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CIRCULATORY SYSTEM DEVICES PANEL

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P A R T I C I P A N T S

Anne B. Curtis, M.D., Acting Chairperson

Voting Members:

Francis R. Gilliam III, M.D.

Tony W. Simmons, M.D.

Consultants Appointed to Temporary Voting Status:

Salim Aziz, M.D.

Michael D. Crittendon, M.D.

Michael J. Domanski, M.D.

Renee S. Hartz, M.D.

James R. Pluth, M.D.

David J. Skorton, M.D.

Cynthia M. Tracy, M.D.

Ronald M. Weintraub, M.D.

Industry Representative:

Gary Jarvis

Consumer Representative:

David A. Gooray, M.D.

FDA Staff:

John E. Stuhlmuller, M.D., Executive Secretary

Thomas J. Callahan, Ph.D.

Wolf Sapirstein, M.D., M.P.H.

Bette L. Lemperle, M.P.H.

Steven W. Allis, B.S.M.E.

Lisa M. Kennell, B.S.

Steven B. Kurtzman, M.D.

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P R O C E E D I N G S

CHAIRPERSON CURTIS: Please take your seats. The first order of business is that the conflict of interest statement will be read by Dr. Stuhlmuller.

DR. STUHLMULLER: The Circulatory System Devices Panel meeting September 15-16, 1997 Conflict of Interest Statement. The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of an impropriety. To determine if any conflict existed, the agency reviewed the submitted agenda and all financial interests reported by the committee participants.

The conflict of interest statutes prohibits special government employees from participating in matters that could affect their or their employer's financial interests. However, the agency has determined that participation of certain members and consultants, the need for whose services outweighs the potential conflict of interest involved, is in the best interest of the government.

We would like to note for the record that the agency took into consideration certain matters regarding Dr. Anne Curtis, Jeffrey Brinker and George Vetovec. Each of these panelists reported interest in firms at issue on

matters not related to what is being discussed today. Since these matters are not related to the specific matters before the panel, the agency has determined that they may participate fully in today's 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 wish to comment upon.

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 September 15 and 16, 1997: Salim Aziz, M.D.; Michael D. Crittendon, M.D.; Michael J. Domanski, M.D.; Renee S. Hartz, M.D.; James R. Pluth, M.D.; David J. Skorton, M.D.; Cynthia M. Tracy, M.D.; George W. Vetovec, M.D.; and Ronald M. Weintraub, M.D.

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. Signed, Debruis Burlington, M.D., Director, Center for Devices and Radiological Health, dated September 15, 1997.

Appointment to temporary status as acting chairperson. Temporary status as acting chairperson is requested for Anne B. Curtis, M.D., for the Circulatory System Devices Advisory Panel meeting on September 15 and 16, 1997. Signed, Debruis Burlington, M.D., Director, Center for Devices and Radiological Health, dated September 15, 1997.

CHAIRPERSON CURTIS: We have no old business left over from yesterday and no new business before the panel so we will move on to the open public hearing. Time to speak has been requested by Gordon Bernard, M.D., chairperson, the FDA/NHLBI Pulmonary Artery Catheterization and Clinical Outcomes Workshop.

DR. BERNARD: Good morning. It's a pleasure to be here to tell you about some work that's been going on over the last several months that deals with a device that falls under the purview of this committee, I believe. This conference or workshop was the Pulmonary Artery

Catheterization and Clinical Outcomes Conference, which was held in August, only approximately a month ago.

This process began about six months ago and has moved at lightning speed, as far as I can tell with regard to such things. The organizing task force involved the Center for Devices, Larry Kessler; the National Heart, Lung and Blood Institute, George Sopko; and also from the Center for Devices, Carole Webb.

The pulmonary artery catheter problem is encapsulated in these points on this slide. The use of this device--and we're talking about the flotation guided pulmonary artery catheter typically used in cardiac cath labs and at the bedside in critical care units and in operating rooms. The use of this device has escalated to approximately one million, some would estimate 1.5 million catheter insertions per year in the United States alone. Use is for both diagnosis and management. It has a wide variety of operators, surgeons, intensivists, cardiologists, even nurses in some circumstances, anesthesiologists. There have been no reports that document decreased mortality through use of this device. There are several reports that associate the pulmonary artery catheter use with increased mortality.

Where are these catheters inserted? These are

data from one of the major suppliers of these catheters. Approximately 30 percent are placed in cardiac surgical patients, mostly in low risk patients. Another 30 percent are in cardiac medical, mostly in the cath lab, but a number of these patients move on to the critical care or the coronary care unit from the cath lab. Another 25 percent in surgery, mostly in high risk surgery patients. And 15 percent in the medical intensive care arena for a total of 100 percent usage.

Does this catheter increase mortality? There are now several studies in these general areas, cardiac surgery, acute myocardial infarction and in mixed ICUs, that suggest that this catheter increases mortality. Most notable is the last on this slide, this publication in JAMA, from 1996, by Conners, et al., and I'll take that study into a little bit more detail.

This study with a title similar to that which is on this slide, "The Effectiveness of Right Heart Catheterization," was a prospective cohort study. The outcome variable was survival in patients--survival. And the study was done in patients who received a PA catheter during the first 24 hours of intensive care stay. Data from five large teaching hospitals were pooled for an N of 5,735 patients, so it's one of the largest of such series, but

what made it unique was the use of the propensity scoring to adjust risk and case match.

Obviously, when patients receive a catheter like this, they receive it because they're sick. They're more likely to receive it if they're sicker, and therefore it becomes very hard to compare patients who--in an observational study--who got the catheter to those who didn't get the catheter because they may not be the same patients. So this propensity scoring was an attempt to try to adjust that and get matched patients who didn't have a catheter. And parenthetically, I'll say that this study showed that--and others have shown, too--that similar ICUs have catheter insertion rates that can range from as little as five percent to as great as a hundred percent.

So the variability of use of this catheter completely covers the scale with regard to utilization. In other words, there's no consensus by the medical community, at least by these numbers, that there are clearly certain patients who need the catheter and clearly patients who don't. There's a large overlap. So with that, I'll move into the Connors study, which showed that the PA catheter, the adjusted risk, as I mentioned before, showed that the PA catheter patients had an odds ratio of 1.24. That is their mortality rate or their odds of dying were 24 percent higher

than those who did not get the catheter.

And the risk was highest for those patients--and there were several subgroups--it was highest for those patients who had acute respiratory failure, which is the acute lung injury or adult respiratory distress syndrome or multi-organ failure. The risk was similar to controls for those patients who received the catheter for management of congestive heart failure and there was no subgroup that had improved outcome as a result of receiving this catheter.

The lay press got a-hold of this report and these are some of the headlines that ran last fall. In the Boston Globe: "Routine Heart Procedure Tied to Mortality." In Newsweek: "Deep in the Heart: Are Catheters Safe?" In The New York Times: "A Medical Procedure Done a Million Times a Year May Do More Harm than Good." "Safety of the Catheter"--and I really like this one--"Safety of the Catheter into the Heart is Questioned, Startling Doctors."

And I'm sure there was this loud outburst of startle across the country when this article came out. These are the professional organizations that called for the workshop and governmental societies that called for the workshop to further discuss this. I just show you these as a list, and, of course, it includes the FDA and the NHLBI as organizers. The societies that you see listed here are very

interested in this problem and are quite concerned both about public perceptions and also the medical realities of what this catheter can and can't do.

So the purpose of the conference that was put together in August was to review the current state of pulmonary artery catheter knowledge, to summarize the indications for the catheter and outcomes in clinical practice, and to address technological issues related to insertion, maintenance, and use of the catheter interpreting the data, and to provide options for research and regulatory action in this area.

The committee was organized along four different subcommittees: respiratory diseases headed by Weideman, Sure and Parsons; trauma perioperative management headed by Demling and Evans; sepsis/multi-system organ dysfunction by Cerra and Masur; and cardiovascular diseases by Williams and Kaplan.

There were three main recommendations that emanated from this conference or this workshop. The first, and this was an overriding theme in all discussions, that the professional societies create mechanisms for improved pulmonary artery catheter training, credentialling and monitoring. There was serious concern that because of the wide proliferation of this device that there were inadequate

mechanisms to ensure that its operators are properly trained, and that the device, equipment and so forth are properly utilized.

The second was that prospective randomized trials be constructed that would assess safety and efficacy in these four patient populations: persistent refractory heart failure, acute respiratory distress syndrome, sepsis/septic shock, and low risk coronary artery bypass surgery patients. These were the areas--the first three areas were those in which the catheter has the highest suggestion of increased risk or increased mortality with its use. In the last category, it's a section of patients where most of the catheters are used, and there is very little evidence that the catheter is offering any benefit to the patient. So it might actually be more like a cost effectiveness study. All of these would require carefully designed control groups.

And lastly, the third recommendation was to use the data emanating from clinical trials in this area and the standardized protocols that would grow from these clinical trials as well as the educational programs that would have to be an essential component of these to improve the methods for evaluation and employment of medical devices in intensive care. This is a much bigger problem than the pulmonary artery catheter. It's just that the onus right

now is to examine the catheter since there are so many reports out there suggesting that this catheter is increasing mortality in patients in critical care. Thank you for your attention.

CHAIRPERSON CURTIS: Do any of the panel members have any questions to ask directly of Dr. Bernard?

DR. DOMANSKI: Yeah, I'd like to ask you one question, if I could. I actually had the pleasure of hearing a bit of this discussion before at NIH, and I guess I'm struck by a couple things. Obviously, people who are not competent to do this sort of thing get into trouble doing it. But I have some, it's not immediately obvious--of course, credentialing, proper training and things are all sort of vanilla. Of course, they probably should be doing more of that, and there are probably too many people putting it in, but I guess I wonder what, you know, one would want to look very carefully to how well they really adjusted risk in those articles before one committed the sort of funding to that kind of clinical trial as opposed to other clinical trials that need to be out there. I guess I'm just not sure whether this, you know, all science not being created equal, whether this is really something that demands that level of attention? I mean what's your thought about that?

DR. BERNARD: Yeah. That's an excellent question.

Most of these studies can be sort of discussed away. As you dig into the methods and the way the patients were divided and the risks and so forth, you could say, oh, well, that's just because sicker patients get PA catheters; hence, of course, they die more frequently. The Connors article did the best, I believe most people would agree now, did the best that we could do with an observational study in which there was no randomization, and it still came out with this excessive risk.

Now, I'm not sure that I believe that the risk is 24 percent greater if you get a catheter. What I'm beginning to wonder, though, is if your risk is anything less if you get a catheter? And so that any risk, any risk at all, would be unacceptable if it's not providing information that we need. Hence, a prospective study--and this, see, this last slide, I hope to articulate what the committee was interested in here--that the whole global issue of methods of using devices in critical care to guide therapy has not been explored adequately. So it's not just the catheter. It's how to use the information that comes from the catheter.

CHAIRPERSON CURTIS: Go ahead.

DR. SKORTON: When do you think the proceedings will be available from the workshop because I'd like to

request that the committee, the panel, receive copies of it?

DR. BERNARD: Sure. We have a draft that's fairly complete now, and our target date was the end of this month to have a final draft. We hope to submit this for publication actually in JAMA, but at whatever point we consider it to be a final draft, we'd be happy to supply you with a copy.

DR. HARTZ: Could I ask a question about data collection? Do you have built into your protocol the determination whether it's the pulmonary artery catheter or the central line insertion itself that's increasing the risk because in many of these patients you're going to have central access, and we need to determine whether it's an acute problem with the insertion, a late problem with the pulmonary artery rupture, so another data collection point is are the catheters wedged? And then the vary late data point about sepsis. The most important thing that whether the patient has to have a central line insertion no matter what, which I think everybody here would agree that a patient having a heart surgery needs a central line--

DR. BERNARD: Right.

DR. HARTZ: --for access. So make sure that's included in the--

DR. BERNARD: No. That's exactly right. And, in

fact, the charge to this committee or this workshop was not to actually design the clinical trials but more to suggest the areas where the questions are most burning. And so we didn't really get into study design except that it was quite tempting to think about it along the lines that you describe, and one of the recurring themes was that there are really two questions that will be tested or should be tested in these studies. One is catheter versus no catheter, and what kinds of complications these patients have. And then management strategies tied to catheter data and management strategies tied to non-catheter data. And so those might actually be factorial designs in a clinical trial to get at just exactly the questions you ask. Because, you know, all of these patients have--at least the critically ill patients and adult respiratory distress syndrome and sepsis have recurrent bouts of sepsis, and so the only way to determine whether that's catheter related is to randomize these patients, for example. I mean there are many other possibilities although sepsis looms large as one of the most likely causes of excess mortality if there is excess mortality.

CHAIRPERSON CURTIS: Okay. Thank you.

DR. BERNARD: Thank you.

CHAIRPERSON CURTIS: Before we move on to the

company presentation, Dr. Domanski wanted to talk about the design of these clinical trials, and I suppose it's a little bit of old business from yesterday.

DR. DOMANSKI: I apologize. I know this is kind of a get-away day, and I'm not going to take a lot of time doing it. But, you know, one of the things that was clear yesterday is that it would be useful to be able to, with something that's been around as long as these prosthetic valves have, to create historical controls. The difficulty is that the literature may well not be there, and it may not be so easy to access people's original data and things. That's another way of trying to do it.

Another approach would be, in fact, to randomize patients, to truly randomize them to one or the other, but accept the fact that it's not practical to ask for a suitably power trial as we usually use that term, but simply randomize them, accept a five percent power or ten percent power or three percent, whatever the power comes out with a reasonable number, and I think that the companies did reasonable numbers yesterday. Accept the fact that the power is low and at least know what you're looking for. You're looking for a truly gross difference, but I suspect that that would at least allow one to quantitate what kind of gross difference one doesn't see or does see rather than

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just having the panel sit around and chat about uncontrolled data, which is just kind of putting your thumb up in the wind and seeing which way it's blowing because I guess we'd see a gross difference, but that would be a cleaner way of doing it, and knowing precisely where we stand in the process and being able to titrate the process, maybe even down in terms of numbers. I'm not sure. Maybe they need to do fewer, not more.

But it's one of handling it and getting away from the problem of being totally uncontrolled, but also not forcing historical controls that probably are not going to be very useful in that field. That's my idea for the morning, but I think it might be something that's worth considering anyway.

CHAIRPERSON CURTIS: Okay. Thank you. I think since we've just started, we'll go right ahead and move on. The presentation this morning is Premarket Approval Application P970030, St. Jude Medical, Heart Valve Division, the Toronto SPV Valve. And we will start with the company presentation. Just before we get started, since there are a large number of you, if you would go down the line and introduce yourselves and your financial interest in the product.

DR. BACH: David Bach, University of Michigan.

I'm a paid consultant to St. Jude.

MR. FLORY: Alan Flory, St. Jude Medical.

MS. McCALLUM: Lisa McCallum, St. Jude Medical.

MS. BURLEY: Fonda Burley, St. Jude Medical.

MS. WENELL: Karen Wenell, St. Jude Medical.

DR. GOLDMAN: Bernard Goldman, University of Toronto, surgeon, principal investigator on the Toronto Board, the Board of St. Jude for the Toronto Valve, and a clinical instructor in the SJM Institute, and I receive a consultant's fee.

