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# CIRCULATORY SYSTEMS DEVICES PANEL

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P R O C E E D I N G S (8:06 a.m.)

**Call to Order**

DR. CURTIS: I'm going to call this meeting to order. We will start with a reading of the conflict of interest statement.

**Conflict of Interest Statement**

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

To determine if any conflict exist, the Agency reviewed the submitted Agenda for this meeting, and all financial interests reported by the Committee participants.

The Conflict of Interest Statutes prohibits special government employees from participating in matters that could affect their or their employer's financial interests.

Due to this prohibition, Dr. Anne Curtis will not participate in this afternoon's deliberations. Dr. Simmons will serve as Acting Chairperson.

The Agency has determined, however, that the participation of certain members and consultants, the need for whose services outweighs the potential conflict of interest involved, is in the best interest of the

government. Therefore, waivers have been granted for Drs. Hartz, Simmons, and Brinker, for their interests in firms that could potentially be affected by the Panel's recommendations.

Copies of these waivers may be obtained from the Agency's Freedom of Information Office, Room 12A-15 of the Parklawn Building.

We would like to note for the record that the Agency took into consideration other matters regarding Drs. Curtis, Brinker, Crittendon, Pentacost, and Tracy.

Each of these panelists reported interest in firms at issue, but in matters that are not conclude or related to today's Agenda.

The Agency has determined, therefore, that they may participate fully in all discussions.

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 participant should excuse him- or herself from such involvement and the exclusion will be noted for the record.

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

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 Circulatory System Devices Panel for this meeting on June 24, 1999

Drs. Brinker, Domanski, and Tracy. For the record, these people are special government employees and are consultants to this Panel under the Medical Devices Advisory Committee.

They have undergone the customary conflict of interest review, and have reviewed the material to be considered at this meeting.

It is signed, David W. Feigle, Jr., M.D., Director, Center for Devices and Radiological Health, dated 6/21/99.

DR. CURTIS: I would like to have us go around and introduce the members of the Panel next. I am Dr. Anne Curtis, and I am a cardiac electrophysiologist from the University of Florida.

MR. JARVIS: Gary Jarvis, industry representative.

MR. DACEY: Robert Dacey, consumer representative.

DR. SIMMONS: Tony Simmons, Lake Forest University, Cardiac Electrophysiologist.

DR. HARTZ: Renee Hartz, cardiac surgeon, Tulane

University.

DR. DOMANSKI: I'm Mike Domanski, cardiologist at HLBI.

DR. CRITTENDEN: Mike Crittenden, cardiac surgeon, Harvard University.

DR. BRINKER: Jeff Brinker, cardiologist, Johns Hopkins.

DR. STUHLMULLER: John Stuhlmuller, I'm a medical officer with FDA and Executive Secretary for the Panel.

DR. Callahan is the Division Director for our Division and he is ill and we are in the process of identifying a replacement for him.

And Dr. Cyndy Tracy is also scheduled to attend. She has a clinical commitment this morning, and will be here this afternoon, and she is a cardiologist at Georgetown University Hospital.

**Old Business**

DR. CURTIS: There is no old business that we need to attend to this morning, so we'll move on to the new business, and we will start with the open public hearing.

**Open Public Hearing**

We don't have any scheduled speakers for today, but we are going to hear now from Dr. Larry Kessler, who is with the Office of Surveillance and Biometrics, and he is

going to talk about surveillance.

DR. LARRY KESSLER: Thanks, Dr. Curtis. Thanks, Dr. Stuhlmuller. Thank you. And thank you, Panel, thank you, Audience, and about -- oh, let's see, is Dr. Gross still here? I'd like Dr. Gross to stand up, because he's going to leave in a few minutes and I'm sorry that he can't be here for the whole presentation.

Tom Gross, the Director of our Division of Post-Market Surveillance, and he and I have been giving presentations to all of the Advisory Panels to the Center for Devices and Radiological Health this year, as a follow-up to a presentation I made around two years go, to the Chairman of the Advisory Panels, and Dr. Curtis was in the audience at that time, and we talked a little bit about post-market surveillance.

And when we did, some of the panel chairs said we should give some of the same speech to all the members of the panels, to help clarify what the Center for Devices and Radiological Health thinks about the post-market surveillance and vigilance arena. And I'll talk about that today, in brief, in the next 15 minutes.

I am going to describe a few of the methods of device post-market evaluation. We use this general tool, because the post-market surveillance generally refers to one section of the FDNC Act, and sometimes people will use post-

market surveillance interchangeably with other terms, and there is some confusion. So, we will use post-market evaluation quite generally, and explain what we mean.

I am going to present challenges and accomplishing post-market evaluation, and then describe the pivotal role that the advisory panels can play in post-market evaluation. And this is very much a presentation directed toward trying to improve what advisory panels can do in post-market evaluation of medical products.

This is the Office of Surveillance and Biometrics' bird's-eye-view of the enter Center's business. Most of the action for devices occurs on the left-hand side of the world; design, modification of medical devices happens primarily by industry in collaboration with their customers, clinicians, users, etcetera.

The FDA gets increasingly involved, as devices move from the design phase, through the evolution, to obsolescence; lab- and bench-testing, clinical testing, of course, FDA is much more involved in. And then once we hit FDA review, the Center for Devices has a much more active role in both the premarket, and certainly the don't evaluation of the device, from marketing approval, through watching what happens while it is on the market.

I have listed here a few of the regulatory mechanisms, and non-regulatory tools we have, for don't

evaluation. The Center's mission, clearly is about public health, and watching for device safety and effectiveness in the don't period. And we are very interested in safety issues, primarily, and we will talk about some in detail.

And we use the following tools to help us monitor products in the market. We use the Medical Device Reporting Program, and that is often thought of synonymously with post-market programs at the Center for Devices, that that's only one of the various authorities we have to look at devices.

We also have the Section 522 authority titled Post-Market Surveillance and I will talk about that -- and the post-approval, or condition of approval function we have, associated with PMA products in some detail today.

I will not talk much about our epidemiology program or our field inspection program, both of which supply important post-market information to the FDA and the clinical community. And the clinical community should be an over-arching group of people that we are interacting with, including the advisory panels, during both the premarket and in the feedback phase of the post-market period.

Why bother with post-market evaluation? There are a variety of questions that we often have about products, once we do market approval, either through the 510(k) or through the PMA process. Certainly, long-term safety of

products, something that we are interested in, and we'll talk a little bit about some of those today.

Performance of the device in community practice. Many of the products, you, the Advisory Panel, see, come from studies or trials that are done in well-controlled environments, with experts such as yourselves.

These products almost never perform the same way in community practice, that they do in the presentations you see by sponsors and the clinical community, at this meeting.

And we see, in the post-market evaluation program, some of the products of devices that are used in the hands of less-skilled practitioners, or in other environments that are less suitable to the conditions under which the device was evaluated and presented here.

Sometimes we will see the effects of change in user setting. As most of you know, for the last 15 years, there has been a dramatic flow of patients out of hospitals, faster and faster. People are going into the community, into their homes, sicker than they ever were, and they are going with medical technology originally used in the hospital setting.

We will often see deaths and serious injuries from patients using products in the home, originally approved for clinical settings in the hospital. Change of user setting brings different kinds of problems.

We are also always interested in the post-market period, about effective changes in technology, that we may or may not anticipate or see here in front of the panels, and unusual patterns of adverse events.

And I will talk a little bit about that for a few minutes, because many people at the FDA and outside, look to the Medical Device Reporting Program, which began about 20-some years ago, but was mandatory, beginning in 1984, for manufacturers, who must, by law, report deaths and serious injuries, that a medical device may have caused or contributed in the event, as well as malfunction for near-incidents, which could cause death or serious injury, if they recur.

All user facilities, since 1990, the passage of the Save Medical Devices Act; that is, every hospital, nursing home, surgery center, ambulance, must report all deaths to the FDA involving medical devices, and all serious injuries, to manufacturers.

This is observed in the breach of the roughly hundred thousand reports we get annually, 95 percent come from manufacturers and less than 5 percent from user facilities. So, most hospitals, nursing homes, etcetera, are not aware of, or do not comply with the regulations, and don't send many reports to the FDA.

Beginning about 1992, FDA was receiving over a

hundred thousand medical device adverse event reports per year. Information includes, or is supposed to include device specifics, event description, event date, patient characteristics. And with that information, we can sometimes draw important signals about problems wiht medical devices in the post-market period.

Unfortunately, reports often have a very limited information base, even though they do often provide critical signals to FDA. And I will talk about a few of those now. And these are actions that are prompted by the MDR Program, and I will give you some examples.

Perforation with pulmonary artery catheter use shows up in the MDR Database on a routine basis, and about a year ago, or two years ago, we started to see telemetry systems, software and hardware failures, which prompted some action from us.

The actions we can take based on the MDR Program, may be a directive inspection of the facility. Just this year we are doing a series of them in the cardiovascular area, including vena cava filter inspections for strut fracture, and AICD charging volt problems, voltage problems.

We can also initiate post-market studies, and I will talk about those in a minute.

And finally, I passed out to the Panel members, a few of the five or sic public health advisories and safety

alerts that we have done in the cardiovascular areas themselves.

We did a safety alert on minute ventilation pacing, stent system problems, vacuum loss, only in the past few years. The cardiovascular area is probably the richest area for post-market evaluation problems and potential solutions, that we have.

And in fact, we are seeing some new problems in hemostasis devices, which we are going to be -- which we are working on right now, and which I expect you will see significant public health post-market activity in the next couple of months.

I want to turn my attention and spend a few minutes trying to help you, in the Panel, understand the role you can play in the post-market period, particularly in regard to post-market study authorities, and post-approval studies. And let me explain first what they are.

Section 522, Post-Market Surveillance, was originally mandated in SMDA in 1990, and changed substantially in the FDA Modernization Act in 1997.

Post-approval refers to PMA products only, and we call these Condition of Approval Studies. 522 covers Class I or III products, whose failure may present a public health problem, and can cover either PMA products, or products brought through by the 510(k) process.

Both authorities are seen as a complement to premarket, and if we use these authorities well, we can mandate studies of the manufacturers -- those are the entities which FDA regulates -- mandate data collection, which will turn around information, which can help us understand what we have done in the premarket period, and help us evaluate new premarket submissions. So, it should be a continuous feedback loop, as I indicated in the diagram a while ago.

Earlier this year, we had a panel present on post-market surveillance, Dr. Brinker presented eloquently at that panel, and we put out some guidance about how FDA is going to tell the industry it is going to do don't studies.

First, we focused on why we would do such studies, or what are the criteria? When would we call for such a study? And it revolves around the critical public health question, which may be for cause; say, for example, exsanguination deaths from retroperitoneal bleeds, following placement of hemostasis devices, and we have a few of those as an example of a for-cause situation.

Newer or expanded conditions of use that we might see in the clinical community, we would call for a don't study. Or the evolution of technology.

Before we finish calling for a don't study of the industry, whether it is PMA, post-approval, or 522, we spend

some time considering other don't strategies to make sure we are asking for the right study at the right time.

For example, a review of the compliant history in a manufacturer, or the MDR system, may adequately address our concerns. Often, they do not. We need to consider practicality and feasibility of conduct, and I'll talk about that in a minute. How the data will be used, and the priority of the issue.

In our publication concerning how we are going to be using the 522 authority in the coming years, after the FDA Modernization Act changed, we signalled to the industry that we would be using a wide variety of study design approaches.

