients and others, you will have an incident component, a component that occurs with activity following eating, with joint positioning, sleeping, other points, where you will have worsening of the pain or you will have a constant pain with intermittent incident pain.

So the point that you measure pain becomes very critical. When you ask a patient, for instance, what their pain level was immediately after eating, for instance, it may be very different than asking them when they have been sitting in an office or waiting room or when they awaken in the morning or other times.

So my question, first, revolves around when these patients were asked about their pain. Was it when they came in for their visits and, if it was when they came in for their visits, I don't understand why, in some cases, pain was measured and opening was not in some patients, if you look at the groups of patients, and, in other cases, opening was measured in some patients and pain was not.

If this was standardized where this standard form is asking both pain and opening questions, why is it that patients didn't either fill it out, or only filled out part of it? Were some of the questionnaires or the standardized form mailed to patients and then mailed back?

I guess the first part of the question is when were the patients asked to fill out the form and then the second part is why is it that there was variability in only part of the form being filled out, apparently from--at least I am extrapolating that from the difference in the numbers?

Finally, the third part of that question is the intermittent nature aspect of pain, the incident pain that occurs, apparently was not taken into consideration, or was it, in a manner that you had them fill out the visual-analogues scales?

DR. MERCURI: Let me start out by saying the optimum word here, or the word we are talking about, is standardized. The form was standardized so it is a standard form. The form was administered to patients preoperatively, obviously before they had their surgery, and then at each follow-up appointment. The patients were told that when they make their mark, the mark should not be at the worst possible pain that they have, as you have characterized, during function, but generally, where is your pain level, generally, during the day.

In order to characterize the pain the way you have talked about it, we would have to take a visual-analogue scale more like a global-pain questionnaire. We would have to say, "At 2 o'clock, what was your pain? At 3 o'clock, what was your pain? At 4 o'clock?" which is an onerous kind of thing for people to do.

Having been in pain research, I know that some of those patients will do that and many patients won't. So, for this particular study, again, because we are dealing with so many different types of surgeries, we wanted to make it as simple as possible.

So we said, "What is your pain level generally; not when you function?" Where we got at the function part of this, because we realized, just as you just stated, that there are variabilities, "Where is your function level? How well do you function?" "I cannot

function," or, "I can function as much as I want on my diet." So that is where we got at the variabilities related to function and chewing.

The third component of your question was--

DR. GONZALES: The study 1 and study 2, you have patients at various months where the numbers vary where some patients apparently filled out the pain questionnaire part and some did not fill out the opening part. It just doesn't fit.

DR. MERCURI: There are two reasons for that, at least two reasons for that. One is, again, the fact that some of these patients were evaluated by the dentist, physician, surgeon who sent the patient to the surgeon who implanted the device at a distant site and just didn't complete the form.

Another was that some of the patients were evaluated by office staff rather than the surgeon who did the procedure and just didn't complete the form. The third reason is that in order to--and this was my particular patients--in order to get data from patients who were out of state that refused to come back, I made up a questionnaire and included a measuring device with instructions on how to measure it.

The patients would fill that form out and send it back to me. Some of the patients didn't understand the instructions. Some of the patients didn't send the forms back. Some of them sent them back not filled out.

Taking all that into consideration, do we throw out all of that data when it wasn't completely filled out or do we put the data in and pool the data as we have done at the various points, the more data the better kind of thing? So that is how it happens.

DR. GONZALES: My concern in this is that the statistics are as good as the basic units of information.

I am just a little concerned about this point of measurement knowing that pain is incredibly variable. You can ask the patient, for instance, to fill it out at one point or at another point and get discrepancies in the measurement.

So standardization is very, very important when you are talking about pain because if you ask a patient what their worst pain is, it is notorious that the memory of pain is not very good. People do not have a good memory of pain. The visual-analogue scales were created for on the spot, at that moment, what your pain level is not what it was in the previous twenty-four hours.

So that is one of my concerns about the data is it is based on this information that could have that variability in it; that is to say, of the pain fluctuation.

DR. MERCURI: All of the patients were given the same instructions so they all gave the report of pain the

same way at each time interval.

DR. GONZALES: And those instructions were written out instructions that every patient received?

DR. MERCURI: No; they were not written instructions.

DR. GONZALES: Those were verbal instructions.

DR. MERCURI: Verbal instructions.

DR. GONZALES: That were given by you, by the nurse, by office members, so it really wasn't standardized, then.

DR. MERCURI: No; I said initially that the form was the standard part of this but each one of the datapoints was based on the same definition of what pain was, the same definition of pain, where your pain generally is.

DR. GONZALES: Another question regarding the ten or greater surgical--I will call them surgical patients, patients who have had ten or more surgical procedures. Your charts show that the patients don't get better over time in terms of their pain. Certainly, with your function measurements, they got better.

You do include a precaution in one of your--I guess this is a handout to patients where you state, "Total TMJ replacement should be undertaken with extreme caution in patients who have undergone ten or more surgeries. Pain-management team consultation should probably be mandatory."

Is that now the case that the patients that come to you--and is that something that you are instructing other physicians--certainly, with patients who undergo, for instance, spinal-cord stimulators or any pain procedures, we find that it is mandatory that those patients be evaluated by a multidisciplinary pain clinic and, certainly, a pain psychologist not because, necessarily, we feel that the patient has premorbid psychological problems but because patients who suffer with pain for such a prolonged period of time, everyone will develop psychological problems, depression, anxiety, on and on and on.

So it would seem to me that, based on what you have already noted and are instructions to patients and, apparently, physicians as well, that any patient with ten surgeries or more procedures like that should be mandatorily directed to a multidisciplinary pain clinic and pain psychologist to be able to evaluate them further as a protection for them, because these patients, also, have a much higher risk of suicide and other pathology that occurs to them psychologically.

The question is what have you learned from doing this in terms of these patients? Are you instructing physicians, or is it part of the plan to have patients be directed to multidisciplinary pain clinics?

DR. MERCURI: Someone asked a similar question before and I addressed it by saying--I wasn't specific for the ten patients or more but I think the question was do you send any of these patients for psychological evaluation. Most of the patients, I would say the vast majority of the patients, that have had ten or more operations are already in a pain-clinic environment.

If they are not in a pain-clinic environment, they get to a pain-clinic environment. So I think that issue has already been addressed.

The problematic patients, though, are the ones that fall in the 5 to 9 category. As I mentioned earlier, a lot of those patients have been so frustrated by their walk down the TMJ path that, as soon as you start mentioning, "I think it is important that you see a psychologist or a psychiatrist or go through our pain clinic," many of those patients turn around and walk out the door.

I don't think we should be scaring patients away. I agree with you because, as I stated before, I have done pain research. I know what chronic pain does to patients and the psychological component to it. But, right now, there is no protocol for that group of patients.

But, to address your specific question about the ten or more operations, the vast majority, if not all, of those patients are already in that environment.

DR. JANOSKY: At this time, I would like to take a fifteen minute break returning at 4:10. We will continue with some more open committee discussion.

[Break.]

DR. JANOSKY: I would like to continue with the open committee discussion with questions from Dr. Patters.

DR. PATTERS: To me, the overriding issue here is whether the subset of 66 patients, where, in my mind, the statistical data suggests clear efficacy or clear effectiveness and safety of the implant, whether that actually reflects the total patient experience.

So I have a question to Dr. Mercuri, if I could, and then to Ms. Cowley or other members of the TMJ Association.

Dr. Mercuri, if I understand correctly, these data were not gathered prospectively in a research protocol but rather as part of clinical practice; is that correct?

DR. MERCURI: According to the 1995 paper, these data were collected prospectively. In other words, the inclusion and exclusion criteria were proposed in the paper. The indications were proposed in the paper and the protocol was proposed in the paper.

DR. PATTERS: But the patients paid for their

treatment and you said that they paid for follow-up visits after 90 days. So the company did not support this care.

DR. MERCURI: That's correct. It was a limited clinical trial.

DR. PATTERS: Did these patients know they were in a research protocol?

DR. MERCURI: Yes.

DR. PATTERS: And they consented to that.

DR. MERCURI: Yes.

DR. PATTERS: And they consented to the follow-up visits that would be required? They were specified up-front?

DR. MERCURI: They were specified up-front as they are now in the PMS.

DR. PATTERS: And there was a fee to those patients for those follow-up visits after 90 days?

DR. MERCURI: I can only tell you about my own practice. To this date, if a patient shows up ten-years postoperatively, there is no fee. I cannot address the other participants.

DR. PATTERS: But it is possible that that had something to do with the loss of patients to follow up from other practices.

DR. MERCURI: It is possible.

DR. PATTERS: Ms. Cowley, I need to understand from you who has a probably a very good understanding of how these patients might feel and think, when patients do not return for follow up, do you believe that that is a subset of patients that are dissatisfied, a subset of patients that are extremely happy, or is that just a random event and it doesn't bias those who return.

MS. COWLEY: I have not heard from anybody ecstatic over much of any TMJ treatment. In other words, no one has called to say, "This is the best thing that has happened to me."

Certainly, we have patients who have called and said, "Yes; I am improved." Unfortunately, we are now hearing from them eight years later and a lot of other problems have set in.

My gut instinct tells me that so many of the TMJ patients have been there, done that, paid thousands, hundreds of thousands of dollars, for treatment. The disillusionment with, perhaps, in a case like not a failed device but the problems associated with the disease and the device and where they are at that point may be very--they just throw up their hands in despair.

DR. PATTERS: But the data from 66 patients clearly shows, in my mind, that these 66 patients got better. So I am trying to find out about the other 150. I want to know, in your mind, since they did not return for all their follow-up visits, if you think that those

were patients who were likely didn't get better, got much better and didn't feel the need to come back, or it is just a random chance and the 66 reflects those also.

Perhaps you can't answer that, but you certainly know the patients better than I would.

MS. COWLEY: I think it would be unfair. I can tell you what I hear from patients. Usually the problems set in and they don't want to go back to the doctor. They are looking for another one. But, on the other hand, many patients in the last three years are tending to not seek any treatment whatsoever. They are trying to just stay where they are because one more surgery equals more pain, and on and on.