MR. SHEPARD: Good morning, ladies and gentlemen. I'm Terry Shepard. I'm the president of St. Jude Medical Heart Valve Division. It's a pleasure for me and for us to be here this morning, and I'd like to thank the panel and FDA for this opportunity. As many of you may know, St. Jude Medical is the world's leading producer of prosthetic heart valves; some 800,000 St. Jude medical valves have been implanted since the company was founded over 20 years ago. And we remain committed today and in the future to providing physicians and their patients with the best solutions for heart valve disease in the broadest sense.

The Toronto stentless porcine valve, or Toronto SPV valve, being discussed here this morning represents an important product development effort for our company and we

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believe an important advance in the management of heart valve disease. It is today commercially available in virtually all other major markets of the world. It is the most widely implanted stentless porcine valve in those markets, and we welcome the opportunity to discuss it with you this morning.

I might also add that we appreciate the opportunity to engage with FDA in what has been a novel interactive PMA process which we believe is a more productive and efficient way of bringing these new products to patients more expeditiously.

We have prepared three brief presentations for you this morning on the Toronto SPV. The first will be a description of the valve implant technique by Dr. Bernard Goldman from Sunnybrook Health Sciences Center in Toronto. Dr. Goldman is one of the main investigators for IDE study and has extensive clinical experience with this particular valve. Along the way, Dr. Goldman will describe some of the novel design concepts that are behind this valve as well as its clinical utility.

The second presentation is the data itself, a summary of IDE clinical study results by Karen Wenell from St. Jude, the principal clinical research scientist for this study.

The third presentation will be by Dr. David Bach, who is associate professor of cardiology at the University of Michigan. Dr. Bach has served as an independent echocardiograph core lab consultant for the IDE study and he will provide a very crisp overview of the unique and important hemodynamic characteristics of the Toronto SPV valve, and with the consideration of the panel, we would like to actually make two other very brief presentations that are not reflected on this particular slide, but which we believe will be helpful to the panel, given yesterday's discussions regarding the importance of training with these new stentless xenografts and the issue of post-market surveillance as well.

Peggy Malikowski, the marketing manager for St. Jude for this product, will give a very brief summary of the comprehensive training programs in place at St. Jude covering this valve as well as other devices, and Karen Wenell, who I just mentioned, will come back and briefly describe our proposal for post-marketing surveillance studies already submitted to FDA.

In addition to Dr. Goldman and Dr. Bach, the investigators listed on this slide are available in the audience to address specific questions that you may have concerning patients or the clinical use of the valve. They

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are Dr. Ed Verrier from the University of Washington in Seattle, one of the larger U.S. sites in the study; Dr. Tirone David from Toronto General Hospital, the inventor of the valve, and I might add the surgeon with perhaps more experience with stentless xenografts than any other; Dr. Harry Rakowski, the chief of echocardiography also at Toronto General; Dr. Michael Petracek from St. Thomas Hospital in Nashville, the other major U.S. center in the study; Mr. John Pepper from the Royal Brompton Hospital in London, the larger of the two UK sites in the study; and Dr. Fred Schoen, professor of cardiac pathology at Harvard and Brigham and Women's.

Finally, several representatives from St. Jude Medical are available to address any questions that you may have concerning the clinical study analysis, the in vitro testing of this particular valve or the manufacturing procedures regarding the Toronto Valve. Responses to your questions will be directed by Fonda Burley, our regulatory submissions manager, and with that, let me introduce Dr. Goldman. Thank you.

DR. GOLDMAN: Madam Chairperson, may I take this moment to remind the panel that the last time a group of Canadians came to Washington we burned down the White House. That was in 1812, and I promise that we'll be more polite

and more civil on this occasion.

The Toronto stentless porcine valve is a subcoronary implant. It is an intact porcine valve. The sinuses are scalloped specifically for subcoronary implantation without the need for surgical modification. Enough aorta is left behind to support the commissural posts and the leaflets. The tissues have been treated with 0.5 percent glutaraldehyde at low pressure fixation. There is a fine polyester covering which is to facilitate suturing and tissue ingrowth. There is, as you can see from the undersurface, a large leaflet coaptation surface, and I'll describe that further.

One can see that the Toronto stentless porcine valve provides a larger orifice to annulus ratio when compared to a stented valve of the same diameter. There is a more favorable internal to external diameter relationship and a larger effective flow area. The rationale behind the Toronto SPV valve is that it is measured to fit within the aortic complex and it is designed to become a functional unit within the host aortic root.

This is achieved by the sizing technique. Commonly a transverse aortotomy is performed. This allows the insertion of a sizer, which is clear plastic which one can look through, which facilitates measuring the

sinotubular junction and the annulus. In aortic valve pathology, the sinotubular junction is commonly larger than the annulus. We choose the sinotubular junction diameter to determine the size of the valve. Sinotubular junction may be 25 millimeters and the annulus 23 millimeters, and that allows us to insert one size larger.

This minimizes the risk of aortic insufficiency by providing a large leaflet coaptation surface. The notches 120 degrees apart on the sizer and on the interior surface of the valve facilitate accurate alignment of the commissural pillars and thus accurate valve positioning. By retaining the normal sinuses of the aorta, of the host aorta, the diastolic pressures allow dissipation of closure stress on the host aorta rather than on the leaflets.

The surgical technique is facilitated by these 120 degree markers on the inflow surface. The inflow suture line is simple and interrupted. The outflow suture line from pillar to pillar to pillar is a continuous running suture. The clinical information and summary will be presented now by Karen Wenell.

MS. WENELL: Good morning. I'd like to present the results of the clinical study conducted by St. Jude. Our clinical study was conducted at 12 sites in North America and England. Two sites participated in England,

The Royal Brompton Hospital in London and Harefield Hospital in Harefield. We had four sites in Canada: Victoria General Hospital in Halifax, Nova Scotia; the Toronto General Hospital and Sunnybrook Health Sciences Center in Toronto; and Holy Cross Hospital in Calgary, Alberta.

There were six U.S. centers: the University of Washington Medical Center in Seattle; Cedars-Sinai in Los Angeles; Barnes Jewish Hospital in St. Louis; St. Thomas Hospital in Nashville; Sentara General Hospital in Norfolk; and Lankenau Hospital in Wynnewood, Pennsylvania.

The first implant of a Toronto SPV valve took place at Toronto General Hospital in July of 1991. Since that time, 577 patients have been enrolled in this cohort. The total follow-up is 1,081 valve years with an average follow-up of 1.9 valve years per patient. The range is zero to 5.2 valve years.

67 percent of the patients enrolled in the study were male. And the mean age was 65.6 years. The objectives of the study were to demonstrate the safety and effectiveness of the Toronto SPV valve and to characterize the patients within the study population. The most commonly identified etiology was calcification followed by congenital defects. Patients with more than one etiology identified appear in multiple columns.

85 percent of the valves implanted ranged between sizes 25 and 29 millimeters. With stented conventional valves, the more commonly implanted sizes are between 19 and 23 millimeters. Approximately half of the patients had concomitant surgery. 40.6 percent underwent coronary bypass. These percentages are similar to those seen with other populations undergoing AVR.

Preoperatively, 54 percent of the patients were in NYHA functional Class III or IV. By six months postoperatively, approximately 98 percent were in functional Class I and II, and these percentages remained constant over the course of the follow-up.

Presented here are early and late complication rates for five serious adverse events associated with valve replacement as well as reoperation and death. Early rates are presented as simple percentages and late rates as percent per patient year. Objective performance criteria for heart valves appear in the far right column. One measure of valve safety states that late rates for these five complications must be less than twice the OPC rates. No OPC rates have been established for reoperation and death. I'd like to mention here that a very broad definition of thromboembolism was used in this study. Centers were required to report any peripheral or

neurological event no matter how short the duration or how minor the symptoms.

When thromboembolism was reevaluated using the current definitions published by Edmunds in 1996, the early rate dropped from 1.7 to 0.9 percent and the late rate from 1.4 percent per patient year to 0.5 percent per patient year.

All rates for the Toronto SPV valve are statistically significantly lower than twice the OPCs with p-values of less than .05.

The next series of slides will present Kaplan-Meier life tables for these events. I'd like you to note that a truncated scale from 80 to 100 percent is used. The 95 percent confidence intervals appear in blue and across the bottom are the number of patients at risk for each interval.

Approximately 12 percent of the patients in this study were discharged on anticoagulant therapy. This included five percent from one institution where the patients were routinely sent home on Cumidan for three months. The rest of the patients were receiving anticoagulants for atrial fibrillation or a history of TIA or stroke. Four anticoagulant-related hemorrhage events occurred within this patient population. One patient had

atrial fibrillation and the other three had history of TIA. All four were being followed by their local physicians and two were known to be noncompliant with their anticoagulant regimen.

Six cases of prosthetic endocarditis were diagnosed within this cohort. Five of the cases occurred within the first six weeks post-op, and the six at 18 months resulted from an abscess in the patient's hand.

17 paravalvular leaks were identified. All the patients were asymptomatic, and the PV leaks were noticed on echo conducted as part of the clinical study. No intervention was required. PV leak was evaluated across valve sizes and across time and no trends were seen.

Using the original study definition, there were 24 thromboembolic events with a one-year freedom from thromboembolism of 96.5 percent and a three-year freedom of 93.9 percent. Based on the current definitions, 13 events were eliminated. Three because they occurred in the immediate post-operative period, and ten were reclassified as TIAs. This slide presents the Kaplan-Meier freedom from embolism for the remaining 11 patients. One year freedom from embolic event is 98.4 percent and three year is 97.1 percent.

Four explants occurred within this cohort. All

were the result of endocarditis. Two patients successfully received a homograft. However, the other two patients did not survive.

This slide presents a breakdown of causes of death within the study. The linearized rate for all cause mortality was 2.3 percent. Of the eight valve related deaths, two occurred in the early post-operative period. One was the result of endocarditis. In the second case, the patient was hospitalized for heart failure and hypertension and died suddenly. The family refused an autopsy so the exact cause of death could not be identified. Of the six late deaths, three were caused by endocarditis and two by anticoagulant related cerebral hemorrhage. One patient was found dead at home. Again, the family refused the autopsy so the cause of death could not be determined.

This slide presents the Kaplan-Meier freedom from death for all cause mortality. 16 deaths occurred within the first month post-implant, 15 between one month and one year, and nine patients died after one year.

This is the Kaplan-Meier freedom from valve-related deaths. Of the eight deaths, seven occurred within the first six months post-implant and one occurred at 18 months as a result of anticoagulant related cerebral hemorrhage.

In summary, 98 percent of the patients were NYHA functional Class I or II throughout the follow-up period. Complication rates were statistically significantly lower than twice the FDA objective performance criteria with p-values of less than .05. And no unanticipated adverse events were reported. Dr. David Bach will now present a summary of the hemodynamic data. Thank you. Thank you.

DR. BACH: Thank you. In the next few minutes, I'd like to demonstrate the echocardiographic appearance of the Toronto SPV valve following implantation, briefly review the hemodynamics including freedom from aortic regurgitation and briefly discuss left ventricular mass regression as a measure of effective relief of outflow obstruction.

This echocardiogram demonstrates the appearance of a normal aortic valve. The characteristics of the valve are those of thin, discrete leaflets inserting directly into the root of the ascending aorta. In systole, the leaflets open fully, nearly disappearing against the wall of the ascending aorta and providing a maximal orifice for flow of blood leaving the left ventricle. The problems associated with conventional stented porcine valves are depicted in this schematic slide.

Shown on the bottom is a conventional stented valve. The prosthetic sewing ring of the valve occupies

space within the aortic annulus and to some degree obstructs blood leaving the left ventricle. Prosthetic stents protruding into the ascending aorta also occupy space and to some degree further obstruct flow. In contrast, the Toronto SPV valve, a stentless valve, has no prosthetic sewing ring and no prosthetic struts. It's molded to the inner wall of the ascending aorta and provides maximal orifice area for blood leaving the left ventricle.

This composite demonstrates the comparison on echocardiography between a normal aortic valve above and a Toronto SPV valve below. The characteristics that these two valves share in common are those of thin, discrete leaflets inserting directly into the wall of the ascending aorta, full excursion of the leaflets, opening fully in systole, nearly disappearing against the wall of the ascending aorta.

The next three slides will summarize the hemodynamic data associated with the valve. All of the data are derived at one year post-implantation. The data are expressed as mean plus or minus one standard deviation and are stratified by valve size. On this slide, there is mean pressure gradient demonstrating excellent low mean pressure gradient for all valve sizes, and as expected lower gradients for the larger valve sizes, somewhat higher gradients for the lower valve sizes.

Peak pressure gradient, again in millimeters of mercury, at one year post-implantation again demonstrates very low transvalvular gradients associated with the valve. Effective orifice area, again, at the one year time point, demonstrates 1.3 square centimeter effective orifice area for the smaller valve sizes to a high of 2.5 square centimeters for the larger valve sizes.

This slide demonstrates the comparison of in vitro and in vivo data for calculated effective orifice area across the range of sizes tested. It shows excellent correlation between the in vitro and in vivo data. This slide demonstrates the very low incidence of aortic regurgitation associated with the valve. The one year time point is depicted here. One and a half percent of patients did not have aortic regurgitation quantified on the one-year time point echo.

Of the remaining patients, 89 percent had no aortic regurgitation. Four percent had trivial aortic regurgitation. Echocardiography is exquisitely sensitive at detecting aortic regurgitation, and I believe this emphasizes the very low incidence of significant aortic regurgitation associated with the valve.

The very low incidence of aortic regurgitation is maintained over time depicted in the early post-operative

period, six month, one year, two year, and three year post-implant time periods. The incidence of no aortic regurgitation in red is maintained; trivial and mild aortic regurgitation remain the same. There remains a very, very low incidence of significant aortic regurgitation throughout the period of study.

Aortic valve disease, and particularly aortic stenosis, result in left ventricular hypertrophy and an increase in left ventricular mass. Following aortic valve replacement, the ventricle may favorably remodel with regression of left ventricular hypertrophy. The degree of left ventricular mass regression is an indication of the functional relief of outflow obstruction and the adequacy of the effective orifice area of the valve.

These data demonstrate the left ventricular mass index, the left ventricular mass index to body surface area, following implantation of the Toronto SPV valve early post-implantation, six months, one year, two years, and three years post-implantation. There is a statistically significant decrease in left ventricular mass index of seven grams per meter squared in the first six months and a further decrease of nine grams per meter squared from six months to one year. This is a measure of the functional significance of relief of all the outflow obstruction.

To summarize the hemodynamics, the echocardiogram demonstrates thin mobile leaflets, their very low transvalvular gradients and a large effective orifice area, and a low incidence of significant regurgitation associated with the valve. Significant left ventricular mass regression is another measure of the functional significance of relief of outflow obstruction. The Toronto SPV valve provides a consistent sub-coronary design with a reproducible implant technique. It has near natural hemodynamics and a safety and efficacy has been established for all valve sizes implanted.

I'd now like to introduce Peggy Malikowski who will discuss the training program at St. Jude Medical.

