

UNITED STATES OF AMERICA
 DEPARTMENT OF HEALTH AND HUMAN SERVICES
 FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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CIRCULATORY SYSTEM DEVICES PANEL

+ + +

December 6, 2012
 8:00 a.m.

Holiday Inn
 2 Montgomery Village Avenue
 Gaithersburg, Maryland

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MEETING

(8:02 a.m.)

DR. PAGE: Good morning. It's a couple minutes after the hour, and I'd like to call this meeting of the Circulatory System Devices Panel to order.

My name is Rick Page. I'm the Chairman of the Panel. I am a clinical cardiac electrophysiologist, and I'm Chair of the Department of Medicine at the University of Wisconsin in Madison.

I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel participating in the meeting today has received training in FDA device law and regulations.

For today's agenda, the Committee will discuss and make recommendations regarding the 515(i) order issued by the FDA on April 9th, 2009, for non-roller type cardiopulmonary bypass blood pumps, one of the remaining preamendment Class III devices. A non-roller type cardiopulmonary bypass blood pump is a device that uses a method other than revolving rollers to pump blood. Discussions will involve making recommendations regarding regulatory classification to either reconfirm to Class III or reclassify to Class I or Class II.

Before we begin, I would like to ask our distinguished Panel members and FDA staff seated at this table to introduce themselves. Please

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state your name, your area of expertise, your position, and affiliation.

And we'll start over here, please.

MS. McCALL: Debra Gates McCall, Patient Representative.

MR. BARRETT: Good morning. I'm Burke Barrett. I'm the Vice President of Regulatory and Clinical Affairs at CardioFocus, and I'm the Industry Representative on this Panel.

DR. GREENFIELD: Lazar Greenfield, vascular surgery, University of Michigan, Professor Emeritus.

DR. DOTY: John Doty, cardiovascular surgeon, Intermountain Medical Center, Salt Lake City.

DR. BRINKER: Jeff Brinker, Professor of Medicine and Radiology and an interventional cardiologist at Johns Hopkins.

DR. CIGARROA: Joaquin Cigarroa, Clinical Professor of Medicine, Oregon Health & Science University, and I'm the Clinical Chief of Cardiology and an interventional cardiologist.

DR. YUH: Good morning. David Yuh, Chief of Cardiac Surgery at Yale University.

DR. DEHMER: Good morning. I'm Greg Dehmer. I'm an interventional cardiologist and Professor of Medicine, Texas A&M College of Medicine and Scott & White Clinic.

MS. WATERHOUSE: Jamie Waterhouse. I'm a Designated Federal Officer for FDA.

DR. NAFTEL: David Naftel, Professor of Biostatistics and Surgery at the University of Alabama at Birmingham, and my area is biostatistics.

DR. HIRSHFELD: I'm John Hirshfeld. I'm an interventional cardiologist at the University of Pennsylvania, and I'm an interventional cardiologist.

DR. KANDZARI: Good morning. I'm David Kandzari. I'm the Chief Scientific Officer and Director of Interventional Cardiology at the Piedmont Heart Institute in Atlanta, Georgia.

DR. ALLEN: My name is Keith Allen. I'm Director of Surgical Research and a cardiothoracic and vascular surgeon at the Mid America Heart Institute in Kansas City, Missouri.

DR. KATZ: Marc Katz. I'm a cardiac surgeon and Chief Medical Officer for the Bon Secours Heart and Vascular Institute, Richmond, Virginia.

DR. SOMBERG: Good morning. I'm John Somberg. I'm a Professor of Medicine and Pharmacology at Rush University in Chicago, and a cardiologist.

DR. SLOTWINER: Good morning. I'm David Slotwiner. I'm a cardiac electrophysiologist at North Shore Long-Island Jewish Medical Center and Hofstra School of Medicine.

DR. ZUCKERMAN: And, finally, Bram Zuckerman, Director, FDA Division of Cardiovascular Devices.

DR. PAGE: Thank you very much.

As you can see, we have really a terrific Panel here representing the necessary specialties to do the work we have before us today.

I'd like to remind everyone, if you have not already done so, please sign the attendance sheets that are on the tables by the doors.

Ms. Waterhouse, the Designated Federal Officer for the Circulatory System Devices Panel, will make some introductory remarks.

MS. WATERHOUSE: The Food and Drug Administration is convening today's meeting of the Circulatory System Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S. Code Section 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to

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special Government employees who have potential financial conflicts when it is determined that the Agency's need for a particular individual's service outweighs his or her potential financial conflict of interest.

Related to the discussions of today's meeting, members and consultants of this Panel who are special Government employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S. Code Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss and make recommendations regarding the 515(i) order for non-roller type cardiopulmonary bypass blood pumps, one of the remaining preamendment Class III devices. A non-roller type cardiopulmonary bypass blood pump is a device that uses a method other than revolving rollers to pump blood. Non-roller blood pumps fall into two device types, centrifugal type pumps and micro-axial pumps. The discussion will involve making recommendations regarding regulatory classification to either reconfirm Class III or reclassify to Class I or Class II.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of

interest waivers have been issued in accordance with 18 U.S. Code Section 208. A copy of this statement will be available for review at the registration table during this meeting and will be included as a part of the official transcript.

Mr. Burke Barrett is serving as the Industry Representative, acting on behalf of all related industry, and is employed by CardioFocus.

Unfortunately, due to unforeseen circumstances for which no time allowed us to find a replacement, we will not have a Consumer Representative at this meeting.

We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all other participants to advise the Panel of any financial relationships they may have with any firms at issue.

For the duration of the Circulatory System Devices Panel meeting on December 6th, 2012, Ms. Debra McCall has been appointed as a Temporary Non-Voting Member. For the record, Ms. McCall serves as a consultant to the Cardiovascular and Renal Drugs Advisory Committee at the Center for Drug Evaluation and Research. This individual is a special Government employee who has undergone the customary conflict of interest

review and has reviewed the material to be considered at this meeting.

This appointment was authorized by Jill Hartzler Warner, Acting Associate Commissioner for Special Medical Programs, on November 21st, 2012.

Before I turn the meeting back over to Dr. Page, I would like to make a few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting. The telephone number is (410) 974-0947. Information on purchasing videos of today's meeting can be found at the FDA meeting registration desk.

The press contact for today's meeting is Michelle Bolek.

I would like to remind everyone that members of the public and press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until after the Panel meeting has concluded.

If you are presenting in the Open Public Hearing today and have not previously provided an electronic copy of your slide presentation to FDA, please arrange to do so with Mr. James Clark at the registration desk.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time you speak.

Finally, please silence your cell phones and other electronic devices at this time.

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Thank you very much.

DR. PAGE: Thank you.

We will now hear from Marjorie Shulman, M.B.A., Director of Premarket Notification for the 510(k) Program.

I'd like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

MS. SHULMAN: Good morning. My name is Marjorie Shulman, and I'm Director of the 510(k) staff. This morning I'm going to talk about device reclassification and why we're here today.

So what is the purpose of this meeting? To provide input to FDA on whether sufficient scientific evidence exists to develop appropriate special controls to reclassify a preamendments device from Class III to Class II.

What is a preamendment device? It's a device of a type that was introduced into interstate commerce prior to May 28th, 1976, the enactment date of the Medical Device Amendments.

What is the classification process? Recent legislation, FDASIA, has affected the classification of medical devices, including Class III 510(k)s, and FDA must now publish a proposed order announcing our proposed classification and seek public comment, hold a panel meeting if classifying or reclassifying a device type, and consider comments and all available

information, including panel recommendations, prior to issuing a final order finalizing the classification of the device.

What are the device classes? Classification is based on the controls necessary, and a device should be placed in the lowest class whose level of control provides reasonable assurance of safety and effectiveness. So Class I is general controls, Class II is general and special controls, and Class III is premarket approval.

What are Class I devices? That's a category for devices which general controls are sufficient to provide reasonable assurance of the safety and effectiveness. Class I devices typically require no FDA premarket review prior to being marketed.

So what are some of the general controls? Prohibition against adulterated or misbranded devices, good manufacturing practices, registration of the manufacturing facility, listing of the device types, recordkeeping, et cetera.

Some examples of Class I devices: general cardiovascular surgical instruments, adhesive bandages, manual stethoscopes, and crutches.

What is a Class II device? It's for devices that cannot be classified into Class I because the general controls are insufficient to provide reasonable assurance of the safety and effectiveness of such a device, and for which there is sufficient information to establish special controls to provide such assurance. Class II devices typically require premarket notification, a

510(k), prior to being marketed.

What are the special controls? They include such things as performance standards, postmarket surveillance, a patient registry, development and dissemination of guidance, guidelines, et cetera.

Some examples of Class II devices: blood pressure cuffs, percutaneous catheters, electronic stethoscopes, vascular graft prosthesis, ECGs, hemodialysis systems, syringes.

How are special controls used? As an example, PTCA catheters were reclassified from Class III to Class II special controls. FDA issued a special controls guidance to mitigate the risk to health. That included information on biocompatibility testing, bench testing, animal testing, sterility and shelf life, labeling that included warnings, precautions, adverse event effects, et cetera. And then the special controls, in combination with the general controls, provide reasonable assurance of safety and effectiveness. So companies must provide evidence in their 510(k) submissions of how the special controls were addressed.

What are Class III devices? That's for devices that cannot be classified into Class II because insufficient information exists to determine that the general and special controls are sufficient to provide the reasonable assurance of safety and effectiveness, and the devices are life-sustaining and/or life-supporting, or of a substantial importance in preventing impairment of human health, or present a potential or unreasonable risk of

illness or injury. Class III devices require premarket approval, also known as PMA, prior to being marketed.

What are some examples of Class III devices? Endovascular grafts, coronary and peripheral stents, percutaneous heart valves, LVAD devices, cardiac occluders, and implantable pacemakers.

So what are Class III 510(k) devices? Those are preamendment devices where FDA issued a proposed rule classifying them as Class III; however, no final rule was issued, or a final rule was issued for Class III but the rule did not contain a date by which companies were required to submit a PMA. Therefore, these Class III devices are allowed to proceed to market via the 510(k) process until such a time as either a call for PMAs or a reclassification is finalized.

What is the reclassification process? FDA may reclassify a preamendment device in a proceeding that parallels the initial classification proceeding, based upon new information respecting the device, either on FDA's own initiative or upon the petition of an interested person, and the Agency classifies or reclassifies intended uses which have been actually reviewed by the Agency.

So for classification of implants, life-supporting or life-sustaining devices, under 21 C.F.R. 860.93, a panel must recommend Class III for implants, life-supporting or life-sustaining devices, unless the panel determines that Class III is not necessary to provide reasonable assurance of

safety and effectiveness, and can provide the reasons for such a recommendation, including references to supporting documentation and data including identification of the risk to health.

What happens after the Panel meeting? FDA will issue a proposed order proposing classification of the devices and seeking public comment on the proposal. FDA may propose that the device type be reclassified into II, remain in Class III and call for PMAs, or split the classification based on indications or technology. FDA will consider the evidence available, including the input of this Panel and public comments. FDA will issue a final order classifying the device either into Class II, Class III, or splitting the classification.

If Class II, existing devices will be subject to any identified special controls and it may continue to market.

If Class III, existing devices will remain on the market but must submit a PMA by a specified time to continue marketing. If a PMA is not approved, devices will be considered misbranded and must be removed from the market, from distribution.

Thank you.

DR. PAGE: Thank you, Ms. Shulman, for that very clear presentation.

Do any of the panelists have any clarifying questions?

(No response.)

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DR. PAGE: Okay, thank you.

MS. SHULMAN: Thank you.

DR. PAGE: That actually puts us ahead of schedule. Let's go ahead now with the FDA presentation.

MS. WENTZ: Good morning. My name is Catherine Wentz, and I will begin the presentation today regarding the reclassification and regulation -- the classification and regulation -- excuse me -- of non-roller type cardiopulmonary bypass blood pumps.

As with yesterday's FDA presentations, we start off with a reminder of why we are here today. We are here today to discuss and seek the Panel's recommendation regarding the classification of non-roller type cardiopulmonary bypass blood pumps for various intended uses.

As with intra-aortic balloon pumps and external counter-pulsation devices discussed yesterday, non-roller type pumps are one of the remaining preamendment Class III medical devices.

For Class III devices, premarket approval, or PMAs, are typically required for marketing. However, non-roller type pumps are currently cleared and marketed through the 510(k) regulatory pathway, which is typically reserved for Class II devices.

The FDA team will present the available evidence that will be used to determine (1) reasonable assurance of device safety and effectiveness, (2) the risks associated with the use of non-roller type pumps

for the various indications, and (3) whether special controls can be established to mitigate the risks to health.

At the conclusion of this presentation, the Panel will be asked to weigh in on FDA's recommendation regarding the regulation of non-roller type cardiopulmonary bypass blood pumps.

The FDA speakers today will be myself, Dr. Avila-Tang, and Dr. Laschinger.