So they may be this much better but not great. I wish we had data.

DR. PATTERS: Then I will ask you, personally. Do you think the experience of the 66 that are presented--do you think that is the representative experience of this device or do you think that 150 have a whole other story to tell?

MS. COWLEY: That is a tremendous responsibility upon me. I would absolutely in no way want to be unfair to any manufacturer.

DR. PATTERS: Then I will ask, perhaps, the representatives of TMJ Association who is not sitting at the table if they have any comments.

DR. ZUCKERMAN: If you don't mind my responding for the National Women's Health Network. I am Diana Zuckerman. Prior to my working in Congress, I was a project director and university faculty member at Harvard and Yale and did research all the time. I would certainly say that my experience was that people drop out for a variety of reasons, but in a case like this when people are in pain, certainly, I don't think that is the time they fill out their questionnaires.

That worried me that people weren't necessarily coming in for exams but filling out questionnaires at home.

When I did follow up--it is always difficult to get people to stay in a study. Usually, you have to provide incentives for them to stay in a study. Certainly, it is the opposite of an incentive to tell people, "Well, come on in but you will have to pay to participate in this study."

People who are happy, people feeling better, might be willing to do that because they are so grateful.

People who are not doing so well, it seems to me, would be the least likely to come in and pay for the experience of telling a doctor, who didn't help them, how badly they feel.

To me, as a researcher, that is just common sense. Also I just wanted to mention what seemed to me

an inherent bias in when the pain was measured. Prior to surgery, it seems to me, is when you feel the worst. When things are really bad and the pain is so bad you can't stand it anymore, that is when you go in for surgery. You've had it and you will try anything.

It seems to me that you come in for your follow-up visits or you fill out a questionnaire in your home when you are feeling a little bit better. When you are writhing in pain at home isn't when you say, "Oh; I have a questionnaire to fill out. I think I'll do that now."

It just doesn't work that way. So that concerned me, that there was that bias, that people weren't coming at regular times with an incentive to come in and objectively be evaluated as to how they feel.

In most studies, of course, people usually participate when they are feeling really strongly either positively or negatively, and that is always a bias. But, in this particular case, when you are dealing with people with so much pain, and maybe Terry Cowley can address this, but when you are in a lot of pain, it seems to me, that is not when you want to participate in a study, usually.

DR. ALTMAN: Can I respond to that as well? I think my experience in fifteen years of public health and doing an awful lot of surveys is just the opposite of that and that people that are the unhappiest are the ones that you do hear from. The people that are happy are the people that tend to not answer things because things are okay.

I think what we have heard from the TMJ Association earlier is, in fact, that people that they hear from are the folks that are having some problems. They don't have a whole big data--they didn't give us examples of people that were happy, but people that are not.

My experience is that people that are not happy with the system are the ones that you hear from.

MS. COWLEY: I think when you have choices of professional providers, it is much easier for you to call the person up who you are not happy with and tell them, "I don't appreciate what just happened," or, "I am just not better."

The TMJ patients, over the last ten years, have had their professional sources limited severely. They are far more limited if you do not have money to travel across the country for treatment which means, if you only have three oral surgeons in your community, you kind of are married to Dr. Love because no one else will see you.

There is sort of what I would explain as a little emotional blackmail going on where you have got to, as patients will tell us--"We have to tell him what

he wants to hear. We can't appear to know too much because then he asks me if I want to treat myself and get out."

So there is this intimidation factor involved. If you happen to find another doctor and that doctor happens to dump you, abandon you, then you might have to go back to Dr. No. 7. We don't have an awful lot of open communication about this.

Why, perhaps, nobody trusts anybody anymore, will not fill out the FDA MedWatch forms, will not complain about their device failure to anyone except us, sort of in an underground manner.

It would be wonderful if all of these people that weren't in the numbers were out there having a life.

Heaven knows, we would like to believe that. We want proof, in a way.

DR. PATTERS: I am looking for scientifically valid data in a relatively complex situation with a very complex patient in a very complex protocol with lots of holes in it. So I am trying to look at it as objectively as possible to ask, "You proved it for 66 selected patients. Is it true for the other 150?" I guess we don't know.

DR. LI: First of all, a follow-up to Dr. Burton's question about comparison to orthopedic devices just as a benchmark. Recognizing, of course, that the patient populations are completely different and the longer history of the total joints, and depending on which statistics are used, in one set, it has been proposed that the failure was 8 percent in the first 300-and-so-odd, if you count them a certain way.

Under those conditions, those would have been an alarmingly high failure rate. Typical for the state of the art to where we call a gold-standard total hip or total knee, the survivorship is around 95 percent at fifteen years. Usually, the first five years, anything above about a 1 to 1.5 percent failure, which are almost exclusively infection, are considered to be too high.

But, again, that is a completely different patient set and experience.

A follow-up question to Dr. Mercuri. Did you do any kind of clinical wear assessment? I saw some very nice looking radiographs there that appeared, for one who spends a lot of time measuring hip and knee wear, would lend itself to radiograph analysis of at least head penetration.

So did you do that on any of your patients, especially when you get out to six, seven years?

DR. MERCURI: As we talked about, and as Mr. Rose presented and the FDA presented, the amount of wear is so small and the imaging that we using is gross, that we can't really measure wear on these particular images

for the factor that, number one, it is so small, and, number two, we don't have a standardized way of doing it.

Now, I realize that there are cephalometric radiographs that can be done to measure wear but, again, because the wear is so small, I don't think we can do that.

DR. LI: But your notion that the wear is small comes from the laboratory data; is that correct?

DR. MERCURI: That's correct.

DR. LI: So if, for instance, the laboratory data was not a true reflection of the in vivo situation, then that assumption may or may not be true. So it is somewhat surprising, I guess, given the fact that the loads are as high as the applicant has specified they are through the finite-element model and the fact that you have, perhaps, down to a 3-millimeter thick piece of polyethylene and that you have got non-zero wear in the hip simulation that you would see no wear in the clinic.

Actually, as I punched through the numbers at seven and eight years, it should be relatively evident. If you take, for instance, the highest wear in your wear test, laboratory test, that would be quite evident in a normal-quality X-ray.

DR. MERCURI: Again, looking at the clinical data, and I will let Mr. Rose address the engineering data, we are not seeing failures.

DR. LI: Understood. But you are not looking for wear, either, apparently, though, I guess is my question.

DR. MERCURI: Wear would show itself up as inflammatory response.

DR. LI: Well before that, you ought to--well, let me take the example of total hips and knees again. Well before you get an inflammatory response, you can see, for instance, the relative migration of the metal component relative to the polyethylene, especially in this case where you have polyethylene with the metal back, it gives you a nice radiographic marker for the back of the polyethylene, would lend itself to that marker.

The other signs of wear, of course, are any kind of loss of radiodensity in the bone. Well before osteolysis, the bone begins to fade. The other portion, and I will sneak another question in in this regard, is that one of the consequences of osteolysis is loosening of the implant which causes pain.

So a question I had for you, and I am not sure you can answer this, but when a patient, several years out, after getting one of these devices, records some level of pain on your scale, how do you know that pain isn't from actually the implant being loose as opposed to the pain they experienced when they first came in to you?

DR. MERCURI: Let me address the issue of the migration of the implant. We make radiographs at each one of the datapoints to look at the relative position, in using a cephalometric radiograph, anterior-posterior cephalometric radiograph, on the same machine, we can overlay the previous cephalometric radiograph, let's say from two years to three years to four years.

So that is kind of a gross mechanism of measuring whether the implant has changed.

The second question you had was how do we know that it is not loose. My experience is not with orthopedic hips and knees but with temporomandibular-joint implants is that when a screw is loose or a component is loose, the first complaint that the patient brings to us is not just pain but also swelling.

You have to understand that these devices lie very close to the skin as opposed to a hip which is buried in a lot of muscle and so any looseness of screws or any looseness of components will manifest itself as an inflammatory response and swelling.

I presented a PMMA-mantled device for the fossa.

I don't have the radiographs here with me but the way that was manifested was not that I could see the crack in the PMMA but the fact that the screws that held it to the zygomatic arch were loose and with radiolucencies, and that the fossa underneath the implant was radiolucent.

DR. LI: Was it possible that pain--and, again, I am drawing on my hip and knee background so this may not hold true so let me ask it as a question, for total hips and total knees, the type of loosening that I am referring to usually cannot be seen by the eye. It is usually in the order of microns, so it certainly would be invisible to the X-ray and certainly would not manifest itself from any movement of the screw.

So well before you actually get a macroscopic visualization, the implant becomes loose enough, and bone doesn't like to be rubbed against, even on the order of microns, and that causes pain. So that is really what I mean by loose, not so much a gross loosening but how do you know these implants are not, on some very micron scale, loose and are causing the pain?

DR. MERCURI: I can't tell you that.

DR. LI: Let me ask the company a question, then. Have you done micro-motion studies in the laboratory where you fix your device in cadaver mandibles and then try to do micro-motion studies to actually see the amount of micromotion as a function of screw placement and the number of screws or the size of the screws or the shape of the device?

MR. ROSE: No; we have not.

I wanted to address your earlier question, Dr.

Li, on the penetrative wear ability, to use radiographs.

Because of the custom nature of these prostheses, the mesh backing to the fossa component is completely irregular and is actually formed to the patient as opposed to orthopedics where there is usually a flat metal plate on a tibial component of some other form of regular geometry which you can assess if you have got migration of two components close to each other.

It is very difficult in this device to come up with any of that because of the irregular nature of this back. Also, if the patient slightly changes their position in which the radiograph is taken, it further complicates that.

DR. LI: One final question. How sensitive is your device to placement and alignment. For instance, in the wear test, I presume you are well aligned in your device where the condyle is basically articulated where you would like it to on the polyethylene.

In surgery, maybe for someone less skilled than Dr. Mercuri, how tough is it to actually get this thing into what you would call an appropriate alignment and what are the consequences if you are out of alignment.