MS. MALIKOWSKI: St. Jude Medical has developed the SJM Institute, which is a worldwide education program designed to train surgeons on the application of a variety of products. This program currently has been utilized to support the Toronto SPV valve, allografts as well as annuloplasty rings.

The objectives of the program for the surgeon are to help the surgeon understand the design, the clinical aspects and clinical advantages of the Toronto SPV valve, to review the sizing and implantation procedure for the valve, understand in more detail the clinical results, and then

finally to apply this in a practical wet lab setting.

The components of the SJM Institute actually are threefold. A lecture session reviews the history and rationale of the Toronto SPV valve and of stentless valves in general, as well as exploring the current clinical experience with the Toronto valve. Teleconferencing and videoconferencing allows time to view a variety of surgical procedures and implementation aspects of the valve. And then finally the program concludes with a wet lab experience which allows the surgeons to work with the valve really in a controlled setting.

The physician's manual that accompanies the Toronto SPV valve includes a very detailed and thorough discussion of the sizing and implementation aspect of the device. The principles used for aortic valve replacement can be adapted for utilization of the Toronto SPV valve. We utilize SJM Institute as an option for surgeons to attend the program based upon their surgical need and experience level. We do highly recommend their attendance at this program and we do support that there is a minimum of one attendee per open heart center for our SJM institutes. If you have any further questions about the SJM Institute, I invite you to direct them to our consultants that are here today as many of them have served as faculty members for the

SJM Institute.

Now, I invite Karen Wenell back to the podium to close our presentation.

MS. WENELL: In response to some comments from the panel yesterday on post-market surveillance and in some discussion that we've had with FDA, SJM has put together a draft proposal of a post-market study for the Toronto SPV valve. In your notes that you receive from the FDA, I think you'll notice that the first three points are identified. The first: to further characterize long-term safety and efficacy SJM would address by following the North American cohort to the year 2002. Presently, patients have still been enrolled since the data closure date of January 31, and there are approximately 450 patients in the cohort in North America.

Safety would be addressed by collecting information on the following complications: bleeding, endocarditis, structural deterioration, nonstructural dysfunction, embolism, valve thrombosis, reoperation and death. Additionally, mortality and autopsy information would be obtained. SJM would make every effort to obtain valves either from explant or from autopsy to be returned and evaluated by a core pathology lab.

To obtain information on detection of rare events,

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SJM is pursuing accurate and cost effective means, possibly the use of Equifax to track mortality for the valve. As far as determining predictors or surrogates for valve failure, we feel there are two methods of doing this. The first, in vivo, on annual echocardiography exam, all patients in the cohort would be requested to have an echo, and this can be used to identify early changes in the valve or valve performance.

In vitro, during the five years of the post-approval study, explanted valves and those obtained from autopsy would be returned to a core pathology lab for evaluation. Additionally, all Toronto SPV valves from North America returned to SJM via our FER, or field experience report system, will be evaluated at the core lab. Once the device evaluation has been performed, a copy of the complete report would be forwarded to the surgeon and/or local physician.

Finally, SJM would provide annual reports to the FDA. This would include adverse events, the use of possibly Equifax to detect rare incidence, and both in vivo and in vitro reports on the function of the valve. Thank you.

CHAIRPERSON CURTIS: Okay. Thank you. We'll move on now to the FDA presentation by Steven Allis.

DR. ALLIS: Good morning. My name is Steven

Allis. I'm the lead reviewer for the Toronto SPV PMA application. Can I have the first slide, please? The Toronto PMA was reviewed by the FDA staff identified on the slide. The information presented in the panel packs provided to you before the meeting represented over a year of work with the FDA review team and St. Jude Medical.

Next slide. This morning I will first present a short description of the Toronto valve. Next, I will review the device's safety and effectiveness data, followed by the study limitations and a review.

Several Toronto valve design features are worth highlighting. The device is essentially constructed of an excised porcine aortic valve that was cross-linked with glutaraldehyde. The device is available in eight sizes and packaged in its finished form ready for implementation.

Next slide. This slide shows the FDA recommendations and what the Toronto study collected. FDA recommends that companies collect the minimum quantity of data in heart valve clinical trials. The heart valve guidance lists these recommendations, the first of which is the collection of at least 800 patient years of follow-up data. The 800 patient year criterion is also a requirement of the objective performance criteria, historical control method.

The Toronto study was successful in meeting the 800 patient year requirement. Go back to the previous slide. The second criterion recommends that at least three centers follow at least 50 patients for one year. The Toronto study had four centers with more than 50 patients followed for a year. The third recommendation instructs companies to collect one year of follow-up data for 15 of each device size. In the Toronto study, the 23, 25, 27, and 29 millimeter valves had one year of data for more than 15 patients. There were zero 19 millimeter patients followed for a year because there were no implantations of this valve size.

Next slide, please. For the safety evaluation, mortality, morbidity in the perioperative period were measured as incidence rates. Late events as linearized rates. The early event rates are compared to values reported in selected literature articles. Late event rates are recorded as linearized rates for comparison to the objective performance criteria outlined in the heart valve guidance. In both respects, the Toronto valve outperformed these historical values for all adverse events.

Next slide, please. In our evaluation of effectiveness, preoperative New York Heart Association functional classification was compared to that one year

after surgery. 352 patients were in Class I at one year compared to only 24 preoperatively. Three patients were in Class IV compared to 48 preoperatively. Only three patients failed to improve functional status. Further evaluation of effectiveness was undertaken with echocardiographic assessment of hemodynamic performance at three months, six months and annually thereafter.

At 12 months valve gradients and effective orifice areas were near normal in value, compared favorably to results reported for stented biografts reported in FDA selected literature articles. Additional data substantiating this performance were provided from concurrent studies of stented homografts [phonetic] and allograft valves at three of the study centers using the same echocardiographic protocol. Median cardiac indices were within normal limits for these studies.

Valve regurgitation was absent in 362 patients which comprised 88 percent of the one year patient population. 16 patients had trivial, 21 mild, and five moderate leak at the three-month follow-up evaluation. One patient had severe regurgitation and no record was available for four patients.

Hemodynamic function tended to improve during the first year before stabilizing at subsequent evaluations.

Regurgitation did not deteriorate during this period. Next slide, please.

The Toronto study was limited in four respects. No data are available for the 19 millimeter valve size. Only limited one-year data are available for the 20, 21 and 22 millimeter valve sizes. This limitation should be taken in context with clinical hemodynamic evidence of increased valve impedance with increasing valve size. A second limitation common to acute heart valve studies is due to the short duration of this clinical trial. Data extending closer to the expected life of this device is necessary for an assessment of durability and calcification. Usually tissue heart valves are expected to last eight to ten years. The Toronto study reports data to four years. A third limitation is the paucity of information related to explanted heart valves. The company attributes this limitation to the difficulty in obtaining explants from the follow-up physicians, most of which are not involved with the clinical centers. Explant data can be critical in the assessment of valve function and device durability.

Lastly, 75 percent of the Toronto study cohort were treated at four institutions outside of the United States. 48 percent of the study was conducted at two of these centers. This limitation restricts our ability to

assess the need for physician training. Last slide, please.

In review, as you discuss the data presented here today, please keep in mind the specific questions presented in Section 1 of the panel pack. These questions generally relate to device labeling, the adequacy of the data presented by the sponsor, post-approval study requirements and the FDA historical control methodologies. Again, I'd like to ask for the panel's comments regarding the use of the non-concurrent historical controls detailed in the panel packs. Both methods, the objective performance criteria and the literature articles, attempt to aid your evaluation by surveying and condensing the available literature.

The objective performance criteria represent the safety data presented in approximately 80 articles published in the 1980s. The new literature article approach that's in the panel packs, in there the articles are selected by FDA reviewers based on how well the article's demographics match the study patient population. Another feature of this method is how the data are presented. Instead of a single simplified linearized rate for each safety outcome, all safety and effectiveness information for the chosen articles are presented for your review.

Please keep the inherent limitations of historical controls in mind when considering the adequacy of these

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methods. Your feedback on these methods as applied to the Toronto study data is critical to FDA's attempts to improve the quality of the information presented for panel review. Lastly, we are also interested in whether the new historical control method should supplement or supplant the objective performance criteria. Since the articles on which the objective performance criteria are based are from ten to 15 years ago, they may no longer represent the current state of the art of stented tissue heart valves.

Because of improvements in heart valve technology, FDA is considering abandoning the method all together. We appreciate your careful consideration of these issues. Thank you.

CHAIRPERSON CURTIS: Thank you. We'll move on to start the panel review. The lead reviewer from the panel is Dr. Michael Crittendon.

MR. CRITTENDON: Good morning. I've had an opportunity to review the panel pack and think that the clinical summary provided by I presume St. Jude was quite excellent. I enjoyed reading it. I reread it again last night and really found it fairly easy to read. I think it was the best of the three that we've had to evaluate these past couple of days and found the information fairly easy to find.

I'm going to comment on five areas. One is the hemodynamics; (2) calcification; (3) the issue about aortic regurgitation; technical aspects of the implantation; and then just design. These are more curiosity points for me approaching it like I would if this was a new device that a salesman were to bring to my office, saying, Dr. Crittendon, would you consider putting this valve in, and I had the unique opportunity, instead of having a guy on the front lines coming to me with his computer and bookbag full of valve sizes, et cetera, I can ask the data from the primary or principal investigators. So this is a unique opportunity.

The first thing I want to ask about was the hemodynamics, and several places in the panel pack, it talks about the rate of the left ventricular mass index regression. And I was just curious to find out is this different than any of the other stented valves or stentless valves, for that matter? Is this something that we see? I'm sure we see this with every type of aortic valve replacement, particularly for aortic stenosis; is this more accelerated for the Toronto valve?

DR. BACH: I don't think we can make a direct comparison. It's never been studied one valve versus another. I think people are beginning to look at left

ventricular mass regression in this field. I have to say that from seeing these echoes, it appears to be very prominent and early, but that's really a gestalt answer to your question.

MR. CRITTENDON: Another question about hemodynamics is that, you know, obviously getting postoperative catheters are going to be difficult so we're going to be relying on echo data to follow these patients either in a post-market analysis or just in general. The question I have on page 4-10 of the panel pack, in the FDA discussion or review of the PMA, there was some discussion about discrepancies between the core lab echocardiographers, i.e., that there was some difference between the core or the larger sites versus the hospitals. And I wonder if that is going to be a problem in terms of further evaluating the data as we go out from this particular cohort? Could somebody maybe from the FDA comment on what they found, just to reiterate that for us? And then maybe have the echocardiographers representing St. Jude comment on that?

MR. DAWSON: Good morning. I'm John Dawson, the FDA's statistician on this application. We had a difficult time when we had the core lab results presented because there was a good deal of variation among hospital to hospital, and in every dimension we looked at there just

seemed to be inconsistency between the hospitals and the core labs, and we basically decided we were just going to have to choose one approach or the other, taking the clinical results or the core lab results. And we opted for the hospital results because at least then we had 100 percent. And if the company had submitted everything to a core lab, we wouldn't have had that issue.

Ultimately, I think it comes down to simply looking at the overall averages or the average results that the core lab attained and comparing that with the overall averages for the hospitals themselves. And on that plane or that sort of very summary dimension, the two were in fair agreement with each other. From my point of view, since we had decided we would use the hospital data, the problem of why the core lab would get something different than the hospitals did, to me was not a very interesting question, or at least it's kind of secondary, I think.

MR. CRITTENDON: Is there a way we can reconcile this, and I guess just from the point of view of being consistent? Obviously, there's inter-observer variation. I see that in my own hospital. So I mean I understand these issues. I don't think it's a point of contention more or less than just resolving it so that we feel confident that when we look at the data that everyone is in agreement that

it represents what we think is the best way of looking at it.

MR. DAWSON: Well, the core lab presented a detailed explanation of the problem and why they thought that there would be disagreements between what they got and what the hospitals got and perhaps the clinical folks can comment on that. It didn't mean a great deal to me.

DR. BACH: There are a couple of sources where the core lab, well, where two observers may get different numbers. One is just inter-observer variability or even intra-observer variability where there will be some random scatter. In addition, there may be some methodologic differences with how things are measured and one example is if a site measure is using M-mode and the core lab measure is using 2-D or vice versa, that may lead to different numbers. The numbers are going to be relatively similar in caliber and comparison for change will be similar to compare different groups at different hospitals. It's nice to have then a single methodology for doing it.

The bottom line, though, is clinically the valve had excellent characteristics no matter what numbers were used, and if there was a few percent variation in one method or another, it did not result in a significant impact on the actual data in the end.

MR. CRITTENDON: Okay. The next issue I want to talk about or ask about was the calcification. As opposed to the valve we looked at yesterday that apparently has zero pressure fixation, this has low flow or low pressure fixation, and I'm wondering if that's going to make a difference vis-a-vis calcification? Is there any--do you have any kind of speculation of whether or not this would be the case or not?

MS. BURLEY: I'm sorry. I missed part of your question. Could you please repeat it?

MR. CRITTENDON: Did the process of zero pressure fixation in glutaraldehyde versus low pressure fixation in glutaraldehyde, would that contribute more or less to more calcification, less calcification, doesn't make a difference?

MS. BURLEY: I would like to ask Dr. Schoen to address this question.

DR. SCHOEN: Good morning. I'm Frederick Schoen from Brigham and Women's Hospital in Boston. I'm a paid consultant to St. Jude, and St. Jude is contributing to my expenses in being here. I'm not aware of any data in the literature or otherwise that relates the pressure at which a cusp is fixed to its propensity to calcification.

MR. CRITTENDON: And then, I'm sorry, Dr. Schoen,

you had an opportunity to look at some of the explants. Did you notice any tissue calcification there?

DR. SCHOEN: I had the opportunity to look at six explanted valves, the longest one going to 145 days. And there was no evidence of calcification in any of those six explants in either the cusps or the aortic wall.

MR. CRITTENDON: Thank you. Now, for aortic regurgitation, I had a little bit of trouble reconciling the data presented on page 5-86 versus that in Attachment 3. In Attachment 3, it details the preoperative diagnosis and some other characteristics of each patient, each of the 577 patients, but on page 5-86, it talks about, I think, 433 patients. When I just did some simple math, I found that there were 47 patients who had regurgitation and principally most of these patients were in the larger sizes in the 27 and 29 sizes. I was just wondering if that is a potential problem or is that seen in patients with homografts with the larger sizes? Can anybody address that?

MS. McCALLUM: When you say Attachment 3, you're speaking to the Patient Information Table?

MR. CRITTENDON: That's correct.

MS. McCALLUM: The Patient Information Table presents data that is current to one year. And also presents severities that are two plus or higher, I believe.

MR. CRITTENDON: Right. These are non-trivial; is that correct?

MS. McCALLUM: Yes, and I think the other thing is if they didn't have the one year visit, then we put the most current data to one year. So if they had three to six month data, that would show up in the Patient Information Table. So that might account for some of the discrepancy between the two.

MR. CRITTENDON: Apparently, there were some patients who were dropped out on the 5-86, the graph at the top of the page. So I guess there are 144 patients who were not put on.

MS. McCALLUM: Yes. And I think if there were three and six month data--

MS. WENELL: The N of 433 represents patients who had echo for which that value was collected. Some patients may not have reached their one year time point.