The outline for the FDA presentation will include the definition of a non-roller type cardiopulmonary bypass blood pump, the device descriptions, the cleared indications and clinical use, and a brief review of the regulatory history, including the current 515(i) order and industry response to that order. Drs. Avila-Tang and Laschinger will then present the clinical evidence, including a summary of the literature search performed and a discussion of the clinical experience with these devices. And I will then wrap up by presenting our recommendation for the regulation of non-roller type cardiopulmonary bypass blood pumps.

Non-roller type cardiopulmonary bypass blood pumps are defined under regulation 21 C.F.R. 870.4360 as follows:

"A non-roller type cardiopulmonary bypass blood pump is a device that uses a method other than revolving rollers to pump the blood through the cardiopulmonary bypass circuit during bypass surgery."

Here are examples of the two types of non-roller type pump

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designs that have been cleared under this regulation, the centrifugal pump design and the catheter-based axial pump design.

The centrifugal pump design is a non-pulsatile, continuous-flow pump that is connected to an extracorporeal circuit between the reservoir and the oxygenator. The pump is available in different sizes and is capable of variable speeds to accommodate the metabolic demands of various patients, for example, neonates and adults. The pump itself is driven by a console that controls the pump via input from the perfusionist. They are labeled for durations of use consistent with cardiopulmonary bypass, which is 6 hours of use or less.

The catheter-based design incorporates the pump and the motor within the cannula, and the entire device is percutaneously implanted into the heart and propels the blood from the inlet to the outlet. For example, this design can be placed with the inlet drawing blood from the ventricle and the outlet positioned in the aorta with the catheter crossing the aortic valve.

The indications for use for non-roller type pumps have evolved over the years, in parallel with advancements in technology and clinical use. An example of the traditional indications for use statement, intended for use as a cardiopulmonary bypass circuit, states that the device is intended to be used in an extracorporeal bypass circuit during cardiopulmonary bypass procedures for periods of up to 6 hours.

The highlighted part of the following indications for use statements have been added to the traditional statements seen in the last slide. These indications for use statements have been cleared more recently, defining circulatory bypass procedures, that is, procedures where no oxygenator is needed. So the circuit is not a cardiopulmonary bypass circuit.

Circulatory bypass procedures are for planned disruptions of the circulation, for example, during surgery on the aorta or vena cava. However, these expanded indications have also given rise, through clinical practice, to temporary ventricular support use during procedures such as high-risk PCI, off-pump coronary artery bypass, and percutaneous valve implantation, which the Agency believes is outside the original intent of the regulation.

The movement away from traditional bypass surgery is illustrated on the next two slides.

This slide shows a schematic of what an extracorporeal circuit looks like when a patient is undergoing a cardiopulmonary bypass procedure. The major components of the circuit include the cannula, reservoir, pumps, oxygenator, heat exchanger, and filters. An extracorporeal circuit used for circulatory bypass, such as surgery on the aorta or vena cava, is a much more simplified circuit including usually only the inlet and outlet cannula tubing and the pump. The pump design cleared and used for cardiopulmonary and circulatory bypass procedures is the centrifugal pump design.

This slide shows two diagrams depicting the use of both a centrifugal pump and a catheter-based axial pump when used for the expanded clinical use of temporary ventricular support.

The diagram on the left shows a centrifugal pump used with specialized cannulae to support the ventricle. For example, the inflow catheter can be positioned in the left atrium via a septal puncture, and the outflow cannula is positioned in the iliac artery.

The diagram on the right depicts a catheter-based pump positioned inside the ventricle, unloading the ventricle by propelling the blood from the ventricle to the aorta.

So as you see, the indications for use for the non-roller type cardiopulmonary bypass blood pump have moved away from the original identification for this device. Additionally, as you will see in the upcoming slides, the risks to health associated with the new technology and the new clinical use differ from the original risks to health identified by the Panel and used to originally classify this device in 1980.

This brings us to the regulatory history for non-roller type cardiopulmonary bypass blood pumps.

Here's a snapshot of the regulatory history for these devices. We are only going to focus on the 1980 final rule, where these devices were originally classified into Class III, and the 1995 reclassification Panel.

Before we do this, however, it is important to note that the

regulatory history, through the 1995 reclassification Panel, only considered the centrifugal pump design because this was the only non-roller type pump design cleared through 510(k) at this time.

The most recent 2009 515(i) order, however, includes both the centrifugal design as well as the catheter-based design, because both technologies have now been cleared under the non-roller type blood pump regulation, with the catheter-based design cleared under this regulation in 2008.

In 1979, the FDA issued a proposed rule to classify non-roller type cardiopulmonary bypass blood pumps into Class III, requiring premarket approval. After a comment period, the Panel's recommendation that non-roller type cardiopulmonary bypass blood pumps be classified as a Class III device was published as a final rule on February 5th, 1980, with the following codified language:

"A non-roller type cardiopulmonary bypass blood pump is a device that uses a method other than revolving rollers to pump the blood through the non-roller type cardiopulmonary bypass circuit during bypass surgery."

The Class III classification was based on the risks to health that were identified for this device at the time. These risks include cardiac arrhythmias or electrical shock, blood damage, variability in stroke volume, and embolism.

The Panel also believed that general controls alone would not provide sufficient control over the performance characteristics of this device, and also that there was not sufficient information to establish a performance standard that could provide reasonable assurance of safety and effectiveness for the device.

In 1993, the FDA issued a proposed rule to establish an effective date of requirement for premarket approval applications for these Class III devices and also to provide an opportunity to request a change in classification in the form of a petition.

A reclassification petition was received in July 1993, and a Panel was convened in August 1995 to discuss the merits of reclassifying non-roller type cardiopulmonary bypass blood pumps from Class III to Class II with special controls.

The Panel believed that there was sufficient information available for centrifugal-type blood pump designs to establish special controls that would provide reasonable assurance of the safety and effectiveness of the device when used as intended, that is, during cardiopulmonary bypass procedures for durations not to exceed 6 hours of use.

This recommendation was based on device experience when used for cardiopulmonary bypass procedures less than or equal to 6 hours, the available data regarding safety and effectiveness, and the special controls that were identified to mitigate the risks to health.

It should be noted that the Panel considered reclassification for the centrifugal pump design only for the cardiopulmonary bypass circuits for periods up to 6 hours.

The risks to health that were identified in 1995 for the non-roller type cardiopulmonary bypass blood pumps include alteration in blood composition, inadequate tissue perfusion, embolism, retrograde perfusion, and duration of use. As you can see, the risks to health changed from the original list in 1980, mainly due to 15 more years of experience in understanding of the technology.

First of all, cardiac arrhythmias or electrical shock were removed because the console and pump heads are being manufactured and marketed separately, and this risk was no longer specifically identified with the pump, but was identified as a risk related to the drive console.

Blood damage was clarified to alteration in blood composition to account for other blood-related issues such as complement activation and coagulopathies.

Variability in stroke volume was clarified to inadequate tissue perfusion, since the ultimate goal is to adequately perfuse the end organs and brain.

Embolism remained a risk to health, and retrograde perfusion and duration of use were added as risks.

A final ruling to the 1993 proposed rule was never issued. And

so, in April 2009, a 515(i) order was issued requesting the non-roller type pump manufacturers to submit safety and effectiveness information to determine whether PMAs should be called for under its current Class III regulation, or whether we have enough safety and effectiveness information to support the down-classification of these devices to Class II, where special controls could be written to mitigate the risks associated with the device.

It should be noted that there is a difference between the 1995 classification Panel and the 2009 515(i) order for non-roller type cardiopulmonary bypass blood pumps. As mentioned before, this 515(i) order now includes both the centrifugal pump design and the catheter-based axial pump design, since both of these designs have now been cleared under this regulation.

Industry response to the April 2009 515(i) order included seven device manufacturers representing a majority of the non-roller type blood pumps cleared through 510(k). The response to the order included the manufacturers' support for down-classifying non-roller type cardiopulmonary bypass blood pumps, as identified in the regulation, to Class II. The recommendation to down-classifying non-roller type cardiopulmonary bypass blood pumps to Class II is predominantly based on the information presented in the 1995 Panel meeting, where the Panel supported Class II, as well as 15 additional years of experience and available data.

The evidence used to support our review to either keep

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non-roller type cardiopulmonary bypass blood pumps in Class III and require PMAs or to reclassify these devices into Class II is based on safety and effectiveness information gleaned from MDR reports, a review of the applicable literature, and clinical experience.

This information is also used to identify the risks to health associated with the non-roller type pumps and to determine whether special controls can be written to mitigate these risks to health.

The MDR reports for non-roller type blood pumps included events related to death, injury, device malfunction, and others. This search was performed on the product code for non-roller type pumps, with 522 reports identified between January 2001 and November 2012.

Assuming a conservative number of cases performed per year is 350,000, the 522 reports identified over approximately 12 years represents a small fraction of cases performed with non-roller type blood pumps. For example, the year 2010 identifies 119 MDR reports for the non-roller type blood pumps. This represents approximately .003% of cases performed that year.

One does need to note the following limitations in MDR reporting, however.

1. Not all events are captured, since this is a voluntary reporting system.
2. These patients undergo a procedure where the pump is one

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component of the extracorporeal circuit. As such, attribution of the event to any single circuit component is difficult.

3. Off-label uses, including long-term use, that is, longer than 6 hours of use, are included in these numbers, since the reports are searched by product code and not by indication.
4. All indications, including bypass and temporary ventricular support, are included in these numbers, again, because the search is done by product code or device and not by indication.

So I'd like to go back to our diagram depicting the use of non-roller type pumps for bypass, including both cardiopulmonary and circulatory, and for temporary ventricular support.

As discussed earlier, the regulatory history, the definition provided in the regulation, and the 1995 Panel discussion and recommendation were based on what was known and cleared at the time, that is, centrifugal pump design and bypass indications. However, as seen here, a potentially new indication for use, for temporary ventricular support, has been introduced for both the centrifugal pump design and the more recent current catheter-based technology.

As we move forward from here, you will notice this delineation in our literature review, in our clinical discussion, the risks to health, and

finally in our recommendation for classification.

At this time I would like to present Dr. Erika Avila-Tang, who will discuss the systematic literature review performed and the methods used.

DR. AVILA-TANG: Thank you, Catherine.

Good morning. My name is Erika Avila-Tang, and I will be presenting the results of our literature review on non-roller pumps that the Division of Epidemiology conducted for this Panel meeting on circulatory system devices.

I will briefly present the objective, methods, and findings, followed by a discussion of the strengths and limitations of this literature review on non-roller pumps.

The objective of this literature review was to provide any safety and effectiveness information on the use of NRPs during surgical procedures not lasting longer than 6 hours for cardiopulmonary bypass, circulatory bypass, and temporary ventricular support.

We conducted two searches of the literature review, published in English, using PubMed. The terms used in this literature review were selected based on the pump type, in this case, non-roller, as well as the type of support these pumps provide. The first search was for the indication of use of cardiopulmonary bypass and percutaneous ventricular assist devices. The second search was for circulatory bypass, using the terms of interest

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listed in item two.

The same exclusion criteria was applied for both searches. Articles were excluded from this review if they were case reports, case series with less than 10 patients, or nonsystematic reviews, for example, letters to the editor or editorials, et cetera. In addition, articles were not included if they were conducted and published before 1990, used NRPs for longer than 6 hours, or provided data only on animals or pumps that were not of interest. Articles that did not present safety or effectiveness endpoints related to the use of NRPs on cardiopulmonary bypass, circulatory bypass, or temporary ventricular support were also excluded from this review.

This slide presents the article retrieval and selection process for cardiopulmonary bypass and temporary ventricular support. There were 930 articles identified using PubMed and the search terms presented before. And out of these, 914 articles were removed from this review based on our exclusion criteria.

In the case of circulatory bypass, we first identified 602 articles, and after using our exclusion criteria, a total of 14 articles were included for the review of this indication of use.

The indications of use of the studies identified included 11 studies for cardiopulmonary bypass, 5 for high-risk PCIs, and 14 for circulatory bypass. In these 14 studies, NRP use was equally distributed for veno-venous bypass in aortic procedures. The 30 studies identified were

publications available from 1990 to this year, and the number of study subjects included ranged from 10 to 4,000.

Eleven studies were identified with relevant safety and effectiveness data on NRP use in cardiopulmonary bypass. The study designs included one meta-analysis, one randomized clinical trial, four cohort studies, and five case series. The studies were conducted among patients in the United States, Europe, and Japan.

The design of the seven studies identified for veno-venous bypass included a randomized clinical trial, a systematic literature review, and five cohorts. Among the seven studies using NRPs for aortic procedures, six of these studies were retrospective cohorts and one a prospective study.

Out of the five studies identified for use of NRPs in high-risk PCIs, one study was a safety and feasibility trial which was not randomized and had no comparison group, and the rest of the studies were case series. These studies were conducted among patients in the United States and Europe.