One of the problems in the early imposition of the 522 authority in the early part of this decade, was that we concentrated on heavy design studies, looking a lot like premarket studies, when we called for 522 studies. And we met with a great deal of resistance and problems in getting those done, and we signalled to the industry that, for some critical public health questions, the less invasive, less detailed, less rigorous studies, may be adequate to address the question, including things as simple as nonclinical testing of device, or use of existing databases, without having to collect new data. For example, the Medicare or HCFA databases that are available.

Nevertheless, we continue to experience constant frustrations in the don't period, for several reasons. First, the rapid evolution of technology makes studies obsolete very quickly. Sometimes by the time a study begins, the companies we're working with and the clinicians you're working with, are already on to the next generation of the device, or two generations beyond that.

Second, lack of incentives for industry. To be quite candid, there is not usually much good news that can come out of a product evaluation in the post-market period for industry. It's not very sexy. It's mostly a stick, not a carrot.

We have been told that the absence of a stick is not a carrot, so telling industry it is not a stick doesn't really help, because it's not really something that's likely to turn up really great and good news.

We did have one wonderful example in polyurethane foam-covered breast implants, where the post-market study did seem to exonerate the product, but that's the exception, not the rule, quite frankly.

There are a lack of incentives and interests in the clinical community, and this is a problem that we all face. It is not as sexy and attractive for clinicians to be testing old product, it's not as interesting, and it is certainly not as publishable. And with all due respect,

that is one of the problems that we face as well, in trying to get able clinician investigators invested in the post-market period.

And finally, one of the problems that we have had, and this is the problem that we had at FDA, and the advisory panels need to help us wiht, is to clearly specify the public health question of interest.

If it's of interest to you, then it should be of interest to us and the clinical community. And if it's not, then we may not be asking the right question.

That's the challenge I want to focus on. When considering post-market studies, whether or not it's a 510(k) or PMA product, whether it's a post-approval study or a 522, ensure that you can clearly specify the public health question.

Tell us what it is you are trying to answer. Try to figure out the clinical or regulatory relevance of answering the question, what will you do with the data? Are you interested in changing the label? Changing the indications for use? Would you suggest a recall? Would you suggest certain restrictions on the device? Would it be important for you, in terms of evaluating future product?

Those are reasons for which we can call for post-market studies, and probably get them done. Questions of secondary interest are not going to motivate the clinical

community, they are not going to motivate the industry, and they are not going to get the data in front of us.

And unfortunately, I reviewed from 1997 and 1998 almost a dozen advisory panels and half of them called for post-market studies for PMA products, and in most of those, I couldn't figure out the real question they were trying to ask.

So, really, the challenge is for you, if you are going to ask FDA to pursue a don't study, try and be as specific as you can, about what is you want answered, and what you might do with such data. We then think we can modify and mandate an adequate study, and get something done.

Finally, the future of where we are going. We didn't talk much about the future of the Medical Device Reporting Program, that's not really a subject for this audience, but for the post-market surveillance approaches, I have illustrated that we are going to try and use a wider variety of design approaches, more flexibility we think will help the industry, and help us get the data we need.

We need more collaboration, both with industry and the clinical community, and expanded access to different data resources, specifically, registries. We have an exciting new development coming.

At the American College of Cardiology Meetings in

New Orleans, we had a panel devoted entirely to post-market, and there was sufficient interest after the panel meeting, that the American College of Cardiology has agreed to hold a three-day workshop, cosponsored with the FDA, on don't evaluation of cardiovascular products, trying to coordinate the vast variety of registry efforts that are now ongoing in the cardiovascular area.

It is going to be sponsored by ACC at Heart House, the middle of November, I believe it's the week of the 15th if I'm not mistaken, and I urge the panel members to try and attend, not only as pivotal people in terms of the role that you play for FDA, but also in the role you play in the cardiovascular community.

We think this is the beginning of a new era in don't monitoring, particularly with cardiovascular products, which occupy a great deal of our time and interest.

I want to thank you for your attention, and hopefully we can have a few minutes for questions.

DR. CURTIS: We often get into discussions here at the panel about the difference between approving something with conditions, asking for further data, further study, versus a post-market study.

It sounds like there are two authorities for that, but practically speaking, what happens is the same, in a way. I mean, the device or product is approved. The

company can market it, and then data is collected afterwards. And reviewed. Is that right?

DR. KESSLER: Absolutely. Both authorities have that similar property. With the condition of approval authority, there is the implied threat to the industry, that if a study is not carried out under a condition of approval, then the approval will be revoked. It doesn't happen. It just doesn't happen, okay? It could happen, it doesn't happen.

When a 522 study is called for, if the company doesn't do it, they violate the law, the product can be deemed as misbranded and adulterated, and it be mandatorily recalled. It doesn't happen, okay?

So, that's the trick here. What's going on is that most of the studies we have called for, whether under the condition of approval studies, or the 522, have been not completed; barely begun. A few have been well-done, mostly they are not.

Part of it has to do with specifying good questions. Part of it has to do with enforcement authorities. And one of the changes we're making in the 522 authority, is this year, unlike what we did for SMDA in 1990, we are writing the a regulation that specifies what we're going to call for and what the penalties will be, for companies not participating in the studies appropriately.

And we're going to start using a variety of our authorities; civil money penalties, warning letters, and when push comes to shove, the FDA is getting close to publicizing companies and products that aren't having studies conducted, and warning the clinical community that we have a post-market concern that has not been evaluated. Hopefully, that will motivate the companies and industry to get moving and the clinical community to respond.

DR. GILLIAM: One question that comes to my mind right away as a clinician, and we're supposed to I guess report some of these things, hospitals and clinicians, assuming that we do not.

How would we -- are there forms that we should have in our office? You know, is there a readily available 1-800 number we can call, or --

DR. KESSLER: Yes.

DR. GILLIAM: How do we do this?

DR. KESSLER: Yes. Okay. The Adverse Event Reporting System has several different ways you can interact. For every, every hospital that has a risk manager in this Country, which is most hospitals these days, motivated less by FDA and more by the tort system, they all have the MedWatch Forms.

There are two separate forms. There is something called the 3500A, which is a mandatory form, it's a little

more complete.

There is also a voluntary form called the MedWatch Form. There is an 800 number for MedWatch. You can report voluntarily by picking up the phone, and there are professionals on the other end, who will take your call, work you through the form and complete it, or send you by fax, information, and you can put it out.

In addition, the MedWatch folks have just put on the worldwide web -- and I'll provide all the executive secretaries, the web site information -- a way to submit data on the 3500 voluntary form, on the web.

So, you have three different ways you can go. Call your risk manager in the hospital; he or she has all the forms necessary. B, you can log onto the web if you have access; and you can pick up the phone. And I will get you all the relevant numbers that you should already have.

DR. HARTZ: Another problem I have run into is trying to get a device back to a company. Whose responsibility is in the hospital, say if we explant a heart valve?

Is it the clinician's, the OR team, the path lab, who is supposed to get that valve back to the company? It's very difficult to track down the packaging.

DR. KESSLER: Right. It's very difficult to track down --

DR. HARTZ: The packaging.

DR. KESSLER: The packaging. That I can not tell you. That is a problem we have heard over and over and over, and when devices get separated from packaging and then something goes wrong, then trying to trace back has been very difficult. I think it's a great challenge.

I can't give you an easy answer. I do know that the responsibility is usually with the OR team giving it to the risk managers, who should send it back to the manufacturers, but I had a great story from --

You may remember the Ventritex recall a few years ago? And the folks from Ventritex who did a wonderful job doing that recall. It was a very difficult situation, came in and talked to us about pacing leads.

And they tell us repeatedly, they go in the hospital, they open up drawers in CCUs, and find drawers full of explanted pacing leads malfunctioned, that no one knows where to send. Theirs, not theirs, and they were just trying to figure out what to do about this.

I think it is a really great problem, and there is a conference coming up at the NIH, which we are participating in, on how to handle explants. An entire conference on explant issues. And Dr. Bill Regnolt is their representative, and this afternoon, I will go back and e-mail him. I will copy it to Mr. Stuhlmuller, Dr.

Stuhlmuller, and try and figure out if we can make sure this issue is handled. Because the NIH is holding a consensus conference on this, and I think it is exactly related to the kind of question you are asking.

DR. SIMMONS: I guess I'm wondering now in retrospect, if some of the protocols that we have seen, we shouldn't have rejected, because I think a lot of us had faith that, you know, when we mandated these follow-ups, and these post-marketing surveillance things, that there was going to be some outcome that was meaningful. And based upon what you have said, I guess my faith in that has been shaken dramatically.

I just wonder, you know, why even bother? Maybe we should just reject it, while we still have the chance to collect data, that's what we should do. I mean --

DR. KESSLER: I'm very glad I have shaken your faith. The spirit of the FDA Modernization Act is to tell us and you, and the industries sitting out there, that in fact, what you have done is what you should have been doing; which is, approve a product which you have good faith in, and with good faith, expect the FDA and the company to get together to address a remaining important remaining public health concern you have about a device, in a post-market period.

That's exactly the spirit of the FDAMA. It has

not been observed. And I would encourage you, if you approve a product, ask for a time-specific return on the answer to that question. And call the company back here. And then we will use a variety of our enforcement authorities, to make sure the study is conducted, while you are waiting for the answer.

And when the answer is brought back, if the answer is, we decided not to do the study, use the authorities we have available, to recall, withdraw an approval, go back to the company and hit them with civil money penalties. There are a lot of things we can do.

And I think that -- I'm sorry to say your faith has been shaken, but you can ask to see the responses from post-market -- we've just done an evaluation of both the post-approval and the 522 studies, and it's -- unfortunately, it is just the way it is. I wish I could have better news for you.

DR. SIMMONS: Well, maybe the better plan would be to do something like just table approval until -- isn't that a -- isn't that one of our options, John?

DR. STUHLMULLER: Absolutely.

DR. SIMMONS: Just table it and ask for more data?

DR. STUHLMULLER: Yes, I mean --

DR. SIMMONS: Rather than reject it?

DR. STUHLMULLER: Well, yes, you have four

options. Approveable. Approveable with Conditions. Not approveable. And you can table it.

The issue would be, you can table it, but it really doesn't effectively deal with the issue. I mean, if you look at the panel options that you get, you know, that handout, if you don't think the data is there to support that it is safe and effective, then you should probably recommend not approveable.

We don't recommend tabling. Yes. I mean, on the scripted text, it's listed.

DR. GILLIAM: Is it possible that we could, say on a regular basis, review things that were done by an individual panel? I mean, you're stating that, like, all of the panels you spoke with, but I mean, is it not possible that we could have associated perhaps with one of our panel meetings, a review of maybe the previous year's of approvals with conditions?

And so we can specifically be informed as a panel which post-market conditions are either being met, or really not being met?

DR. KESSLER: I have to tell you that we've just figured out in the past few months, this is not happening. We would have, in a post-market side of life, it's part of the problem with the vulcanization of FDA.

In the post-market side of life over in OSB and

the Office of Compliance, we would have assumed that, once you approved products with conditions, you would want to see the results.

And I think we are discovering that that is not something you have asked for. That is something, certainly, Dr. Stuhlmuller can help provide. But you haven't asked. You know, we have got so much business in front of the panels on the pre-market side, and it's part of our life. There is so much to do, that squeezing this in is always an after-thought.

I really encourage you to ask us to review what you have asked for over the last three or four years. We've just done a review, so Dr. Kimber Richter is available. She is the Deputy Director of ODE, and she is asked for updates on all the post-approval studies.

So, she can provide that at your next panel meeting, very briefly. I'm sure she could do so without taking a lot of your time, and give you some insight into things that have been accomplished and things that have not.

DR. CURTIS: And I also think, though, that tabling things or turning them down, isn't really in the best interest of the public, for the most part, because what we are usually struggling with is a clinical study that was done over a period of one year or two years. We have got that data, it looks good, but we don't know what happens

five years later.