MR. CRITTENDON: I understand. Okay. It was remarkable that nearly 80 percent of the regurgitation noted, if we look at Attachment 3, if you go through that data, 78 percent of those patients had sizes 27 and 29, and I'm just curious is that a characteristic--is that just part of the pathology of the process we're trying to deal with as to why there is more regurgitation in those sizes or is that

just a red herring?

DR. BACH: At least in looking at the echocardiograms, I wasn't struck with a trend toward that. And I don't know of any correlation with valve size to severity of regurgitation.

MR. CRITTENDON: I have several questions about the technical aspects. One, Dr. Goldman, would you mind talking about who could or who couldn't put these valves in in your institution, and for those who were not initially trained and who subsequently were able to do it, what kind of process they went through?

DR. GOLDMAN: I had had experience with homografts, and so it was relatively easy for me to make the transition to the Toronto SPV valve. As a matter of fact, it was an easier valve to implant because it wasn't as flexible and difficult to orientate as a homograft. Also, once I had learned to do a transverse aortotomy and understood the relationships between the sinotubular junction and the aorta as a functional unit in facilitating leaflet coaptation and valve closure, it became quite straightforward.

I taught one other colleague of mine, a relatively junior surgeon who had had no experience with homografts, and he has put in at least half of the 130 valves that we

now have. I've been involved as an instructor of other surgeons in Canada and this country and abroad, and have really found no trouble in helping surgeons make the transition once they have had the sizing and functional unit sinotubular junction to aorta explained to them.

MR. CRITTENDON: Why were there so few 20, 21 and 22 valves put in? Surely in that time frame, we must have encountered some patients with those. Did you decide to use a different prosthesis? Why is that?

DR. GOLDMAN: Well, I'm sure that happened on occasion, but the mechanism of sizing has allowed us to put in a larger valve so that in those patients who we encountered with a 19 to 21 millimeter annulus, we were able to put in a 21 to 23 millimeter valve and obtain superior hemodynamics, and my associate, George Christakis, presented this at the American Heart last year in patients who had annuli measured at 17 to 19 millimeters and he showed that he was able to implant 23 millimeter SPVs in nine of these patients and achieve superior hemodynamics to a conventional stented valve.

MR. CRITTENDON: You describe using the size of the measure, the diameter at the sinotubular junction, and then again at the annulus. Could you use these same dimensions or measure these dimensions with echo

preoperatively? Is there any correlation between the two?

DR. GOLDMAN: Well, there is excellent correlation and we invariably use transesophageal echo perioperative. We're involved in resident training, and we're involved, as I said, as preceptors. So we tend to use both, and we also like to, we enjoy digging our elbows into the ribs of the echocardiographer when there is discrepancy. But often surgeons will just use the TE without spending any time sizing with the sizer.

MR. CRITTENDON: Is there a technical modification for bicuspid aortic valves?

DR. GOLDMAN: There is no technical modification of the valve, of course, because it comes premade. We were concerned initially about bicuspid valves, but as you know so many of them have a rudimentary cusp in any event, and the only concern really is the proximity of the coronary arteries which, of course dictates the placement of the critical commissural pillar. We have not had any problems once we learned how to cope with adjacent coronary ostia.

MR. CRITTENDON: And one last question about technical aspects. In Attachment No. 1, and this is the St. Jude physician's manual, just a minor point, but it's something I couldn't fathom yesterday. On page three of the physician's manual, it says, note: although an oblique or

hockey stick aortotomy can be performed, it should not be extended below the aortic rim. I'm not familiar with the term aortic rim. And I apologize for my ignorance. Can you describe that, please?

DR. GOLDMAN: I'm not sure what they mean either other than the sinotubular junction.

MR. CRITTENDON: Right.

DR. GOLDMAN: Some surgeons still use an oblique incision. I believe Dr. Pepper does, Mr. John Pepper. Most of us have switched to a transverse aortotomy now for all aortic valve replacement because it gives us such an interesting third dimensional view of the aortic root. And certainly that was one Dr. David's contributions was an understand of the ST junction in sizing the valve in aortic valve pathology.

MR. CRITTENDON: Well, I thought the idea of a physician's manual was great. Just that particular part of it was not clear to me so it probably just needs some reworking. And finally the design. How does this valve differ from the Freestyle Medtronic? I mean I realize that the scallops are cut out, but more specifically I guess about how it's harvested and put together. And then as well maybe the Cryolife O'Brien valve, if you know about that? And then the last question about design, then I'm done, is

we don't see the muscle bar that I think ought to be there. Is that covered, that teflon patch or felt, whatever it is?

DR. GOLDMAN: Taking that question last. In early versions, as this valve was evolving and in Dr. David's experimental work, in a bare valve without any cloth cover, he found that resorption of the muscle bar was a significant problem in the sheep model and came up with the concept of covering the muscle bar with Dacron. So the muscle bar is trimmed as much as it can be, and as you have noted, it can't even be seen because it is covered by that fine polyester Dacron which is wrapped around the bottom which also facilitates the inflow suture line and the orientation at the 120 degree markers.

I can't tell you much about the harvesting except that it is from a well-known laboratory in Saint Hyacinthe, Quebec, which is a large pork producing area, and where other porcine valves had been harvested for a different company in the past. The essence of this valve is that it comes as a scalloped valve and it is meant to be only a scalloped valve for a uniform and reproducible insertion technique without variation.

MR. CRITTENDON: I'm done, Madam Chairman.

CHAIRPERSON CURTIS: Okay. Why don't we stop now and take a 15 minute break before we go around to the other

panel members?

[Whereupon, a short break was taken.]

CHAIRPERSON CURTIS: Okay. Dr. Tracy, could we start with your questions?

DR. TRACY: Okay. Thank you. I'd like to congratulate the company on a very excellent presentation, and the data is very clearly laid out here. I just have a very few questions to ask. Would you in your indications/contraindications, is there any contraindication you can think of? What about a porcelain aortic valve? Is there any place where this particular valve cannot be implanted?

DR. GOLDMAN: We were concerned about calcified aortas or proximal aorta and we were concerned about redos, and neither of those became a problem. Obviously, a porcelain aorta with the entire aorta being calcified is a problem for any kind of valve and any kind of an incision. I would probably not put in this valve or any form of stentless valve in that setting. You may well need to put in a root replacement of some kind.

DR. TRACY: Do you think the issue of calcification, how is that going to play out over time? Any thoughts on that, and would there be any reason to think there would be less calcification with this valve?

DR. GOLDMAN: Calcification of the pig aorta?

DR. TRACY: Of the valve, yes.

DR. GOLDMAN: There is no reason to think there will be less. There is no reason to think there will be more. There is very little aorta left, as you must realize from the design. We are not preserving any other portion of the aorta. And our belief is that the durability of this valve will be enhanced as much by its design and its relationship to the host aorta because the stresses and buckling and abrasion that normally occurs in a stented porcine valve, of course, won't occur in this valve. The leaflets open fully because of the better central flow. The leaflets close more easily with the diastolic pressures being absorbed by the native aortic sinuses. So the mechanisms that we understand for destruction of the collagen and ultimately damage including tearing of leaflets in stented valves are not present because of the design, and we anticipate that that will be the hallmark of prolonged durability.

DR. TRACY: I noticed in the FDA review versus what you have here the percentage of the glutaraldehyde was different. I think it was .2 in the FDA review, and I think you talk about .5. What is it?

MS. BURLEY: It is 0.5 percent glutaraldehyde.

DR. TRACY: Okay. Was there a change or was that just a typo?

MS. BURLEY: No, it always has been. It's a typo.

DR. TRACY: Okay. You present pretty much no data on the smaller sizes, and I take it that's because of the way the sizing is done? You just never use those smaller sizes. Is there really any point in gaining approval for those smaller sizes?

MR. FLORY: I'll answer that from the company's perspective. We readily admit that there was very little data on the small sizes, and there is not a huge patient group that's applicable to those sizes. When we brought the PMA to the FDA, we decided to include those sizes for five reasons. One, that the design and tissue processing and materials are identical across models. Two, that the implant technique is identical across models. Three, that the hemodynamic performance of the valve is excellent across all sizes and the correlation between our in vitro results and in vivo results was very good. So we felt that the in vitro results were predictive of good hemodynamic performance even in the small models.

And fourth, when we did our multi-varied analysis, there was no statistically significant difference across valve sizes that would indicate a problem from one size to

the other, and the last thing is in our Canadian and European sales, these valves even though they're very rarely used do account for somewhere around one percent of the sales, and so we felt that there was a patient group that could benefit from these size valves, and we recognize that there aren't many in the study.

DR. TRACY: I'd just like to get back to a comment that I had made yesterday. I think the data that has been collected on the valves that are presented today would be a very useful starting point for comparative studies in the future, but that's going to be dependent on continued data acquisition as time goes by with these different valves. And one thing I would particularly be interested in--the lead reviewer had questioned whether or not the degree of AR was greater on the larger size valves, and just sort, I agree, glancing through without any kind of statistical analysis, it looks like the high degrees of AR are seen with the larger valves, and I think that maybe an answer can be given to that specifically with what you have or something you can come up with, and that certainly would need to be followed over time.

MS. BURLEY: Dr. Harry Rakowski would like to address this question.

DR. RAKOWSKI: Good morning. I'm Harry Rakowski.

I'm a cardiologist from the Toronto Hospital. I'm a paid consultant for St. Jude and St. Jude has paid my way here. If you look at the--we did the largest cohort of 165 patients at the Toronto Hospital. If you look at the implant sizes for men, they're almost exclusively 27s and 29s; for women, 25 and 27 predominate. And so I don't think that there's a statistical difference between the degree of AI and the various valve sizes.

It would be reasonable to expect that more of the AI is going to occur in the large valve sizes since they were the largest numbers implanted.

DR. TRACY: That's all I have. Thank you.

DR. WEINTRAUB: Most of the questions that I had were asked by other members of the panel or Dr. Crittendon. First of all, I'd like to say again that this was really an excellent book. Reading the PMA, again compared to the three or four years ago when we had three feet high piles of data, was a pleasure. Also, and perhaps this is the difference between Canada and the United States, a comment on the relatively high autopsy rate. It's too bad that Dr. Schoen couldn't get more of those valves back, but the rate seemed to be really quite good.

Perhaps Dr. Sapirstein could answer. I wonder in your review of all the many articles that would be used as

OPC controls, now the freedom from deterioration, Kaplan-Meier curve is really not applicable, I guess, because most tissue valves deterioration doesn't really occur till four, five, six years out, and this is really basically a three year study. Do we have any information on allografts or comparable articles from the allograft literature? There really wasn't anything in the panel pack except for reference to one article.

DR. SAPIRSTEIN: Wolf Sapirstein, FDA. There were some articles associated with allograft implantations in the articles that we provided. And as far as deterioration was concerned, this was picked up in terms of regurgitation and valve replacement and that sort of thing.

DR. WEINTRAUB: Again, address a question about bicuspid valves to Dr. Goldman. Do you, as is recommended with cryopreserved valves, just don't use it in a true 180 degree coronary bicuspid valve?

DR. GOLDMAN: No. We have not abandoned any bicuspid valve in any situation that we were planning to use the SPV valve.

DR. WEINTRAUB: How do you slip around that?

DR. GOLDMAN: Well, the cusp sizes of the pig aorta are not uniform. They are slightly different.

DR. WEINTRAUB: So you can juggle it a little bit?

DR. GOLDMAN: Right.

DR. WEINTRAUB: Question about explants. I didn't tote up the number of explants that there were, but with the fabric outer lining around the valve, I would think it must be awfully hard to get those things out if you have to explant them for some reason; is that true or not?

DR. GOLDMAN: Well, we worried about the same thing, and we had the opportunity to take out one at my hospital. A patient who had typical SBE with I believe a strep or staph albus from a different hospital. The leaflets were destroyed in the manner that a native valve leaflets would be destroyed. The aortic portion was exactly as a normal aorta, and taking it out, we found a cleavage plane where the Dacron had adhered, not dissimilar to taking out an old aneurism graft and it took a little bit of chipping, but the remaining aorta was intact and viable, and a new valve was inserted without any consequence of the patient's native aorta.

DR. WEINTRAUB: On page 3-2, under Indications, it says the Toronto SPV valve is indicated for the replacement of malfunctioning native or prosthetic--oh, I'm sorry--I thought I read somewhere it said bioprosthetic. Is that true somewhere in there?

MR. WENELL: Yes, Dr. Weintraub, there was a typo

in the original panel pack.

DR. WEINTRAUB: Oh, okay.

MR. WENELL: It's been corrected.

DR. WEINTRAUB: Okay. And further to that question, when one explants a prosthetic valve, you're left with a single planar rim. Have you placed many of the Toronto valves in that situation, and how easy or difficult is it?

DR. GOLDMAN: Perhaps other surgeons here have replaced more old valves with the Toronto SPV. We've done a few, and that ridge, which you kind of like to use for your new suture line, we are more aggressive about removing just as we are more aggressive debriding the calcification in a calcific aortic stenosis in order to put this valve in just as you would with a homograft. So we have cut out that ridge in order to get a more flat outflow. And often as not, that's not the level that you want to put this inflow suture line. This inflow suture line is below that.

DR. WEINTRAUB: Below that.

DR. GOLDMAN: It's below the lowest cusp usually or at the level of the lowest cusp.

DR. WEINTRAUB: In looking at Attachment 3, which is the compendium of hemodynamic data, I was struck in looking at some of the other hemodynamic data in the pack,

there were a number of patients who had post-operative what we would call critical aortic stenosis, and they tended to be in the smaller valves, 23s, largely. And the cardiac outputs, as I noted, tended to be somewhat low. For instance, I'm looking--they're not paginated so I guess I can't--but they're in order--192 and 193. These are patient numbers, 303, 311, and I wonder if Dr. Bach could give us some insight into that? Those are, I mean we would say those valves ought to be removed, the patient has got critical aortic stenosis.

DR. BACH: I think in general the valve performed well across sizes. There was a trend that I don't know if the data is in the package that the gradients tended to go down in the first few months out to six months and a year post-implantation and effective orifice area increased. Actually, it was more than a trend. It was a statistical difference. It wasn't a huge change, but a lot of these gradients that were sort of borderline in the smaller valve sizes in the three days post-implant became very acceptable and even attractive gradients and orifice areas by three months later.

DR. WEINTRAUB: Okay. And that's about all I had. With Dr. Allis' comment, did I misunderstand? Did you say there was some talk or at least some thoughts about

abandoning OPCs for valves? That was sort of a throw-away comment at the end of your comments, and I didn't hear it right or would you clarify that?

DR. ALLIS: Steven Allis. The OPCs, they need to be either updated or adjusted in how the method is, and so we're faced with the possibility of doing that or perhaps starting with a new method like I tried to do with the control articles. So with those two choices, you know, I was thinking of going one way or the other or using both, depending on your comments. Abandoning is a possibility; adjusting is another possibility.

DR. WEINTRAUB: Well, using control articles is sort of, I mean it is establishing new OPCs, I guess, isn't it?

DR. ALLIS: Yeah, and they're catered to each valve submission that comes in.

DR. WEINTRAUB: I see.