Before presenting the results of safety and effectiveness, let me take a minute to review some factors that need to be taken into account when interpreting the results of the studies in this literature review.

The lack of a comparison or control group in a study is a big limitation in the interpretation of its results. From its results, we cannot conclude if using NRPs is safer or more effective compared to other types of

support systems or other NRPs. If standard definitions are essential for the comparison of studies using different endpoint definitions, for example, severity, it could lead to erroneous conclusions. If the study is not a randomized clinical trial, the characteristics of the subjects, including the risk profile, had to be controlled for.

Differences in the group subjects' characteristics can introduce confounding, which could result in incorrect results and conclusions. The region where the study was conducted is important to consider, especially if we want to use the results of the studies conducted abroad in patients in the United States, as patients in other countries have access to other types of healthcare systems, as well as potentially different risk profiles.

Finally, although a study could have a comparison group, if its sample size is small, the study could lack enough statistical power to detect differences in endpoints, if an actual difference exists, between the different methods of support used during the surgical procedures.

I would like to start with the results on safety on NRP use for cardiopulmonary bypass.

A meta-analysis of 18 randomized clinical trials obtained pooled estimates for a number of safety outcomes. Patients that underwent a CPB procedure, either using NRPs or roller pumps, had most statistical significant differences in mortality, bleeding, or blood transfusion by the end or one day after procedure. Similarly, most statistical significant differences

were found on other safety endpoints, including cerebral damage, hemoglobin, hematocrit, and other endpoints listed in this slide.

Among the studies evaluating NRP effectiveness for CPB, the most common indicators were duration in the ICU, in the hospital, and on intubation. Among the studies that had comparison groups, most statistical significant differences were found between NRPs and roller pump estimates in the duration of ICU, hospital, or on intubation.

A controlled clinical trial randomly allocated 77 patients receiving liver transplants to have support with veno-venous bypass or not. In this clinical trial, veno-venous bypass was useful in decreasing renal impairment during the anhepatic phase, early postoperative renal dysfunction, and arterial pressure. However, the renal function parameters were similar among both groups at the seventh postoperative day.

The main endpoints regarding safety and effectiveness for aortic procedures were paraplegia/paraparesis, renal failure, mortality, and other cardiac events. All seven studies examined P/P, which could be permanent, temporary, or late onset and range from 0 to 7.5. All seven studies examined mortality, and the rate of mortality was 2% for 30 days, 5% to 9% in hospital, and 9% in the operative period. Only two studies reported renal failure, and the proportion of patients in which this was reported ranged from merely 6% to 7%. A number of other cardiac-related adverse events were also reported. The event rates noted here are acceptable due to

the mortality, and were really expected in this patient population.

These are studies evaluating the use of NRPs among patients undergoing high-risk PCIs. The first two studies had a small sample size and were conducted both in the United States and Europe. Since the completion of this literature review, the PROTECT II study, a randomized clinical trial with 450 enrolled subjects, has been published. Dr. Laschinger will discuss the results of this study, as well as the aforementioned smaller studies, during his clinical review presentation.

We found limited evidence of NRP use compared to roller pumps for high-risk PCI, veno-venous bypass, and aortic procedures. Out of the studies identified, few had a comparison group, and also few studies were conducted among patients in the United States. An additional limitation is that severe adverse events were either not defined or had different definitions.

The data on NRP use for CPB has a number of strengths. First, the CPB review includes a meta-analysis of randomized clinical trials which evaluated the use of NRPs against roller pumps. Secondly, the pooled estimates were obtained from a large sample of nearly 2,000 patients. And, finally, confounding is eliminated if there is a random allocation of the pump to be used for CPB.

Dr. Laschinger will now present the clinical review for NRP use on the indications of use of interest.

Thank you.

DR. LASCHINGER: Thank you, Dr. Avila-Tang.

My name is John Laschinger. I'm a cardiac surgeon and a medical officer in the Division of Cardiovascular Devices at the FDA.

As you are aware, we are here to discuss the classification of non-roller pumps used for cardiopulmonary bypass. As part of this clinical discussion, I will first summarize the clinically important regulatory issues that are essential to consider for the classification and recommendations that will be made in today's presentation.

The definitions of safety and effectiveness are summarized on this slide. There are two important common elements which are highlighted in each definition. First of all, the determination should be made based upon "valid scientific evidence," and second, the determination should be based upon the "intended uses and conditions of use" for the device.

The safety determination is then made based upon whether the evidence shows that the benefits "outweigh the probable risks," while effectiveness is determined by whether or not there is evidence that use of the device will provide clinically significant results "in a significant portion of the target population."

21 C.F.R. 860.7(b) is reproduced on this slide. In the determination of safety and effectiveness for the purposes of classification, four key relevant factors are cited for Panel consideration. These are the

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population of use, the conditions of use and intended use, the benefit/risk profile, and the reliability of the device.

Benefit/risk analysis is a key part of both the safety and classification determinations and is summarized here. Information to be considered in determining overall benefit include whether benefits of a device are clinically meaningful, factors related to the patient and the disease, and the availability of other treatment options.

Overall risk is determined by the type, number, severity, probability, and duration of harmful events and whether mitigations are available.

Using this background, the remaining clinical presentation will focus on the use of non-roller pumps in two general contexts, culminating in a classification recommendation for each.

But first we'll summarize the long history of use and stable technology for non-roller pumps used for temporary bypass indications. In the second we will explore differences in population and indications for use, as well as differences in historical experience and technology, that affect the safety and effectiveness determination and the risk/benefit profiles for non-roller pumps used for temporary ventricular support indications.

Our clinical discussion will focus on standard cardiopulmonary bypass and the types, risks, and roles of non-roller pumps used in these extracorporeal circuits.

Cardiopulmonary bypass, as a whole, is an inherently pathologic state. The major physiologic disturbances elicited while on bypass affect every organ system and are summarized on this slide. Fortunately, these abnormalities have been substantially mitigated, though not eliminated, by constant improvements in circuit technology and biocompatibility and limitation of exposure to periods of less than 6 hours.

Procedures such as percutaneous coronary intervention and off-pump coronary artery bypass have been introduced where a substantial portion of their benefit is specifically derived from avoiding the need for cardiopulmonary bypass.

The necessary components of a cardiopulmonary bypass circuit are shown on this slide, with each component fulfilling its specific need for performance and completion of complex intra-cardiac operations.

Here is how all of those pieces fit together in a typical temporary cardiopulmonary bypass circuit. The extracorporeal circuit provides for the complete bypass of the heart and lungs, to allow the quiet and bloodless field necessary for surgery on or within these structures and their major vessels, while simultaneously oxygenating the blood and providing the blood flow necessary for peripheral organ perfusion.

Despite the complexity of the overall circuit, we are here solely to examine the classification of non-roller pumps for temporary use within this cardiopulmonary bypass circuit.

The role of these pumps is to provide the propelling force needed for pumping blood through both the circuit and the body.

Ideal temporary blood pumps for cardiopulmonary bypass are required to pump blood against resistance at substantial and measurable flows that are adequate for whole-body perfusion. The pump must be manually operable in cases of electric or battery failure. The pump design must be optimized so that trauma to the blood and blood components is minimized and thrombosis is prevented. The ideal blood pump should also be disposable, safe, and reliable.

Roller pumps were first described in 1885. The roller pump was later modified by a 23-year-old medical student adding flanges to prevent tubing creep, and it has remained essentially intact since, as shown. The roller pumps have enjoyed a long history of continuous use within temporary cardiopulmonary bypass since their first use in 1953.

Non-roller centrifugal pumps were first described in 1960 and have several notable advantages, as summarized on this slide. Rafferty used these concepts to devise the magnetically coupled forced vortex centrifugal pump in 1968, which led to initial commercialization for use within a temporary extracorporeal cardiopulmonary bypass circuit in 1976. Centrifugal pumps have finned or vaned impellers, magnetically coupled to a driving console, that are inflow and pressure sensitive so that separate flow measurement devices are

required to assure adequate output.

Within a 6-hour time frame typically employed for temporary cardiopulmonary bypass, centrifugal pumps have the advantage of being less traumatic to the blood, resulting in lower levels of hemolysis than typical for roller pumps used for the same duration.

The way in which the impeller is magnetically tied to the drive console has a significant effect on heat generation and hemolysis with prolonged use. But within the 6-hour temporary time frame being discussed today, these effects are minimal.

Here is a partial list of the most common procedures where use of temporary cardiopulmonary bypass is required or considered within the standard of care. In most of these situations where the procedure is inside the heart or inside the great vessels, open exposure is required, and use of cardiopulmonary bypass is required to make the surgery possible.

Non-roller pumps have also been used to provide the propelling force for blood within temporary extracorporeal circulatory bypass circuits, primarily for open surgical procedures on the extracardiac great vessels.

The most common applications for temporary extracorporeal circulatory bypass are for open surgical procedures on the descending thoracic or thoracoabdominal aorta, where prolonged interruption of the distal circulation is expected. The primary goal for use of these circuits is to

prevent complications related to distal organ ischemia, especially for the kidneys and the spinal cord.

These temporary bypass circuits are simple, with just a pump and inflow and outflow cannulae, and the use of centrifugal pumps in these temporary circuits allows for use of biological coatings so that systemic anticoagulation may be avoided.

Non-roller pumps for temporary circulatory veno-venous or veno-atrial bypass have also been selectively employed during open surgical procedures requiring either reconstruction or prolonged interruption of either vena cava.

When used as a propelling force in temporary extracorporeal cardiopulmonary bypass or circulatory bypass circuits during open surgical procedures on the heart or great vessels, non-roller centrifugal pumps have been proven over a 36-year history of use to fulfill all of the criteria for an ideal blood pump. Importantly, hemolysis is minimized and additional safety advantages are gained, including the ability to trap air and minimize priming volumes.

The four major factors to be considered for classification panels for the determination of safety and effectiveness for classification purposes are again summarized on this slide.

The review of non-roller pumps as the propelling force for blood within temporary extracorporeal cardiopulmonary or circulatory bypass

circuits has shown that the population of use is well known, the conditions of use and indications for use have been well described, the benefit/risk profile associated with temporary use within bypass circuits is well known and favorable, and 32 years of additional experience with non-roller pumps has been obtained since the original 1980 classification determination. The proven technology of these devices is shown to be extremely reliable.

Based on classification considerations specified in 21 C.F.R. 860.7(b), sufficient evidence exists to make a robust and favorable determination regarding the safety and effectiveness of non-roller pumps used as the method to reliably propel blood in temporary extracorporeal cardiopulmonary and circulatory bypass circuits during open surgical procedures on the heart and great vessels. Special controls are sufficient to mitigate risks associated with continued use of these life-supporting devices for these specific populations, conditions, and indications for use.

Since their introduction, clinical use of temporary non-roller pump devices has expanded well beyond the purposes of serving as an extracorporeal blood pump in circuits during procedures requiring cardiopulmonary or circulatory bypass, to procedures where the intended use of the non-roller pump is support of the ventricle during episodes of impaired function.

The use of temporary non-roller pump devices for these ventricular support devices can be divided into two broad categories,

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therapeutic ventricular support and temporary ventricular support.

In general, ventricular support devices for therapeutic purposes are required for ongoing ventricular dysfunction that is not immediately reversible. The general purpose of these uses is to initially stabilize overall hemodynamics and, if possible, allow for elimination of the proximate cause, under ideal hemodynamic conditions, so that natural reparative processes can begin.

In these situations, continued use is then required to support hemodynamics while providing the time and conditions necessary to allow recovery of native heart function or, in the absence of recovery, to serve as a bridge to a decision or to another therapy.

Use of support devices in these situations is anticipated to be greater than 6 hours for hemodynamic stabilization and the recuperative processes to occur, or for a decision for a more invasive therapy to be made, a time period not qualifying for consideration as part of this classification determination. A PMA is required for device approval for these indications.

Today we are concerned with whether adequate information exists to provide sufficient evidence of safety and effectiveness of non-roller blood pumps used for temporary ventricular support indications. In order to be used for these purposes, there are three requisite conditions that must be fulfilled.

First, there must be either ongoing or anticipated ventricular

dysfunction of a transient nature that requires support.

Second, the cause of ventricular dysfunction, whether due to mechanical or physiologic causes, must be immediately reversible so that immediate restoration of normal ventricular function is anticipated and temporary use is achieved.

And, third, when used for these purposes, the device and/or access cannula should ideally be designed to allow percutaneous placement.

The history of temporary support for reversible ventricular dysfunction began with the use of the intra-aortic balloon pump in conjunction with reperfusion for treatment of ST elevation and myocardial infarction accompanied by cardiogenic shock. It was theorized that early intra-aortic balloon pump placement would favorably affect the conditions of reperfusion and maximize coronary artery blood flow, resulting in less myocardial damage and multi-organ failure so that improved survival would result.