I guess this would be at any plan, either A/P, medial-lateral, or even if there is a tilt especially to the polyethylene because the stresses, if you get out to the edge of the polyethylene can be enormous if you are out of alignment on such a small component.

DR. MERCURI: That's correct. That is one of the advantages of a patient-fitted device. At surgery, the model, which I hope you have taken advantage of looking at, is available. When I do the surgery, as I discussed at Dr. Altman's question, monitor or proctor the surgery, the design is drawn on the model.

The surgeon has the model at surgery. There are various landmarks. From my presentation, you may have seen that the anatomy is so different than the normal anatomy that it is almost, in many cases, like a lock and key mechanism, that this implant will only fit in one particular plane of space.

Also, the instrumentation that has been developed for placement of the implant assures that once the implant is placed technically, at surgery, that it is seated in the proper position so that there are no rocking motions to it. So the patient-fit component of it is one. Two, the instrumentation.

The third thing is the fact that when these devices are placed in a patient, the patient's occlusion has been predetermined and the patient's jaws are wired together so that immediately you will know if this thing is not in the proper position because you will be able to see that the patient--it won't fit.

And then you have to go back, be assured that

you are in the proper occlusion, and you have to place it to its home position based on the occlusion.

So, for those three factors, it is unusual--rare--that these devices, with this particular implant system, do not fit.

DR. JANOSKY: One final question for Dr. Heffez and then we will move to the open public hearing.

DR. HEFFEZ: Could I have some idea of the breakdown of the indications for intervention between correction of iatrogenic disease versus non-iatrogenic disease? How many patients were treated in order to correct a problem that was created by, for example, a Proplast/Teflon or Vittek implant?

DR. MERCURI: If you would just give me one second to--

DR. HEFFEZ: While you are working on that question, if I could ask Mr. Rose, what is the CT scan that is obtained to generate that model? What is the thickness of the scan that is used in order to reconstruct that image?

MR. ROSE: The area of interest, near the fossa geometry, I believe we are using 1-millimeter slices on the scan. As we proceed down through the mandible, depending on the type of scanner that is used, that is opened up slightly.

DR. MERCURI: In response to Dr. Heffez' question, I would like to refer the panel back to the failure data that was reported on these 162 patients based on study 1 and study 2. We can see here, these are the patients with failed surgery, either grafts or devices. It will kind of give you an idea of the percentage of patients that are in each one of these categories.

I think this is the best characterization that I can give you.

DR. HEFFEZ: But those 162 patients, were they operated with this TMJ Concepts?

DR. MERCURI: Yes.

DR. HEFFEZ: They were operated because of those reasons?

DR. MERCURI: For these reasons; right.

DR. HEFFEZ: Have you broken out your data according to each of those? Let me backtrack. You're classifying it as failed devices, failed grafts. I would like to know how many were treated for inflammatory disease, for example, or traumatic disease?

DR. MERCURI: How many rheumatoid arthritis?

DR. HEFFEZ: Yes; as opposed to how many of those are--many of those are iatrogenic problems, basically.

DR. MERCURI: Yes.

DR. HEFFEZ: I want to know how many were virgin

joints and how many were inflammatory disease, tumor. What is that subset?

DR. MERCURI: I don't have that data with me. This is the best I can give you to characterize that. I would be happy to provide that to you. I have that data. I just don't have it with me.

DR. STEPHENS: One question on that graph, does the failed graft group represent grafts that been done for Vittek implants that had failed? On other words, are there some failed Vitteks in that failed graft group?

DR. MERCURI: Yes.

DR. BURTON: One other question which goes off that graph as well. This 162 patients, can you give us at least a somewhat demographic breakdown of when they were done in terms of how many were done three to five years ago and how many have been done one year ago, two years ago, three years ago?

MR. ROSE: This is actually the data from our active postmarket surveillance study, so these 162 patients have been done since December of '97.

DR. BURTON: Thank you.

DR. JANOSKY: At this time, we would like to open the public hearing again.

Open Public Hearing

DR. JANOSKY: I would ask that anyone who wishes to speak state their name, their affiliation, any current or previous interests, financial interests. Can I see by a show of hands if there are.

It looks like the list from this morning, if I am correct. Do you want to do the same order from this morning? Each of you will be given three minutes to address the panel. We will start with Ms. Lisa Brown from TMJ Association.

MS. BROWN: I will be real brief. A lot of people, after five to nine surgeries, these surgeries could range anywhere from \$3,000, \$30,000-plus, each. They run out of money. Although they would really like to go and have the follow ups, they don't have the money to do it. Insurance companies as well, they will cover three to four follow ups and then, after that, these people are no longer covered.

Three to four follow ups, I don't know that that would constitute a year of follow up for someone. I think there is more than I would like to say--a number of people out there that fall into this category that cannot afford it. They are on disability, social security. They would love to have the follow up but they can't afford to get there.

I gave a few examples this morning of that very thing from comments from people saying that they couldn't afford it and they didn't know what to do.

That's all.

DR. JANOSKY: Thank you.

Next is Mr. Kevin Clark from TMJ Association.

MR. CLARK: Kevin Clark with the TMJ Association. I would like to follow up, I guess, what Dr. Patters, your questions to Terry and anybody in the TMJ Association with respect to the science behind this particular study.

I don't think we are in a position to validate or invalidate the science that you have heard about today. I think that is the panel's job to do so. But I would take exception to something that you mentioned over here. In any business, an unhappy customer is more likely to complain something like ten times. You hear ten times over the negative, versus the happy customer that walks away and says, "That is a great product."

With respect to the TMJ patients who have been hurt or wronged or whatever you want to phrase it, I don't think they typically go back to their surgeon to complain. Sometimes they do, but maybe they get a kind of a, "Maybe it is possibly your fault," or, "It is in your head. It will get better," whatever answers they hear.

But typically, and I have been through this for thirteen years with my wife who has had six surgeries and five of those were bilateral. She has two different types of implants right now. I have to admit that for the first several years, we were very intimidated to go back to complain to the surgeon. We didn't know quite what to do.

Since then, we have gotten close to some surgeons and hooking up with the TMJ Association and really taking matters into my own hands and getting into this to understand it better has made me more confident to be able to ask the questions that we need to ask.

But that is not your average patient. Your average patient is paranoid, extremely intimidated, of their surgeon. So I am not sure those are the ones that are coming back to follow up. So I just wanted to throw that in.

Lastly, Dr. Patters, you asked what we would like to see from the Association, or maybe even personally. I think it is the panel's job to decide whether the science is there for any of these implants being presented this week. But, personally, obviously, as I mentioned earlier, my wife has got two different types of implants and they appear to be failing.

We do need something if they are failing. If speak for her. I speak for thousands of other patients that I believe that are out there that are in the same predicament. I don't know what the answer is. Would we like to see approval of one of these two products? That is up to the panel to decide. I would like to see

approval at some point at some time of something that is going to help my wife out and the other patients across the country.

I don't know what shape or form that comes in and I don't know the FDA process real well, but I understand there is conditional approval, there are conditional approvals for certain indications and maybe some combination thereof is the answer. Again, that is up to the panel.

Obviously, if you approve a device for certain indications, that device, once approved, as I understand it, can be used kind of as a blanket device. It is approved for this indication or that indication but anybody can implant it for other indications that it is not approved for, as I understand it again. I am not an FDA person.

With that, maybe I can ask the company just one question. In the case of virgin joints, at what point--and maybe Dr. Mercuri, as a practicing clinician can answer this best, what do you need to see before a device is put in? How bad off, if you will, does a patient have to be?

Thank you.

DR. MERCURI: Unfortunately, that is a very difficult question to answer because all patients are completely different. What may be an indication for one patient may be a contraindication for another patient. When we look at the indications that I discussed earlier, I think those are solid indications for placement of a patient-fitted temporomandibular-joint device such as the TMJ Concepts device.

But I can't tell you, as I sit here today, without having a specific patient in front of me--and that is why I find this particular device to be the most useful because it is patient-specific for the specific patient and the specific problem that that patient has. So I am hoping that that answer will satisfy you.

DR. HEFFEZ: Those indications that you listed, which ones of those are imperative, in your mind, that this device would be required, that there would be not another alternative method of reconstructing that joint if indicated?

DR. MERCURI: I believe all of them are.

DR. HEFFEZ: So you feel that there is no other viable means of reconstructing the temporomandibular joint in those indications listed besides using this device.

DR. MERCURI: I would like you to remember my characterization of these patients. These are multiply operated, anatomically mutilated, patients or physiologically mutilated patients such as a rheumatoid patient, or an ankylosis patient.

I believe on the basis of principles of orthopedic joint placement that these devices must be stable in situ and they must be made for the specific indication, the specific problem, that is there. Right now, in my clinical experience, the only device that I feel comfortable with, as a clinician, in placing is a specific device such as the TMJ Concepts device.

DR. HEFFFEZ: I am not necessarily talking about the device. I am saying there is no other alternative means of reconstructing the temporomandibular joint besides using this device on those indications that you listed.

DR. MERCURI: There are other ways to reconstruct the temporomandibular joint using autogenous tissues.

DR. HEFFFEZ: Right. So which one is imperative, in your mind, that even autogenous material wouldn't be indicated and that you would have to use this device.

DR. MERCURI: As I said, I think for the patient population that I characterized, it is this device. If you are going to talk about ankylosis, primary ankylosis, in a child, this device is not a reasonable device to place in a child.

DR. HEFFFEZ: Yes, but you didn't list that in your indications.

DR. MERCURI: No. It is one of the contraindications.

DR. HEFFFEZ: I am saying in the indications, as ankylosis, or the indication is rheumatoid arthritic, is the only way of reconstructing that individual using this device, in your mind, or there are other alternative means? I want to try to identify if there is a specific indication in your mind where there currently is no alternative reconstructive method.

DR. MERCURI: Certainly the patient who has had, because of the data that was presented in the Wolford and Cottrell paper, it appears that an alloplastic device such as the TMJ Concepts device is the only device that can deal with that situation. That is certainly one of the absolute indications, but I have to stand by what I said before that I believe that this device is the device for reconstruction of the patients the way I have characterized them.