DR. ALLIS: Because we look at the demographics before we select the articles instead of just picking them blindly.

DR. WEINTRAUB: I've got it. Thank you. That's all I have. Thank you.

CHAIRPERSON CURTIS: Dr. Skorton.

DR. SKORTON: Thank you. I want to join my

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colleagues in congratulating the company and the consultants on an excellent presentation. Before I have just a couple questions, I also want to comment on Dr. Allis' discussion just now and earlier. I repeat my feeling from yesterday that when possible, and it very well was not possible in this case, but when possible, I think the FDA should continue to emphasize the need for randomized prospective trials, and when they're not possible, I think that in a case like this, control articles are the best secondary decision aid, but I think we should not derive statistical data from them nor try to derive p-values, because it's just not a valid way of doing it. So I support your use of control articles as a decision aid understanding that what we're doing is a consensus conference here and not really review of statistically valid controls of any kind.

I have two questions for the company or consultants. I'm sorry these are a bit redundant, but things I'm still a little bit uncertain about. In answer to a question from Dr. Tracy, you said there was no change in protocol for sterilization. Yet, in two places in the book, it talks about difference. On 4-4, in the engineering summary of the process of manufacture, I want to differentiate the fixation, which is obviously .5 percent glutaraldehyde from apparently a change in sterilization

procedure in bioburden reduction where you say in your own document that it was changed from .5 percent glutaraldehyde to two percent glutaraldehyde ethanol and formaldehyde. So for the public record, can you straighten that out for us?

MS. BURLEY: I believe Dr. Tracy referred to the fixation concentration of glutaraldehyde, and that was in error. It's 0.5 percent. We did make a sterilization change early on in the development of this device, and it was at one point two percent glutaraldehyde, and we did change that to a multicomponent sterilant consisting of two percent glutaraldehyde, three percent formaldehyde, and 20 percent ethanol.

DR. SKORTON: I know that that was approved by the FDA and was considered a non-significant change, but can you reassure us and the public that it made no difference in your subsequent microbiological tests?

MS. BURLEY: This multicomponent sterilant showed extremely fast antibacterial reduction. Within minutes normal flora of the native porcine tissue is dead.

DR. SKORTON: Okay. Thank you. And the other one, one more time I want to ask about the issue of calcification. Perhaps Dr. Schoen can comment on this. I understand that in the explants from your statements, you didn't find any evidence of calcification. However, in the

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preclinical studies, which I understand are an animal model, a juvenile sheep, there was substantial calcification. Can you comment on two things for us? One is the applicability of these animal studies? Whether you think that this should cause us very careful surveillance of the valve in the future, and, secondly, I would ask Dr. Rakowski to tell us whether--or Dr. Bach--whether there was any evidence of early calcification in any of the echo studies, and whether you think echo would be a reasonable post-surveillance mechanism, post-approval surveillance mechanism to look for early even if hemodynamically inconsequential signs of calcification?

DR. SCHOEN: I was not the pathologist participating in the animal studies, and I honestly do not have access to the detailed data. So I can comment on specifics that you might tell me, and would be glad to, but I honestly don't know the details of them. In general, we feel that juvenile sheep in a sense represent the most severe environment for a bioprosthetic valve implantation, equivalent to a rather young child, so that this model has grown up as the best measure of calcification both to study the process and to look in a circulatory system at anticalcification therapies.

DR. SKORTON: Thank you.

MS. BURLEY: Can I make a comment, please? We have to reiterate that at the time this animal model was used, an orthotopic aortic stentless valve animal model was not fully developed, and the numerous problems associated with this animal model could likely be the cause of the results that we observed.

DR. BACH: From the echo standpoint, there was no evidence on the echocardiograms that I reviewed of calcification of the leaflets as they were seen. I think the general question is echo a good screening tool to look for calcification? I think it's a fairly good screening tool to look for calcification. There's obviously not the ability to quantify degree of just calcification within a leaflet. It's an excellent tool for looking for hemodynamic consequences of calcification, and that's really the clinical parameter that perhaps needs to be measured is do the gradients change, is there regurgitation, and for that it's an excellent screening tool.

DR. SKORTON: Thank you. In response to your comments, which are the points are very well-taken, I would still have to say that the burden of proof is on all of us to make sure that this doesn't result especially as the FDA summary pointed out and as is expected in this kind of trial, there are not a lot of very long-term endpoints, and

because the hemodynamics of the valve appear so excellent--they really look superb--that's going to be sort of a late phenomenon. And so I think that the burden is on all of us to make sure, given that this is the best animal model and the one that's in the public record, suggesting sort of exuberant calcification, that some follow-up occurs, as you suggested already, in your plans for post-approval surveillance. So in no way to be argumentative with you, but I think the burden of proof is on us to show that this is not going to be a problem as it appears to be worse than in stented valves. Anyway, that's all I have.

CHAIRPERSON CURTIS: Dr. Pluth.

DR. PLUTH: I guess I would like a little more clarification on that calcification and why the comparison between the stented and the non-stented valve is not an accurate assessment in the preclinical trials?

MS. BURLEY: I'd like to ask Bill Mirsch to address this question, please.

MR. MIRSCH: Bill Mirsch, St. Jude Medical, St. Jude Medical shareholder. I'm the director of Tissue Development Programs. At the time that the animal study was done, stentless valves were really just at their inception, and it was felt very strongly that an orthotopic implant would play an important role. Typically, heart valves had

been tested in a mitral position, stented valves being used. But that wasn't possible with a stentless aortic valve. Many of the problems associated with the animal study were related to the animal model. If you look at it, there were issues with the aortotomy healing, fibrosis, and what we found over time is that the growth associated with using a juvenile animal contributes to hemodynamic problems over time.

The cardiac output of the animals go up, and so that sizing the valves is very difficult because you size a the time of implant and that's not the appropriate size for the end of the duration of the study.

DR. PLUTH: Isn't that the same problems with the stented valve?

MR. MIRSCH: Except that the stented valve leaflets are constrained by the stent. They're supported by the stent, and so the hemodynamic profile changes in terms of cardiac output, but the movement of the leaflets is continued to be restrained by the stent. With a stentless valve, as the host aorta grows, the valve is opened up so that the hemodynamic properties of the valve change over time, and we think that may have contributed to the calcification in the first study.

DR. PLUTH: But isn't there not somewhere in this

brochure the fact that you felt that the stented valve or non-stented valve would take some of the stress off the leaflets and therefore decrease calcification?

MR. MIRSCH: That's exactly right in a non-growing aorta. You have an elastic compliance effect that supports it. However, if the aorta grows a disproportionate amount over the duration of the implant, then you no longer have the original sizing in place, and that places stresses on the stentless valve.

DR. PLUTH: I think I also heard this morning that there was a polyester coating, as Dr. Weintraub brought up, that's used to facilitate suturing and tissue ingrowth, and yet I see in this attachment as far as page 17 on Attachment 1, it says it provides a dissection plane making it easier to remove the valve. I guess my question is which way is it? Dr. Goldman, I think you mentioned that you could chip the valve up, but how long after the original valve was it implanted that you took the explant?

DR. GOLDMAN: I believe it was two years. The hope, of course, is that no one has to explant any of them.

DR. PLUTH: Well, it relates to the fact of the calcification, which I don't think has really been totally satisfied to my thoughts, and if this continues, whether or not explantation is going to become a problem in the future.

I also noted that there was limited data on the 19 and 20 millimeter sizes, but I also note that in the sizes say 19, there was a 20, a 21, a 22 and a 23 valve. Yet I heard from you, Dr. Goldman, this morning, that it doesn't make too much difference as far as size. You can take an annulus that's say 17 or 19 and put in a 23 valve. Why do we have all the various sizes at the 17, 18, 19, 20, 21 sizes if you don't need them all at that point, or does this suggest that it's extremely critical as far as sizing is concerned to the insertion of the valve?

DR. GOLDMAN: The last issue that you just mentioned is the essence of the valve, and that is sizing, but the sizings, as you know, are 19, 21, 23, et cetera. And so most of us have experience with those odd numbers. the answer that Mr. Flory gave before about the pig sizes of 19, 20, and 22 are just a matter of what they harvest and there has been some use in the marketplace. I think it's one percent for each of those sizes in terms of their global sales. I'd best leave that up to him. We have not had the occasion to use anything less than a 21.

DR. PLUTH: My question is does it make that much difference between a 19 and a 20 or between a 20 and a 21 if what you stated was correct before?

DR. GOLDMAN: I can't answer that. I have no

experience with those numbers.

MS. BURLEY: It really is just a manufacturing process that those valves are available from the abattoirs, and it's just simply that we can stock them.

DR. PLUTH: Did I also hear this morning on the St. Jude Medical Institute that it was planned as far as lab experience or wet lab experience was concerned, that this was going to be optional depending upon experience?

MR. WENELL: I think what Peggy Malikowski referred to was that that would always be offered as part of the SJM Institute, and dependent on the physician's experience with homograft and their own personal training, additional training could be made available to them.

DR. PLUTH: Well, I bring that up for another reason is that I noticed in your brochure that before you started the clinical trials that all participating institutions had undergone a training session for valve insertion. And I also note that Hospital V, which I think is Victoria, had an eight percent per year incidence of perivalvular leak and yet it had the fewest implants, 58 patient years. Now my question is is this related to a learning curve or is this related to the fact that perhaps their experience wasn't adequate?

MS. McCALLUM: I think it might be a statistical

aberration. We looked at the data. There doesn't seem to be any reason for this. We also looked at the learning curve issue in terms of cross-clamp and bypass times over time, and from the time of each surgeon's first implant through their last implant, there did not seem to be any trend of at the beginning they had high cross-clamp times and over time it decreased. There was no trends noted.

DR. PLUTH: My last question regards that of left ventricular mass, and I think it was stated that there was no data provided on this yet. I would like you to direct your attention later on to an article that came out of 1981 by Cody and all from Massachusetts General Hospital in Boston, and this is 1981, at which they looked at left ventricular mass after aortic valve replacement in patients who had Hancock, Carpentier-Edwards valves, Starr-Edwards valves, and Bjork-Shiley prostheses inserted, and the left ventricular mass index dropped from 170 to 117 from pre-op to post-op. So there is data in the literature regarding that, and I would caution you to use this as a reason for non-stented valves.

CHAIRPERSON CURTIS: Dr. Aziz.

DR. AZIZ: Well, I too must, I think, echo the statements of the other speakers here that it was very well presented data and information, and most of the, I think,

good questions have been asked, but there are a few still left. Again, as I think the data shows that there were very few patients who had size 19 aortic valves implanted. Most surgeons, I think, in the right patient population would obviously try to enlarge the aortic root. What percentage of patients here, despite I think what we've heard, had root enlargement procedures done or would there be any problem in doing the root enlargement procedure where your ST ratio to annulus ratio might be affected?

MR. WENELL: As part of the protocol, we did request that surgeons do not do other concomitant procedures enlarging the root during this study, and I'd like to have Dr. Goldman answer from his clinical experience.

DR. GOLDMAN: We have not done any root enlargements with this valve.

DR. AZIZ: But would you see any problems? I mean obviously when this valve, or similar valves in the past, there may be surgeons who might want to do that. Could Dr. David maybe have something to say about that?

DR. DAVID: Tirone David, the inventor, consultant for St. Jude. I have a contract with them on this valve. The rationale behind the stent is to avoid the enlargement aortic cannulas. As far as sizing is concerned, sinotubular junction is important, but you can't implant this valve if

the annulus is 17, the sinotubular junction 25. At 25, the valve won't go in. There's no, sure, it's flexible. It doesn't have a rigid stent. But you're going to produce severe aortic stenosis by puckering the inflow in the arch cannulus. In my experience, discrepancy by two or three millimeter can be overcome by the flexibility of the inflow, but you can't oversize more than two or three millimeters. I have never done an enlargement with the stentless valve. We use the stentless valve to avoid enlargement.

DR. AZIZ: Actually while you're there, maybe I could ask you another question. I think two percent of the patients had the valve replaced for endocarditis. I guess this valve is sort of somewhat similar to putting an allograft in. Would you, if you had the option, what would most surgeons be advised to do, put an allograft in or is there a suggestion that this may be suitable for patients with endocarditis?

DR. DAVID: In a setting for active endocarditis, I don't think this valve should be used. It contains a Dacron graft. It would be just like a stented St. Jude mechanical. Leaving this topic aside, I happen to believe that homograft is not better than any mechanical valve in endocarditis. If you as a surgeon clean the environment

properly--we have published extensively that extensive debridement and reconstruction of the infected areas is by far more important than the prosthetic valve that goes in. Having said all that, I never implanted the Toronto SPV in an infected environment. I have done the opposite. I have removed one that was infected and implant a mechanical valve.

DR. AZIZ: Yeah. I think it's just two percent of the cases were actually placed in patients who had endocarditis.

DR. DAVID: That wasn't done in Toronto. I don't know if Bernie did any. It was not done in my unit.

MR. WENELL: We collected endocarditis as a medical history, but none of the patients had active endocarditis.

DR. DAVID: I should correct then. If the endocarditis is healed, it doesn't matter which valve you put in, but in view of pus in the arch cannulus, I do not believe this valve is the best alternative.

DR. AZIZ: I think I would probably sort of echo what Dr. Pluth is saying. I think technically this is obviously a little more challenging to implant, and I think

that there probably should be some mandatory stipulation that, you know, surgeons who are going to be putting in, clearly if you've had a lot of homograft experience, this is probably easier, but if you haven't, I think there should be some for surgeons who haven't done that training or participation in a training course. Thank you.

CHAIRPERSON CURTIS: Dr. Domanski.

DR. DOMANSKI: Well, I'd like to revisit the echo data and kind of how that was compiled and thought about and so forth. We talked yesterday about these OPCs and looked at the data and when the data with the valve didn't look quite as good as what was there, we said, well, their baseline variation is such that it's not--baseline, the two populations are really not the same so that's the reason for the difference, and I think that was probably correct. But I think that the data, you know, the data are really just very much observation data.

Now, we go to the echo thing, and I really am concerned about the way that was kind of thought through.

You know we use in clinical trials, one uses core labs in order to assure the data are uniformly evaluated and that the data are as good as possible. In fact, one of the real criticisms of the clinical trial when you present data is that there was a failure to use a core lab. Here there

was a lot of variation in your clinical sites, and you threw out, you decided that, you looked at that and you looked at your core lab, and you threw out the core lab because it was more data, more bad data, but more data nonetheless, at least more variable data.

And I guess I have some real concern about that approach, and I'd like to hear it discussed a little bit more. I'd like to know why that was done because I'm concerned about the quality of data that are presented here as a result.

MR. FLORY: Essentially the history on the core lab, FDA requires a certain number of echoes to be collected from the center and the tapes submitted to FDA. And our feeling was if we are going to collect that sample of echoes, we may as well have those evaluated by a core lab. And so it was not intended at the beginning of the study to have a core lab, and our feeling was that information was good to have. That's when we contracted with Dr. Bach and set up the core laboratory.

As far as the differences between the core lab and the sites, I don't believe that we feel that that's as much of an issue as perhaps you do. Our assessment was that the results weren't different between the core lab and the sites, and as a matter of fact, if we had used the core lab,

I believe the core lab was more conservative in their estimates than the sites were overall.