The initial results of this strategy of early intra-aortic balloon pump combined with reperfusion, accomplished using thrombolytics, were positive for reduction in mortality. However, subsequent studies and meta-analyses examining a strategy for IABP use during reperfusion of acute MI, accomplished by different treatment modality, specifically percutaneous coronary intervention, have not demonstrated any significant benefit for reduction of infarct size, prevention of multi-organ dysfunction, or reduction

in mortality.

It was then theorized that in the setting of acute MI and cardiogenic shock, a percutaneous temporary ventricular support device, placed at the time of PCI-mediated reperfusion, would be superior to intra-aortic balloon pump due to the improved hemodynamic stability and the additional theoretical improvements in conditions of reperfusion provided by these support devices, and that these benefits would result in improved survival.

Three different technologies for percutaneously placed temporary ventricular support devices have been tested for these enhanced reperfusion strategies, including two using centrifugal pumps with special cannulae to allow either percutaneous placement of ECMO or left atrial to femoral artery bypass. A third technology using a transcatheter approach for insertion of an intra-ventricular, transvalvular axial flow pump has also been used.

In addition to these three, FDA is also aware of literature reports describing other novel catheter-based technologies designed for temporary ventricular support, which reside in different anatomical locations and rely on different mechanisms for propulsion of blood, as well as isolated reports of temporary support devices used for other purposes such as support during high-risk transcatheter aortic valve replacement.

Despite these theoretical advantages, percutaneously placed

temporary ventricular support devices have, unfortunately, not been shown to provide any additional benefit over intra-aortic balloon pump when used during reperfusion of acute MI associated with cardiogenic shock and have been associated with additional risks from both leg ischemia related to the insertion site or bleeding.

In addition, the time of support required for devices used for these temporary support indications with ongoing cardiogenic shock far exceeds the 6-hour window for which temporary ventricular support devices were cleared, ranging from a mean of 24 to 84 hours of support in the studies shown on this slide.

With no proven benefit being able to be shown for either intra-aortic balloon pump or temporary ventricular support used during PCI-mediated reperfusion of acute MI associated with cardiogenic shock, attention has been turned to even earlier use of both balloon pumps and percutaneous ventricular support devices for temporary prophylactic support during non-emergent, high-risk percutaneous revascularization procedures.

In this paradigm, high risk is no longer defined by ongoing myocardial ischemia, cardiogenic shock, or severe hemodynamic instability, but rather by anatomic criteria, including the location of coronary lesions and their severity, in conjunction with depressed LV ejection fraction of less than 35%.

Unfortunately, initial trials evaluating the use of elective

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initiation of intra-aortic balloon pumps in patients undergoing high-risk PCI revealed no substantial benefits for MACCE at 30 days or mortality at 6 months. A recent report of late follow-up of these same patients at 5 years suggests that a late mortality benefit may exist.

Subsequently, trials and registries focused on the theoretical benefits of the prophylactic use of percutaneously placed temporary ventricular support devices during catheter-based revascularization of non-emergent, high-risk coronary lesions has been reported.

It should also be noted that the definition of high-risk lesions used for these trials include those lesions and those ventricular function states where absence of severe contraindicating comorbidities, a Class I indication for surgery, exists.

In this strategy, it is predicted that prophylactic use of a percutaneously placed temporary ventricular support device in a non-emergent, stable patient prior to and during PCI for high-risk lesions diminishes the threat of hemodynamic instability while unloading the left ventricle, thus enhancing the operator's ability to safely perform the more aggressive and thorough catheter-based coronary interventions required for a superior outcome to be achieved.

In order to test this hypothesis, PROTECT II was undertaken as a prospective randomized trial comparing temporary prophylactic percutaneous ventricular support using Impella 2.5 to intra-aortic balloon

pump during non-emergent, PCI-mediated revascularization of high-risk lesions, specifically patients with markers of ST elevation. Myocardial infarction, hemodynamic compromise, severe disease of other organ systems, including renal, hepatic, or peripheral vascular disease, were all excluded.

Despite these inclusion and exclusion criteria where high risk was clearly defined by lesion location and severity, in conjunction with depressed ejection fraction, the average SYNTAX Scores of 30 for each group were in the middle tercile of lesion severity typically seen in the SYNTAX classification system. And this is generally considered, based on SYNTAX trial data, to be a low-risk group for early major adverse cardiac events following non-emergent PCI, especially for left main patients.

Despite the non-emergent status and the exclusion criteria preventing enrollment of patients with several markers for extreme risk for CABG, the actual risk profile for the enrolled patients was notable for the presence of comorbidities sufficiently severe to obtain an STS-predicted risk mortality score of 6%, with diabetes noted in 50%, a history of heart failure in 80% to 90%, and prior placement of an ICD in close to one-third of patients. A significant portion of patients in both groups had undergone prior cardiac surgery. And although heart team evaluation was not part of this study, it is reported that close to two-thirds of patients were turned down for surgery in both groups.

The primary outcome measure for safety and effectiveness

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with a composite endpoint, which included the 10 different clinical outcomes shown here, superiority for the Impella 2.5 device over balloon pump was to be judged for this composite endpoint at 30 days. Data from the publication of the PROTECT II study showed no overall benefit for the Impella 2.5 temporary percutaneous ventricular support device at 30 days, when compared to intra-aortic balloon pump.

As noted on clinicaltrials.gov, the study was confounded by statistically significant differences between the two arms, with regards to the use of atherectomy and the duration of support.

The sponsor terminated the trial after the data safety monitoring board recommended stopping the trial for futility for meeting the primary endpoint based on analysis of data from 50% enrollment. The following major observations by the paper's authors are quoted from the published PROTECT II study, based on the final evaluation of data from 69% of the expected enrollment.

First, Impella use may have allowed or fostered more aggressive use of atherectomy, although the appropriateness and effectiveness of this use remains unknown.

Second, definitive statements regarding the primary endpoint remain speculative.

Third, hypothesis-generating observations were possible, though unproven.

And, fourth, no mortality benefit for the temporary ventricular support device was demonstrated, and the observed mortality in each group was similar to the STS-predicted rate of mortality.

The authors concluded that the 30-day incidence of major adverse events was not different for patients with intra-aortic balloon pump or Impella 2.5 hemodynamic support. However, trends for improved outcomes were observed for Impella 2.5-supported patients at 90 days.

Consideration of all the available evidence brings us back to the four major factors to be critically considered by classification panels for the determination of safety and effectiveness for classification purposes, and they are once again summarized on this slide.

Comparison of each of these four factors for temporary bypass, on the left, and temporary support indications, on the right, shows marked differences. While the population of use for non-roller pumps used for temporary bypass indications is well known and supported, the proper population of use for non-roller pumps used for temporary support indications remains undefined.

Furthermore, use of a temporary percutaneous support device reintroduces risk, related to the use of the device, to procedures whose known benefits are partially or substantially conferred by avoidance of the need for support or bypass devices.

The conditions and indications of use of non-roller pumps in

temporary extracorporeal cardiopulmonary and circulatory bypass circuits are known, and the open procedures on heart and great vessels are only possible with their use. The anatomic location of non-roller pumps used for temporary ventricular support varies in position, based on the device and the technology, and often requires special catheters and cannulae using peripheral vessels for access.

Importantly, the conditions where the use of a temporary support device is appropriate, either for hemodynamically unstable patients undergoing reperfusion or for prophylactic use during revascularization of either high-risk lesions or in high-risk patients, remains unknown.

Evaluation of available evidence shows that the benefit/risk profile for non-roller pumps used for temporary bypass indications is known and favorable.

The benefit/risk profile for non-roller pumps used for temporary ventricular support indications is unknown due to the lack of demonstrated clinically meaningful benefit and an undefined risk profile resulting from relatively short history of use, a lack of clinical evidence regarding safety, and the implications of reintroduction of device risk to procedures designed to avoid their use.

Finally, the technology of non-roller pumps used in temporary extracorporeal bypass circuits has a long history of reliable use with stable technology, while non-roller pumps used for temporary ventricular support

indications have variable and evolving new technologies without a long track record necessary for adequate assessment of reliability.

All of these factors lead the FDA to conclude that there is insufficient evidence of safety and effectiveness for non-roller pump devices intended for use for temporary ventricular support indications. This opinion is mirrored by the current societal guidelines, where a low-level recommendation has been assigned to the use of temporary ventricular support devices for high-risk percutaneous coronary interventions.

In addition, depending on their technology and amount of access, variable additional safety risks may be reintroduced by percutaneously placed support devices intended for temporary ventricular support. The future addition of new technologies, locations, and indications for temporary support devices will also introduce additional risks that may not be anticipated based on currently available devices or technologies.

After reviewing all available data for all non-roller pumps intended for use as life-sustaining temporary ventricular support devices, FDA concludes that the evidence that exists for these device types, as a whole, is insufficient to determine the safety and effectiveness of non-roller pumps used for temporary support indications. FDA recommends retaining Class III status for devices used for these purposes, requiring approval when an intended use is for temporary ventricular or circulatory support.

I'd like to thank you for allowing me to present this. And I'll

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reintroduce Catherine Wentz, who will wrap things up.

MS. WENTZ: Thank you, Dr. Laschinger.

So to wrap up what we know about the safety and effectiveness of cardiopulmonary bypass, circulatory bypass, and temporary ventricular support.

Regarding the safety and effectiveness for cardiopulmonary bypass, there do not appear to be any safety concerns regarding the use of non-roller type cardiopulmonary bypass blood pumps for CPB. And the effectiveness of non-roller type pumps, as compared to roller pumps, which are regulated as Class II medical devices, was similar regarding length of stay in the hospital, in the intensive care unit, and mortality.

For circulatory bypass, the use of centrifugal pumps for temporary circulatory bypass have (1) provided additional margins of safety by allowing for completion of these procedures in a less rushed fashion, avoidance of full cardiopulmonary bypass, and full heparinization; (2) provided for maintenance of distal organ perfusion or RV filling; and (3) reduced transfusion requirements, all without significant reports of device-related complications such as pump thrombus, thromboembolism, or cannulation-related injuries.

Regarding the temporary ventricular support, conclusions cannot be reached with respect to the safety or effectiveness of non-roller type pumps used for temporary ventricular support, such as high-risk PCI, due

to the paucity of publications, lack of non-roller pump-specific adverse event reporting, and the minimal clinical experience.

Based on the literature review and the clinical discussions related to cardiopulmonary and circulatory bypass, the following risks to health are identified for the bypass indications: alteration in blood composition, inadequate tissue perfusion, embolism, duration of use, fluid leakage, adverse tissue reaction, and infection.

Again, as you can see, there are differences between the risks to health identified in 1995 and the risks to health identified today. For example, retrograde flow has now been incorporated into the embolism risk, which now includes both thromboembolism and air embolism and is associated with the proper use of the device.

Fluid leakage, adverse tissue reaction, that is, making sure that the material, surface finish, coatings, et cetera, are biocompatible, and infection, with respect to device sterility, have all been added since 1995, based on the last 15 years of experience and additional data available.

FDA believes that these risks to health can be sufficiently addressed with special controls, as identified in this table. For example, alteration in blood composition can be addressed through bench studies evaluating dynamic hemolysis potential, complement activation, blood cell counts, et cetera, as well as labeling that will outline proper use of the device to assure that the device is operated in a way that best mitigates alteration in

blood composition and function.

It should be noted that future device evaluation for this recommended use will not generally include clinical data.

Based on the literature review and the clinical discussions related to the use of non-roller type blood pumps for use in temporary ventricular support, the following risks to health are identified: alteration in blood composition, inadequate tissue perfusion, embolism, duration of use, fluid leakage, adverse tissue reaction, infection, structural/tissue damage, local heat generation, and flow dynamics.

Fluid leakage, adverse tissue reaction, and infection are the new risks associated with non-roller type pumps as compared to 1995 and as discussed in the risks to health associated with the bypass indications also.

Structural or tissue damage, local heat generation, and flow dynamics are new risks associated with the non-roller pump designs when used for ventricular support.

FDA believes that the risks to health associated with non-roller type cardiopulmonary bypass blood pumps used for temporary ventricular support cannot be sufficiently addressed through special controls. That is, the lack of information and clinical understanding regarding the use of non-roller type cardiopulmonary bypass blood pumps for temporary ventricular support precludes our ability to write the special controls needed to assure safety and effectiveness when used as intended.

It should also be noted that under the circumstances where we are not sure of the clinical benefit, the Class II paradigm is not well suited to assess this point. The 510(k) paradigm will suggest that a device is equivalent to another Class I or Class II device legally on the market. However, clinical benefit will not be established.

So we conclude our findings. The FDA would like to recommend that non-roller type blood pumps, when used for cardiopulmonary and circulatory bypass procedures, be down-classified to Class II with special controls with the following identification provided in the regulation.