And so, you know, to make a product wait for five years before you can approve it, is -- that's not a good answer, either.

DR. KESSLER: Absolutely. Things like long-term safety and performance of a device in community practice are those things that you don't want to hold it up for that, but you want to see that information.

I understand Suzanne Kuen, one of my statisticians today, was telling me that we are going to hear long-term performance data in some presentations today -- is that right?

Okay, so that's the kind of thing you have asked for, and is typical of post-approval. Post-market monitoring of cohorts of trialists is often done, but the other news-specific conditions of approval you have asked for, is less often done. Monitoring patients that are in trials is more commonly done.

Part of it is because it's done for the protocol reason. In the original protocol, you want to look at five-year outcomes of heart values or a new pacing device, and so those data usually are available. But it's the new issue that you may raise at a meeting, or at a panel session, that may not get done.

So, I would not, for these kind of issues, not

approve something and wait for five or ten years, but certainly, asking for updates, asking to see if people are accruing the studies, and if not, why not?

You play an incredibly critical role. I don't know everybody here, but I have been working with Dr. Brinker on the Teletronics issue, and his Chairmanship of the Physicians Advisory Committee has made a difference in what gets done in the post-market period by that specific manufacturer.

And you play a very critical role specifically in Physicians Advisory Committees, but also more generally, in the clinical community. And I really urge you to weigh in, find out what's going on, and when things are or are not being done, you can use, like we can, letters to the editor, editorials, commentary, and I really think this is Panel that can make an enormous difference.

I encourage you to get invested and work with us. Please feel free to call me and my staff anytime. And please come to the November meeting.vancomycin

DR. CURTIS: All right. Thank you very much.

DR. KESSLER: Thank you very much.

**Open Committee Discussion**

DR. CURTIS: Is there any other members of the public that wanted an opportunity to speak before we get

started with the first application?

If not, then we will move ahead. We are going to be discussion now premarket approval application P980043, Medtronic Cardiac Surgery Hancock II Bioprosthesis Heart Valve. And we will start with the Company presentation.

**Company Presentation**

DR. THOMAS ARMITAGE: Good morning, Madame Chairperson, Panel members, ladies and gentlemen. My name is Thomas Armitage. I am the Director of Clinical Research and Regulatory Affairs for Medtronic Heart Valves.

The purpose of the presentation today is to share with this audience data that support the safety and efficacy of the Hancock II Bioprosthetic Valve.

The presentation is going to be broken into four pieces. I will discuss the data from the Medtronic Long-Term Clinical Study.

DR. Tirone David from The Toronto General Hospital will discuss the Toronto Case Series of Hancock II patients.

DR. Fletcher Miller from the Mayo Clinic in Rochester will discuss the Hemodynamic Evaluation of the Hancock II.

And I will conclude with some remarks about the analyses performed on our Worldwide Explant Database, and make some concluding remarks.

In addition to the presenters, we have some consultants here with us today, who will be available to answer your questions. Dr. Frederick Schoen from the Brigham and Women's Hospital in Boston. Dr. Barclay Gilpin from California State University in Long Beach. Ms. Susan Armstrong, Clinical Researcher and associate of Dr. David's in Toronto. And Professor Ajit Yoganathan from the Georgia Institute of Technology.

In addition to these consultants, we have a number of Medtronic personnel who are experienced with regard to Hancock II, the design, development, in vitro and clinical testing of the product.

The Hancock II is intended for replacement of either diseased native or diseased prosthetic valves. The valve itself is derived from porcine aortic tissue. It is fixed in glutaraldehyde. It is treated with a chemical, sodium dodecal sulfate, in a process that Medtronic refers to as the T6 process.

The purpose of this is to mitigate the calcification potential of the valve. The process has been demonstrated effective in animal models.

The stent is plastic; specifically, it is an acetal homopolymer.

The stent and the valve are made radiopaque by their placement of markers, one each at the tip of the stent

post, and then around the periphery of the annulus, on the inflow of the valve.

The entire stent is covered with polyester fabric, and the polyester fabric is also used to craft the sewing cuff.

The valve comes in two basic designs. I think it is a little bit difficult to distinguish in the photograph here, but the aortic model, the stent and the sewing cuff are scalloped. And the mitral model is plainer. And the reason being that we want the valves to adapt most readily to the natural anatomy of the patient.

The history of the Hancock II valve, with regard to the FDA and pursuit of approval in the United States is a lengthy history.

The valve was originally developed by Johnson & Johnson Cardiovascular. They conducted a clinical trial in the early to mid-1980s.

They put forth a PMAA and indeed took that submission to Panel where it was not approved, or rejected.

Medtronic acquired the Hancock II as part of an acquisition in 1987, and we elected at that time to continue follow-up of the patients from the Johnson & Johnson clinical trial.

And as we followed these patients further, we also elected to submit a PMAA, which the FDA told us was not

approveable, and then we electively terminated the IDE in 1993.

The most important message on this slide is one that is not identified here as a specific bullet, but it's that the data we are presenting today are not from a formal clinical trial.

You have two cohorts of patients, one that were followed by the sponsor, one that were followed by a clinical researcher. And the data are very long-term clinical data; however, they don't meet the clinical requirements as stipulated in the Heart Valve Guidance. The presenters will talk about the limitations of the data, as they share their information.

In 1996, we approached the FDA and put forth a proposal saying that we believed we could demonstrate the safety and efficacy of this valve, using long-term clinical data, and they agreed, assuming of course that the data were satisfactory, that that would be a route, a potential route to approval.

So, today, we are going to present that data. As I said, we have two cohorts of patients. The Medtronic Long-Term Clinical Study is a group of nearly 400 patients at seven sits in the United States.

DR. David will present the Toronto Case Series of patients. Dr. Miller will discuss Hemodynamic Evaluation of

a Sub-grouping of the Toronto Case Series. And I will discuss the Worldwide Explant Analysis Program we have, and talk very briefly about our Worldwide Clinical Experience with this product.

Moving into the Medtronic Long-Term Clinical Data, the Study was a prospective study, multicenter. We looked at isolated AVR and MVR, and when we withdrew the IDE in 1993, we elected to follow the patients every other year, looking specifically at long-term mortality and the valve-related morbidity.

We have used the NYHA classification as an indicator of effectiveness of the valve.

As far as references or controls are concerned, we will be discussing the Objective Performance Criteria, established in the Heart Valve Guidance, and we will also be referencing some published literature, and using also our Hancock Standard PMAA data.

Looking at the aortic valve replacement arm of the Medtronic study, there are 267 patients. The mean age at implant was 64 years. There is a preponderance of males, 79 percent.

The majority of these patients required valve replacement due to stenosis of their native valve. There were also patients who had insufficiency and mixed disease in roughly equal proportions; 23 percent, 19 percent,

respectively.

From this grouping, 77 percent of the patients were in either NYHA Class III or IV, preoperatively.

The primary, or the most frequent etiology of native valve disease was calcification, 69 percent. Here you see a delineation of the valve sizes implanted. The most frequent valve size being the 23 mm, 43 percent, and the most common concomitant procedure was Coronary Artery Bypass Grafting, in 32 percent of the cases.

From these 267 patients, we have 1889 patient-years of follow-up. The mean follow-up is 7 years. We have a maximum follow-up of 12 years. And the completeness of our follow-up is 94 percent.

There have been 12 early deaths and 120 late deaths in this group. Zero of the early deaths were valve-related; 13 of the late deaths were valve-related, I'll discuss those in a moment.

If we look at the Kaplan-Meier estimate for freedom from death for all causes, we see at ten years, 49 percent, freedom from death.

Looking at the causes of valve-related death, four cases due to cerebral vascular accident; two endocarditis; two deaths occurred during reoperation; four deaths occurred do to hemodynamic dysfunction of the valve; and one death occurred due to congestive heart failure, which itself was

secondary to periprosthetic leak.

Looking at the Kaplan-Meier estimate for freedom from valve-related or unexplained death, we see at ten years, there is an 82 percent freedom, and on this slide, you also see marks regarding literature references. They are here for comparison.

You can see the Hancock II is similar to the literature references.

Looking at the listing of adverse events. The most common adverse event, thromboembolic complications, occurred at a linearized rate of 1.98 percent per patient year.

The other events occurred at lower rates. We have performed the appropriate calculations to compare these linearized rates to the OPCs. And we have found that all of these linearized rates fall below the Objective Performance Criteria stated in the Heart Valve Guidance.

And here we looked at the Kaplan-Meier estimates for freedom from the different categories of adverse events. I'll just take a look at thromboembolism, the most common adverse event at five, eight, and ten years.

Freedom from this complication is 93 percent, 86 percent, and 81 percent, respectively.

Looking at structural valve deterioration, the Kaplan-Meier estimate is 94 percent freedom at ten years,

and you see here for a reference, three publications from the literature.

It's generally accepted that a structural valve deterioration is an age-related phenomenon; younger patients typically suffering structural valve deterioration more frequently than older patients; therefore, we have broken the cohort of patients into two subgroups.

Those 60 years of age or younger, and here you can see that for that younger group, the freedom from structural valve deterioration is 88 percent at ten years.

For the older group, those over 60, the incidence of structural valve deterioration is exceedingly low. There is a freedom of 90 percent at ten years.

Here you see the Kaplan-Meier estimate for freedom from valve-related reoperation. At then years, it is 90 percent. You also see again the three references from the literature for a comparison.

There were 23 cases of valve-related reoperation. Twelve of those were for structural valve deterioration. Seven were for endocarditis. Three for thrombosis. And one of the valve-related reoperations was a prophylactic replacement of the valve.

Concluding my discussion of the aortic data, we look at the NYHA classifications to demonstrate the effectiveness of the valve, and we have taken a subgrouping

of the original 267 patients. This grouping was selected -- well, these are the people who were available for follow-up at the most recent time point, 1996, for the 213 people who were in that classification at the time, 15 percent of them were in Class III or Class IV at the most recent time point.

And that means that 81 percent of these patients maintained an improvement in their NYHA classification over the time during which they had the Hancock II valve implanted.

I will now discuss the mitral arm of the Medtronic Long-Term Study. There were 102 patients in this group. The mean age at implant, 63 years, with a roughly equal split between males and females.

In two-thirds of these cases, the reason for valve replacement was insufficiency and roughly equal split between stenosis and mixed disease; and here you can see an overwhelming majority, 89 percent of the patients, being in Class III or Class IV, preoperatively.

The primary etiology of native valve disease was rheumatic in nature, 36 percent. Again, you see the delineation of valve sizes in the mitral position, the most common size is 31 mm, and as with the aortic population, the most common concomitant procedure was Coronary Artery Bypass Grafting, 31 percent.

From these 102 patients, we have 649 patient-years

of follow-up. Mean follow-up is six years. We have follow-up out to 12 years. And the completeness for this grouping is 98 percent.

There have been 13 early deaths and 48 late deaths in this group. One of the early deaths was valve-related. Four of the late deaths were valve-related. I will discuss those in a moment.

Looking at the Kaplan-Meier plot for freedom from death for all causes, we see that the estimate is 38 percent at ten years. Looking at the causes of death, there were two deaths related to cerebral vascular accident, one occurred during reoperation for structural valve deterioration, one due to a leak, which cause congestive heart failure.

In the early case, the valve-related death was due to puncture or rupture of the left ventricular wall by contact wiht the stent of the heart valve.

Looking at the freedom from valve-related or unexplained death, we can see the Kaplan-Meier estimate at ten years for the Hancock II valve, at 77 percent. There are two Journal references listed here for a comparison.