DR. HEFFFEZ: The Wolford paper was regarding the Proplast/Teflon implants.

DR. MERCURI: Yes.

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

DR. ZUCKERMAN: Thank you. I actually have a question for Terry Cowley. She said something and I want to make sure I understand it correctly. It was my understanding that what you said in the follow-up study

where there are only two doctors taking patients that one of them--that you know of at least one patient who said he wouldn't see her for follow up because she owed him money.

So the concern was that if patients owed--out of only two doctors in the study that if patients owed one of them money, they couldn't come back for follow up. So it wasn't just that they had to pay to see the person but also, if they owed money, they couldn't come; is that correct?

MS. COWLEY: If they had a balance on the account.

DR. ZUCKERMAN: Balance due.

MS. COWLEY: Yes. The staff sort of kept the patient out. We did hear that quite a few times.

DR. ZUCKERMAN: I guess my concern is, as a researcher--I mean, this is just against everything that you do. In research, you try to get as many people in for follow up as possible. You don't create barriers to them coming back in. I guess that is why there are only three people at the end of some of these studies, or six.

You don't know, as you pointed out, whether that is a random three or a random six, or whether the people who owe money are the worst off or not.

MS. COWLEY: Have I answered your question?

DR. ZUCKERMAN: Yes.

MS. COWLEY: Am I able to follow up on that? I think this brings into discussion one of the--another can of worms of all of this TMJ mess and that is patients will call us with complaints. We have to keep their patient confidentiality. Many times, I ask, can I tell the FDA about this? They say, "Absolutely not because they will know I am the patient with the device implanted sideways," or whatever.

So I think one thing that we desperately lack is a network where we can communicate openly, honestly, where the patients are not living with this emotional blackmail if they complain to the FDA they are going to be marked, their surgeon will never see them again.

We have to be able to communicate openly with the manufacturers. My ideal situation would be where we have one implant registry, period, for all TMJ devices. I would like to see all the devices sent to one central location where they are sent to the hospital only for that patient because I hear of patients waking up with a device they didn't know they were getting.

We somehow have got to clean this system up and we have to be able to work with the good manufacturers. We have to get some funding from the FDA, from the NIH, to set up some type of registry, some type of studies.

The gentleman over there said it is imperative we have pain control and go to pain clinics. I would

like to know why we have a medical doctor who doesn't understand anything about temporomandibular-joint diseases, disorders, as well as particle disease so many of these patients are suffering from.

We routinely hear now of vision damage where particles are in the eye, they are migrating. We hear of seizures. This is constant. If you ask a patient, "Can you open your mouth?" "Yeah, but I am seizing every day."

We need a network of medical people, dental people, manufacturers that can start putting together a picture of what is this TMJ patient. If we are able to have manufacturers willing to do this, I think this will be the beginning of getting a leg up on some of these problems.

DR. ZUCKERMAN: I just have a quick comment. When I was talking to patients, when I was doing this investigation in Congress, it was really clear that people contacted me who had been very happy at one point, had gotten an implant, had really felt great, thought finally their problem was solved and then, a year later or two years later, they felt completely differently.

That is why I made the comment earlier about long-term safety data. When I said that, I didn't know what the studies looked like. I never dreamed that the dropout rate was so high after even two months let alone after twelve months.

So I just want to say, based on my experience of talking to patients, a year's worth of data just doesn't really tell you anything about what is going to happen to them. So many of these people thought, "Well, things can't get worse. If my doctor says, "Try this new implant. It will make you better. It is worth a try," only to find out that things could get worse.

So that really concerns me. That is obviously the purpose of doing studies with some kind of long-term follow up.

Thanks.

DR. PATTERS: Dr. Zuckerman, in the people that you have contacted, do you have any anecdotal experience about what the percent of the success rate of TMJ implants is? I am having a problem--I read letters of testimonial here from people that are put in front of my that say, "Oh, I have done 48 of these and every one has worked perfectly." These are from oral surgeons.

Ms. Cowley gave me sort of a different opinion that very rarely does it work well and most of the time it doesn't. Do you happen to have any objective or even subjective data of how many patients get better and how many patients don't.

DR. ZUCKERMAN: Let me just be clear that the people who contacted me generally were people who were

unhappy because I was working for a Congressional oversight committee and we were having hearings and they wanted me to know how bad things were.

We did get some calls from people who were happy. They were almost always people who had implants for a very short period of time. They said, "I had a terrible experience in the past but now I have got this new implant. I have had it for three months and I am really a lot better."

So we certainly did hear from people like that.

I can't say I ever heard from a patient who had their last implant or set of implants for several years and called to say how happy they were. Personally, I didn't.

I don't have a big n. This isn't a sample. It is not a study. I can only say that the people who contacted me, there was a real relationship between latency, how long they had had it.

DR. PATTERS: In your talk this morning, you laid out three criteria which you thought the panel should follow. I have a feeling you knew that that didn't exist, that the long-term safety and effectiveness data did not exist, when you laid out the criteria that suggested that we needed to see it.

DR. ZUCKERMAN: Honestly, it was just a best guess. I actually had no idea what the data would look like. I really did think that since some of these implants have been on the market for quite a long period of time, I really did think that there would be data for at least a few years.

In fact, there are data for a few years. It is just that there are only four people in that sample. But, had the manufacturer really wanted to follow a larger number of people, it seems to me they would have created incentives for those people to come back instead of disincentives.

DR. PATTERS: I agree. I think this is an issue of trying to collect data as part of clinical practice versus doing an actual placebo-controlled, double-blind, clinical trial which is not what was done here.

DR. JANOSKY: At this time, we are going to close the open public hearing and move into the open committee discussion and vote.

Open Committee Discussion and Vote

DR. JANOSKY: We have in front of us three questions that the FDA would like us to answer. Are these available on overhead or everyone has them? If you look through your packet of information, in the agenda, it is about the seventh or eighth page in the agenda.

Question 1. I will read the question. It says, "Based on the engineering data, the sponsor has predicted an implant lifetime of greater than ten years for their device. Does the fatigue and wear testing presented in

the PMA support this predication?"

Panel members? General discussion or comments and then I will go around assessing assessments of this.

DR. LI: On the issue of the engineering data for implant life, I presume, actually, you calculated the hundreds of years of life based on the fact that you had some wear rate and then you added up the number of years it would take, then, to wear away the entire polyethylene component? That is kind of a nonsensical projection of the life of an implant.

Well before you get to that point, you are going to generate billions enough particles in such a small joint space that I would say osteolysis is probably a given. So the idea of multiplying the wear rate times the number of years it takes to generate that volume of polyethylene, I think is just plain nonsensical although I guess it has some attraction in other realms.

The fatigue testing is kind of interesting. As I understand it, you had a dynamic fatigue test where you loaded something repetitively for millions of cycles at 12 Hertz and it didn't break and then, separately, you took brand new implants and then you did a yield test and provided a yield number.

Both of those tests are adequate but, typically, if you really want to test this, you would have taken the devices that you cyclically fatigued and then get a yield strength because the issue isn't how strong it is when you start. The issue is if it gets loaded that many cycles, does it, in fact, lose its strength.

This material is relatively strong and probably would have likely passed that test. But that would have been a more appropriate, I think, view on that. So the way I look on the dynamic fatigue test, it may or may not have been a sufficient indicator. I really couldn't tell.

As far as the wear testing goes, I guess I am troubled by the wear testing results mostly because of the lack of retrieval devices. So we don't really know how these things wear. I think, as Ms. Blackwell pointed out in the commentary, even for hips and knees, devices which have been around and tested for a lot longer, there is still no really great laboratory test that guarantees that that will be the performance in a patient.

The real test is, in fact, analysis of retrieved devices or sequential follow ups on radiographic devices.

So I would say, in this sense, we actually don't know what the wear of these devices is. But I was a little taken aback looking at the individual datapoints in wear that, when you assessed wear by penetration, there was a factor of about 4 between your lowest wearing sample and your highest wearing sample.

When you did it by volume, there was actually a factor of almost 8 between your best-wearing and your worst-wearing sample. So, as one who has done wear-testing for a number of years, that is an alarmingly high standard deviation for what should be a relatively repeatable test. And I am unsure where the source of that data comes from.

But that data is where I got my earlier comment that if I took your highest wear rate and then did a volume calculation, you ought to be able to easily see that on a radiographic analysis.

The fact that Dr. Mercuri doesn't find polyethylene in the tissue is somewhat surprising given the fact we know the implant does wear. But this may be a function of how one looks at the tissue and could be under the conditions that he is looking at, they are very hard to see. Unless you go out of your way to see them, you actually may or may not see the tissue.

So I put all that together saying the dynamic fatigue doesn't really exactly tell me if it is going to survive fatigue although Dr. Mercuri did show pictures of broken plates and screws of other devices indicating that there is plenty of force there to exert very high stresses on this device and that the wear testing, in the best view, is non-validated and, in the worst view, it does not mirror what actually happens in vivo.

DR. JANOSKY: Additional comments?

DR. REKOW: The other potential pitfall to complement what Dr. Li said very elegantly is that, over time, wear mechanisms could change and you may get a wear pattern early on that subsequently then becomes a three-body problem with the particles getting in the way and creating an extra problem.

So just to extrapolate linearly over time can be dangerous.

DR. LI: One last issue I think which is important, that is key right now in the area of total hips and knees, is a method of sterilization. You picked ethylene oxide as a method of sterilization which has the benefit of not causing any long-term degradation to the material which gamma irradiation can do if a component is allowed to age prior to implantation.

However, the price you pay on that is that several, now I think about a half a dozen hip-simulator studies, have shown that if you compare an ETO product versus a gamma-ray sterilized product, ETO products wear 20 to 40 percent higher from brand-new components.

So the question is, without knowing how retrieved devices fail--in other words, if they fail by a mechanism of delamination, pitting or fracture and not wear, then ETO would be very appropriate. However, if they are failing over long term because of wear

mechanisms, then the ETO sterilization, in fact, would not be the recommended method.