"A non-roller type cardiopulmonary and circulatory bypass blood pump is a device that uses a method other than revolving rollers to pump the blood through an extracorporeal circuit for periods lasting 6 hours or less for the purpose of providing either (a) full or partial cardiopulmonary bypass" -- that is, the circuit includes an oxygenator -- "during open surgical procedures on the heart or great vessels, or (b) temporary circulatory bypass for diversion of flow around a planned disruption of the circulatory pathway necessary for open surgical procedures on the aorta or vena cava."

The FDA would like to recommend that non-roller type blood pumps, when used for temporary ventricular support procedures, be classified as Class III, requiring premarket approval with the following identification provided in the regulation.

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"A non-roller type cardiac support blood pump is a device that uses any method resulting in blood propulsion to provide the temporary ventricular assistance required for support of the systemic and/or pulmonary circulations during periods when there is ongoing or anticipated hemodynamic instability due to immediately reversible alterations in ventricular myocardial function resulting from mechanical or physiologic causes." The duration of use, again, would be less than or equal to 6 hours.

Thank you very much. And this concludes the FDA presentation regarding the recommendation for the regulation of non-roller type cardiopulmonary bypass blood pumps.

DR. PAGE: Thank you, Ms. Wentz.

I want to thank the FDA for a very clear and efficient presentation.

I'd like to now ask the Panel if there are any brief clarifying questions for the FDA. Please keep in mind that the Panel may also ask FDA questions during Panel deliberations later in the day. So I'll now open questions up to our panelists.

Dr. Hirshfeld.

DR. HIRSHFELD: One very quick clarification. The third indication, which is temporary ventricular support lasting more than 6 hours, not associated with procedures, could you clarify what the FDA's position is on that indication?

MS. WENTZ: Sure. Thank you.

COURT REPORTER: Would you say your name, please?

MS. WENTZ: I'm sorry. Yes, this is Catherine Wentz.

So the use of the devices for greater than 6 hours is not within the scope of today's discussion. So today's discussion is just the short-term use, 6 hours of use or less. The greater than 6 hours of use is already regulated as a Class III device that requires premarket approval.

DR. PAGE: Dr. Allen.

DR. ALLEN: So as a follow-up on that, because they are interrelated, less and greater, are there current non-roller pump devices that have gone through the PMA process and the FDA has approved for use for durations greater than 6 hours?

MS. WENTZ: With the current centrifugal pump design, no, we have not approved the current centrifugal pump design for longer than 6 hours. There are ventricular assist devices that have been approved and are on the market, but not of this design.

DR. PAGE: Dr. Kandzari.

DR. KANDZARI: Thank you.

Catherine, a couple quick questions and then one comment, just to follow up on the 6-hour issue. I didn't hear it in the regulatory presentation.

What is the history around 6 hours? We understand that there

may be greater risks beyond that, with regard to thrombosis and other issues, but what is the magic number of 6?

MS. WENTZ: That's a great question and something that we've asked ourselves as well.

So when we dug back into the definitions and the regulations, the regulation, as you saw in my slide, was originally designed for cardiopulmonary bypass, and the general length of that procedure was 6 hours maximum. So that's where that 6 hours of use or less number came up, because it was originally designed -- that regulation was originally designed for cardiopulmonary bypass.

DR. KANDZARI: So mostly on the historical precedence of things?

MS. WENTZ: Correct.

DR. KANDZARI: My question for you is that yesterday, in our discussion of other devices that may provide circulatory support, FDA had suggested one of the risks was failure to identify the appropriate patient population, and I notice that that is missing here.

And given that there may be other indications or uncertainties regarding the contraindications of this technology, would FDA recommend that that be included into the risks for this technology?

MS. WENTZ: That's a good question. That's something that we hadn't considered, but we certainly can.

DR. KANDZARI: And my final is -- I'll reserve the rest of it for deliberation, but my final, just as a comment for Dr. Laschinger, as a fairly minor point but, I think, important one is that in these high-risk PCI trials, when we have patients who have advanced left ventricular dysfunction, a high rate of chronic kidney disease, the SYNTAX Score itself is predictive of late-term outcomes but not necessarily of procedural outcomes. Still, at the higher end of the intermediate tercile, we would consider this a high-risk patient population, not a low risk.

DR. PAGE: Thank you.

Dr. Yuh and then Dr. Naftel.

DR. YUH: Thank you very much for a very thorough presentation.

A question in terms of your analysis. Did you find that combining the catheter-based, i.e., Impella, device with other types of pumps in that classification, and the different characteristics, non-roller pumps, i.e., centrifugal heads, the difference in characteristics might be problematic in making further comparisons and classifications since the characteristics of those two classes of devices are quite different?

MS. WENTZ: Right. So this is a little unique in that we are distinguishing that there are now two different technologies as well as indications for use. So there is a distinction in the technologies, and the centrifugal pumps can only be used for the bypass indication. The micro-axial

pumps are not currently designed for use with an oxygenator and cannot be used for cardiopulmonary bypass. But both designs can be used for the ventricular support. So we had to make a distinction in intended use, as well.

Does that answer your question?

DR. YUH: Yes, thank you.

MS. WENTZ: Okay.

DR. PAGE: Dr. Naftel.

DR. NAFTEL: I'm going to try not to take it personally, but I didn't get a microphone today.

(Laughter.)

DR. NAFTEL: I'm sure that's no reflection on yesterday.

Just a quick detail question. The literature review looks really complete. Whenever you do a literature review like this and you come across a meta-analysis, that makes you real happy because you look at all of the papers they found and you can match it to the papers that you found. So I see that because you ended up with a very few number of papers to actually look at, and the meta-analysis found 18.

So I'm just wondering if you excluded those 18, if you called those duplicates, or did you review them formally and also the meta-analysis formally?

DR. AVILA-TANG: Yes, thank you for a great question.

No, we --

COURT REPORTER: Your name, please.

DR. AVILA-TANG: I'm sorry. I'm Erika Avila-Tang.

No, we, yes, checked the trials that were included in the meta-analyses, but we just considered the results of the meta-analyses since they were already covering or including consistent or more consistent outcomes, if that answered your question.

DR. PAGE: Dr. Naftel, did that answer your question?

DR. SANSING: Hi, I'm Dr. Veronica Sansing, and I also worked in regards to the literature review.

For the systematic literature review, we had extremely tight inclusion and exclusion criteria. We did compare the ones that were included into the meta-analyses, but we have listed our exclusion criteria for those points. So yes, a comparison was made, but we did have several cutoff points which limited our scope in terms of the meta-analyses scopes.

Does that answer it? Okay.

DR. PAGE: Thank you.

Dr. Somberg.

DR. SOMBERG: Could the FDA take me through the rationale of their dichotomy between for bypass surgery versus for these other uses of the pump systems?

And what I mean specifically is that yesterday we down-classified the intra-aortic balloon and we felt there were adequate special

controls for that situation. Now we have here a very large study compared to what we've dealt with in the past, with PROTECT II looking at the intra-aortic balloon versus these pumps, and there really was not a significant difference. I know they were looking for superiority, but there really wasn't. They looked at multiple factors here.

So if we have one group that behaves similar in terms of outcomes here, et cetera, then we're really saying that it's not that they're not comparable, it's just that we're lacking special controls.

Why are we lacking? What is the difference between the two situations, between intra-aortic balloon and the centrifugal pumps?

MS. WENTZ: I expected that this is going to be the majority of the discussion today, because this is a very difficult concept.

So yesterday we had a discussion about intra-aortic balloon pumps, which have been on the market for over 30 years. We've got significant information and data for that device type, and the risks are known and low. So we're able to understand that device better and we're able to come up with the mitigations or the special controls that mitigate those risks.

For the new technology, for the non-roller type cardiopulmonary bypass blood pump, this PROTECT II study was published 2 months ago. We have very little data. That's pretty much it that we've got on that device type, so we don't know the risks. We're unable to write the special controls to mitigate risks because we don't know the risks.

Does that help?

DR. SOMBERG: I'm still a little confused because, yes, the PROTECT study was the comparative component, but we're talking about these devices, and they go back to '95, if I'm correct, in the centrifugal pumps for these indications and when they were approved, et cetera. So we're talking about drugs that were -- drugs, I always say drugs. I'm sorry. It's in my genes.

(Laughter.)

DR. SOMBERG: But we're talking about, what, 17 years or so. So I would think that's a long exposure and that you have -- the engineering people would have the compatibilities, the other characteristics, the inflations, the pressures, the leaks, the ventings, et cetera, et cetera.

MS. WENTZ: Okay, I see where you're coming from. So you're not talking about the new technology introduced.

Again, this is Catherine Wentz from the FDA. I'm sorry.

So you're specifically talking about the centrifugal pump technology that's been on the market longer, correct?

DR. SOMBERG: I'm talking about the special controls that would permit you to mitigate the risks and provide for a down-classification, because now we have new data saying, you know, that the intra-aortic balloon pump and these centrifugals from the PROTECT II seem to be about the same in terms of outcomes and risks.

So I'm saying, with that new information that's out there, plus a decade of experience with the centrifugal pumps, why is it different that we don't have the special controls?

MS. WENTZ: Okay. So the risks are different for the different devices. All right. So the risks are not going to be the same for an intra-aortic balloon pump as they are going to be for the non-roller type pumps. Okay. So there's the difference there.

For the non-roller type pump of the centrifugal design, yes, they have been on the market longer and probably used for this indication since the late '90s or so. Again, we don't have data. There haven't been studies. We don't have data that shows us -- that validates for us that the use of centrifugal pump designs or the micro-axial type pump designs used for temporary ventricular support is safe or effective. And, again, we don't have -- it's unknown what the risks are because we don't have that data.

DR. PAGE: Dr. Somberg, does that satisfy your question?

DR. SOMBERG: We'll get into this in the discussion, but it's obviously a PA point.

MS. WENTZ: I'm sure we will.

DR. SOMBERG: I don't agree.

DR. PAGE: One other, perhaps, clarifying issue might be that I think you were asking about the comparison. You made note of the fact that the balloon pumps, yesterday, were granted a Class II, but we have a

comparison in PROTECT II of the non-roller pump with the balloon pump.

And I think I might ask Dr. Laschinger to just comment on the fact that the indication, in terms of the PROTECT II, for balloon pump was in the setting of specifically for ventricular support for elective procedure and where that fits relative to the data for balloon pumps, in the first place, relative to the non-roller pump.

DR. LASCHINGER: Yes Yeah, I think --

DR. PAGE: Dr. Zuckerman.

DR. LASCHINGER: John Laschinger, FDA.

DR. ZUCKERMAN: After Dr. Laschinger, if I could explain.

DR. LASCHINGER: Okay.

DR. ZUCKERMAN: Thanks.

DR. LASCHINGER: Yes, I think we have a few different things going on here. First of all, remember, yesterday we down-classified the balloon pump due to a couple of important factors, mainly not that the data was overwhelmingly positive for the outcomes being changed by intra-aortic balloon pump use.

In fact, I think most of the studies we discussed yesterday, and the Panel yesterday, all recognize that robust data for a favorable effect on outcome wasn't present, but rather that there was a 35- to 40-year history of use, that the technology was stable, it was no longer evolving in any meaningful way, and that special controls for the manufacture of these

devices and the use of these devices could be adequately determined such that the practice of medicine could determine its use appropriately.

In the case of non-roller pumps we have primarily two devices. A total of three studies have been done with less than 600 patients total, and none of the studies have shown a benefit of any of the devices over currently available technology.

There are differences also in how these devices are used. Some of these are used for reperfusion. Primarily, the intra-aortic balloon pump studies are used for reperfusion in those with ongoing cardiogenic shock. And those uses, even if you want to use the other devices, as we saw with the TandemHeart and the Impella device, that when you use it for reperfusion with ongoing cardiogenic shock, the expected use is well outside the 6-hour window. It ranges from 24 to 84 hours. And when you use it for prophylactic use in revascularization, that's what we're talking about here today, is the temporary, less than 6-hour support device. So I think those are all important distinctions.

For the temporary uses, again, we have one study, the PROTECT II study. It was recommended to be stopped by the DSMB. The company followed those recommendations. And we don't think that the data from that trial gives us comfort in being able to write special controls necessary for the device or knowing how it's going to function when it's used in a general form in the general population.

DR. PAGE: Thank you.

Dr. Zuckerman and then Dr. Katz and Dr. Allen.

DR. ZUCKERMAN: Okay, Dr. Somberg has raised a very important question. Certainly the Panel, after hearing the industry presentations, also will need to think about this very important question. But I do want to underline two key things that the FDA speakers have noted.

Number one, when talking about a reclassification to Class II, we're talking about a class of devices. Reference has been made to the PROTECT II trial, which involved one device. But remember that there is more than one device that we're talking about, and that's a challenge.

As Dr. Laschinger and Ms. Wentz have pointed out, do we know enough clinically and from an engineering preclinical perspective to really define the box that we're talking about for appropriate Class II regulation? So that's one point.

The second point that may be helpful to Dr. Somberg and others is, when we go back to Slide 98, Ms. Wentz has defined the differences between risk to health between bypass and ventricular support.