This is the delineation of adverse events. For the mitral population, the most common adverse events in this group was thromboembolic complications which occurred at a rate of 3.12 percent per patient-year.

We have calculated the -- we have done the appropriate calculations, I should say, to compare this linearized rates to the OPCs of the FDA, and for all of the categories where there were adverse events reported, we are within the OPC threshold.

There are two categories where no events were reported: valve thrombosis and major periprosthetic leak.

Looking at the Kaplan-Meier estimates for these different adverse event categories, at five, eight, and ten years. We see for thromboembolism the most common complication, that at ten years there is a 73 percent freedom.

Looking at structural valve deterioration. The Kaplan-Meier estimate was 91 percent freedom from SVD at ten years. Here you have three literature references for comparison.

As with the aortics, we looked at the incidence of structural valve deterioration as a function of age, and again, the younger patient population suffers this phenomenon more frequently. For the patient 60 or below, you have a freedom from SVD of 84 percent at ten years. For the patient grouping 60 years and above, it's 95 percent.

For freedom from valve-related reoperation, the Kaplan-Meier estimate is 88 percent at ten years, and there are two literature references shown here for comparison.

There were eight cases of valve-related reoperation, seven for structural valve deterioration, one for endocarditis.

And concluding the mitral discussion, I will show the NYHA data, and as we did with the aortic population, we selected the subgroup of 74 patients who were available at the most recent follow-up, which is 1996.

We see that 87 percent of that group were in Class III or Class IV preoperatively. Thirty percent of that group were in Class III or Class IV at the 1996 follow-up, and that means 69 percent of the patients showed an improvement over the time course during which they had the Hancock II valve implanted.

And that concludes the discussion of the Medtronic Long-Term Clinical Data. And I will ask Dr. David to come up and discuss the Toronto Case Series.

DR. TIRONE DAVID: Dr. Curtis, members of the FDA Panel, I'm Tirone David. I'm a surgeon in Toronto. I am a paid consultant for Medtronic. Medtronic is also paying for my travel expenses to come to Gaithersburg, but I have no financial interest in Toronto -- I'm sorry, on the Hancock II valve prosthesis.

The series of patients represented to you have been followed by our research personnel, not in a mode that FDA requires for other devices. They are followed for an

entirely academic purposes, publication in an academic unit.

The follow-up was done at periodic intervals, largely by sending patients questionnaires. And if the reply was not entirely clear, a research assistant would call back the patient by telephone, and discuss the details of the information, and sometimes the physician was also consulted.

We believe that this mode of follow-up is adequate to detect hard data endpoints, like death, stroke, a major morbid event following valve surgery. We have done this for a large population of valve replacements in our unit.

And also to assess the functional capacity to our detailed questionnaire, we present our data and also show how it compares to the Objective Performance Criteria, other published series in the literature, as well as the Hancock Standard PMAA data.

From September 1982, when we first implanted this valve, to the end of 1994, we had replaced the aortic valve in 710 consecutive patients. The mean age was 65, the range age 18 to 86. Most of them were men.

The majority of patients had aortic stenosis and the remaining mix of insufficiency and mixed lesions. The majority of patients were in Class III or IV at the time of operation.

It was the first aortic valve replacement in 94

percent of patients, and in 6 percent, they had had previous aortic valve surgery.

Most valves were a size 23 mm, 25, and 27 mm, and this differs a bit from the previous presentation, and it is a reflection of the approach in our unit. We do believe that the largest possible valve should be implanted to minimize trans-valve regurgence.

Because of our elderly population, 42 percent required concomitant Coronary Artery Bypass Grafting.

Of the 710 patients, the total follow-up was 4,064 patient-years, with a mean of 6, and the maximum follow-up of 14 years. We have lost only 1 percent of patients to follow-up.

There were 34 operative deaths, most of them due to cardiac causes, related to myocardial infarction or low cardiac output syndrome. Very few other causes.

In 156 late deaths, equally divided among cardiovascular causes and noncardiovascular causes, and the cardiovascular causes were predominantly myocardial infarction, and 17 valve-related.

The Kaplan-Meier estimate of survival showed 54 percent at 12 years, 64 at ten years.

The valve-related deaths were 17, seven of them due to stroke, and ten with the prosthetic involvement of carditis.

The freedom from valve-related or sudden death was 93 percent at 12 years. We compare our series in Toronto with the other published in the literature.

The linearized rate for thromboembolism, valve thrombosis, perivalvular leak, and prosthetic-involved endocarditis are listed here, was 1.2 percent per year per patient. No valve thrombosis could be diagnosed, but perivalvular leak, 0.08 percent, and endocarditis, 0.43 percent per year. All well below the OPC.

The Kaplan-Meier estimates of five, eight, ten and twelve years are shown here for the morbid valve-related events. The freedom from thromboembolism at 12 years was 86 percent; valve thrombosis 100 percent; prosthetic-involved endocarditis, 95 percent, and periprosthetic leak 99 percent.

The freedom from primary tissue failure was 94 percent at 12 years, as compared with other prosthetic valves published in the literature, we have the distinct impression that these are more durable valves.

Because age plays a major role in the duration of a tissue valve, we divided by age below and after 60 years. For patients below 60 years, at ten years, the freedom from was 90 percent; 99 percent for patients that were over 60 years.

The freedom from valve-related reoperation was 90

percent at 12 years. Of 24 patients requiring explantation of the prosthetic valve, ten of them because of primary tissue failure; eight because of prosthetic-involved endocarditis; three for perivalvular leak; one for aortic dissection; one because of inadequate hemodynamic performance; and one because of unexplained, recurrent TIAs, for which we decided to explant the valve.

At the time this follow-up was closed in December 1996, 489 patients were available for follow-up, and 88 percent were Function Class I or II, 12 percent were Class III.

We used this device to replace the mitral valve in 308 patients. Like in the aortic valve, in the elderly population, typical for mitral valve disease in North America, is the shift towards gender, to the female gender.

The majority had mitral insufficiency, and the remaining 38 percent had mixed lesions and stenosis. 91 percent of the patients were very disabled when they had the mitral valve replaced.

It was the first time mitral valve replacement in 89 percent; 11 percent had had a previous surgical intervention in the mitral valve, either repair or replacement.

Most valves were sizes 29 mm, 31 mm, and as with the aortic valve, given the elderly population that we

operate on, 42 percent required concomitant Coronary Artery Bypass Grafting.

The total follow-up on these 308 patients sum up to 1,720 patient-years. The mean follow-up is six, maximum 14 years. And again, only 1 percent of our patients were lost to follow-up.

There were 24 perioperative deaths, most of them, again, cardiac failure. And 89 late deaths. Unlike the aortic valve disease, the mitral valve disease, there is a large proportion, 230 patients from myocardial or valve-related deaths. Only a third had non-cardiovascular deaths.

The survivors at 12 years, as estimated by the Kaplan-Meier method, was 42 percent; at 10 years, that being 58 percent.

The valve-related deaths were: strove in seven; endocarditis in five; bleeding due to anti-thromboembolic-related hemorrhage in two; structural valve deterioration in one; and valve thrombosis in one.

The freedom from valve-related or unexplained deaths following mitral valve replacement was 89 percent at 12 years. This compares favorably with the published series of other biological porcine valves in the market.

The linearized rates were 1 percent per year for stroke; 0.06 percent for valve thrombosis; 0.12 percent for perivalvular leak; and 0.6 percent for endocarditis. All

linearized rates below the OPC.

The freedom from morbid events is estimated by Kaplan-Meier here is shown at five, eight, ten and twelve years, was 90 percent for thromboembolism; 99 percent freedom from valve thrombosis; 95 percent from prosthetic-involved endocarditis; and 99 percent for perivalvular leak.

The freedom from structural valve deterioration is not as good as in the aortic position, as shown in the other series, as well. At 12 years, only 82 percent of the patients are free from primary tissue failure, but still compares favorably with the other porcine valves on the market.

Age, again, played a role on the freedom from primary tissue failure. In younger patients, the freedom was 76 percent; at ten years, in patients older than 60, it was 89 percent at ten years.

The freedom from valve-related repeat mitral valve replacement was 78 percent at 12 years. During this time interval, 21 patients required a redo of mitral valve replacement, 15 of them, because of primary tissue failure, 2 for prosthetic valvular endocarditis; 2 for perivalvular leak; and two are incidental because the aortic valve required replacement, and they had old mitral valve prostheses, so the surgeon electively replaced it.

At the time of the closure of this follow-up, 172

patients were available and 79 percent were Class I or II; 20 percent were Class III.

Thank you.

DR. FLETCHER MILLER, Jr.: Dr. Curtis and Panel members, I am Fletcher Miller, Junior. I am from Mayo Clinic, Rochester. I am a cardiologist and echocardiographer.

I am also a paid consultant to Medtronic and my expenses are being reimbursed for participation in this Panel meeting.

I am going to discuss with you the Toronto Hemodynamic Evaluation from the patients, a subset of patients, that Dr. David has just described the clinical outcomes on.

There are 343 patients. He discussed over 1,000 patients with you, moments ago. These 343 patients represent that subset that was followed clinically by the Cardiologists at the Toronto Hospital, and had at least one echocardiographic study within the first five years after valve implantation, and you can see the study dates here.

If there were multiple echos performed within that five years, the first echocardiographic study was selected for providing this data.

The reason that this particular subgroup was selected was because the echocardiographic studies for these

patients were performed by a core group of sonographers who are very experienced at assessing prosthetic heart valves by echocardiography, and their work was supervised by a core group of echocardiologists who similarly have great expertise in the echocardiographic assessment of prosthetic heart valves.

All studies include a complete 2-D imaging with appropriate M-mode imaging, and complete spectral and color Doppler information.

As in the PMA, a comparative analysis was carried out between this group of patients and the group from Dr. David's experience, that did not undergo echocardiography for preoperative and operative demographic variables, and there were no significant differences.

For the aortic data, there were 226 patients of whom 205 had at least one echo during the first five years. The mean age was 63, and with aortic valve disease, the preponderance in gender was men.

The hemodynamics will be expressed in the same way for aortic and mitral; the small square represents the mean value; in this case, the mean of the mean gradient; the bars represent 1 standard deviation in either direction, and it is broken down by valve size with the patient number in parentheses underneath.

As you can see, across all valve sizes, there was

an entirely acceptable mean gradient, and acceptable standard deviation.

You will notice that there is a relatively small number of patients in the size 21 mm valve, and I will address that as I reach my summary.

For comparison with the literature controls that were provided, it is broken down by size, the Hancock II versus control, and you can see that on a size-by-size basis, there is a very satisfactory comparison for mean gradient in these aortic prostheses.

The aortic effective orifice area for these patients was calculated by the simplified continuity method, the ratio of the left ventricular outflow tract and prosthesis velocities was multiplied times the left ventricular outflow tract area.

The left ventricular outflow tract diameter was measured for this particular calculation. Again, it is broken down by size, and you can see that on a size-by-size basis, for an aortic prosthesis, there is a very satisfactory mean value for effective orifice area, and a very small standard deviation.

For purposes of regurgitation analysis, this is standard, semiquantitation, using complete color Doppler information, supplemented with spectral Doppler criteria, when appropriate. And for the purposes of this

classification, if the word moderate was mentioned in the description, whether that is moderate or mild to moderate, that falls under Class 2+ out of 4+.

All of the 1+ included mild, but also include terms like trace, trivial, mild, physiologic. If it's none, there were no pixels of regurgitation identified. And as you can see, 82 percent of the valves had no regurgitation; only 2 percent had moderate or mild to moderate.

For the purposes of making the comparisons with the control articles that were provided, all regurgitation was lumped together, so this includes both the 1+ and the 2+ regurgitation, and you can see, again, by comparison with the controls, very favorable.