DR. JANOSKY: Additional comments or responses?

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?"

Panel members?

DR. LI: I guess this is really a shorter answer to the question if you don't have any--I'm surprised that, given the number of laboratory wear tests that you did, that you didn't once, at least, look to see if the particles are of the appropriate size.

For instance, it would be a good validation of your test if you generated particles of the same shape and size as found in vivo and, in fact, it would be a good reason to completely ignore the test if the particles that were generated were, in fact, different in size and shape than found in vivo.

So, in the absence of that data, it is another question--you have got a big question mark you have got to put over the laboratory data about whether or not it was appropriate. So the lack of that information, I don't think there is any way would could tell anything about the fate of these particles or how many were generated or anything along those lines.

DR. JANOSKY: Additional comments, responses?

Moving on the 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."

Let's start this way and work our way around.

DR. PATTERS: Quite clearly, some patients do benefit from this device. I think that that has been very well shown. However, a lot still is unknown. I do not believe that effectiveness data can be generated in the type of clinical research that has been performed to date because it is all--in my mind, it is quite anecdotal and it is a series of anecdotes taken from a whole bunch of different practices following a protocol but, really, it is part of clinical practice and it is not defined separately for research.

For instance, in periodontology, when we test a device, the manufacturer sponsors that test and we pay patients for their inconvenience to come back for our follow up. In that way, our purpose in doing this is actually to test the device in a double-blind, placebo-controlled clinical trial and get all the data that is possible.

That is not what was done here. These were implants that were placed in patients who clinicians believed, in their clinical judgement, would benefit from

these and data was collected as possible in that framework.

I don't think you can really develop scientifically valid data if that is really your only measure. So, quite clearly, I think people benefit. The long-term data is not here regarding the effectiveness in my opinion and a lot remains to be done.

I would not like to see this alternative for patient care removed. But I believe this alternative needs to be available. However, it needs to be presented to patients, I think, as a treatment of last resort with a relatively high failure rate.

DR. GONZALES: I feel that the pain measures were not done properly in my mind. Efficacy for pain reduction was not determined. Therefore, I think you have to throw out the pain data. At least, I'm less strong in terms of function and diet in terms of the measures, but certainly for the pain measures, it was not done properly.

I don't feel that this device is efficacious for pain in patients with ten or greater prior surgeries and, therefore, those patients should be excluded or those patients should be warned that this procedure is not a procedure for pain reduction.

I think that if this device is approved, it should be approved with those conditions.

DR. REKOW: In spite of what you said about double-blind placebo studies which, I agree, are ideal, I don't see how you could conceivably do one of those when you have radiographs that show quite clearly which device you have in place. So there are some practical issues with this design of the study.

But, having said that, I am concerned with the amount of data that is available for patients who clearly are most likely going to have a device for a very, very long time. I, too, think that it has its place. There are some patients that need it but I don't think that we can clearly say that the patient who is between 35 and 45 can look forward to a pain-free life for a really long time with this device.

I don't think that the data, as presented, shows that clearly.

DR. HEFFEZ: I think you have to separate safety from effectiveness. I think what is most important is safety. The effectiveness is hard to judge because every patient has a different constellation of symptoms that one has to address. For me, the primary thing to look at is safety.

I am concerned that the construction of prospective studies that are currently underway, that study protocol needs to be looked at or we are just going to amass data that is still going to be difficult to

interpret later on.

Do we need such an option? I think we do and I think that this option should have certain exclusivity and I do think that it should be looked at possibly as a temporary device, temporary meaning five to ten years. On other words, the patient should be aware that the likelihood of replacement is there.

The key, as far as safety is concerned, is, I believe, are we able to retrieve this device with minimal damage to the patient, any damage being local and not systemic and that it does not remove the ability to reconstruct the joint at a future date.

DR. BERTRAND: These are a desperate group of patients. What we haven't done is really characterize how or what these patients are suffering or how this has affected their lives before we do something to them again. I think it is really incumbent upon us, if we are going to use devices like this, to really characterize what that patient is experiencing, how they view what they are going to do in the future, whether types of situations affect who they are.

There are instruments that can measure that, predictably and reliably that would address what Dr. Gonzales was talking about, the effect of pain and what the pain is upon their lives. I think that has to be done from the baseline and has to be done with follow ups.

Additionally, dealing with these types of patients on a daily basis, there are some patients for which an ankylosis does need some type of appliance to be placed to help that people. So this looks like we have pilot data for this point. And we really don't know the long-term effectiveness. I would hate to close the door on this at this point, but I think definitely think we need to characterize the patients more thoroughly at every juncture.

DR. LI: Just an issue on the length of follow up, and again, to follow up Dr. Bertrand's question. Typically, an orthopedics, larger joints in orthopedics, osteolysis takes a minimum of about four to five years to occur. It is highly rare to get osteolysis in the short times of the clinical follow up provided.

So, as far as the long-term consequence of the wear, it is virtually unknown for this device. It may or may not be an issue but we can't tell by the follow up presented so far.

DR. BURTON: I think that, again, we have a device which is necessary in terms of treatment of a small group of patients. But I am not sure that the data we currently have--I think it shows some safety but we don't know the long-term safety issues because we don't know what those wear byproducts are, how much they are

going to accumulate and what their long-term effect is going to be.

Secondly, we are not sure about the effectiveness. I think that is what Dr. Bertrand and Dr. Gonzales were alluding to. I think that this product needs to be there. The question is whether patients are made aware of what its true effectiveness. It may be functionally effective in terms of dealing with range of motion and potentially masticatory issues, but, again, this is a very definite group which may be driven more by pain in many cases than it is strictly by functional issues.

They may be getting something which may be effective in addressing a portion of the problems but ineffective in dealing with the other ones, and they need to be made aware of that such that when they are making the informed-consent process, they are truly aware of when we say it is effective what it is effective for.

DR. JANOSKY: Additional responses, comments?

DR. STEPHENS: I think that clearly some type of temporomandibular-joint replacement is absolutely essentially. I think that part of the effectiveness problem is that I don't know that you can expect to have a consistent effect in this group of patients because they have such a wide group of symptoms and etiology.

My experience with total-joint patients is that, after two or three operations, somewhere along the line, the percentage of them that have, as an example, neuropathic pain associated with this disease is very high and that even in patients with joint replacements, these symptoms are going to persist after the joint is in place.

I think the key is what this therapy is mated to is most important. I think the joint replacement benefits are fairly predictable. The intra-articular pain that patients have from sclerotic bone against bone is likely to improve and the stability of their occlusion is likely to improve.

But a lot of these side issues, the neuropathic pain, muscular pain, problems are not going to be--there is not going to be a level effectiveness. So I think that we definitely need the devices and we probably will need additional studies in whatever way that it is approved. Hopefully, it would be approved and we would need additional studies to go with it.

DR. JANOSKY: Dr. Runner, are there any additional questions you would want us to consider at this time?

DR. RUNNER: I would just say that, in your deliberations, you should be very specific in terms of what you would like.

DR. JANOSKY: Okay. Before we move for a motion

and a vote, are there any responses from the sponsor or a few minute for final comments.

MR. ROSE: I have several comments I would like to make. I would like to address Dr. Li's questions about characterization of the wear particulates. I have to confess I am not current on the literature at what point wear particularization became an important feature. This wear study was done quite some time ago.

To that end, it may have preceded a lot of the recent knowledge that has been developed in that area on wear particulates. This device was developed as a salvage procedure to deal with conditions that exist. It was not a device that was developed to see if a market could be found for it. It had a definite indication in a situation that really had very little alternative.

In earlier discussions here, I think people have mentioned that there was only--we have dwindled to four patients, or very small numbers and a very short number of years. We did present information that we have 29 patients that we followed out at the seven-to-eight-year time frame. So we do think we have an indication at least that the device is lasting for a long period of time and it is functioning for some people and it is greater than four.

This device also suffered for a period of time in which there was no sponsor. There was nobody to be following up that information and actually it was never known at that point if it was ever going to be made available. So I think a situation existed where there has been a lot of effort to collect the data that has been shown.

I agree that it is not optimal and it is not done in an appropriate research method, but I think there is evidence or indication at least that there is some value that has been obtained on this.

As far as the comments about pain, it has never been our contention that this eliminates pain. In fact, that is one of the reasons that this was done by the group of clinicians who was looking at that, is they wanted to find out how it was effective for people and the fact that the larger the number of surgeries, the pain level has statistically been shown to be reduced.

It just hasn't been reduced to as great a level of those patients who have fewer prior surgeries. This information has all been included in our literature that we have developed directly for patients to inform them of that exact condition. I don't remember who brought that point up but there has been a strong effort to label this device appropriately so that patients are fully informed of the risks and the problems they might encounter.

We think that has been very important given the past history of patients having unnecessary surgery or

surgery and they weren't really understanding what was taking place or what implants they were about to get. We take that very seriously.

Function is something we aim to restore. We know that there are problems with pain restoration. But, for many of these patients, I have spoken with them personally. They say they have realistic expectations. They understand that they are going to be living with pain for the rest of their lives and they say, "I just need some functioning."

They have a realistic expectation that that is the best they can hope for at this point given their surgical history.

Those are all the comments I have.

MR. ULATOWSKI: I have two comments. The first comment is I certainly want to remind the panel about the discussion this morning regarding valid scientific evidence and the flexibilities provided under the regulations on what might be considered to be such type of evidence and the types of devices we are dealing with today in terms of the history of marketing of the products, availability of the products.

I think there is another aspect here. As you move toward your vote, you will be voting up and down depending on what the applicant has presented to you today or tomorrow. I think it is going to be helpful to the FDA that, if there are areas of problems in terms of the data or the types of patients, concerns that you may have, if you have directions for us in terms of in what subpopulations or what conditions or what areas there might be viability to this product or other products that will come along, certain labeling restrictions, other areas that will help us in some scientific negotiations or other discussions with the company so we can perhaps seek an acceptable middle ground with the company on a condition of use.

So although companies tend to come to you asking for the whole ball of wax, quite often there is a niche there, there is an element of acceptable performance and knowledge base that would be worthwhile. So, in your discussions, consider that.