Do you need any more clarification on that, Dr. Somberg, or anyone else?

DR. SOMBERG: If you're trying to say that there are additional concerns between the two categories, the point is taken. But that still doesn't address the issue that if we down-classify one system because it's

been around for a long time, there was very little information, but there was adequate special controls. And then this other system's been around for a long period of time as well. It's hard for me to understand. And that's my question. I was trying to get the basic rationale behind, after a decade of availability of this system, that we don't have special controls and now we have a study, which is fairly large, showing similar outcomes.

So I was just trying to focus in on the special control differences. Yes, there's a list of them there, but I'm surprised, after a decade, we don't have some parameters to be able to establish special controls for that device. And so I don't think having more on a list on the right side and the left is really the answer.

Sorry, Bram.

DR. PAGE: Ms. Wentz.

MS. WENTZ: Yes, I'd just like to make maybe one more clarification point that might help.

So in yesterday's discussion we determined that the risk profile for the intra-aortic balloon pump was known because of all the data that we had, correct? Right. In that patient population.

So even the older technology for the centrifugal pumps, even though they may have been around for 10-plus years in temporary ventricular support indications, we have no clinical data. We've got nothing to go to, to review, to analyze and determine that we understand the risks for that device

in that patient population.

DR. PAGE: Next is Dr. Katz, then Dr. Allen, then Dr. Kandzari.

DR. KATZ: Given that the centrifugal pumps in a variety of different designs for extracorporeal use have been used for quite some time and those are recommended to be down-classified, and that the FDA recently approved an implantable centrifugal pump for long-term use, I wonder why the extracorporeal group is being looked at as being kept as Class III and what the differences are there.

MS. WENTZ: Okay, I'm actually not familiar with the implantable one. That wasn't in my review pile. But if we --

DR. ZUCKERMAN: Okay, but for clarification to help Ms. Wentz, I think you're referring to a recent LVAD approval for a micro-axial type design.

DR. KATZ: Well, it's a centrifugal design, the most recent one.

DR. ZUCKERMAN: Okay.

DR. KATZ: HeartWare.

DR. ZUCKERMAN: HeartWare, yeah.

MS. WENTZ: Okay. So an approval is based on a clinical study and data that we've reviewed and analyzed and understand, and it comes to panel and we discuss the merits of approving it.

Again, this design being used in a different patient population does not have a study. We don't have any data to go to, to make an analysis,

to make a determination.

DR. ZUCKERMAN: Or perhaps, Dr. Katz, does this help you?

The device that you're talking about, and technology that you're talking about, went through the regular PMA process because we just don't have the tools available to consider it appropriately through a Class II regulatory pathway. It's a good example.

DR. KATZ: I understand that that device went through it, and I understand there are pictures of three different extracorporeal centrifugal devices that were shown that have been used and that are being suggested to be down-classified for cardiopulmonary bypass-type utilization.

But I guess I'm not understanding the difference in the thought process, saying those same extracorporeal devices, when used for ventricular support, are not adequate, when here's a device of similar technology in an implantable scenario, that's being suggested to be used for a long-term device, well over 6 hours, is approved. And maybe it's my lack of understanding of the physics here, but there just seems to be a real dichotomy in the thought process of how we're classifying things.

MS. WENTZ: Again, this is Catherine Wentz. I keep forgetting to tell you my name.

So, again, the HeartWare device was in a very specific patient population, okay, and the PMA was designed to demonstrate a clinical benefit for clinical utility. The temporary ventricular support using a similar design is

used in a very different patient population. You can't extrapolate the fact that even though it's used longer and it's in a different patient population, you can't assume that that's going to work for a shorter amount of time in a patient population that's different than what has been approved.

So we need that PMA data. We feel that we need that PMA data, that clinical data, to demonstrate a clinical utility and demonstrate clinical benefit in that patient population, even though the design is the same.

DR. ZUCKERMAN: Okay, Dr. Katz and other Panel members, I think that that's very helpful, Ms. Wentz's comments. We have Matt Hillebrenner, our Deputy Director for the Division of Cardiovascular Devices.

I think, did you want to make a statement, Matt?

MR. HILLEBRENNER: Sure. Matt Hillebrenner, Deputy Director, Cardiovascular Devices.

So I think that we may be miscommunicating on kind of how -- the questions we're trying to answer here, as well as how the approval process may go.

So the HeartWare device was approved as a Class III device through the premarket approval pathway. What we're asking for your input here on today is not whether or not certain technologies can be approved based on available data, or cleared, but to make sure we're distinguishing the

right pathway. And so there's nothing to suggest that an extracorporeal device technology couldn't be approved for a use less than 6 hours.

But the question is, should it go through the Class II 510(k) pathway and have a clearance process pathway versus are we not in a position where we can create special controls such that premarket approval is required and that that is the threshold for getting on the market?

And so I think that there's been a lot of information provided by the team to suggest that our recommendation is that we don't have sufficient information to down-classify this device class in those uses. So we would put it in that Class III bucket, and it would be regulated similarly to how longer-term support devices, such as the HeartWare, might be regulated. We're not trying to preclude that possibility. We're not saying it can't be approved for that, but that we need the data to support that.

Does that answer your question?

DR. PAGE: I think that satisfactorily answers the questions right now.

Dr. Allen.

DR. ALLEN: I think I want to get back to what Dr. Zuckerman said, because I think what he said really is important. And maybe as a surgeon, if I could kind of summarize what at least I think the FDA's position is, at least as I understand it.

I think there is still a lot of confusion among panelists about the

bucket that includes non-roller pumps. So, for example, when Dr. Somberg is talking about the PROTECT II, he references centrifugal pumps. The centrifugal pump was not used in the PROTECT II trial. It was an axial flow pump.

So these are not interchangeable devices. They are put in differently, they function differently, they have different outcomes, and we have to continue to think about that and not confuse what's in the bucket, which I think is what's happening.

So what I'm hearing the FDA say is that you have a wealth of information about centrifugal pumps, over 30 years, for short-term cardiopulmonary bypass in conjunction with an oxygenator, or without an oxygenator, to do a ruptured aneurysm of the descending thoracic aorta or to resect a portion of the IVC in a kidney tumor, for example. And you're asking, based on that wealth of data just looking at centrifugal pumps, is that that be reclassified as Class II.

You then move on to this little bigger bucket of non-roller pumps, which includes both centrifugal and axial flow pumps that are being used for short-term left ventricular support. The axial flow pump can't be used for cardiopulmonary bypass. You can't tie that into an oxygenator. It doesn't fit in that category I just talked with you about.

So now what the FDA is saying, we don't have a wealth of information about using a centrifugal pump or an axial flow pump for short-

term left ventricular support. And in the FDA's opinion, because we don't have that comfort like we had with an intra-aortic balloon pump yesterday, that that should remain as a Class III device, Class III indication, and those devices should go through a PMA.

Does that summarize things for you?

MS. WENTZ: Do you want a job?

(Laughter.)

MS. WENTZ: That was fantastic. That's exactly what we're trying to portray.

DR. PAGE: Dr. Allen, thank you very much for synthesizing very well the problem at hand today. So I think you got it exactly right, and I hope everybody was listening to that carefully.

Dr. Kandzari.

DR. KANDZARI: Dr. Allen, can you repeat that, please?

(Laughter.)

DR. KANDZARI: Catherine, in our endeavor to reconcile what seems to be inconsistencies, I do want to ask you, it does seem clear about the paucity of data with regard to many of these other more complex indications. But whereas yesterday we were talking about the balloon pump and acknowledging that the data had been, at best, inconsistent with the use of the balloon pump, everyone agreed that the device itself has a merit in improving hemodynamics and there's a lot of data that would support that.

Similarly, for the non-roller pump devices we do have, I think, fairly convincing evidence suggesting the same, and I think that should be pointed out to the Panel. And, in particular, maybe it's a matter of nomenclature, but instead of ventricular support, I'm still a little challenged on the indication or the classification regarding circulatory support for this, or hemodynamic support.

And, in particular, although it was not addressed in Dr. Laschinger's slides, there is a small study, ISAR-SHOCK II, that has suggested that non-roller pump technologies may provide similar, if not superior, hemodynamic metrics compared, again, with the balloon pump, sample size notwithstanding.

So do you discount that we don't have sufficient evidence to say that these devices do provide hemodynamic circulatory support?

MS. WENTZ: Again, a very good question.

So yesterday's discussion did revolve around, towards the end, if you remember, the initial studies with IABP. Before all the new technologies and new drugs were introduced and PCI was introduced, the IABPs actually showed mortality benefits. And then, as these other therapies were introduced, the ability of the IABP to show a benefit was reduced down to what we could find, is that it still provides hemodynamic support.

So what I'm understanding that you all did yesterday is you accepted that amount of effectiveness based on the fact that we knew the

risks very well for intra-aortic balloon pumps, correct? Do I summarize that pretty well, from yesterday?

So the intra-aortic balloon pumps did show, early on, that there was a clinical benefit, that there was a benefit in mortality. So that mechanism of action was understood and it showed a clinical benefit.

The devices that we have today for the temporary ventricular support, we don't have that history. We don't have information on the clinical benefit and we don't understand the risks, so we can't write special controls for risks that we don't know. We're unaware of the risks as compared to intra-aortic balloon pumps, where we knew the risks and we could accept the hemodynamic effectiveness. We don't know the risks for the devices used for temporary ventricular support, so we can't write special controls. And then we don't know what kind of effectiveness to accept for unknown risks.

DR. KANDZARI: So you would say that the devices do provide hemodynamic support, but you just don't understand the risks?

MS. WENTZ: Okay.

DR. PAGE: We'll have time for discussion, hopefully.

DR. LASCHINGER: Yes, I think you can say, yes, that in theory the devices do -- they're designed to provide hemodynamic support. In theory, that's what they're designed to do. Whether or not they are successful in that, you know, obviously intuitively you would say yes, they

are, but I'm not sure that there's data to say definitively, yes, they are. Certainly not one that provides a mortality benefit based on that hemodynamic support.

DR. PAGE: May I remind the panelists not to speak among themselves. Everything should be limited.

DR. LASCHINGER: So the question becomes whether or not the hemodynamic support was (a) necessary and (b) whether or not the fact that it was delivered had a desired effect. And that's what we need to find out by doing further studies.

And, secondly, -- in order to establish what degree of effectiveness you need to see to justify the risks, we have to know both of those sides of the equation, and right now we don't have enough data for either side of the equation in MI.

DR. PAGE: Dr. Allen, your microphone is still on, but I'm going to move on to Dr. Cigarroa.

DR. CIGARROA: So, in contrast, in terms of IABP versus these newer devices, either the centrifugal or the micro-axial devices, it is clear that the newer generation devices -- and there is data, physiologic data -- improve hemodynamics to a far greater extent than intra-aortic balloon pumps. And they certainly unload the left ventricle to a far greater degree than the intra-aortic balloon pumps.

Similar to intra-aortic balloon pumps, the ability to

demonstrate in today's era, over a high-risk patient population, which patient will actually benefit in terms of a reduction either in biomarker myonecrosis or death is challenging.

Is it the FDA's position that the distinction here, unlike the intra-aortic balloon pump, is a discomfort with downgrading because our clinical experience is distinctly different, i.e., decades of experience with the balloon pump versus a relatively recent introduction to the marketplace of these other devices?

MR. AGUEL: Fernando Aguel, FDA.

I wouldn't say that it is just based on that. But I think the 35, 40 years of experience with the intra-aortic balloon pumps gave us a comfort level that we knew all the risks involved, which we don't have with the relatively short history in the catheter-based micro-axial type pumps.

DR. CIGARROA: When we look at registry data that has been reported both in the United States and in Europe, and when we look in the clinical trials, to me it seems that risk with the different types of devices, whether it's transseptal with two cannulae or whether it is retrograde with a micro-axial system, is known and that is we know that there are inherently vaster complications associated with delivery. We know that there are infection issues, we know there are bleeding. And one can go on down the line. And those have been well delineated.

It seems to me that, in the published data, what is challenging

is which patient actually benefits, not the issue of risk. The risk is well known for all of these different components.

So as I hear the concerns focused on risk, to me, more of the issue is, apart from the hemodynamic benefit based on the public literature, who is it that actually benefits in the hard endpoints of periprocedural infarcts and/or survival, relative to a technology that's been around for three or four decades? And that is IABP. Can you comment on that?

MS. WENTZ: So I'd like to comment on your statement that the risks are known. I understand. And what you just repeated were adverse events. And we're going to go back to that discussion that we had yesterday, risks versus adverse events.

So the risks are related to the device type in the certain patient population, and that's what we don't have enough information on. Adverse events we may understand in that population. But the specific device type used in that patient population can bring up different risks than adverse events, and that's what we don't know.

DR. PAGE: Thank you.

Dr. Slotwiner. And then Dr. Katz has another question.

DR. SLOTWINER: Thank you.