DR. DOMANSKI: Well, I'd like to hear about the variation then. Perhaps from the echo folks.

DR. BACH: I'll just briefly reiterate one thing that Al Flory said, and that is that at the time the protocol was set up, it's my understanding that core labs were not asked for, and even now I'm not sure that core labs are universally asked for in trials like this. And the core lab provided a measure of certainty that that data that were collected at the individual sites were reasonably derived.

DR. DOMANSKI: But they said that there was a lot of variation at the centers, and there was less at the core lab, so they threw out these sites. I mean I'm not sure why the core lab is, you know--

DR. BACH: The one thing that a core lab can surely offer compared to individual site analyses of echoes is a consistency in how the measurements are done. I think no one would argue that there is some amount of inter and intra-observer variability in any measure no matter how it's derived, invasive or noninvasive. If techniques are performed the same way for all studies, there will likely be less variability than if three different people used their own measurement techniques. That leads to some amount of

variability in individual data.

But if the clinical message that comes from the data is unchanged, I think it's sort of a mute point whether which data are actually used in the cohort. I agree with you. I think that core labs are a good idea. I think that they provide more consistent data. Despite whether core lab data is used or whether site data is used, I think the message is the same though.

DR. DOMANSKI: Well, I think the message for this valve is the same because if you look down the list--in fact, I'd like to do that. If you could go to the attachment--what is it--Attachment 3. It's actually kind of interesting to look at that. I think what we're saying is that the message is the same despite the fact that we don't have really a control population to compare it to, and I think you're right, by the way. I think this is a good valve, probably--I think anyway--and I think when one gets the gestalt of this, or at least when I do, I think this is at least as good a valve as the ones we approved yesterday and stuff like that, and I'm certainly in the end going to be very supportive of approving this valve.

But I am concerned about the data that are coming in because what we're looking at is very--we're looking at devices that have very low complication rates that are

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already out on the market. We're now looking at another device, which has a very low complication rate. In point of fact, the data that are presented would not allow us to know that it wasn't a complication rate that was substantially higher than the stuff that's already out there. So what I'm pushing on and what I'm going to spend probably three or four more minutes pushing on is the quality of data that are being presented to evaluate this kind of device.

As far as your device is concerned, I'm quite supportive of putting it out on the market, but I do want to go through the data. One of the things that strikes me about this is if one looks to the mean gradient, and I'd like your comment about this, if one looks to the mean gradient, that means that what you did was you took a Doppler trace, and you planimetered it. Gradients down in the one or two range are very small Doppler signals, and I wonder if a lot of the variation that you're seeing isn't just the difficulty of people trying to planimeter tiny things. In fact, I even think it make sense to do that?

DR. BACH: I agree. The smaller the number, the likelier there will be a larger percent variation. Electronic maneuvers can be done in obtaining the Doppler envelope.

DR. DOMANSKI: Change the gain.

DR. BACH: Right. Change the gain. Change the scale so that the number looks bigger. That is done variably and can lead to some amount of error. Whether the mean gradient is two or three is a 50 percent variation but clinically of no importance.

DR. DOMANSKI: Right. And the other thing is do you think a continuous wave Doppler across a valve that's giving you a one millimeter mean gradient really is an accurate number at all? I mean you're summing everything along the path. I mean does that mean anything?

DR. BACH: I think so.

DR. DOMANSKI: Other than it's low?

DR. BACH: I think so. And the calculation of the mean pressure gradient took into account the proximal velocity, a frequent assumption that forgotten is that blood has a velocity proximal to the valve, and the mean pressure gradient relies on the assessment of the acceleration--

DR. DOMANSKI: So they did that?

DR. BACH: So we did that.

DR. DOMANSKI: I know it's in the guidance.

DR. BACH: So that one millimeter mercury really is that there was a trivial acceleration of blood across the valve, not that there was no flow across the valve.

DR. DOMANSKI: Okay. Well, I think the variation

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is probably accounted for by the fact that you were looking --this valve has remarkably low gradients. I mean it's, I'm not sure if I just--you know, I mean one doesn't usually planimeter just normal valves. But I suspect you get numbers like this if you just took a normal valve and, you know, kids or something and got this because we can't get much lower than one just doing it. And there is some variation, but there's not very much. And these aren't peak gradients. They are mean. So it's a little bit lower than a peak.

But I would encourage--I must say that I would encourage--where the data are less--these data are so obvious. I mean it's so low that it doesn't, you're right. It doesn't matter from a clinical point what we say with respect to it. But I must say to throw out core lab data to increase the volume of data doesn't strike me as a good maneuver scientifically. I don't have any other questions. I think it's a nice looking valve.

CHAIRPERSON CURTIS: Dr. Gilliam.

DR. GILLIAM: I applaud the presentation by the company. It was indeed very easy to follow this morning. I don't have very much to say. I think many of the questions have been addressed already. I'll just share the concerns that I think all of us have in the back of our minds that

the jury is still out on the overall safety of all of the valves we've looked at, this one included. And there is no way for us to know. Ten years from now we'll all be smarter. I'll defer questions.

CHAIRPERSON CURTIS: Dr. Simmons.

DR. SIMMONS: Yeah. I think everything has been covered, and it is a very nice booklet. I applaud the FDA for putting it together. The only one question I had that I'd like an answer to is the issue of anticoagulation, and you had four hemorrhagic events, but I didn't see in here what the hemorrhagic events were and what the outcome of those four hemorrhagic events. Was it in here somewhere?

MR. WENELL: I'll let somebody else look for it, and I can just tell you we did have four patients that had anticoagulant-related hemorrhages, two of the patients died, and two of the patients--one patient had a series of GI bleeds, and the other patient had very, very severe anemia followed by a GI bleed at a later time.

DR. SIMMONS: So are you still--I mean part of your recommendation is that the patient still be anticoagulated for I think--what was it--six months or three months or something? Is that something that's--

MR. WENELL: I think what the company recommends is that indefinite anticoagulation be used based on the

patient's condition and the recommendation of their physician.

DR. SIMMONS: I have no other questions.

CHAIRPERSON CURTIS: Dr. Hartz.

DR. HARTZ: I have a few comments and questions.

The first is on the labeling in which there is anticoagulation therapy, but I don't see the disclaimer concerning antibiotic therapy for dental prophylaxis. And in regard to that issue, we discussed yesterday this issue of a temporary wallet card, and amazingly to me I find that there is a temporary wallet card dispensed with all of the heart valves that I've never seen before in my entire career. At least maybe in Canada these are distributed to the patient.

We all spend some time with FDA, and I think we'll try to modify this to reflect what anticoagulant therapy and what antibiotic prophylaxis the implanting physician recommends because, again, as we mentioned yesterday, this crucial first 30 days is when the patients have nothing, and hopefully this will begin to address some of the early valve related complications. Maybe we can lower that rate.

All my other questions relate to the issue, and I think I'd like to ask Dr. David specifically some questions, relate to the sinotubular junction. Specifically in

relation to the use of this prosthesis in bicuspid valve which has been alluded to by all the surgeons on the panel already. Are the relationships between the sinotubular junction and the annulus different in bicuspid stenosis than they are in calcific aortic stenosis because that's the group of patients who is most likely to need a reimplantation if there is a problem or later calcification? Is it the exact same relationship and do you change size?

DR. DAVID: Bicuspid aortic valve is a complex disease and I don't think we know enough about bicuspid aortic valve. I would like to submit to all physicians here the bicuspid aortic valve is not a disease of the leaflets. It is a disease of the aortic root. We are looking at this prospectively now because the interest in Ross procedure. The principal indication for Ross procedure in children and young adult is bicuspid aortic valve, and those in Toronto are dilating at five to ten years, dilating because the pulmonary artery is the same origin as the aortic trunk, when the trunk arteriosclerosis, I think, is biochemically abnormal, the fibril and the arterial wall of the pulmonary artery is abnormal.

So bicuspid aortic valve is a complex disease. It's not only a change in leaflets. Truly bicuspid aortic valve is rare where there are two sinuses and two coronary

arteries diagonally opposed from each other. I have operated on over 400 bicuspid aortic valve. I don't think I had ten truly bicuspid aortic valve. Most of them have an anterior and a posterior leaflet, and the anterior leaflet almost invariably has a raffe [phonetic] which is a vestige of a primitive septation that was never completed.

The relationship between size of the annulus and the sinotubular junction bicuspid aortic valve varies. If the patient has--I'm speaking as a clinician now--if the patient has aortic stenosis, it's the same as anybody else. The aortic annulus is slightly larger than the sinotubular junction early in life. As you get older, the sinotubular junction dilates and by the time you are 70, it's larger than the aortic annulus. If the bicuspid aortic valve is being operated on because of aortic insufficiency, almost invariably they have aortictasia [phonetic], and a surgeon can be very aware of this, and something ought to be done to the sinotubular junction of this patient, but frequently, even at 29, it will be too small for them.

So what I do, I tailor the sinotubular junction in these patients. I do not recommend the average surgeon goes out and do that.

DR. HARTZ: My next question relates to do you feel that every implanting surgeon can accurately locate the

sinotubular junction especially when there is post-stenotic dilatation?

DR. DAVID: No. If it exists you can see it. The left sinus is very easy to identify. In Marfan's patients, the sinotubular junction left sinus is almost always there. Left sinus is protected. There's not too much wall tension as in the non-coronary sinus which is the worst one. It's the first of three that disappears as a human acquires the aortic valve disease. It's not very difficult, however, to identify, and then to imagine a horizontal line based on the level of the left sinus. I would say in one sinus, it can do just about every patient regardless of the underlying pathology. Even Marfan's, on the left sinus, usually one can tell where the sinotubular junction is. In other words, where the sinus end, where the ascending aorta begins, and that's a sinotubular junction.

I don't think this valve should be used in Marfan's. I do not believe it should be used in any aortictasia because it is a disease of the aortic root. This valve is really for the old patient who has idiopathic aortic stenosis. That's a perfect valve for those patients.

DR. HARTZ: Now I'm wondering if you've considered a sizer which is shaped more like a ring sizer when you go

to the jewelry store, a blunt-tipped, and the gradations are ten percent apart so that when we sized, if they were within ten percent of each other, we would know that instantly on the basis of one sizer rather than the typical valve sizers that we're so used to using? And if that was the case, if we could keep them within ten percent of each other, sinotubular junction, I mean the annulus being smaller than the sinotubular junction, is there a limit at which over a certain diameter, you would just not use a prosthesis? In other words, the annulus is greater than 27. Would you still--but they're still within ten percent?

DR. DAVID: If it's 29 or 30, I can put a 27, 29 valve in and be happy with that. The coaptation margin is so extensive in this valve because the root is not pressurized unlike what you saw yesterday, where the sinus are pressurized during fixation. So increasing the ratio between leaflet and annulus, this one there is no pressurization of the root at all. So the root actually shrinks during the fixation method. As a consequence, there is more leaflet per square centimeter of orifice than the leaflets had to seal. So minor discrepancy, ten, 15 percent, doesn't produce aortic insufficiency. It's a bit more forgiving like a homograft where the ratio between annulus-sinotubular junction, in there the leaflets are very precise

geometric formula. This one is more forgiving, and when I developed this valve in the early '80s, we developed it with this intention to be more forgiving to the implanting surgeon. So you could use a freehand.

DR. HARTZ: And my final question relates to explantation, especially since the valve is used in relatively large sizes for redo, does this valve really need to be explanted? You're going to go back into an aortic root where the fabric has literally been incorporated and endothelialized into the aortic wall, and you have a fairly big annulus. Has anyone just literally excised the leaflets and placed a mechanical prosthesis when the patient has early calcification? Has that been done yet or would you recommend that? I worry about excising the fabric in the non-coronary sinus and getting into the situation where one might injure the mitral valve.

DR. DAVID: Yeah. I have removed only three stentless valve early. All three, none of them Toronto SPV, by the way. All three are custom devices. I made them myself, implant--from technical errors from one to eight years, I had to explant them. And all three, the whole thing came out very easily to be quite honest. I was concerned, as you, because of the experience. I used a teflon felt, for instance, in the ascending aorta. If you

remove the felt, there is no aorta behind anymore. By analogy, I thought if I remove the Dacron from the intima of the aortic root, the sinus is going to be totally gone and be destroyed, but to my surprise in all three patients I reoperated on, once I removed the xenograft tissue first, Dacron was left in the arterial wall. I peeled the Dacron and the arterial wall was like in a patient Dr. Goldman described, making four in Toronto now, the arterial walls are normal. One patient received another SPV. Another two patients opted for a mechanical valve which did not do anything to the root. It did not seem to be damaged or weakened by the removal of the stentless valve.

CHAIRPERSON CURTIS: I wanted to make a couple of comments. One was that the post-approval study that you all outlined I thought is a perfect model for what we ought to use, and if we just had that page out and handed it to the FDA, I think they could go ahead and do that. It basically summarized what we were talking about yesterday in terms of clinical follow-up, echo, mortality, autopsy data. And I think doing that and just plugging in N equals whatever would be appropriate. I think will work. And it would be a nice way to follow these things up.

Next issue, I'm always interested in hearing about this as a non-surgeon, but some different issues have come

up. For example, one was alluded to was coronary artery anomalies. Would it be contraindicated to implant this valve if the patient had coronary artery anomalies?

DR. GOLDMAN: We haven't found any yet. We've had some interesting times from high take off with right coronary right at the ST junction to coronaries that are very much in close proximity with difficulties getting a commissural post in between in them, but we have not abandoned any because of any coronary artery problems.

CHAIRPERSON CURTIS: Could you envision that? I mean should that be a precaution? Should somebody be concerned about implanting the valve if they knew that somebody had an anomaly?

DR. GOLDMAN: You know like any new technique there is all sorts of events and anatomies that you encounter or pathologies. And a low lying coronary artery requires some adjustment of how you suture the valve in and care has to be taken to avoid injury to the ostia of either coronary in suturing the upper layer. That's no different than a homograft or any other valve.

CHAIRPERSON CURTIS: Okay. The issue of root enlargement came up, and if that is something that is done from time to time in doing aortic valve surgery that roots might be enlarged, it sounds like it's probably not

necessary or not as necessary with this valve because of the fact that it's stentless and you've got the larger orifice. Would it be wise, though, to discourage the idea of doing a root enlargement? Let's say, you know, it sounded like it was a very obvious thing to the surgeons here, but should that be part of the labeling that root enlargement procedures would be discouraged in conjunction with the use of this valve?

DR. GOLDMAN: Well, it's an interesting point because it might distort the anatomy of the aortic root. It hasn't come up in discussion because--

CHAIRPERSON CURTIS: Well, you have to worry about the guy who doesn't know, you know.

DR. GOLDMAN: I know. I know. I respect what you're saying. I don't know that it has to come into labeling or as warnings. I think it comes into part of the teaching program.

CHAIRPERSON CURTIS: Teaching and the education.

DR. GOLDMAN: On how to use this valve because root enlargement comes in because of rigid obstructive stented valves that are 19 or 21 millimeters, and as I've said, we're able to get larger valves in often by using the bulge of the non-coronary sinus and making a portion of this stentless valve superannular.