DR. JANOSKY: Dr. Floyd, do you have some comments for us being the industry representative?

DR. FLOYD: It has been a very interesting discussion. From my perspective, obviously, my background is not orthopedic surgeries or joint-replacement surgeries. But I do have a strong engineering background and a strong anatomic pathology background.

The thing that has impressed me about this is we are dealing here with a poorly characterized disease process. We have heard a lot of anecdotal patient

information that I think all of us can sympathize with and react strongly to. On the other hand, much of that information does not directly relate to the condition and the device we are talking about here.

We are talking about a device that is really for rescue of the patient for which there are very, very few other options. We are talking about a device that is built upon--and, remember, it is a preamendent device--but it is built upon a lot of information derived from other major joint-replacement mechanics, engineering. We can quibble about the engineering data and I appreciate all those arguments.

However, we have a device that has a couple of very unique--one extremely unique property and that unique property is tailoring to a patient who has had severe anatomical changes from surgery or other disease processes. And, therefore, we have a device that is custom for that patient and, in fact, may be the only kind of option that patient has at this particular time to have any semblance of function.

I don't think anyone has ever claimed that the use of this device will return a patient to their pre-disease state. In any of the medical specialties that I am aware of, it would be foolish for any practitioner to ever claim that to a patient because we don't have those kinds of capabilities are our fingertips at our current state of the art.

But what we are talking about here is a device that, for a limited number of people, may be the only option possible. We have heard that there is a mechanism in place to track these patients, to follow up data. And we have had a suggestion from the company, and I suspect the FDA will reinforce this, that that follow up will become even more strenuous in the future so that we will collect some of the data that we don't have at the moment.

I am a non-voting member of this group but I would urge all of us to seriously consider what the options are for these patients and what the threat of this device is because we are talking about safety and effectiveness--what the threat of this device is for this limited subset of patients who really do have very few other alternatives.

DR. LI: Maybe one question for the dental surgeons or maybe Dr. Mercuri; if, down the road, it turns out--let's say that worst of all worlds happens and, for some reason, this device actually does cause osteolysis at five, six or seven years when you get out to several hundred patients at that time.

So now you have a patient that originally came in with a compromised joint and you are going to put this device. The ramification of osteolysis is loss of even

more bone. Now, if you try to move the device, you are going to have lots of screws in there as well.

So I guess my question is what would the surgical or the medical treatment be on a patient that got one of your devices and, heaven forbid, got osteolysis out in eight or nine years and you had to, then, do something.

DR. MERCURI: It is a good question. I think the patient-fit aspect of this device--in other words, I showed you some clinical examples of devices that had failed and left the patient with basically no ramus and those are the kinds of cases that a patient-specific device is made to deal with.

In your own field of orthopedics, when you have a hip that has had a device fail where you have lost the stock bone, you go to a "custom" device to be able to deal with that situation. So I would say that this is the perfect, although in this world there is nothing perfect, but this is certainly the alternative for a patient who would be in that situation and where you are seeing those patients right now.

We see patients with other devices that have failed that we are now able to give a semblance of function to that they would normally not have because there is no other device available right now that can handle that situation.

DR. REKOW: But what happens when yours fails? Then what does the patient do?

DR. MERCURI: I look at this as an evolutionary process. I am not talking about evolution of this particular device. We have talked about that enough today. But I look to the future as there being an evolution to maybe the next level of biomimetics, maybe the next level.

DR. REKOW: Can you get yours out?

DR. MERCURI: I have not had to take one of mine out. I can tell you that the people that I mentioned before who had removed the device were able to remove the device without doing significant damage to the underlying bone.

DR. PATTERS: I think what I am troubled mostly by is I have not been able to get a handle here on what the true success rate is, whether patients five years after treatment, whether the majority feel benefit from the treatment or feel worse from the treatment. I just don't have a good handle on that from the discussion.

I do hear, over and over again, about people being on their fifth set of TMJ implants. That is obviously four sets that have failed. And that is of great concern to me.

DR. MERCURI: Is that a question?

DR. PATTERS: It can be if you like.

DR. MERCURI: I didn't know quite how to work this answer in but this gives me an opportunity to answer the question. As someone else said, I appreciate, obviously, the problems that these patients have. I have been dealing with these patients on a clinical basis, on a daily basis, for the past ten years so I think I can speak from experience.

These patients are the most difficult patients to deal with, not from a character flaw. They just have a significantly difficult clinical problem to deal with and it is multifactorial, as we have talked about.

I hear the good side of this. We talked about bias before. Maybe it is a bias that these patients come back and they say they are doing very well. When I see a patient that comes back in eight years and the patient says that they are doing extremely well, it is a much different experience than what we have been hearing.

I would like to panel not to think that all of the patients who have temporomandibular-joint implants, be they be TMJ Concepts implants or be they be the Christensen implants, are not doing well. My biggest concern is that we may be overstating how bad these patients are doing.

These patients do well, or as well as they possibly can do, based on the disease process. I think Dr. Bertrand and Dr. Gonzales have a very good point. This is a different group of patients that we are dealing with here.

The other thing is that someone made the point that we need to inform these patients. It states right in the documentation that the patient gets as well as the consent that they get, and I am quoting, "Unfortunately the complete elimination of pain is not possible." It is not possible. We never go in with the idea that these patients are going to have their pain completely eliminated.

So I will leave it at that unless there is another question.

MR. ULATOWSKI: I had to make a bureaucratic point of order but I think that, this being the closed committee discussion, we need to keep the discussion within the panel so that the manufacturer isn't turning a one-hour presentation into a two-hour presentation over time here.

DR. PATTERS: Could I address that, then, to the oral surgeons that are on the panel as to what they think the success rate of these generic devices are.

DR. STEPHENS: I am not sure that I know the answer to that across the board but I can speak from personal experience. We have, in the group with which I work, a very high success rate but it is really tied, I think, in large part, to the fact that they are mated to

a very aggressive chronic-pain management group because, clearly, in the group of patients who have that first operation, for example, for ankylosis, they do very well.

In fact, a great reason that they do well is the fact that they have not had multiple procedures which, in themselves, generate problems. In the patients who have had multiple operations, we have always looked at the total joint, itself, as the one point that you can use as a starting point to stabilize their occlusion, to approve their function, to make them look better, to get patients to generally feel better about themselves as a part of a chronic-pain management approach.

We have found that they very well. I would say that our success rate is--I know that it is greater than 90 percent, but it is very hard to know, across the board, because I think that also the surgery is very much surgeon-dependent. I think that it is very technique-sensitive.

DR. HEFFEZ: I have had so many patients who have come to me who have been multiply operated and they just tell me, "Get me back the way I was when I first walked in to the office before I got my first surgery."

So I would say today the majority of treatment that we are doing is to correct iatrogenic disease. I would say that is the majority of times that we are operating.

As far as success, I take it patient-by-patient. I try to identify the patients complaints and try to gauge what I can do for that particular patient. It is not that easy to be able to say how that patient is going to benefit from a procedure. There lies, I think, experience and where 6 p.m. it sort of crosses the border between art and science and it becomes more of an artistic sense of knowing when to operated on a patient and when to say, "I can't offer you anything anymore."

We have to, I think, identify the complaints and then see, in our minds, if we can identify the etiology for that complaint. Sometimes, the etiology is a closed vertical dimension. If you can direct that vertical dimension, that patient may be okay. Sometimes, a patient's chronic complaints of pain are due to foreign microbe particulate, foreign body material, where there is no way you can remove all that foreign body material.

You can remove the gross amount but there is no way you can remove that micro-particulate matter. Sometimes they have parafunctional habits that are not properly controlled. And that impact on the symptomatology is difficult to know.

So it has to be patient-by-patient. I have a good number of failures, I will tell you, and I have a good number of successes. But for me to just bring it and lump it up into one study would be very difficult.

Hence, the problem with all these studies is that it is a heterogeneous population. I truly believe you need an option, you need an alloplastic option for the patients.

You wish you could control the practitioner to determine when it should be used or not.

DR. JANOSKY: Dr. Burton, do you have a response?

DR. BURTON: I would just like to add to that I think that the other issue is just time frame and length of time. I think that what Dr. Heffez says is very true, it is a multifactorial problem and there certainly is not question, at least in the institutional setting where we see patients from a broad number of practitioners that it certainly is surgeon-specific to a degree.

I think that, in the short term, the success with these types of devices looks pretty good. I think that the problem is that there has been a real paucity of any data that is very long-term. When you talk about a group which demographically is very commonly either 30 to 40-year-old age bracket, and you are looking at something that has a one or a two or a three-year time frame, it doesn't give you much of a feeling for what is going to happen at that five-year, ten-year or fifteen-year point.

I think that that is when you ask about what is the success. The real question is what is it at that point. Our job is really not to make that determination, maybe to give some insight into that if it was possible.

But I think that that is where the real question of whether it is successful or not--I think that short-term, probably, from what I have seen, the success of these devices is well up in the 90 percent brackets.

Was it as high as, perhaps, hips? I don't think that it is. It is probably more like the low 90th percentile rank. But the problem is that most of those, again, are short-term data. When you start to get beyond two or three years, the numbers drop off so radically that you really probably don't know what the five-year-or-greater success is.

I don't think anyone knows the answer to that right now.

DR. PATTERS: Can you address the people that have had multiple implants and have had them replaced over and over again. Can you address those issues? Do you think that was poor surgical judgment?

DR. STEPHENS: I think, frankly, in patients who have had multiple procedures, oftentimes one of the major problems is that they are not followed. When they come into the group--and, again, this is a personal approach to doing it in the center with which I am associated, but I find that one of the things that is most settling for patients is assuring them that they are in a group that is going to stay with them, that is going to stick with

them if there is a problem.

There are so many factors. As an example, in a total-joint patient who, a year or two down the line, is having uncontrolled pain, the joint really doesn't matter if it is really a muscle-spasm problem. But, on the other hand, the patient doesn't know either.