I just wanted to point out that it's sort of been implied as we've talked about the technology changing from the bypass pumps to the centrifugal pumps and then the non-rollers and the micro-axial. But along

with that change in technology, there's been a vast change in the size of the device and the ease of use. And we're already starting to see that because these micro-axial ventricular support devices are so easy to use, that they're being used in situations where they would never -- the other devices would never have been used before. And I know, in the electrophysiology laboratory, they're now being routinely used for, for example, ventricular tachycardia ablations.

So I think that this change in patient population that we're going to continue to see evolve is another reason why writing special controls at this point would be difficult as the technology is evolving.

DR. PAGE: Thank you, Dr. Slotwiner.

You said that in EP labs it's universal. Can you expand on that, in terms of what frequency is being used? Is the device being used in high-risk VT ablation and whether there are any data to support that?

DR. SLOTWINER: Sure. It's certainly not universal and I would be reluctant to give you a percentage, although it certainly is somewhere in the double digits. Patients who have ventricular tachycardia, that's difficult to map. And so the ease of use of these, the Impella, for example, allows the electrophysiologist to induce the ventricular tachycardia and have the patient remain in the arrhythmia while we use our three-dimensional mapping techniques to try to understand the mechanism and critical portion of the circuit for that particular patient.

DR. PAGE: Thank you.

Dr. Zuckerman.

DR. ZUCKERMAN: Yeah, I think, not going off on a tangent, but Dr. Slotwiner's comment again underlines the key point that Dr. Allen reminded us of. We're not here to just talk about one device, as opposed to a class of devices in this discussion today. And while it's interesting that for particular devices we might see interesting applications, it just underlines the problem that the FDA team has when you go to does this apply to all devices or special controls and then indication and et cetera. And I would just ask the Panel to remember that we're trying to talk about a class of devices today.

DR. PAGE: Thank you.

Dr. Katz.

DR. KATZ: So that's a good segue into where I think my thoughts are finally getting.

I'm just wondering if -- it seems to me like the centrifugal pumps and this micro-axial technology are very different, both in how they work and the longevity that they've been on the market and do they have to be considered in one basket like that, because I think they may fall out very differently in both the experience level, the amount of data that's available, the utilization, all of those factors.

MS. WENTZ: So the way we set it up, they do need to be considered in the same basket, because it's the basket -- the basket is the

intended use. Now, don't forget, those centrifugal pump designs are currently out there on the market for the bypass indications but can be used for the other. So if the other goes Class III, the centrifugal pumps will still remain on the market for the Class II indications. This will just give them two regulatory pathways for two different types of intended uses, that's all.

DR. PAGE: Did that answer your question, Dr. Katz?

And if I may amplify, if I'm correct, that also implies that the baskets would be separated if, subsequently, any devices -- if this were a Class III, they'd be coming in independently with separate PMAs, separate panel deliberations for that specific technology, for that specific indication; is that right?

MS. WENTZ: Correct.

DR. PAGE: Yes, Mr. McCall.

MR. BARRETT: Burke Barrett.

DR. PAGE: Barrett. Sorry.

MR. BARRETT: That's okay.

This may be a little difficult to answer, but I think it would be interesting to get some insight into this challenge you had of drawing the distinction between well known and not well known and you had to make a call.

But can you give us some insight into any -- how the process happened and the thresholding? Were there any quantitative measures?

What would've made the difference in you saying the risks were not well known, to making them more well known? Is it the years of experience? Is it the amount of literature?

I'm sure that it was challenging, but just for the industry to try to get some insight into that process.

MS. WENTZ: So I'll let Dr. Laschinger speak to some of that. But all of the above. We don't have written down a specific threshold and what we use to get to that threshold. This is complicated by the fact that there is only one study, and that one study was stopped early and showed no effectiveness. And they missed their primary endpoint, and that's why it was stopped.

So there was nothing there for us to hold onto, either, and there was nothing before that. And we have no other data. I think if the other study had a different outcome or if we had additional data, it may have changed the picture.

Do you want to --

DR. LASCHINGER: Yes, I think in the one case you have 35 years of use in probably close to 300,000 patients per year and less than 100 MDRs in those patients, which suggests that, overall, the device has a wealth of experience out there with very few reported risks to health. It serves a specific function within a larger bypass circuit and performs that function very well and very reliably.

And also, in the first group we know the patients it's to be used in. They are patients who are requiring open procedures in the heart or the great vessels, and you need it to divert the blood or bypass the organ that you're operating on.

In the second case, we don't know the indication. We don't know if it's best used for reperfusion or revascularization. We don't know if it's best used electively or for patients with a real hemodynamic need. We have, as Catherine said, basically one study in the case of the Impella to hang our hats on and two studies in the case of TandemHeart to hang our hats on, none of which showed any significant benefit over an intra-aortic balloon pump. And the Impella, in particular, is hard for us to evaluate because of the circumstances of how that trial came to an end.

So when asking us what we had to evaluate, I think there are two totally different groups of data. We don't have a threshold to say one is good and one is bad. When you look at the totality of all of the data available on both sides of the coin or however, I think we're comfortable on the one side, that we can write special controls for a pump in a bypass circuit so that we can reasonably say that it is safe and effective when used in that fashion. And the other side, we do not have sufficient information that would allow us to write special controls to guarantee the safety and effectiveness of that device in any known population or for any specific use.

MR. AGUEL: Fernando Aguel, FDA. If I could just add one other

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comment to that, to what John was mentioning.

I'd just like to remind the Panel that we're here to talk about the whole class of devices and not just individual devices, and based on some of the data that were collected on individual devices, whether or not we can apply that to the whole range and classification of devices.

And just to add another note to answer your question, it is a difficult decision, figuring out what that benefit/risk is, and that's the reason we're here today before a panel of experts.

MR. BARRETT: Could I add one quick follow-on, Dr. Page?

DR. PAGE: Yes, please, quick.

MR. BARRETT: Yesterday, when we were discussing special controls, one of the special controls that's available are postmarket studies.

In this process, given the ventricular support indication, did you consider the possibility of a Class II with a special control of some sort of postmarket work?

MS. WENTZ: So it's correct, we did discuss that. And if you remember, postmarket studies are not to be used to collect safety data. And that's what we're missing. We're missing the information needed to make a determination on risk and the safety of the device. So I don't think we can use postmarket studies to gather that information.

DR. PAGE: Thank you.

We're scheduled to break in 5 minutes, but in the meantime,

let's see if we can handle questions from Dr. Somberg and Dr. Yuh.

Dr. Somberg.

DR. SOMBERG: Yes. This is to Dr. Laschinger. I've heard you several times talk about, well, the study was incomplete, it didn't show superiority, which is its intent, et cetera.

But why are you focusing on that, as opposed to that we have a sizable controlled population where we show there's not a distinct increase in adversity and there's a similarity of effect in the database?

Sure, the DSMB recommended stopping for futility, because their goal was superiority. But if we say the intra-aortic balloon has a certain degree of efficacy and all of this extent, and then we have that it's futile to try to show superiority, but it's not a formal non-inferiority study, but it does provide that sort of insight, why are we focusing on superiority?

DR. LASCHINGER: If you look at the 10-component endpoint that the futility was for, it also included safety measures, which we got incomplete data on. And in any prospective randomized trial that is stopped early, it's very hard for us to use that as definitive information to make a complete judgment on the benefit of the device, as opposed to its risks. So the data itself, for us, although interesting, it's really at this point in time insufficient to stand on its own to make that determination.

DR. ZUCKERMAN: Could I just add something?

So, Dr. Somberg, there are two principal responses. Number

one, the study is a difficult one to analyze on its own for this particular device. And then two, given that, can it really be generalized to tell us risk versus benefit profile for the whole bucket of devices in non-roller pumps?

And those are some of the difficult questions that the Panel will be asked to think about this afternoon.

DR. PAGE: Dr. Yuh.

DR. YUH: A quick question. If non-roller pumps were down-classified to Class II today, and let's say an axial flow pump was then developed that was robust enough to compare it to a centrifugal pump in flow characteristics, what would be the predicate device to which it would be compared to?

MS. WENTZ: Sorry, I missed the first part of that question. Could you repeat that?

DR. YUH: So if we down-classified non-roller pumps for cardiopulmonary bypass today, and in the future, the near future, let's say, an axial flow pump was then developed that was robust enough to compare it to a centrifugal pump in flow characteristics, what would be the predicate device to which it would be compared to?

MS. WENTZ: Okay. This is Catherine Wentz from the FDA.

So I'm assuming that when you're saying can be compared in flow characteristics, that the intended use would be the down-classified Class II intended use for bypass uses.

DR. YUH: Right.

MS. WENTZ: Okay. So, again, as we discussed yesterday our decision-making process, we would go down our decision-making tree, and the first question is intended use. And if the intended use is the same, the next question is technology. And if the technology is different, we then ask the question of does this raise new types of safety and effectiveness questions? And if it does, then it gets put into the Class III bucket. If it does not, then we can continue down the 510(k) pathway and use the device that they chose as the predicate.

DR. YUH: Thanks.

DR. PAGE: Thank you.

Dr. Allen and Dr. Cigarroa, you both had your hands raised.

A quick question, Dr. Allen, or did you want to wait until our later discussion?

DR. ALLEN: I'll wait.

DR. PAGE: Fair enough.

Dr. Cigarroa.

DR. CIGARROA: She just addressed the issue, and that is the distinction with technology and opting out, if there's a fundamental change in technology, of the pathway to Class III. So I'm great.

DR. PAGE: Thank you.

With that, then I'd like to thank the FDA for their presentation.

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And we'll now take a 15-minute break.

(Off the record.)

(On the record.)

DR. PAGE: All right. I'd like to now reconvene and proceed with the Industry Open Public Hearing portion of the meeting.

Public attendees are given an opportunity to address the Panel, to present data, information, or views relevant to the meeting agenda.

Ms. Waterhouse will now read the Open Public Hearing disclosure process statement.

MS. WATERHOUSE: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. PAGE: There have been requests to speak by the following: Thoratec and Abiomed. Each of these companies will be given 30 minutes to address the Panel. Once you have been asked to approach the podium, please be sure to state your name, company, and any affiliation you may have with the entities presenting today.

Please go ahead.

MR. MIDDLEBROOK: Thank you, Dr. Page.

Before I begin my prepared remarks, I'd just like to thank the Panel and the FDA for allowing me this opportunity to speak to you today on behalf of my company, Thoratec Corporation.

My name is Don Middlebrook, and I am the Vice President of Corporate Regulatory Affairs and Quality Assurance for Thoratec. I am a full-time employee for the company.

This is an outline of the presentation that I prepared, but I think, in the interest of time, I've given copies to all the Panel members. In the interest of time, I'm just going to jump right into my slides here.

A little bit about the company. Our company is committed to the development of mechanical circulatory support devices to improve the outcomes of patients with end-stage congestive heart failure and other cardiovascular diseases.

The company is headquartered in Pleasanton, California. We have products and services facilities in a number of locations in California, also in Massachusetts, Florida, the United Kingdom, and Switzerland. The company employees over 800 employees worldwide.

We are a leader in the field of mechanical circulatory support. We're the only company with MCS devices that are aimed to treat acute, intermediate, and chronic support. We have devices approved for left-sided support, right-sided support, and for biventricular support. And with over 25,000 implants worldwide, we are the world's leading manufacturer of mechanical circulatory supports.

The company is committed to significant R and D investments and furthering the field of mechanical circulatory support, as evidenced by the fact that we have a fully magnetically levitated LVAD system in development for chronic support that will be entering clinical trials in 2013. We also have a percutaneous heart pump for acute support, which is a micro-axial non-roller type pump. It's in development and also will be entering into clinical trials in 2013.

I thought, given some of the questions this morning and some of the confusion and also, I think, to very clearly illustrate the differences between devices that are approved via 510(k) and those that are approved today via a PMA, that it would be helpful and illustrative to go through the current products portfolio that Thoratec has.

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This device here is the HeartMate II. It was approved in April of 2008, and it is a PMA device. It is indicated for a bridge to cardiac transplantation and for destination therapy, and generally it's used to support -- for durations of support that are considered intermediate to chronic. Patients that are ineligible for cardiac transplantation would be on the device essentially for the rest of their life. This device is configured for left-sided support.

We also manufacture the Thoratec Paracorporeal VAD system. This device was also approved via PMA in December of 1995. It's used for a bridge to cardiac transplantation and postcardiotomy recovery for support durations that range from acute to intermediate. It can be configured as a left, right, or biventricular support device.

This is the CentriMag device. This particular slide is illustrating the CentriMag right heart support system. This device is a non-axial centrifugal-type pump. And I think it's very important for me to point out that this device is approved for periods over 6 hours. It's approved under an HDE.

There was a question earlier this morning -- I can't remember from which Panel member -- about devices, centrifugal devices that are approved for over 6 hours of use. This one is. This device is approved through an HDE, which is Humanitarian Device Exemption, for sort of orphan and limited patient populations of less than 4,000 patients per year. This

device is used for intermediate support for periods of up to 30 days and is configured as a right-sided support device.