CHAIRPERSON CURTIS: I think maybe if that were specifically included in the educational process that it was just explicitly stated that that shouldn't be done, and that it's not necessary because of the design of the valve. That would probably cover it.

Along the same lines, the issue of Marfan's, that you would not implant it, and all that came up, and it was interesting. I started to wonder if that, too, should be an exclusion but it sounds like from the wording of the sinotubular junction can't be "x"--you know, it's too much of a mismatch from the aortic root. It sounds like that basically covers it. That's all. It's just not quite as explicit a way. And any surgeon would know that the aortic root is going to be larger in some of those conditions. I think it does include that.

Endocarditis. That was also, it sounded like, oh, no, we wouldn't use that valve if somebody actually had active endocarditis. Is that a contraindication or is that just a surgical decision?

DR. GOLDMAN: I think as Tirone said, it's a surgical decision not to put any artificial material in active purulent endocarditis and the concept of cleaning it out and repairing it and covering it with pericardium then allows you to put whatever you want in. So I don't think

this is any different.

CHAIRPERSON CURTIS: Okay.

DR. GOLDMAN: I think you're right that it's part of teaching and it's part of the literature that we create. One shouldn't think that this is the same as the homograft because there is glutaraldehyde preserved tissue and Dacron.

CHAIRPERSON CURTIS: Right. When there was a discussion before about the OPCs and that some of the literature is outdated, I think today we've had three sets of data between yesterday and today about heart valves, and obviously a lot of this winds up coming, the clinical studies will be part of the publication with the labeling. I think that's a good database to work from for future, and in some cases may be superior to using ten or 15 year old data from the medical literature so that as long as there is no problem with that in terms of confidentiality issues and that sort of thing, I think there could be creation of a very nice data base. It's not peer reviewed in the sense of being in the published medical literature, but there is certainly a lot of people here looking at it very closely and able to come up with a lot of thoughts about analyzing all this information.

Let's see if there are any other comments I wanted to make. I wanted to point out that in the labeling that

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you have for the patient booklet, I really like the description of the valve. I thought it was very clear. It's on page 3-15. I think it's a very nice description for a patient to know what it is they're getting, and it's said in nice lay terms at the top of the page exactly what it is they're getting.

The issue about the echocardiograms has already been discussed. Oh, and then overall with the study compliance on 5-25, even though, I mean I think the presentation was nice. We've got good information and all that. It really comes down to a similar issue to what we talked about yesterday. I'm not quite sure how I understand we could have completed visits, yet the very basic information from a patient about what New York Heart Association class they are doesn't wind up getting obtained. I don't know what the study coordinator is talking to the patient about if they're not talking to them about what they're able to do and what their functional status is.

And so we should aim for as close to 100 percent on all these as possible, and although it's reasonably good, it's not quite as good as it could be in some cases for the longer follow-ups.

MR. WENELL: Dr. Curtis, I'd like to make a comment on that.

CHAIRPERSON CURTIS: Okay.

MR. WENELL: When our case report forms were designed, we put NYHA down as part of the data to be collected at the early post-operative visit which is before discharge. After we started the study, our investigators told us that it's almost impossible to assess NYHA two days after the patient has had heart surgery.

CHAIRPERSON CURTIS: Sure.

MR. WENELL: As far as some of the other ones go, oftentimes at a follow-up visit, the patient was seen by just a study coordinator. At some centers, these were not nurses. We tried to make sure that the surgeons or cardiologists saw the patients for their follow-up visit. However, occasionally they were seen just by the study coordinator, and in those situations often they didn't feel comfortable assessing the NYHA.

CHAIRPERSON CURTIS: Okay. Those were all the comments I had. And we'll go around now and ask if anyone has any further questions for anybody from the company?

DR. HARTZ: I missed one question. You've been pretty explicit about the suture choice but not the needle type. Now, a 4-0 grade of suture is not the usual inflow suture line on an aortic valve replacement. So I want to know if the implanters feel that the size of the needle is

as important as the suture and also obviously for the 4-0 proline diastole? And are you going to make a recommendation?

DR. DAVID: I practice on a capitated system where they get one suture, one needle so they have no choice.

[Laughter.]

DR. DAVID: No, I'm not being sarcastic. I'm very serious. I think they are so bad in Canada they say that's what you can get, the cheapest one you can buy, and we try to make the best of it. It works all right. It's not the--it should be a small needle, a cardiovascular small needle. Bernie is richer. He has a few more--let me say something about this--

DR. GOLDMAN: His hospital is in the downtown. Mine is in the suburbs. We have more choice. We're just using the same 4-0 Tycron as most others are using with a small needle because we're just taking an endocardial bite. It's really just a fixation suture. It's not a hemostatic suture.

DR. HARTZ: I'm thinking there is just less to sew to than we're used to so a smaller needle may cause less injury to the prosthesis.

DR. DAVID: I should add, Renee, in the smaller root, a small needle. Remember the space between a leaflet and the arterial wall is very small in small valves. So if you try to pull a bigger needle it might damage the leaflet. Once you damage the leaflet, the valve you have to replace again. So it has to be a small needle that fits between the cusp and the arterial wall of the xenograft. I imagine what--five millimeter, six millimeter long at the maximum length of the needle. In a larger valve, you can do just about any needle.

CHAIRPERSON CURTIS: Go ahead.

DR. SKORTON: It's not a question, but I'm going to make a suggestion that is slightly counter and so I want to give the company a chance to rebut it now because you'll be away from the table. In general, I'm very much against adding gratuitous stuff to labeling that limits physician's choice, but I think there should be a contraindication about endocarditis because this type of device is still relatively unusual in the U.S. I don't think it's going to hurt the marketing efforts at all, and I think it's an extra safety net for the patient.

So I'm going to suggest that the labeling under contraindications include contraindication to this valve

being put in in active endocarditis, and I want to give the company or consultants a chance to argue with me now as opposed to later when there will be nobody at the table.

MS. BURLEY: We don't have an issue with that.

CHAIRPERSON CURTIS: Go ahead.

DR. PLUTH: Before a question was asked regarding the use of anticoagulants, and I sense that there was a difference of opinion at the table because some people were looking around wondering what the answer was. I wonder if Dr. David would tell us what his practice is as far as the use of anticoagulants in these valves?

DR. DAVID: If my patient requires anticoagulation, I don't use this valve. I put a mechanical valve in and send the patient Cumidan for life. If a patient has a transient bout atrial fibrillation or if he had a stroke where aspirin is better than Cumidan, sure, I will put this valve in. None of my patients were anticoagulated permanently. Two of them had a perioperative stroke, one interoperative and they thought was embolic due to a clot in the atrium. So those patients received Cumidan for the first three or six months and then changed to aspirin. I do not believe this valve requires anticoagulation.

DR. PLUTH: Do you put any anticoagulation on the

first week or two?

DR. DAVID: We do for the first three months. It's routine in the hospital for every patient they are going aortic valve replacement, with any tissue valve, be on aspirin.

DR. PLUTH: Aspirin?

DR. DAVID: Aspirin only. If they can take aspirin. Some of them can't. They take nothing.

MR. VERRIER: Can I make just one further comment about the anticoagulation. Ed Verrier from the University of Washington, and we had one patient who had a hemorrhagic complication from the Cumidan, and if you look at the tissue literature, there is a clear controversy on whether or not you should Cumidanize patients with tissue valves in the first three months. And you can find literature substantiating it or refuting it. In fact, at the recent STS, there's an abstract saying that that's probably not indicated to use anticoagulation just because they have a tissue valve. And most of the time the early thromboembolic events are probably platelet related to the suture lines.

One of the things that you should understand that is an advantage of this valve is that there is no internal suture line that is sitting in the root, i.e., everything is

basically buried essentially in the wall. It goes up against up the wall. So in terms of the theoretical reasons, there's good reason to believe that there will be less of that platelet thromboembolic event in the first three months. We've stopped using Cumidan completely after our initial ten patients and have just used aspirin and have had no complications since that time.

CHAIRPERSON CURTIS: Any other questions or comments directed to the company?

DR. SIMMONS: Well, maybe the recommendation should be reworded some way because right now it says as there is insufficient information to indicate otherwise, St. Jude Medical recommends that patients implanted be maintained on the short-term anticoagulation therapy unless it's a contraindicated. So if you're actually saying you don't recommend anticoagulation but maybe there is a role for antiplatelet agents, maybe it should be changed.

DR. HARTZ: I think that's a crucial point. Do you mean anticoagulation because to us that means Cumidan? It doesn't mean antiplatelet therapy.

MR. WENELL: The copy of the labeling that you have is not the most current copy. I'm not sure how we were working in the interactive fashion with FDA. In the last days we were sending multiple copies back and forth. What I

stated earlier about the company's policy is that it should be up to the individual physician based on his patient's needs is what St. Jude would recommend.

CHAIRPERSON CURTIS: Should it say anticoagulant or antiplatelet therapy then?

MS. BURLEY: If you look under Section 2, the pagination says 3-5, under 8.1, this is the correct language.

MR. SPYKER: Dan Spyker, FDA. Based on what I've heard this morning, I would like to consider including a bit more data under clinical studies as to what antiplatelet agents had been used. I don't know that I have access to it right now, but I'd like to encourage the sponsor to provide it. Put a little bit of data under clinical studies and just refer to that under individualization of treatment because what I've heard today sounds pretty appropriate to me to at least--so rather than make a recommendation, I'd like very much to show the data.

CHAIRPERSON CURTIS: Okay. Okay. I think the company representatives can step back from the table now. Any other internal discussion we want to have here before we start going through our questions? I think that's actually the easiest way to do it. The first thing we've been asked to discuss is do the data presented permit assessment of the

safety and effectiveness of this device?

I gather a consensus that there is enough data here for us to make a judgment about this and if anybody objects to that? Since no one does, let's go ahead and answer the specific questions. The first one is does the following indication section adequately define an appropriate population for use based on the data presented? This is on page 1-3. The Toronto SPV valve is indicated for the replacement of malfunctioning native or prosthetic aortic valves. Any comments from any members of the panel about the indications? Okay.

And then the number three, the proposed--so in other words, we would agree with that. The contraindication section. The Toronto SPV valve is contraindicated for use in patients where the diameter of the aortic annulus is larger than the diameter of the sinotubular junction or where the diameter of the aortic annulus is more than ten percent smaller than the sinotubular junction. Excessive mismatch may cause central incompetence and/or stenosis of the bioprosthesis.

And that would basically cover anybody who has got a dilated aortic root in the wording there. And I had asked some of the questions about the anomalies and all that, and it sounds like it's a fairly apparent thing to a surgeon,

that operation, and would have to be dealt with but doesn't need to be in the labeling. Any comments?

DR. PLUTH: We should include endocarditis in that area.

CHAIRPERSON CURTIS: I guess that's a question. Do we think that active endocarditis ought to be a contraindication?

DR. WEINTRAUB: Perhaps it could be worded it is not recommended that--

CHAIRPERSON CURTIS: Yes.

DR. WEINTRAUB: In other words, there's really no data one way or the other, but it's not recommended that be used.

CHAIRPERSON CURTIS: Is that a warning or a precaution?

DR. HARTZ: That's an interesting phenomenon because unless the surgeon has a homograft, which valve should they use? If you tell them this one is contraindicated, should we put that contraindication on every other prosthesis and insist that--

CHAIRPERSON CURTIS: Surely a mechanical valve is a lot of hardware.

DR. WEINTRAUB: This is different because it's got fabric that's going to be actually sutured over the entire

aortic wall.

DR. HARTZ: But other bioprostheses have fabric.

DR. WEINTRAUB: But--well--

DR. DOMANSKI: Do we have any evidence that that fabric makes a difference?

DR. SKORTON: With all due respect to my colleague, I think what other labelings have occurred in the past is irrelevant to this decision. If you believe it's the standard of surgical practice not to put this valve in active endocarditis, we're talking about aiming these instructions to the lowest common denominator, low experience person, and I think we should call it a contraindication unless you think it isn't contraindicated. I'm only reacting to the bulk of surgical opinion that I heard this morning.

DR. HARTZ: In trying to put this in perspective, the known literature on the early phase of endocarditis after implanting a prosthesis and hearing what Dr. David said and why he would use a homograft as an alternative to this prosthesis, but I'm trying to think what other prosthesis does not carry a risk of infection in acute endocarditis?

DR. WEINTRAUB: If I understand him, he didn't say that he would definitely use a homograft, that he would, the

important thing about acute bacterial endocarditis is debridement.

DR. HARTZ: Right.

DR. WEINTRAUB: But he wouldn't use this valve because it sutures Dacron to the aortic wall around the whole circumference of the aorta. I believe I understand that is what he said, and I would just a priori agree with that. It sounds, it makes sense.

CHAIRPERSON CURTIS: But would a mechanical valve be less risk?

DR. WEINTRAUB: Yeah, because you're only suturing the sewing ring, not the entire valve, to the aortic wall. At least, again, without any experience, that makes logical sense. So perhaps we should just say that it's not recommended that it be used.

DR. DOMANSKI: Could you explain why that? It's not obvious to me.

DR. WEINTRAUB: Well, in any, whether it's a stented biologic valve or a mechanical valve, your point of contact with the potentially infected tissue or at least where there are bacteria are the sutures, the interrupted sutures or the running suture, and the annulus and the sewing ring. With the Toronto valve, you're plastering an entire fabric around the whole circumference of the aorta,

and, you know, we obviously don't know what will happen with that, but I'd certainly worry about it.

DR. DOMANSKI: Well, I mean I would have worried about the other valve, too, but if you need to put in a valve.

DR. WEINTRAUB: Well, but we do.

DR. DOMANSKI: If you need to put in a valve, of course, one does, you know, for hemodynamic reasons, one would, even in a fairly active setting, and I guess I wonder--one wouldn't put that contraindication on every valve because you've got to put something in. The question is what data do we have to suggest that this one is worse is it is just--

DR. WEINTRAUB: We don't.

DR. DOMANSKI: Okay.

DR. SAPIRSTEIN: And precisely addressing that question, Dr. Domanski, we've tried to distinguish in developing this labeling, distinguishing between endocarditis and sepsis as Dr. David brought up. In endocarditis of any form, we just slip in another valve, don't we, and usually if infection recurs, it's a different organism anyway, whereas, in sepsis and actual purulent infection, you have to do this gross debridement. So we didn't think there was a need to contraindicate the device

for endocarditis specifically, but maybe we were incorrect in that.

DR. SKORTON: Let me offer sort of a compromise on this. I think we're intellectualizing too much about this. I think it's relatively contraindicated to put this valve in active endocarditis, period. And so I think that since we gave them a chance to argue, since the person who invented the valve and the company didn't argue, they know more than we do, I would say, and no surgeon here has contradicted the idea that it's relatively contraindicated, so I would suggest that we say active endocarditis is a relative contraindication of this valve, and the reason for doing that is an educational process so the relatively new surgeon doesn't think this is a homograft.

CHAIRPERSON CURTIS: Sounds like we have a consensus there.