So it is very important that there is continuity in their care. So I think the problem with the multiply operated patients is--I think there are many reasons for it. I don't know that you can really pin it down.

DR. BERTRAND: I think, if there have been multiple surgeries, the primary etiology was never addressed in the first place and people are just overlooking whatever may have caused that problem initially. I think that is what Dr. Heffez is talking about. We are trying to correct a desperate group of patients who have had the change and they can't function.

But I think it is very important to go back and ask, what was the original group of problems that have been magnified by the repeated surgical insults that do created post-surgical neuropathies as well as saying, "This area hurts. I am not going to let you use that part of my body and I am going to look for other patterns of muscle activity." That is what we are not seeming to look at and that is what we need to characterize right from the beginning.

With the group of patients we are talking about in this dataset right here, they have not been characterized enough as to what is interfering with their life and how their pain is affecting them from day 1 through day 1,000. There are ways to do that. There are people that can characterize this.

It is not psychogenic or psychosomatic. It is neurogenic or neurosomatic and what is actually happening.

DR. JANOSKY: Before calling for a motion, Ms. Scott is going to remind us of the recommendation options. We will move into the motion phase now.

MS. SCOTT: This document that I am about to read is in the panel packet so if you would like to pull this from your packet and read along as I read it.

"Panel recommendation options for premarket approval applications. The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act require that the Food and Drug Administration obtain a recommendation from an outside expert advisory panel on designated medical device premarket approval applications that are filed with the agency.

"The PMA must stand on its own merits and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information. Safety is defined in the

Act as reasonable assurance based on valid scientific evidence that the probable benefit 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 when labeled will provide clinically significant results.

"Your recommendation options for the vote are as follows: approval; there are no conditions attached. The resulting agency action; if the agency agrees with the panel recommendation, an approval letter will be sent to the applicant.

"The second option is approvable with conditions. You may recommend that the PMA be found approvable subject to specified conditions such as resolution as clearly identified deficiencies which have been cited by you or by FDA staff prior to voting. All of the conditions are discussed by the panel and listed by the panel chair.

"You may specify what type of follow up to the applicant's response to the conditions of your approval recommendation you want; for example, FDA or panel follow up. Panel follow up is usually done through homework assignments to the primary reviewers of the application or to other specified members of the panel.

"A formal discussion of the application at a future panel meeting is not usually held. If you recommend post-approval requirements to be imposed as a condition of approval, then your recommendation should address the following points: A, the purpose of the requirement; B, the number of subjects to be evaluated; and, C, the reports that should be required to be submitted. Agency action; if FDA agrees with the panel recommendation, an approvable with conditions letter will be sent.

"The third option; 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 labeling to be false or misleading. If you recommend that the application is not approvable for any of these stated reasons, then we ask that you identify the measures that you think are necessary for the application to be placed in an approvable form.

"Agency action; if FDA agrees with the panel's not-approvable recommendation, we will send a not-approvable letter. This is not a final agency action on the PMA. The applicant has the opportunity to amend the PMA to supply the requested information. The amended application will be reviewed by the panel at a future meeting unless the panel requests otherwise.

"Finally, tabling. In rare circumstances, the panel may decide to table an application. Tabling an application does not give specific guidance from the panel to FDA or the applicant thereby creating ambiguity and delay in the progress of the application. Therefore, we discourage tabling of an application. The panel should consider a not-approvable or approvable with conditions recommendation that gives clearly described corrective steps.

"If the panel does not vote to table a PMA, the panel will be asked to describe which information is missing and what prevents an alternative recommendation.

"Following the vote, the chair will ask each panel member to present a brief statement outlining the reasons for their vote."

DR. JANOSKY: At this time, I would like to call for a motion.

DR. GONZALES: I would like to make a motion. Since pain is not an indication by the company, I would motion that if the device is approved regarding the nonclinical aspects and now focussing on the clinical aspects that the device should be approved if, one, a prospective study that measures pain and pain relief and medication to be used to modify pain be performed, since pain is still a significant factor in patient's going to oral surgeons for this device that, two, patients should be told that the studies do not yet reveal that pain is significantly modified and that, three, patients with ten or more surgeries should be told that the implant will not help them since the information provided by the company indicates that.

So the motion is a little bit complex in saying that, first, if the device is approved in terms of its characteristics, device characteristics, non-clinical characteristics, that, then, the device be approved but with the conditions one, two and three that I have just stated.

DR. JANOSKY: If I am understanding you correctly, then, you are proposing a motion for approvable with conditions; is that correct?

DR. GONZALES: Yes.

DR. JANOSKY: The conditions being one, a prospective study with very detailed information concerning pain be assessed. Two--I am reading this as a labeling concern in terms of the device not modifying

pain or not having an impact on pain.

DR. GONZALES: That means you should be told that the studies at the present time do not yet reveal that pain is significantly modified. That isn't to say that, in the future, the study won't show that. And that, three, patients with ten or greater surgeries should be told that the implant will not help them with their pain because those individuals may end up going through the surgery for other reasons, function reasons.

DR. JANOSKY: Just to get it clear in my mind; is number 3 a suggestion for a labeling issue or for an indication-for-use issue, where you are talking about patients with greater than or equal to ten surgeries?

DR. GONZALES: I think that patients should be told, however that would take place, whether it is a labeling issue or some mandatory issue. But it is clear that patients with ten or greater surgeries do not have improvement in their pain and, therefore, they should not be told that that is going to be the case, that they will not have improvement.

DR. HEFFEZ: Could I make a suggestion. Could we maybe limit the motion to whether it falls into one of these three categories and then be specific on what we want the conditions to be?

DR. JANOSKY: I am understanding him to say that it is approvable with conditions and that he is listing the conditions. I don't want to speak for you, but--is that correct?

DR. GONZALES: That's correct.

DR. HEFFEZ: Are we voting on the entire package or just the fact--

DR. JANOSKY: Right now we are just discussing the motion. It is just a discussion of the motion currently.

DR. HEFFEZ: His motion is very specific. Could he initially just make his motion approvable with conditions and then, later on, be more specific because it will be hard for everybody to want--they may want to add additional conditions as well and make it very hard for the panel.

DR. BURTON: In past votes, though, in other panels, this format of making a motion with conditions; that's fine. I can also make the motion now that the device be approved with conditions.

DR. JANOSKY: As I am understanding it again, the motion currently is approvable with conditions and then, so far, three conditions were proposed. Any other discussion? A second?

DR. BURTON: I would like to make an amendment to that. I was going to make a motion for approval with conditions. However, one, I think that there should be a study done looking at particulate levels in a test-lab

situation so we would have some kind of a feeling for what is produced particulatewise in a lab-bench situation and, secondly, since, at this point in time, the current study is only approximately three years old, that that be continued to the five-year point for reporting purposes and that, again, lastly due to the small number of patients involved with these devices that there be a maintained registry of patients so that there be some longer-term issues so that we have some way of identifying both the numbers placed and the type of implants placed.

So my three conditions are one, particulate levels being done on a lab-bench; two, longer-term follow-up with completion of the current study to five years; and, three, establishment of registry of all patients where these implants are utilized.

DR. JANOSKY: Any additional modifications? We will go through the motion again and call for a second.

DR. LI: I'm sorry. I am confused a little bit now. Are we adding our conditions now? Is that what we are doing?

MR. ULATOWSKI: I would agree with the comment about a clean vote on one of the three types and then discuss the conditions separately.

DR. JANOSKY: Let's return, then. There was a motion that was placed on the table that said approvable with conditions.

[Seconded.]

DR. JANOSKY: That has been seconded. Let's call for a vote. Let's start on this side. Again, it is approvable with conditions.

DR. PATTERS: Point of order. How could one vote if they don't know what the conditions would be?

DR. JANOSKY: Could you give us some direction again, please.

MR. ULATOWSKI: You can discuss at this point in time before you vote as you go around.

DR. JANOSKY: So approvable with conditions, again. Discussion.

DR. BERTRAND: I have some discussion. I am very curious about the patients who there isn't follow up on. I would like for any future patients in a prospective study to be characterized by life interferences, depression, anxiety, things like that. I would recommend that if we are going to do prospective studies, employ somebody who can assess it in patients so you can see before and after.

Perhaps that would give us an idea of why certain patients are not doing follow up. There may be also a way that we can assess what is the degree of financial constraints that prevents people from doing follow ups in situations like this.

The best of all worlds would be to do studies where there is some financial incentive. I don't know if that is really possible.

DR. PATTERS: I would like to see one of the conditions being that, in order to gather the follow-up data that the sponsors take the responsibility of the surgeon's fee rather than the patients. To me, that is an enormous detriment to collecting absolutely critically needed follow-up data.

DR. HEFFEZ: Do you mean the actual initial surgery or the follow up.

DR. PATTERS: The follow-up data so patients are not lost to follow up because they have to pay the surgeon to return to the office. I think the company should bear that, the sponsor should bear that, burden so that we can get the follow-up data out to multiple years.

DR. HEFFEZ: When you talk about cost, do you include transportation costs and fee for a consultation?

DR. PATTERS: That is how we do it? Our sponsors compensate the patient for their inconvenience for them to come in for us to collect this data.

DR. HEFFEZ: I understand. I just want to be clear whether you are including transportation costs.

DR. PATTERS: Yes.

DR. HEFFEZ: I feel it would be important to study the material as it pertains to different diagnoses, whether it is related to the failed Proplast/Teflon implant, whether it is related to an inflammatory disease, tumor reconstruction. I think the data has to be separated out.

DR. JANOSKY: We have two motions on the table, both of them with different conditions, but the motions, themselves, have been approvable with conditions. In our discussion, we have suggested other conditions. So I am asking that Dr. Gonzales and Dr. Burton either revise their motion or withdraw them and someone else present one with the additional conditions.

DR. BURTON: I will withdraw mine.

DR. GONZALES: I don't understand. You want a retraction?

DR. JANOSKY: A modification to include all of these. But we need to call for it as an additional motion and withdraw the other two.

DR. GONZALES: Can you state all of the conditions and modifications and then we can actually vote?