Looking at the mitral demographic data from this particular patient cohort, there were 138 patients followed at Toronto, 130 of whom had at least one echo during the first five years after implant.

The mean age was 64, and as expected with mitral disease, the breakdown by gender was close to 50-50.

If we look at the hemodynamic information, the chief variable that was used to ascertain that the prosthesis was functioning normally at Toronto General, was the effective orifice area.

This was calculated by the pressure half-time method, and broken down by size. You can see that there was

only a single patient with a 25 mm -- I'll address that again, later.

If we go to the other sizes, you can see a very, very acceptable pressure half-time derived effective orifice area, and again, a small standard deviation.

Because the valves had been -- this is a clinical study, and the valves had been certified as being normal by pressure half-time method, a lesser number of patients had mean gradients measured, which requires tracing the spectrum, but for those patients, you can see that, again, there is a very acceptable mean gradient and acceptable standard deviation for all valve sizes, except for the 25, which didn't have a measurement.

Again, if we compare wiht the control group, you will also notice that there were no 25s available in the control-provided, but if we compare the other sizes, size-by-size basis, for mean gradient, a very favorable comparison.

Regurgitation was scored the identical way that I described for the aortic prostheses; again, only 2 percent of patients had either mild to moderate, or moderate regurgitation, and 74 percent of patients were free from any regurgitation by echocardiography.

And again, lumping patients with any degree of regurgitation together, either 1+ or 2+, for purposes of

comparing with the literature control, and in this case, the type of porcine prosthesis was unspecified in the article, but a favorable comparison in terms of the percentage of the patients with any degree of regurgitation.

In summary, for this cohort of patients that was followed at Toronto General Hospital, in their echocardiographic laboratory and by their cardiologists, for aortic valve replacements, we had a mean gradient of less than or equal 25 mmHg for 99 percent of echos, and an effective orifice area greater than 1 $cm^2$ for 87 percent.

Valvular regurgitation was less than or equal to 1+ for 98 percent of these studied.

With mitral valve replacement, the mean gradient was less than or equal to 8 mmHg for 96 percent of echos. The effective orifice area by pressure half-time, greater than 1.5 $cm^2$ for 95 percent of echos, and valvular regurgitation, again, was less than or equal to 1+ in 98 percent of cases.

Which leaves me only to comment on the relatively low number of patients with the size 21 mm aortic prosthesis, or the size 25 mm mitral. I think that the small amount of in vivo echocardiographic data in these particular patients for this particular study, long-term study, needs to be interpreted in the light of two other considerations.

Number one, those valve sizes were tested thoroughly by Dr. Yoganathan, who is available in the audience, in the Hydrodynamic Laboratory, and bound to be equivalent to other bioprostheses, porcine prostheses, that are on the market.

But, more importantly, you will recall, as in the OMA and what Dr. David has just presented, there was very complete long-term in vivo clinical follow-up on these patients, and if we take the entire cohort of the Toronto group, there were 49 patients that had the size 21 mm valve implanted.

In the long-term follow-up that he has described, there were four thromboembolic events, one late death related to endocarditis, and one valve explanted, secondary to structural valve deterioration.

For the size 25 mm mitral prosthesis, there were 11 total implants. There were five deaths, none of which were valve-related, or uncertain in their etiology.

And so, we have long-term in vivo data that is other than echocardiographic, that would certainly strongly imply that there were no significant, clinically-significant, stenotic or regurgitant lesions, even among those patients that didn't undergo echocardiography.

Thank you.

DR. ARMITAGE: I will conclude now with some brief

comments about the analysis of our explant database, as shown on the slide, here.

There are a total of 109 human explants that we have had the opportunity to review. Almost half, 52 of these, came from the Toronto Case Series. Twenty-nine of them came to us from the clinical trial, that's from the 17 sites originally started by Johnson & Johnson. Twenty-eight devices came to us from centers around the world who chose to send their explants here.

The two most common causes of explant were, number 1, structural valve deterioration in 41 cases, and secondly, endocarditis in 27 cases.

I don't intend to provide detailed information. Dr. Schoen is here, as I indicated previously, if there are specific questions about the pathology of these valves, I am sure Dr. Schoen would be delighted to answer them.

But we have worked with Dr. Schoen. He looked at all of the Medtronic explants. He has reviewed some of the Toronto data, as well. And so he has seen a majority of the explant information, and we have jointly come to the conclusion that you see presented here.

That is, if you look at the time to failure. If you look at the pathology of these explants, meaning the thrombus, endocarditis, leaflet tears, calcification, the Hancock II explants are similar to explants of other Hancock

bioprostheses, the Hancock Standard and MO, as well as being similar to other commercially-available porcine bioprostheses.

So, to summarize, I want to hark back to a comment I made at the beginning of my presentation, and that was that we acknowledge that we have not presented data here today that fit the formal clinical trial format.

We have provided long-term clinical data. We have several bodies of data. I presented the Medtronic long-term cohort. Very satisfactory clinical experience in that group, almost 400 patients followed out to 12 years.

DR. David presented on over 1,000 patients, followed in his Toronto Hospital system, with a maximum follow-up of 14 years for that grouping.

DR. Miller presented hemodynamic data on 340 patients, and found those hemodynamic results to be very satisfactory.

And finally, we have the explant findings, which indicate that the long-term explants for Hancock II are similar to other commercially-available bioprostheses.

On an anecdotal note, admittedly anecdotal, there have been well over 22,000 implants of the Hancock II valve, worldwide, over a 17-year time period.

If you take the sum of these pieces of information, it is our opinion in total that the safety and

efficacy of the device has been demonstrated, and we believe that the safety and efficacy has been demonstrated across the full range of valve sizes.

Thank you for the opportunity to present this information.

DR. CURTIS: We'll move on now to the FDA presentation.

**FDA Presentation**

MS. KENNEL: Good morning. First, I want to take a brief moment to acknowledge the members of my team that helped me on this project, and they are listed on this slide. Many of them are here today.

My first several slides give some details about the history and chronology of this project, since it has had a long history with the Agency.

This valve was the subject of a 1983 IDE, and as you can see, the first PMA was submitted in 1985 by a different sponsor, Johnson & Johnson.

That 1985 PMA was taken to the Circulatory System Devices Panel for review and recommendation in March of 1987, and it was recommended that the file be disapproved, on the basis of a lack of safety and effectiveness information, and suspicion of fraudulent information.

In July of that same year, the former sponsor

withdrew the PMA, and in October of that year, Medtronic purchased the device, and data from the previous sponsor. Both FDA and Medtronic performed audits of the data.

In April of 1990, Medtronic submitted a new PMA with a new application number, but FDA found it to be inadequate.

The firm made a total resubmittal, under the same PMA number, in April of 1992, but this again was deemed insufficient, and the sponsor withdrew the PMA in January of 1993.

In August of 1996, Medtronic asked FDA to reconsider this valve for the U.S. market. At that meeting, we indicated to the firm that we would not be looking at acute data, as suggested in our Guidance Document, but rather we asked the sponsor to focus on data addressing durability; that is, failure mode and time to failure. We asked that they submit current data and that they focus on the long-term complications, explants, and long-term echocardiographic data, and also whether or not the anti-calcificant worked.

We worked with the firm informally, and then in October of 1998, this current PMA was filed and reviewed again. That brings us up to today, the second Panel meeting for this valve.

This slide is a very brief overview of the

clinical data in Medtronic's submission. The PMA was divided into four main sections: the Medtronic Long-Term Cohort, which is the U.S. study; the Toronto Case Series; a subset of the Toronto Series who had echo data; and the explants, and these were just discussed by Medtronic.

The Medtronic Long-Term Cohort involved 406 of the original 647 patients, enrolled at seven of the 17 original centers.

The Toronto Case Series involved 1,112 patients at three Canadian centers, which were eventually merged into one center.

Follow-up ranged from two to 14 years in these cohorts. Pooling was not warranted for a variety of reasons.

The next several slides go over limitations of the study that we would like you to take into account as you discuss this submission.

The first two slides relate to the Medtronic Long-Term Cohort. There was no echo data presented for this group because it was taken during the time when echo was in the developmental period, and there was no standard protocol.

There was a heterogeneous mixture of cath data, M-mode, 2-D and Doppler data. Echo data is only available for 0.7 percent of this cohort. For this cohort, the most

recent follow-up is broken down in this slide. The majority, 63 percent of the U.S. patients were followed with a clinical exam, with the remainder being followed by phone or mail survey or both.

In the Medtronic Long-Term Cohort, poolability wasn't justified for endocarditis and valve-related reop.

The next three slides relate to the Toronto Case Series and explain why the data from this Cohort is not poolable with the Medtronic Long-Term Cohort U.S. data set.

The STS/AATS definitions for complications were used, except for primary thrombosis, primary perivalvular leak, and structural dysfunction.

In addition, there were different definition for complications and reporting schemes for the Toronto Case Series compared with the U.S. Medtronic Long-Term Cohort.

Specifically, thromboembolism did not include peripheral or MI events, only valve-related events were presented. The sponsor did verify, however, that this represented all events.

Also, multiple events were not available for TIAs and patient years were calculated to the occurrence of the first event, which was different than in the Medtronic Long-Term Cohort.

In the Toronto Case Series, most of the patients, 96 percent, were followed by a mail survey. The sponsor

provided an article assessing the accuracy of this survey, which revealed that the male survey, combined with the phone follow-up, was more accurate.

The next two slides relate to limitations in the subset of the Toronto Case Series who had echo data.

The data was retrospective, and only 35.1 percent of the 1,112 Toronto patients had echocardiographic assessments.

In addition, the percentage of the patients who had both a baseline and a late assessment was low. The mean gradient was calculated from the peak, but there was a good correlation.

The continuity equation was not used for calculation of mitral effective orifice area. There were less than 15 assessments of gradient for aortic size 21, and for all mitral sizes.

Additionally, there were less than 15 assessments of EOA in the aortic size 21, and in the mitral size 25.

In summary, we would like to review FDA's questions to the Panel relating to the labeling, sizes and post-marketing studies issues. And we can put these up on the screen later when you're actually deliberating, but I will just read this, so that you, the audience, can see if they're not showing up. It says:

No. 1. Do the data presented permit assessment of

the safety and effectiveness of this device? Specifically, does the use of a mailed patient survey allow for assessment of safety and effectiveness of the long-term Toronto case study?

No. 2 The sponsor wants to include information in their labeling, (Instructions for Use) about studies performed in animals. Would this information be meaningful to the user?

Given the long history of human implantation with this device, would it be preferable to include results of the human explants and adverse event rates for structural valve deterioration, rather than information from the animal studies?

No. 3. The sponsor wants to market the Model T505, which is the aortic, in sizes 21, 23, 25, 27, and 29 mm, and the Model T510, which is the mitral, in sizes 25, 27, 29, 31, and 33 mm.

Do all the data presented support approval of all sizes, and if not, what additional data would be required to establish the indication for sizes not approved? And then there is a reminder about the echos.

No. 4. Does the following Indications section adequately define an appropriate population for use, based on the data presented?

And that section reads, "Hancock II bioprostheses

Models T505 and T510, are indicated for the replacement of pathologic or prosthetic aortic and mitral valves."

No. 5. Is the proposed Contraindication section appropriate? Are there any other contraindications for the use of this device?

And that section reads, "Use of the mitral bioprosthesis in patients with a small, hypertrophic left ventricle may be contraindicated because of the potential for perforation of the ventricular wall by the stent posts.

"Accordingly, the physician should carefully consider these potential hazards when selecting an appropriate bioprosthesis for such patients."