DR. DOMANSKI: I'm kind of missing something on that. You don't have a consensus, as a matter of fact, and I apologize for extending this, but I really don't understand that point. I'm not convinced that this valve is any worse than any other valve based on anything that's been presented. The fact that the company didn't argue about it doesn't--maybe they should have--but I don't understand. I don't understand why we're denying this one when you

wouldn't deny the mechanical, and I understand the point about how you sew it in around there, but I'm not sure why that's a cogent reason for being concerned about infection.

DR. SKORTON: I guess when all of us practice, whether we're talking about drugs or devices, we have a portfolio of choices in every patient care situation, and my reading of regulatory compliance on contraindications is that there's two levels of contraindications. There's ones where the manufacturer and the governmental agency feels it's very strongly a bad idea to use the device. The company has suggested and the inventor that a mismatch between annulus and sinotubular junction diameter area is such a one.

The second is gentle guidance that the regulatory agency gives a practicing clinician, helping him or her decide the relative order of choice, and that's what a relative contraindication is: leaving choice to the person but gently reminding them that this might not be their first choice. And to answer your question, the better choice would be one where there is no artificial tissue like a homograft, meaning that that would be the first choice after debridement.

MR. SPYKER: Dan Spyker, FDA. We've had a tendency over the last few years where I've been working

with labeling to be very careful about, very reluctant to put things in, contraindications that are really warnings, and I don't think I can get the idea of a relative contraindication past my colleagues at the next level. This is not something that we've been doing lately, at least. So I think we have every support of putting that in as an indication to the surgeons and users of this device, but I'm reluctant to use the term--we're going to have trouble with the term "relative contraindication." This sounds like a warning to me.

CHAIRPERSON CURTIS: Yes, I was just going to make that point. It sounds like we don't do relative contraindications. It's either a contraindication, a warning or a precaution. You've got to put it in one of those bins, and if so, would you have any problem with putting it as a warning? Okay. I think now we have a consensus.

All right. Number four, patient counseling information. Exact same things we saw yesterday. We might want to strengthen the one about the antibiotics for dental prophylaxis, as we mentioned before, and the wallet card issue has already been discussed. I mean that's all we've gone through, and I don't think we have to rediscuss that unless somebody has any other points.

All right. Number six. I think this may be somewhat more important. Do the data presented support approval of all seven valve sizes? If not, what additional data would be required to establish the indication for the other sizes? As you remember, there were 13 implants of the 22 millimeter and then smaller numbers for 21 and 20 and nothing for 19. Do we want to recommend approval for all the different sizes even though the smallest sizes have no to very limited experience? Go ahead.

DR. SKORTON: As opposed to our earlier discussions we had, I don't perceive any basic manufacturing difference between any of the sizes, the size availability mainly being what's available at the abattoir, and so I'd be happy to suggest approval with a special emphasis on post-approval surveillance, particularly of the small sizes.

CHAIRPERSON CURTIS: Other comments? If you remember, though, yesterday, there were some valves that we turned down simply on the basis of lack of data, and the first valve we talked about, there some difference in possible manufacturing, but there were also some other valve sizes that were similar manufacture, but we basically said if we didn't have the data, we couldn't approve it.

DR. GILLIAM: There were zero implants with those.

CHAIRPERSON CURTIS: Well, the Mitral, the 25, had

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a few, had three follow-ups on, which is more than zero, which is what we're talking about here for at least one of the sizes.

DR. TRACY: The Table 7.2 in their--

CHAIRPERSON CURTIS: Where is that?

DR. TRACY: That's in Tab 2, Table 7.2, on page 3-5, Effectiveness Outcomes. I think unlike one of the other valves we looked at yesterday, I agree this is created the same way. You can expect different hemodynamic outcomes just on the basis of size, but it doesn't sound like there's any different processing or handling of the valve. So the place where the lack of information should be stated, I would think would be in this table that would include something to indicate that there are no data available on sizes smaller than the 20. I mean it should be--I agree that we should allow the flexibility of having the greater number of sizes, even though the data aren't presented, but I think the data doesn't exist, that is, but that should be indicated clearly in this table that data simply doesn't exist on the smaller sizes.

CHAIRPERSON CURTIS: Well, certainly on the 22, there's as much information as anybody had asked on any of the other ones.

DR. TRACY: Right.

CHAIRPERSON CURTIS: But the 21 and 20, I mean we've got one and four.

DR. TRACY: Right.

DR. GILLIAM: Five.

CHAIRPERSON CURTIS: Five. Okay. I don't know if we are being entirely consistent, but it doesn't sound like anybody's got a problem with that.

DR. SKORTON: Well, I just have a question. Are you suggesting a labeling change to indicate to the surgeon that limited or no data are available at small sizes?

DR. TRACY: Right.

DR. SKORTON: Just as a reminder?

DR. TRACY: Right.

DR. SKORTON: I think that's consistent with what we did, if I recall, with the second.

DR. TRACY: It should just be added to that table maybe as an additional item at the bottom.

CHAIRPERSON CURTIS: Okay. Number seven: Is the proposed Specific Patient Populations section specifying three years appropriate? So we don't have any data on patients who have been implanted longer than three years.

DR. WEINTRAUB: Could you put the size statement in that data--there are no data or there are limited data for valves of such and such a size? Does that make sense?

CHAIRPERSON CURTIS: It sounds like it would work to me. Okay.

DR. TRACY: The other question there, why are nursing mothers there? Is that because of anticoagulation? But if we're not recommending anticoagulation, why does it matter?

MR. SPYKER: Dan Spyker, FDA. There have been a couple of categories of special populations that we've been admonished to consider so we just didn't want to leave them out, and this was the logical place in our view to put that information. So we're open to your suggestion, but this will probably be something that will be the same for all the valves.

DR. TRACY: I'm not sure I understand what a nursing mother is supposed to do if she needs a valve?

[Laughter.]

MR. SPYKER: Well, as you probably have perceived, this category of limited data might logically be thought of by some as the next few indications that we're going to support with data. So it's a way of exactly as the situation is here, we don't feel, when we wrote this label with the sponsor, we didn't feel that we didn't want to allow the smaller valves or nursing mothers to be used, but we do need to call attention to the fact that we don't have

the data supporting it either way. So we had nothing special against nursing mothers.

CHAIRPERSON CURTIS: I do note that I think you were looking at page three, 3-5. There it says implants longer than four years, but then on our page 1-5, it talks about three years. Is that a typo somehow or--

MR. SPYKER: Four.

CHAIRPERSON CURTIS: Four. All right. So it should say four in both places. Any other comments on that issue? All right. Number eight: Is the proposed Physician Training section appropriate? Are there any additional points you believe should be included, and we've talked a lot about the fact that there's going to be formal physician training for this.

DR. GILLIAM: That's mandated.

CHAIRPERSON CURTIS: That's mandated, and that covers in better detail more than anything we're going to write down here. Sounds like no one has any problem with that section. Any other suggestions for labeling? Have we forgotten anything?

DR. PLUTH: Is it still mandated or is still optional in some instances?

CHAIRPERSON CURTIS: My understanding was yesterday we were mandating it.

DR. PLUTH: We're mandating it.

CHAIRPERSON CURTIS: I guess it would raise an interesting point, though, if you, this is now the second stentless valve, aortic valve, we've seen for subcoronary implantation. Do you need to attend both training sessions? Are there differences in the way these two things are implanted? Is it different enough?

DR. HARTZ: Actually, the issue that we raised yesterday was that that prosthesis had to be trimmed, and that was the specific new point on the learning curve. In other words, if you attend that one, then the next step is to sew it in like you sew this one in.

CHAIRPERSON CURTIS: Right.

DR. HARTZ: So, no. In that regard, if you've trained on that Freestyle, you would be able to implant this prosthesis. But not vice versa.

CHAIRPERSON CURTIS: Ah, how do we handle that?

[Laughter.]

DR. HARTZ: Sorry.

CHAIRPERSON CURTIS: Suggesting that they attend both programs. I'm sure the second one would be fairly simple if you did know how to do the first. Okay. All right. We're down to Final Questions. Do the data presented adequately demonstrate the safety and

effectiveness of the device as labeled, which would mean we're coming to panel recommendations. In case anybody forgot what we heard yesterday.

DR. STUHELMULLER: All right. Panel recommendation options for premarket approval applications. The Medical Device amendments to the Federal Food, Drug and Cosmetic Act require that the Food and Drug Administration obtain a recommendation from an outside expert advisory panel on designated medical device premarket approval applications that are filed with the agency. The PMA must stand on its own merits and the recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information.

Safety is defined in the act as reasonable assurance based on valid scientific evidence that the probable benefits to health outweigh any probable risk. Effectiveness is defined as reasonable assurance that in a significant proportion of the population, the use of the device for its intended uses and conditions of use when labeled will provide clinically significant results.

The recommendation options for the vote are as follows: option number one, approval, there are no conditions attached; option number two, approvable with conditions. You may recommend that the PMA be found

approvable subject to specified conditions such as resolution of clearly identified deficiencies which have been cited by you or by FDA staff. Prior to voting, all of the conditions are discussed by the panel and listed by the panel chair. You may specify what type of follow-up to the applicant's response to the conditions of your approvable recommendation you want. For example, FDA or panel. Panel follow-up is usually done through homework assignments to the primary reviewers of the application or to other specified members of the panel.

A formal discussion of the application at a future panel meeting is not usually held. If you recommend post-approval requirements be imposed as a condition of approval, then your recommendation should address the following points: (a) the purpose of the requirement; (b) the number of subjects to be evaluated; and (c) the reports that should be required to be submitted.

Option number three: not approvable. Of the five reasons that the act specifies denial of approval, the following three reasons are applicable to panel deliberations: (a) the data do not provide reasonable assurance that the device is safe under the conditions of use prescribed, recommended or suggested in the proposed labeling; (b) reasonable assurance has not been given that

the device is effective under the conditions of use prescribed, recommended or suggested in the labeling; (c) based on a fair evaluation of all the material facts in your discussions, you believe the proposed labeling to be false or misleading.

If you recommend that the application is non-approvable for any of these stated reasons, then we ask that you identify the measures that you think are necessary for the application to be placed in an approvable form.

Option number four: tabling. In rare circumstances, the panel may decide to table an application. Tabling an application does not give specific guidance from the panel to FDA or the applicant, thereby creating ambiguity and delay in the process of the application. Therefore, we discourage tabling of an application. The panel should consider a not approvable or approvable with conditions recommendation that clearly gives described corrective steps. If the panel does vote to table a PMA, the panel will be asked to describe which information is missing and what prevents an alternative recommendation.

CHAIRPERSON CURTIS: Dr. Crittendon, would you like to go ahead and make a recommendation?

MR. CRITTENDON: I move that the panel approve this device with conditions, and the conditions are as

follows: (1) that the FDA and the sponsor agree on some method of uniform collection of echocardiographic data; (2) that the labeling be consistent with the other conditions we laid out yesterday vis-a-vis the temporary card and the mandating of antibiotic prophylaxis for dental procedures, endoscopy, et cetera; (3) that to the warning section that we add the warning for endocarditis, acute infective endocarditis; (4) that the post-marketing analysis should be detailed as described by the St. Jude presentation this morning, and in particular to include post-approval surveillance of the smaller sizes; and then (5) that there be mandated physician training.

CHAIRPERSON CURTIS: I mean it sounds very clear to me. And you're recommending approval for all the sizes?

MR. CRITTENDON: I'm recommending approval for all the sizes.

CHAIRPERSON CURTIS: Okay.

DR. TRACY: Yeah, the only additional thing to that, I would make it clear that the--

DR. STUHLMULLER: From a parliamentary point of view, there's a motion that you need to make a decision to second it.

DR. WEINTRAUB: Second.

[Motion made and seconded.]

DR. STUHMULLER: Now you can amend it.

DR. TRACY: I second or he seconded. But the additional comment that the lack of data on the smaller sizes be contained in the labeling.

CHAIRPERSON CURTIS: So that's an amendment you're proposing?

DR. WEINTRAUB: I'll second that on Robert's Rules of Order.

MR. CRITTENDON: And I'll accept that amendment.

DR. PLUTH: It was brought up before that there was not data as far as anticoagulation was presented regarding this particular group. Was that part of the condition before we accept this or was that or for the future?

CHAIRPERSON CURTIS: I think that's part of the post-marketing.

DR. PLUTH: Okay. That's what I wanted to know. I didn't know if we wanted that prior to that or not.

DR. SIMMONS: I think you had also brought up some points about the physician manual had some errors that you wanted to change about the aortic root.

MR. CRITTENDON: Just the description of the anatomy. This was not the usual anatomic terms. That ought to be included as well. So I would amend a paragraph in the

physician's manual as currently detailed in the panel packet ought to be amended to make the anatomic descriptions more standard.

CHAIRPERSON CURTIS: Do we have a second for that?

DR. SKORTON: Second.

[Motion made and seconded.]

CHAIRPERSON CURTIS: Okay. Everybody's concerns.

No other amendments? All right. Let's go ahead and have the vote. Dr. Hartz?

DR. HARTZ: Approve with conditions.

CHAIRPERSON CURTIS: Dr. Simmons?

DR. SIMMONS: Approve.

CHAIRPERSON CURTIS: Dr. Gilliam?

DR. GILLIAM: Approve with conditions.

CHAIRPERSON CURTIS: Dr. Domanski?

DR. DOMANSKI: Approve with conditions.

CHAIRPERSON CURTIS: Dr. Aziz?

DR. AZIZ: Approval with conditions.

CHAIRPERSON CURTIS: Dr. Pluth?

DR. PLUTH: Approval with conditions.

CHAIRPERSON CURTIS: Dr. Skorton?

DR. SKORTON: Approve with conditions.

CHAIRPERSON CURTIS: Dr. Weintraub?

DR. WEINTRAUB: Approve with conditions.

CHAIRPERSON CURTIS: And Dr. Tracy?

DR. TRACY: Approve with conditions.

CHAIRPERSON CURTIS: All right. And Dr. Crittendon, apparently you have to specifically vote.

MR. CRITTENDON: I approve with conditions as well.

CHAIRPERSON CURTIS: Okay. So the recommendation is accepted to approve the valve with conditions. And before we adjourn--

MR. SPYKER: Could I get a little clarification? Dan Spyker--

CHAIRPERSON CURTIS: Sure.

MR. SPYKER: On your first condition, be working out the echo.

CHAIRPERSON CURTIS: Yes.

MR. SPYKER: Are you talking about follow-up?

MR. CRITTENDON: We've had the discussion about the discrepancy between the core lab and the hospitals. I'm sure there's just some consensus that the FDA staff and the sponsor can arrive at so that you're happy, and then I think if you're happy, we'll be happy with the type of data that's collected in--

CHAIRPERSON CURTIS: I think possibly, rather than saying get echoes on everybody, maybe there should be some

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standardization about the way the data is obtained? Is that what you're saying?

MR. CRITTENDON: Right.

MR. SPYKER: For the future?

CHAIRPERSON CURTIS: For the future.

MR. CRITTENDON: For the future, for the post-market analysis. And is Dr. Grundemeier still here? All right.

CHAIRPERSON CURTIS: He's not here. Okay. Then I think we're finished with our business today. We'll go ahead and the meeting is adjourned. Thank you all.

[Whereupon, at 11:36 a.m., the panel meeting was adjourned.]

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MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
Washington, D.C. 20002
(202) 546-6666