DR. JANOSKY: I can state them--

DR. LI: Excuse me; a question before we do that. Do I understand that we should say all our conditions now if we have them? Yes? Then I have got some conditions.

DR. JANOSKY: Okay.

DR. LI: I thought we were voting in the general sense. So I think my wish list, some of which Dr. Burton already said, was to bring the materials and wear testing up to what we would consider to be state of the art for today, not from whatever the understanding that the test might have been done long ago.

But it is 1999 and we know a lot more about wear and performance of materials now than prior. So, with that preamble, I think I would want more wear testing with more appropriate measures of wear. This would include by weight loss. It would certainly would include analysis of particles.

An area we haven't talked about is that they have a cobalt-chrome component attached to a titanium-vanadium-aluminum component. The issue of mixed metals, crevice corrosion has not been raised. I don't know if this is an issue they find clinically or not but is one that occurs in total hip replacement and has been unmentioned for most of today.

This has a ramification of either weakening the titanium taper that it is on or, in the worst of cases, could create another form of particulate debris.

I think the materials testing should be, for lack of a better word, a little tightened up. The material source is specified right as simply 4150HP polyethylene but its source, whether or not it is extruded or compression molded, who does that, whether or not it was preaniled. Those details at least were not in the packet of information that I had and should be included and/or specified, the ramifications of altering from those material sources.

I think analysis of retrieved devices is going to be the only way that you can, in the end of it all, validate any laboratory testing that you do. For whatever reason that comes out, whether or not be it for infection after a week or somebody just wants it out after some time, I think it behooves you to analyze those devices. Otherwise, you won't really know how the device fails.

Lastly, I think the applicant should take all the technologies available today as going on in reducing wear in total hips and knees to see which of those technologies actually would apply to your joint today rather than using a device or a method that you picked some time ago and just sticking with it because that is what you started with.

MR. ULATOWSKI: I think Dr. Runner might want to summarize all the bullets once we get them all down here.

DR. JANOSKY: Maybe we can do it together. Do we have an overhead we can write on?

DR. RUNNER: I think I have them all down if you want me just to list them again.

DR. JANOSKY: Yes; if you can, that would be fine.

DR. RUNNER: I had the list starting with a prospective study that would measure pain; that the patients would be told with ten or greater surgeries that this will not help their pain; patients should be told that studies have not been completed to indicate that there is a decrease in pain long-term; there should be an additional particulate study. I am sort of combining a few here now with state-of-the-art wear testing, weight loss, analysis of particles, tighter material sourcing, addressing the issue of diverse metals with specs being tightened; the continued follow up of patients that are presently in the study to five years; a registry of patients; any prospective study should study life interferences; there should be some payment for patients participating in follow-up visits; and there should be some attempt to study the different conditions and their relationship to the type of success or failure that happens and separating out the conditions that lead to implant placement.

DR. REKOW: And one more; the analysis of retrieval.

DR. RUNNER: Oh, right; analysis of retrieved implants.

DR. LI: And sterilization methodology.

DR. JANOSKY: So as I understand the motion, it is approvable with conditions, with the conditions that were just read to us by Dr. Runner. Any other discussion?

DR. PATTERS: Yes. Dr. Runner, I just suggested that the sponsor bear the cost. It doesn't mean to compensate the patient necessarily, but to bear the cost of follow-up visits rather than the patient bear that cost.

DR. HEFFEZ: I would like to ask the rest of the panel members how they feel, if they feel that the device is a temporary device or a permanent device.

DR. BURTON: I think, in my consideration, it is a permanent device. I don't think we should be considering it at this juncture as a temporary device. The patient would need to understand that potentially it could be replaced at some point in time but I don't think that the intent, at least from what I can gather and certainly what I have seen thus far that it would be considered a temporary device.

We have looked at that issue in the past but I don't think that is the case here.

DR. HEFFEZ: How does the orthopedic literature view hip prostheses? Do they feel that it is a temporary or permanent device, or is that age-specific?

DR. LI: It is a shifting question. The average

age of a double-hip patient ten years ago was 72 and now it is 67 and dropping. So, before, the life of the implant was near the life of the patient but that is rapidly changing. So, now, in a 40-year-old, it is a totally different question.

So I think it is an evolving question for total hips. But, clearly, if you are under the age of 60, chances are you are going to get more than one in your lifetime.

DR. BURTON: I understand that. But I guess my question is, even though it may not last the rest of your lifetime, I am not sure that that makes it a temporary device.

DR. HEFFEZ: Perhaps "temporary" is not an appropriate word, but I think the patient should be at least advised that the younger you are when you have this implant placed the more likely it is that you will need another operation.

DR. REKOW: Maybe the way to resolve that is to say, "a projected lifetime of the implant is--" or, "the expected service life of it is--"

DR. HEFFEZ: I think you are always concerned as a surgeon when you have that because if you fall below that, you are at risk.

DR. JANOSKY: Additional discussion? Dr. Gonzales or Dr. Burton, would you state the motion? We can list the conditions as read into the record by Dr. Runner.

DR. GONZALES: Do you want the motion that--

DR. JANOSKY: That this is approvable with conditions, I think.

DR. GONZALES: This is approvable with the conditions that have been listed. I guess that is all of ten conditions.

DR. JANOSKY: Right; that Dr. Runner had read into the record. Do I have a second on the motion?

DR. BURTON: I will second it. My question is is the FDA able to live with being able to clean--my thing right now the language is a little confusing, even listening to this. Is this something that you can, then, work with to produce something that is--

DR. RUNNER: The recommendations are--the panel's vote is a recommendation to the agency. We, then, take into consideration the intent of what you have said in the panel proceedings and proceed to work with the company to come to closure.

DR. BURTON: I second the motion.

DR. JANOSKY: So the motion is approvable with conditions, the conditions as Dr. Runner had read to us.

It has been seconded by Dr. Burton. I would like to call for a vote, please, starting on the right with Dr. Patters and working around.

DR. PATTERS: I vote in favor of the motion because I believe the data, as presented, supports approval with the listed conditions.

DR. LI: I vote for approval with conditions.

DR. GONZALES: I vote for approval with the conditions.

DR. REKOW: I vote for approval with conditions but I have to say that telling a company they have to pay for it, I think, is micromanaging.

DR. BURTON: I vote for approval with conditions.

DR. HEFFEZ: I vote approve with the conditions listed.

DR. STEPHENS: I vote for approval of the motion.

DR. BERTRAND: I vote for approval with the conditions.

DR. JANOSKY: So the motion carries.

Can we, then, please go around the table once again and state again the reason for why you voted, if you hadn't stated it earlier.

Dr. Patters. You had stated. Dr. Li.

DR. LI: I think this device is obviously necessary for a group of patients that have little alternative. The device may or may not be actually suitable for the task right now. Unfortunately, the data just really doesn't lend itself to make a decision. So my additional amendments, hopefully, given that data, would be a much clearer picture on the outcome.

DR. GONZALES: I voted in favor of approval because I think this is the best that is available right now. But I think that the caveat of continuing to measure patients in terms of their pain, their function, is still very important. I think it is also very important to caution patients what they can expect, and what they can expect is improved function but not necessarily other improvement such as pain.

DR. REKOW: I think that there is a definite need and I agree with Gilbert that this is probably the best that is available but the data is very limited and that is of particular concern to me because of the relative young age of these patients and the lifetimes that they are going to have to deal with an implant that will never be as good as the ideal situation. That is what prompted my decision.

DR. BURTON: I voted for approval with conditions because I again felt it is a very necessary device for a small number of patients. However, the data as presented was not conclusive enough to show that it had been adequately studied in terms of both its efficacy and its design factors. I think that the guidance that we have tried to give back to the company will,

hopefully, improve that.

DR. HEFFEZ: I voted approval with conditions because there is a small subset of patients who definitely need this option. The data still needs to be collected and, therefore, doesn't merit an approval-without-conditions status.

DR. STEPHENS: I voted for approval with conditions. I think this is clearly a necessary therapy for a group of patients and that the conditions that we have attached to protect patient safety and efficacy is still to be established.

DR. BERTRAND: I voted for approval with conditions based on the need for this desperate group of patients and the fact that the conditions start to outline data collection that can make us better understand what is afflicting these patients.

DR. JANOSKY: One final decision. For the information for follow up, return to panel or can the FDA evaluate? I hear a response to FDA evaluate, follow up for the information that we have requested.

DR. BURTON: I think we can return it to the FDA.

DR. JANOSKY: Any requests to return it to panel? No? So the recommendation is to return it to FDA.

Thank you.

One other item of business; any more information that the panel feels must be made of those conditions premarket?

DR. HEFFEZ: Is there a time limit that is placed on acquiring these conditions?

DR. RUNNER: Because these are 515(b)s, we have 180 days to review the data and we would, therefore, have to complete the negotiations within 180 days of when we received the application which was sometime in January, I believe. So it will be completed with the company by sometime in July, I believe. July 6.

DR. BURTON: Point of clarification; is the product currently on the market at some level?

DR. RUNNER: Yes.

DR. BURTON: That is my understanding, anyway.

DR. RUNNER: The product is on the market.

DR. BURTON: The product is currently on the market so I guess I am not sure what the question is.

DR. RUNNER: The question is, after the 180 days, they would not be able to remain on the market unless they met these conditions of approval or agreed to a plan to meet these conditions of approval.

DR. JANOSKY: The recommendation of the panel premarket?

MR. ULATOWSKI: Some, by their very nature, are premarket. Some are labeling statements and things of

that sort. Some of the other things are, by their nature, postmarket in terms of the follow-up studies and so on.

DR. JANOSKY: So it is sufficient as we have it stated, then?

MR. ULATOWSKI: It is kind of self-regulating premarket/postmarket in a sense.

MS. SCOTT: This concludes our meeting for this evening and I thank all of our panels for their participation today. Tomorrow, we will reconvene at 8 o'clock a.m. to continue or panel meeting to discuss the next submission that has been submitted to the FDA.

Thank you.

[Whereupon, at 6:30 p.m, the meeting was recessed, to be resumed on May 11, 1999 at 8 o'clock a.m.]

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