No. 6. At this time, the sponsor has not submitted any patient literature counseling the patient about their valve, although they just indicated to me that they have some, and appropriate activity after valve implantation.

And we would like to know if you recommend that such literature be developed for this valve?

No. 7. Have you any other suggestions for the labeling? And

No. 8. Do the data presented adequately demonstrate the safety and effectiveness of the device as labeled?

No. 9. Are there any other issues of safety or

effectiveness not adequately covered in the labeling which need to be addressed in further investigations before or after device approval?

No. 10. Do you recommend any post-marketing studies, and if so, for what purpose? And I believe there might be one more. No? Okay. That's it.

That concludes my presentation. Thank you.

**Panel Discussion**

DR. CURTIS: I believe reviewers for this PMA were Drs. Hartz and Crittendon. Dr. Hartz, do you want to start?

DR. HARTZ: This valve was introduced for two reasons. The standard Hancock valve did not have as good hemodynamics because it had a muscle bar from the pig aorta. Both, what was called MO and Hancock II valves are created from two pig aortas, so that there are better flow characteristics because the muscle bar has been removed and the bar has been fashioned from two actual pig aortic valves.

The stents were designed to be lower -- is that correct?

DR. ARMITAGE: You are correct. The statement you made regarding the MO, which is in fact crafted from two separate valves, but with regard to the Hancock II valve, that is not the case. It is a single porcine aortic valve.

DR. HARTZ: And what do you do about the muscle valve in the bar in the valve, because I didn't see that in your --

DR. ARMITAGE: I would like to deflect that question to Carol Eberhardt. Carol, can you please come up and comment on the manufacturing process, and just relate to this group how the muscle bar is treated with Hancock II?

DR. EBERHARDT: The muscle bar for the Hancock II is --

DR. CURTIS: Could you identify yourself and what your financial interest is in the product?

DR. EBERHARDT: My name is Carol Eberhardt, and I'm an employee of Medtronic Heart Valves in Irvine.

And the manufacturing process for Hancock II removes the muscle bar by use of fixturing of the fresh valve, where the valve is pressurized against a plastic tube, where the muscle bar can be removed, as opposed to trimming it out, like MO.

DR. HARTZ: This becomes important because of the indications from planting a tissue, versus a mechanical valve, eventually.

The second point being to have a lower profile than the previous stents on the other valve, which had a higher incidence of AV groove separation in the mitral position.

Now. FDA requires 800 patient-years of follow-up for a valvular prosthesis, and some points that I found that are in the United States we have 889 patient-years for the aortic and 649 for the mitral. So we are just underneath the threshold for mitral on the U.S. experience.

But, outside of the United States the patient follow-up years are over 4,000 for aortic, and almost 2,000 for mitral.

Regarding the Medtronic Long-Term Study, I think that the data is excellent in some -- you heard the 267 aortic valve replacements and 102 mitral valve replacements with good long-term follow-up.

I'm concerned of course about the structural deterioration in patients less than age 60, both for aortic and mitral.

If you will refer, please, to pages 5 -- most of the key data is reflected on pages 5-2 and 5-3, under Clinical Studies. And it points out what I believe are some of the inherent problems in use and labeling of the prosthesis.

Structural deterioration is good. Thromboembolism, although it is low and within the OPC's, was 1.98 percent for aortic valve, and over 3 percent for mitral valve. So, that a fairly significant number of patients implants with this tissue valve, have

thromboembolic events in both the aortic and mitral positions.

If you look further into this data, there were either 59 or 70 -- and I can't determine an accurate number, it's listed in two different ways -- of these patients at the time of implantation who are in atrial fibrillation. And most of these patients remained on anticoagulation in the long-term, even coumadin anticoagulation.

And that raises one of my serious concerns, not about the prosthesis, but about the use of the prosthesis, and that is, why is this tissue valve being used in patients who are in atrial fibrillation? And it has nothing to do with the manufacturer, or design of the valve, but the Indications for Use, which we should address a little bit later.

I should also point out that the long-term deaths that are cardiac-related in this group, especially the mitrals, are usually related to left ventricular dysfunction and coronary artery disease. So, that we have to be careful and focus in only on structural deterioration for this prosthesis.

For the Toronto Series, I was impressed that there were only 1 percent of patients lost to follow-up. I do have a question for Dr. David about the explant of a tissue valve in a patient with multiple TIAs.

No. 1, what was found at the time of explant on the valve? And No. 2, what were the options for re-replacement in that patient?

DR. DAVID: The patient continued having TIAs and --

DR. HARTZ: Wiht the new prosthesis.

DR. DAVID: With the new prosthesis, a mechanical prosthesis, then, he was fully anticoagulated, but we never resolved the patient's problem.

DR. HARTZ: So, did you determine that the TIAs were --

DR. DAVID: The transverse view suggested that there be a calcified leaflet, which is wasn't, in this one case in a series of well over 1,000 patients replaced for this reason.

DR. HARTZ: The thromboembolic events in the Toronto Series was 1.2 percent per patient-year, but freedom from TE for both the aortic and mitral was good at ten years.

I could not determine from reading if there was a major difference in the rate of atrial fibrillation in the patients implanted in Toronto and in the United States.

Concerning the hemodynamic data, it was not pointed out that there is indeed a 25 mm peak systolic rate across a 21 mm aortic valve, and so that should just raise a

word of caution and the numbers aren't large, but there is indeed a significant peak systolic rate at all of the mean gradients, and effective orifice areas appear to be good.

I did not see addressed, the issue of the anti-calcification process, which was raised by the FDA review, and as a matter of fact, explanted valves did not have quantitative calcium evaluations and I wonder why that was not carried out.

The comparisons, the overall comparisons of the Medtronic prospective study use extensive literature controls. Excellent definitions by the combined STS/AATS Ad Hoc Committee for Valve Performance Criteria, those were not exactly followed in the Canadian Series, but the patient-years in Toronto Series much more than offsets the exact definitions of those complications.

The performance of the valve was excellent for all freedom from all adverse effects, except as I mentioned, the thromboembolic rates, which I do not think should be this high for tissue valves.

I think my other comments will be reserved for when we make suggestions on the labeling, and the specific questions to the Panel.

DR. CURTIS: Dr. Crittendon?

DR. CRITTENDON: Well, I have a series of questions and a couple of issues that I wanted to bring out,

and I'm sure a lot of these issues are going to come out wiht the general Panel discussion, but I think I'll go ahead and start it out.

The first one was a methodologic issue, and that was that this study that is presented by the sponsor today, perhaps met the spirit of the OPC criteria, and in fact when you look at the primary endpoints, I think it did meet the OPC criteria, but the way the study was conducted was not within the letter of the law, so I have somewhat of a problem with that.

The OPC criteria were developed because we did not -- it was an undue burden to industry to have them come up with the ideal study that we would all like to see, you know, a randomized control type of trial. But it was just too burdensome for them to do that, so the OPCs were developed to sort of make it a shorter study, and where everybody would be happy because the data was looked at very rigorously.

The problem is, by breaking those rules, I kind of wonder if we're kind of subverting the process even further, in terms of trying to make sure the science is as exact as we can get it.

So, that's just a comment, and I just kind of throw it out for discussion. I'm sure someone else is going to bring it up.

Anyway, in terms of just following the letter of the law for the OPC, could I have someone from the FDA kind of comment on that, whether they thought this meets the OPC criteria exactly. Am I'm being maybe a little too fussy about it, or do they have some similar concerns?

DR. SAPIRSTEIN: We were concerned about the methodology and the nature of, the retrospective nature of the Study.

We felt, however, that they had met the OPC criteria, in terms of that isolated study for the long-term cohort.

DR. CRITTENDON: And then this is for the sponsors. Why this valve, now? To be quite honest with you, I use the other valve, so to speak when I use tissue valves. And to be honest with you again, being fairly conversant with the literature, I was surprised to find out that the Hancock II was not FDA-approved. I thought it was, I just was always using, quote, unquote, the "other valve."

And there have been plenty of other, you know, nice reviews about Dr. David and people from Stanford about the Hancock II, so I thought people were using it and that it had been approved.

So, I guess, you know, the first part of a series of questions is, well, why this valve, now? Is it just because it's better for several reasons, at least we think,

over the Hancock I, and the Hancock I Modified Orifice?

DR. ARMITAGE: When the PMA submitted by Medtronic was rejected because it was considered to be non-approveable, I can say in hindsight that Medtronic make a mistake not to pursue a formal clinical trial at that time, because we would have liked to have had this valve in the U.S. market several years ago.

And by continuing to follow the cohort of patients in the United States, what we learned over a period of time, and the only way you can learn it is by looking at patients over a period of time, that the long-term performance of this valve is quite excellent.

And the reason that we want to bring the valve now, is that, the FDA was very open-minded and gave us the opportunity to use long-term clinical data, so that the opportunity was there. We knew more about the product. We were more confident about it. And we believe it is an excellent prosthesis, and based on the clinical follow-up, we believe that it is more durable than other devices with satisfactory hemodynamics.

And putting those two pieces together, the opportunity being there and our belief that we have an excellent device, we've decided to pursue this opportunity.

DR. CRITTENDON: To kind of follow-up and maybe Dr. David could answer this, or anybody you select. Do we

really feel this is more durable? If we look at some of the data -- or some of the text, anyway, that was put in the Panel packet, it says the thing -- and this is an exact quote from Section III, pages 24, 25.

"The Medtronic Hancock II bioprosthetic heart valve meets specifications for performance and is comparable to existing approved heart valves."

So, are you going to make a claim that it is durable and better than heart valves, or is it just comparable to approved heart valves?

DR. ARMITAGE: It's exceedingly difficult, and perhaps impossible to make any claim. We have no intention to make a claim that it is superior. Because the basis of comparison between different studies, you are looking at different timeframes, you have got different population groups, different means of practicing medicine.

I mean, there are a myriad of reasons why use of other published literature, etcetera, just isn't a fair way to make a comparison, and the data that you have in the Panel packet and the PMAA, you know, states what we think is very defensible, and that is that the valve has comparable structural valve deterioration rates to other valves.

DR. DAVID: May I make a remark, Dr. Curtis?

DR. CURTIS: Yes, go ahead.

DR. DAVID: I think Dr. Armitage has to be humble,

since he represents Medtronic. I have no interest in this. I sincerely believe this is more durable. It is remarkably more durable? No, it is better than the traditional porcine valves.

DR. Miller, myself, and Erika Jameson, together we have some 7,000 patients who have undergone aortic mitral valve replacement, porcine valve prostheses in the past 20 years.

We just did an abstract to the American Heart Association which we present in November, comparing them. And we analyze it inside and out, including propensity scores, to eliminate the bias of the investigator, or the surgeon who chooses the valve.

Like you said, your valve is different than this one. Mine is different than this one now, but it at one time was my valve of choice, so even including propensity scores, at 15 years, it is a more durable valve, than Hancock I, than the porcine valve.

So, it is a more durable valve for the same patient population. Again, it is with respect to data, but analyze the best possible way.

So, I think it is a better valve than the commercially-available porcine valves in the States.

DR. CRITTENDON: Now, there are a couple of other design issues that went into this. You know, one, we

changed the stent, around the stent material was changed. Also, the way it was mounted, I understand, alluded to earlier by someone else from Medtronic about this whole muscle bar issue.

So, are we going to make it -- are you going to make any claims about this T6 process in terms of that leading to more durability, or I guess that's the question. Is the durability due to the T6 process, or is it everything, or do we know?

DR. ARMITAGE: Again, it is exceedingly difficult to understand why the valve is as durable as it is. I personally consider it to be a multifactorial issue.

The stent for the Hancock II valve is more flexible than it is for the Hancock Standard Valve. The more flexible stent, therefore it absorbs some of the energy that needs to be dissipated at the moment of closure, that relieves the tissue of some of the stress.

I think that the slightly different way of processing the tissue; that is a different glutaraldehyde fixation process for Hancock II than it is for Hancock I. It's a two-step process, may have some role in the improved durability. And the T6 process may also have a role.

Your question was, you know, are we going to make any claims in that regard, and the simple answer is, no, we aren't going to make any claims in that regard. We do not

have the data that could act as proof to support such a claim.

DR. CRITTENDON: And then I have a couple of engineering issues that I would like either Lisa Kennell or perhaps Steve Hilbert to address.

And one, just a general question, are the issues regarding creep in stent deflection been adequately resolved? I've read that section in the Panel packet a couple of times and I would just like to hear from you. I've read what was in there, I would just like to hear from you, what your thoughts are about that.

MS. KENNELL: Well, we have requested additional information and the day before I came here, it arrived at my desk. So, we haven't looked at it yet, but we're hoping they've been resolved. It is ongoing at this point.

DR. CRITTENDON: Well, it's just that there were some troublesome comments that Dr. Letzing made, and that's another issue I wanted to address.

Has that been resolved? If you look on pages 23 to 24, and page 28 on the FDA Review, Dr. Letzing makes some pretty -- some comments that are pretty disturbing, I guess, is the best way to put it.

Has that been resolved internally, as far as you guys are concerned?

MS. KENNELL: No, that I believe is what is in

this submission that just came in. So, we will have to look at that and see what has been done.

DR. HARTZ: Can I just interject? The one major comment, even the Shiley valves do better than this. Was that supposed to mean the Ionescu Shiley, or the Bjork Shiley, because it is unclear to me what they were comparing the valve to in this.

MS. KENNELL: I don't know that I can speak to that.

DR. HARTZ: Okay. Completely different modes of failure.

DR. CRITTENDON: And then, finally, and then we'll make some other comments when we get around to discussing the FDA questions.

Just labeling, in Section II, page three, there is discussion about reflux and that you may notice some reflux after you insert the valve, and if you see some reflux afterwards, don't get too disturbed -- and I am paraphrasing now -- and put in sutures.

And I am just wondering if we are kind of playing games with words. Do we describe this as a perivalvular leak, as opposed to reflux? Could someone from the sponsor's table address that?

Believe me, there are times when I'm looking at the post-bypass echo, and gosh, I'd like to go and say, oh,

this is just reflux, don't call this a perivalvular leak.

DR. ARMITAGE: I'm not 100 percent sure if I am going to be answering your question, you will have to help me out.

I agree with you, in the sense that the word, reflux, would generally be considered to be, you know, transvalvular, as opposed to perivalvular flow, and we ought to be specific. If the echo image indicates that there is perivalvular leakage, depending on the magnitude of it, that may be repaired and sometimes it's subclinical and it can be left.

That of course is up to the discretion of the physician and with transvalvular reflux, again, it's a qualitative decision that needs to be made by the echocardiologist as to whether or not it's physiologic.

There is always some closure volume that goes backward through the valve, so we're open to rewording of that, in order to make it more clear.

DR. CRITTENDON: The impression I had from the text, was this was near the annulus, as opposed to being central, the closure volume that you're talking about. That's why I brought it up, it just, I mean, it seems like we ought to call a spade and a spade, and it's a perivalvular leak, it's perivalvular leak, versus reflux.

DR. ARMITAGE: Agreed.

DR. CRITTENDON: And then one last question in terms of -- this is for the physician's part of the labeling. There was no comment made about the mitral insertion.

I'm just wondering. I know the stent profile is 2 mm shorter for the Hancock II, but I was just wondering what comment ought to be made, and maybe Dr. David, you can comment on that, the orientation of the stent is to prevent left ventricular outflow tract obstruction.

DR. DAVID: It's the same for any stent, the biological valve, surgeon who implants the mitral prosthesis must might make sure that the space underneath the aortic valve is not obstructed by one of the stents.

It is up to the company to say one stent should be just below the left lateral fibrostrygon and then the rest falls into place.

DR. CRITTENDON: If I remember correctly, in the literature it says, which you know, obviously, is pretty obvious to surgeons, that the annulus needs to be below in the aortic position, the coronary osteal.

If we're going to talk about putting it below the coronary osteal, maybe we ought to talk about orienting the stent appropriately so that it is not in the left ventricular outflow tract.

And that's all I have for now.

DR. CURTIS: All right. Before we go around to the rest of the Panel members, I think we will go ahead and take a 15-minute break.

[Brief recess.]

DR. CURTIS: What we are going to do at this point is go around to the other Panel members to make comments and to ask any questions they want of the sponsor. I'm going to start with Dr. Brinker.

DR. BRINKER: I think this is one of these issues where this particular valve has stood a test of time, that rarely see for any other kind of device that comes up for a PMA approval. And therefore, many of the objections and concerns that we would have with a device with a limited follow-up, the way it is usually presented to us, and perhaps this was the way this was presented to us in 1985 and then again in 1990, at least to the FDA, is obviated by the fact that we have a pretty good idea of what this valve will do.

And the only real concern that I have I think is wiht the thromboembolic phenomenon that was raised by previous speakers. And I hope that this will be addressed more thoroughly by someone else with more valve experience.

The only comment that I would like to make is that some of the FDA points as to study limitations seem to me, after an almost ten-year period of time, to be unacceptable

that these things hadn't been worked out.

For instance, it's not clear to me why standard definitions couldn't be retrospectively applied to the different cohorts, or why efforts made to achieve other kinds of follow-up might be made to address some of these issues. And in fact, perhaps some of the original echos could have been relooked at, or others obtained, in some of the long-term patients.

So, I'm not sure that that is a meaningful comment now, because I do think the valve is reasonable for those patients that would benefit from a tissue valve.

But, I think it would make like easier for everyone if we didn't have a preamble of study limitations that seem to me to be avoidable at this stage. So, I'll just pass on.

DR. DOMANSKI: Yes. I guess I -- I guess I have a -- I have a couple of -- I have a number of concerns about the data that are being presented. I mean, one of the things about this valve is, it has been around for a long time. It appears to be in widespread use in a variety of places.

And so the feeling is that, well, it must be okay, because it is being used widely, etcetera. This is kind of a general -- it seems to me that that's a general background on which we're -- against which we're operating.

But one would expect that with any reasonable valve, the event rate would be far too low to detect a problem in any particular practice. So, that one has to rely on data put together in, you know, in an aggregate sort of setting.

Therefore, the materials, I guess this general background of, gee, the valve's out there and it's doing, "okay," I guess resonates a little less than it might with some other devices.

And I do have a few questions as one looks through the data. I'm looking, just so it's easy to follow what I'm tracking on, I guess it's page four of the FDA summary. There is no grander thing -- there is no -- I don't see any other page number on here.

But, if one looks, for instance, at the Toronto Cohort, it says, "Only valve-related events are presented." This is, oh, I don't know, it's a couple of bullets down.

"Historically, the FDA has asked that all events be reported and related events may be reported as a subset for facilitating comparisons."

I guess, who is it that is deciding whether it's a valve-related event in that study? Perhaps -- Dr. David, perhaps you could answer for Toronto.

DR. DAVID: I should have referred this question to my research associate. She is very experienced in

following patients. The questionnaire is a quite comprehensive and extensive questionnaire that patients receive, and if the answer is unclear, she follows-up the answer with a phone call.

DR. DOMANSKI: Yes, but that's not really the question. Somebody adjudicated those events, now, I -- we do clinical --

DR. DAVID: In an explained event that is an cardiovascular event, we blame the valve. That's how the SGS and the HES databases -- unexplained myocardial infarction of patients with valve coronary disease, we blame embolic events.

DR. DOMANSKI: But who decided whether it was explained? I guess, there is no independent endpoints committee, it was the investigating --

DR. DAVID: No, I'm sorry, one person only. The research associate who reviews the data.

DR. DOMANSKI: So, it was somebody who in effect was being paid out of funds generated by Medtronic --

DR. DAVID: No, they are not. They are being funded by the University of Toronto for the partnership with the cardiovascular surgeons. She is part of the personnel of the program. She doesn't do only follow-up for Medtronic. She does follow-up for all the heart valves that we implant at Toronto Hospital.

DR. SAPIRSTEIN: Perhaps I could add some clarification on the division. It has four groups, four cohorts of -- and let me explain how the Agency adapts to these four cohorts.

We initially said that we would evaluate the Toronto Cohort for the hemodynamic data that was not available at the previous PMA applications that were rejected, and for the reason that there was inadequate follow-up.

So, the Toronto data was only initially requested for hemodynamic information, and the original IDE cohort was going to be followed for adverse events, in terms of OPCs.

And then we utilized what we had from the Toronto, for additional sort of information on adverse events, but that's why there is a difference between the adverse event tabulation with Toronto and the -- The Toronto was independent of any IDE, and was a study performed by the center --

DR. DOMANSKI: Yes, I guess I'm addressing a little bit different issue, though. I understand the business of OPCs. What I'm concerned about is not the house of the OPC, but the foundation it's built on in terms of the data.

And this was actually probably a very simple question, not a complicated one. I am just wondering who it

is who is adjudicating these events as being valve-related? I mean, it's clearly the key issue.

How they were adjudicated. Because otherwise, they don't get reported and they are not an event. I guess, right, Wolf, I mean --

DR. DAVID: Dr. Domanski, really, I've been doing this for 22 years now. The only issue in follow-up with a heart valve is, about the congestive heart failure, which becomes unclear, is the heart failure due to valve dysfunction, myocardial dysfunction, coronary artery disease, or a TIA, is it truly TIA?

And these are the cases that Sue Armstrong called the patient or called the doctor to clarify the event. Remember, the rate of the event is very low. Very few patients told us, yes, I was hospitalized because I short of breath.

In those patients, are the 23 percent or so, who are followed-up with the phone interview, and frequently, the physicians who attend the patient, spoke to the research personnel, to determine if it was a heart failure due to what? Is the valve failing, is the --

DR. DOMANSKI: Sure.

DR. DAVID: So, the hard endpoints, the New York Functional Class, valve failure and death, these are very hard endpoints, I don't think our questionnaire or a

telephone interview would miss.

I agree that TIA, we may have missed a few of the patients who forgot to mention that one day, two years ago, for two minutes, my left eye was blurred, or something like that.

So, the TIA, I have to agree that it is contentious. The other ones, I can't agree --

DR. DOMANSKI: Well, congestive heart failure may -- you know, I -- there is a whole business that goes with adjudicating. It's always easier to determine total mortality of course than to -- you know, than to decide what the mortality was due to. I mean, it's a problem that any committee that is set up to adjudicate events has a difficult job with.

Okay, well now, you have answered the question, though . The other thing is, I guess in that section. They talk about multiple events not being available for the Toronto Cohort. And I guess I don't understand why multiple events weren't reported.

Does that -- and maybe I'm just being stupid. Was it that if you had a TIA and you had an MI, multiple events weren't reported?

DR. DAVID: That's how Kaplan-Meier methodology works for actuarial, the determination for events. If a patient has a stroke, the moment the patient had the stroke,

the patient is no longer followed for continued events. So, the patient who had five strokes is not depicted here.

DR. DOMANSKI: All right. But if they had a stroke or they had an MI, or they had something, then they had --

DR. DAVID: Then it was entered, but subsequent events, they are not.

DR. DOMANSKI: So, you could have a TIA -- what if -- suppose you had a TIA, and then, a year later, you had a massive stroke, or you had an MI. What would happen?

DR. DAVID: Well, since we are -- this was pointed out to us, I think, Susan, how did you manage this, would you explain?

In TIAs, specifically. I know that death, of course the patient ends with the death, but how about in morbid events that do not result in removal of the valve, or continued follow-up?

MS. SUSAN ARMSTRONG: My name is Sue Armstrong. I'm from the Toronto General Hospital. I'm a paid consultant to Medtronic and they are reimbursing me for my expenses here.

In answer to your question about a TIA which was followed with a subsequent stroke. That TIA was overruled, and that was then coded as a stroke.

I felt that the stroke was a much more important

event, so therefore, I wiped out the TIA and coded the stroke, and that was the one that would have --

DR. DOMANSKI: So, actually --

DR. DAVID: -- second stroke, if there was a second stroke, was the second depicted in the data or not?

MS. ARMSTRONG: No, if there was a second stroke, it wasn't. Only first events, unless it went from a TIA to a stroke.

DR. DOMANSKI: Okay, so if there were a stroke, and then there were an MI, or there were congestive heart failure death, or there valve endocarditis, would -- you know, how would that come out?

MS. ARMSTRONG: Well, those were all recorded separately. The first event for endocarditis, first event for thromboembolic -- yes.

DR. DOMANSKI: Okay. Sure. No, that helps. Well, good. Thanks.

The other thing -- the other thing that struck me, I guess, and I would defer to the engineering talent present, but you know, I was bothered by -- let's go to page -- I'm on page 28, which is a memorandum by William Letzing, in which there is a -- under No. 3 in italics, it says that, "Medtronic has argued that during the fatigue test, the stents were loaded as they are during in-service loading. This is not really accurate, since the test was run at high

initial stresses, 4600 psi, cycle rate of 100 Hz.

"Since dalryn becomes viscal elastic above 2500 psi, this raises issues about linearity, phase lags between stress and strain, etcetera."

And then it goes on to say, "As a result, we can't really rely on the fatigue lifetime test results." I guess the question that I have, and maybe Mr. Letzing, or Dr. Letzing could answer the question for himself, and I guess I wonder how important data like those are.

That is, if they are really wrong about -- you know, are they really wrong, and if they are wrong, so what? I mean, I guess I'm not a good enough engineer anymore to answer those questions, but I'm very bothered by -- I am bothered by the fact that, you know, we're seeing a statement, highlighted in quite that impressive a fashion.

It also goes on in that memorandum, you know, if I were reading this late, or if there were major problems with this valve after its release, after it is approved by this Panel and released, and then somebody had a major problem, and I was looking at it, I would be -- I'd sort of stop on this and ask for some explanation.

And then under No. 5 it says, "What more can I add to the accelerated wear testing issue, except to say that we have recently seen another tissue valve pass the FDA protocol for accelerate wear testing and gone on to fail

clinically, in a manner that was unnecessary, and should have been predicted by the test."

I mean, I guess I would like to know what all that verbiage means, and what the significance is. How can we answer that? Shall we have -- I mean, we can have the author do it, or we can have some other FDA people, but I'd be interested in knowing, in just having somebody explain all that to a country, sort of a country doctor.

DR. ARMITAGE: The sponsor would certainly like to comment on this, but I assume right now you are looking for a comment from the FDA.

DR. DOMANSKI: Well, I think it would be interesting to hear, maybe hear the guy who wrote the memo explain all that.

DR. SAPIRSTEIN: Well, let Dr. Letzing give his interpretation of it.

DR. LETZING: Yes, I'm Bill Letzing, I'm a heart valve expert in the -- in ODE.

DR. DOMANSKI: Can you speak more clearly into the microphone for the purposes of the transcript?

DR. LETZING: Sure. Is that better?

DR. DOMANSKI: Yes.

DR. LETZING: What was your first question, let me try --

DR. DOMANSKI: Well, I guess maybe under No. 3, if

you could explain, help me understand the importance of the test that you are referring to, and whether -- and if it's not important, then fine, I guess that's the end of that discussion.

But, if it is important, then why would it be safe to ignore what's being -- ignore the problems that you say are there with that test?

DR. LETZING: Well, if you are concerned about long-term durability of a heart valve, in particular, the stent of that valve, then these things are very important. And they have to be dealt with in one way or another.

And as I understand it, we now have the data, they have just submitted data, additional data, over what I've had the opportunity to review.

But in some of these cases, you can only look at the long-term durability by long-term durability testing of -- the cyclic testing of a stent, which is what they did, and they did it at fairly high loads, but the question is, they emphasized the loads were applied just during initial, the initial load. They didn't give me the final load.

So, it's difficult for me to say just how valuable that test is. So, there, I don't have good data as far as the long-term durability of the stent.

There are other ways of dealing with this problem, too. You can look at crack propagation or damaged tolerant

analysis, where a crack is supposed to propagate to the point of failure over the lifetime of the stent. Again, we need more information in that area, and I hope that that's been submitted.

In addition, some of the loading of the valve that they have done up to this point has been non-conservative. And so, hopefully, they have improved on that; hopefully, they've given us some additional data to deal with that. But at this point in the game, we don't really have a lot that shows the long-term durability of that stent.

DR. GILLIAM: Okay. Let just interject here. What you're saying, Dan, is that you haven't information that it's not durable, you just don't have enough information that it is. Is that fair to say?

DR. LETZING: No, the information I have at this point shows that certain sizes of that valve, and certain types -- for example, you take a dimensionally-challenged stent, even Medtronic does not make a perfect stent each time. There are going to be certain worst case within tolerance stents.

If you take the worst case with intolerance in a certain size, the data currently predicted that that valve will fail, the stent will fail, in a fairly short period of time.

That's concerned me. And what I need to know is,

just how they are going to deal with that. What kind -- you know, what kind of analysis they are going to provide. What additional engineering data, what additional loading data, that can convince me that we are going to get a little bit more than actually less than two years on a stent.

There is a certain size in there that, according to the current data that I have, shows that that stent will fail in less than two years. This is a dimensionally-challenged stent. This may not be the perfect stent, but then I don't know how many stents they make that are perfect dimensionally, and how many they make that are worst case dimensional.

So, if I had that information, I'd be better able to predict just how many problems we are going to have.

DR. DOMANSKI: All right. Well, I would be interested in hearing -- I think five doesn't bear directly on this -- on this particular -- your No. 5 in that memo, doesn't bear directly on this particular stent, except to raise one's concern about No. 3, so I won't ask specifically about that.

But maybe the company could respond and perhaps refute that, because what I'm hearing said, and maybe, again, correct me if I'm not right, but I'm hearing you say that you don't think we really have adequate data on the long-term durability of this stent.

DR. LETZING: From an engineering point of view, that's correct. But, we may have it now. They've just recently submitted some additional data, but I haven't had the chance to review it.

DR. DOMANSKI: Does the Company want to join this discussion?

DR. ARMITAGE: Yes, please. We've been interacting with the FDA over, well, approximately two, two and a half years, on all aspects of the Hancock II submission, and one of the more challenging aspects has been the stent testing.

DR. Letzing has brought up some very challenging questions for us. Some of these questions deal with methodology. Some of these questions deal with materials, the raw material of the stent, the acetal homopolymer, something that has to do with actual measurements, or the way the calculations are performed.

And we have made significant progress over that period of time. And now there was a teleconference on April 30th, give or take a day, where the FDA, specifically, Dr. Letzing, identified the remaining questions he has. And it took us the better part of seven weeks to do the testing, to answer those questions, and as Ms. Kennell pointed out, that information has only recently been submitted to the FDA. They haven't had a chance to review it.

It is difficult to, you know, rebut the issues, unless you go through them individually. And I won't try to do that, unless you specifically request it.

DR. DOMANSKI: Well, did you do -- did you do -- did you do your seven weeks of testing because you thought he was right, or because you -- because that was just what looked like what was going to be necessary to try to get approval, I mean -- either is reasonable --

DR. ARMITAGE: The -- we -- we do not agree with several of the assertions of Dr. Letzing. We didn't do the additional testing because we thought he was right, but we did the additional testing because we thought it was necessary to get approval.

And in fact, if you look inside the Panel pack, I just would like to make sure, you know, that the audience knows, and I think the Panel members know this, that the stent data have been reviewed by other technical personnel at the Heart Valves Organization, and Dr. Hilbert and Mr. Chwirut, who is a professional engineer, reviewed all of the concerns of Dr. Letzing, and in each individual case, they have indicated their belief that the response of the sponsor is correct, and if I may, I'll just read the final recommendation from Mr. Hilbert's memo. And this is on page 17 of the FDA's Summary.

"The sponsor has adequately demonstrated the

preclinical in vitro safety of the Mosaic, bioprosthetic valve," I'm sorry, Mosaic is a valve in evaluation at the time. The stent for the Hancock II, the stent for the Mosaic, are identical. They are exactly the same device.

". . . has demonstrated the preclinical in vitro safety of the Mosaic bioprosthetic valve, based on the engineering and material science findings reported in this submission, and the attached correspondence.

"The final assessment of the safety of the Mosaic dalryn stent will only be determined by monitoring the long-term clinical safety and performance of this valve, as reported in the medical literature, and annual reports submitted to the FDA."

Now, this is very consistent with the opening presentation this morning on the public's behalf, and that is, the acid test in any device is, how does it perform over the long haul, in the hands of the average clinician?

In the case of the Hancock II valve, the stent in particular, there are 17 years of clinical history, as I said before, over 22,000 implants. We do not have a single reported case of stent fracture.

Now, you can slight that observation by saying, well, you weren't actively going out and collecting that information.

It's true. It was a passive data collection

system. But I would ask Dr. David to comment, it's my opinion, that a stent fracture, witnessed or observed by a clinician, would be a significant event, one that they would bring to the attention of the manufacturer.

Is that a fair statement, Dr. David?

DR. DAVID: I think so. You know, we have never documented any yet, in 1700 implants.

DR. DOMANSKI: Well, I think that's a compelling response. I thank you, I mean, it's clear -- clear, concise, and complete from my point. i don't have any other questions.

DR. STUHLMULLER: As a point of order, would you like Dr. Hilbert on this, or Dan Chwirut, if they're available, to address these issues for you, if we can --

Betty, are they here?

[Response away from microphone.]

MR. CHWIRUT: Yes, I'm here.

DR. DOMANSKI: Sure.

DR. STUHLMULLER: Since there is this variation in the FDA opinion, I think we should hear form both sides.

DR. DOMANSKI: I think that's right.

MR. CHWIRUT: My name is Dan Chwirut. I'm a mechanical engineer in the Office of Science and Technology in CDRH, and as has been mentioned, I was the engineering consultant-reviewer on the Mosaic prosthesis, for which

Steve Hilbert was the lead reviewer, and again, as has been mentioned, the stent design for the Hancock II and the Mosaic are identical, and probably 90 percent of the data that were submitted in the two applications, were identical data.

I feel like a statistician when they say, being a statistician is never having to say you're certain. You know, we all have different thresholds. I reviewed the data. Based on my experience, I thought the sum of those data indicated that I had no outstanding concerns with respect to the durability of the stent, as applied to the Mosaic valve.

DR. Letzing reviewed much of the same data, had some concerns. He expressed them. We come to, obviously different thresholds, as what is reasonable.

I can just stand on my experience and the conclusion that was reflected in Steve Hilbert's memo. Thank you.

DR. ARMITAGE: May I make one additional comment, please?S

DR. CURTIS: Sure.

DR. ARMITAGE: Dr. Letzing did indicate that the initial calculations showed some of the valve stent sizes, if you had a, as you called it, a dimensionally-challenged stent, or one that had the minimal dimensions, it would fail