As you can see from the picture, this is the identical device. This device was cleared through a 510(k) in March of 2003. It's used for acute support for durations of up to 6 hours. This is our version or our device that we manufacture that falls into the category of a non-roller centrifugal-type blood pump, and it can be configured for left, right, or biventricular support. This device was recommended this morning by the FDA to be reclassified into Class II.

We also make a pediatric version of this pump. It's just a smaller version. Again, this device was cleared via 510(k) on 10/10/2009 for acute support, for durations of support up to 6 hours, and it can be configured as a left, right, or biventricular device.

We also have the same device, which we call the CentriMag Ventricular Assist System. This device is an investigational device. It's under study right now. I've given you the reference to the IDE number. It's being studied for intermediate use for support durations up to 30 days, and this device, like the CentriMag that is cleared for 6 hours of use, can be configured for left, right, or biventricular support. This study is under way. It is not completed, but it is enrolling currently today.

We also have in development a micro-axial non-roller type blood pump. It's called the HeartMate Percutaneous Heart Pump. It is not

510(k) cleared. We have not submitted a 510(k) yet. We're in discussions with FDA currently on the regulatory pathway to bring this device to market, and also on the clinical trial design for this device. It is designed for acute support for periods of up to 6 hours of use, and it is configured, at least initially, to be used only for left-sided support.

I also would now like to turn to some regulatory considerations.

The current FDA regulatory requirements, as we heard this morning -- I'm going to try to make it as simple as I can -- for mechanical circulatory support devices that are labeled for short-term circulatory support for periods of less than 6 hours, and that have similar mechanisms of actions and intended uses to devices that are already on the market, can be brought to market via the 510(k) clearance process. That's the standard today.

For mechanical circulatory support devices that are labeled and intended for use for support durations greater than 6 hours, those require a PMA. That's why you saw that we have the CentriMag that is a 510(k)-cleared device for less than 6 hours, and we have it under investigation for uses beyond 6 hours today.

That's our current regulatory framework. I think it's a good way to look at it, and I think this makes sense. And I'll say more about that in a few minutes.

So a little bit of history here. As was alluded to this morning,

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non-roller blood pumps have been safely used since the mid-'70s. FDA classified these devices as Class III in February of 1980, and under the 1996 Medical Device Act Amendments to the Food, Drug and Cosmetic Act, FDA was given the authority to reclassify these devices from Class III to Class II, if FDA determined that special controls would provide reasonable assurance of safety and effectiveness.

So, importantly, under the Safe Medical Device Act, the new definition of a Class II device explicitly references devices purported or represented to be for use in supporting or sustaining life. Under this new definition, the Secretary examines and identifies special controls, if any, that are necessary to provide adequate assurance of safety and effectiveness and describes how these special controls provide such assurances. And I've referenced the U.S. Code of Regulations where this is stated.

In 1993, Ed Basile from King and Spalding working with us at AdvaMed -- and I was actually -- it was HIMA at the time, but it's now known as AdvaMed. And I was actually a member of this committee that put together a Section 515(b) petition to reclassify centrifugal non-roller type pumps from Class III to Class II. And as we heard from the FDA this morning, an Advisory Panel similar to this one, in 1995, heard testimony from a number of experts, including surgeons, perfusionists, hematologists, and other subject experts on the safety and effectiveness of non-roller type blood pumps for use for periods of less than 6 hours, and also on recommendations

for special controls.

In July of 2009, in response to a *Federal Register* notice and a letter the company received from the FDA, Levitronix, which has been acquired by Thoratec, at the time submitted a reclassification petition providing a significant amount of data on the safety and effectiveness of these type of pumps for periods of up to 6 hours of use, and also recommending special controls within that petition.

So what about the pre-clearance testing and special controls? The definition of special controls may include 510(k) testing requirements, labeling requirements, FDA guidelines, international standards, which in the device industry have become very important and deal with things like electrical safety, sterilization, biocompatibility -- are all addressed in international standards that we typically have to comply with for devices, whether they're Class II or Class III, performance standards, postmarket surveillance, and patient registries. These are all considered as categories of special controls.

The testing required for a 510(k) clearance for non-axial -- excuse me -- for non-roller type centrifugal and micro-axial type pumps is illustrated here in this list that I put together. I pulled this list together from the 1993 petition for reclassification and also the 2009 petition for reclassification that was filed by my company.

And so these are the types of tests that are typically done in

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order to get a 510(k) clearance for a device for use in a surgical procedure for up to 6 hours. And some of the things that were identified as new risks, such as retrograde flow and heat generation, are clearly addressed here as potential special controls that FDA could develop and define for these devices to facilitate reclassification.

So looking at the complaint history and MDR history for non-roller type centrifugal flow pumps, I've provided here for you just a trend of data. We have been distributing the CentriMag pump for 6 years. We have data on the complaint history, and as you can see, it's very low for this type of device. And I've included both a numerator and denominator here for you so you could look at that. And also I've included the number of MDRs reported for this device for those types of uses. Actually all uses, regardless of duration of use. And you can see, there's only been one MDR reported through the third quarter in 2012.

I also want to mention compliance and recalls. I know those are important matters in considering reclassification.

So for the manufacturing operations relative to the CentriMag, in the past 5 years there have been three factory inspections by the FDA, resulting in eight FDA 483 observations. All of those have been adequately resolved. There are no open matters from any of those inspections today. And from those inspections, there were no warning letters that were issued to our company.

In that same 5-year period there has been only one voluntary device correction. That was initiated in March of 2008, to warn of possible interruption of the CentriMag system when it is used with a Valleylab electrocautery unit. There was a new black box warning added to the labeling as part of that correction, and there was a software modification submitted as a 510(k) that was also part of that correction.

So turning to the micro-axial non-roller type blood pumps. There was a lot of discussion this morning and there was mentioned in particular to the PROTECT II trial. But I think, if I've learned one thing in my 30 years in this business, is you look at data. The FDA has taught me to look at the totality of the information that's available.

So I'd just like to point out here that the FDA has 510(k) cleared these types of devices for use in extracorporeal bypass circuits during cardiopulmonary bypass, and for partial circulatory support during procedures not requiring cardiopulmonary bypass, for up to 6 hours of use. Micro-axial devices have been used clinically for these indications since 2004, when they were first brought to market in Europe, and then later 510(k) cleared in the United States in 2008.

FDA referenced an MDR history in their presentation this morning, and I believe that you must take that into consideration as well, because that provides additional evidence of safety for these devices for their intended use.

There was also mentioned, as I said, of just the one study. But as I looked through the FDA summary, there were five micro-axial literature articles for high-risk PCI that were mentioned by the FDA, that provide clinical outcomes on 215 patients. All of those studies suggest safe use of a micro-axial blood pump for surgical procedures.

The special controls that I showed you before, that list that was proposed for centrifugal non-roller type blood pumps, that list is also appropriate for these micro-axial type blood pumps as well. There's no reason why we cannot develop -- that I can see, that we can develop special controls for both of these categories of devices.

The new risks that were identified by the FDA, structural and tissue damage, local heat generation, and flow dynamics, those can all be detected in pre-clearance special control testing, either in vivo, in vitro, or in clinical evaluations that FDA can impose for any new device, whether it's 510(k) or PMA. The FDA has the authority to impose or require clinical testing for those types of devices.

FDA alludes to the point in their summary materials that clinical trials, as a special control, are in some way a lower bar because you only have to demonstrate substantial equivalency to a clinical trial to develop independent data demonstrating a reasonable assurance of safety and effectiveness for a PMA, for a PMA-type device. If these devices were reclassified or remain in Class III, that there would be a call for PMAs and we

would likely have to do prospective, randomized controlled trials for these devices. And, ironically, the standard of care that we would compare against is an intra-aortic balloon pump, which this Panel yesterday voted to reclassify to Class II. So I think that's an important thing that should be taken into consideration.

So summary and recommendations. The centrifugal non-roller type blood pump has been used for more than a quarter of a century and proven safe and effective for clinical use as a life-supporting and life-sustaining device. The CentriMag has a decade of clinical use and excellent performance and safety profile. The totality of the data, including clinical evidence for micro-axial blood pumps, is not insignificant and supports an acceptable safety profile for uses up to 6 hours.

The current FDA pre-submission testing requirements for centrifugal pumps and micro-axial non-roller type blood pumps intended for less than 6 hours provides a reasonable assurance of safety and effectiveness and could easily be formulated into a specific pre-specified set of special controls. The current regulatory requirements via 510(k) clearance are adequate to ensure safe use and are appropriate for both centrifugal and micro-axial non-roller type blood pumps for intended uses of less than 6 hours.

Thoratec is currently seeking, as I mentioned earlier, to gain a PMA approval for use of the CentriMag non-roller type blood pump for

periods of greater than 6 hours; in this case, 30 days of support. So any indication for these devices that are beyond 6 hours do require a PMA and should be brought to market via the PMA process.

So Thoratec's recommendations, based on the excellent safety and performance record, the comprehensive current pre-clearance testing requirements, and the need for regulatory differentiation between MCS devices intended for less than 6 hours compared with those intended for long-term chronic support, that industry, AdvaMed, and the FDA should work together to develop the necessary special controls to facilitate reclassification of centrifugal and micro-axial non-roller type blood pumps intended for less than 6 hours of support.

Thoratec strongly recommends the reclassification to Class II of both centrifugal and micro-axial non-roller type blood pumps for the indications during cardiopulmonary bypass, circulatory bypass, and for temporary ventricular support, again, for durations of less than 6 hours.

This concludes my prepared remarks. Thank you for your time and attention.

DR. PAGE: Thank you, Mr. Middlebrook, for that very clear and concise presentation.

We're going to hold questions until both industry presentations have been delivered.

Next is going to be led by Dr. Weber from Abiomed. And I think

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I'll ask you to introduce your colleagues, if they're speaking, as well. And, again, you have 30 minutes, sir.

DR. WEBER: Thank you, Mr. Chairman.

And I think I need to get my slides up here. Thank you.

So thank you again. Good morning, everyone, and thank you for the time to present today. My name is David Weber. I am responsible for operations at Abiomed, where I am a full-time employee.

As a brief introduction to the company, we are a medical device firm located in Danvers, Massachusetts. We employ about 450 people, and our products range from extracorporeal ventricular assist devices that have PMAs for heart recovery, all the way to the family of Impella micro-axial pumps, which are under discussion today.

We'd like to use our time today as follows. I'll begin by discussing some considerations for the classification of Impella for durations of support up to 6 hours. I'll be followed by Dr. Jeff Popma from the Beth Israel Deaconess Medical Center in Boston, who will discuss the supporting scientific evidence on Impella. And then I will close with some discussion of controls and make some concluding recommendations.

I also want to note that joining us today, in addition to this, is Dr. William O'Neill. Many of you know that Dr. O'Neill has been a leader in the field of hemodynamic support for many years and has also been the principal investigator in the Impella trials and registries.

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So I'd like to begin with just some perspective on the category of non-roller type blood pumps and particularly the role of Impella within that category.

As noted by previous speakers and the earlier discussion this morning, this category has evolved over time to include different types of technologies, from the early centrifugal pumps used in surgical cardiopulmonary bypass circuits, all the way to percutaneous cardiac-only support circuits that use centrifugal pumps and then now micro-axial pumps.

Innovation, over time, within this technology has reduced the pump and cannula size, it has reduced the amount of invasiveness of these technologies and provided faster setup times, and in doing so has expanded the settings in which that support is provided, essentially expanding the general concept of pump beyond the surgical suite into the cath labs and EP labs.

And in accordance with this, the original clearance for the Impella 2.5 device, which was the first micro-axial pump cleared in the category in 2008, was based on the submission of clinical data comprised entirely of patients provided circulatory support in a cath lab setting, and in particular in the setting of high-risk PCI. This was 129 patients in total, 20 of which were from the original FDA safety and feasibility study of Impella in high-risk PCI, and the rest were from a European registry of Impella-supported high-risk PCI patients.

And the 510(k) summary included in this clearance acknowledges that it was these data collected in the setting of high-risk PCI that were the basis on which the safety of the device was evaluated.

The Impella device itself is a catheter-based device. It is percutaneously inserted through a 13 French sheath. It's advanced over the aortic arch and across the aortic valve so that the motor or pump head resides in the ascending aorta and the inflow end of the cannula resides in the ventricle. It then draws blood directly from the ventricle, deposits it in the ascending aorta, thereby directly unloading the ventricle while also providing support to the systemic and coronary circulation.

And since its clearance, this family of Impella devices, which includes not only the 2.5 but also two other higher-flow devices ranging up to 5 L a minute, have been used over 15,000 times around the world, with 12,000 of those implants in the U.S.

For use up to 6 hours in its labeled duration, 90% of that use is for temporary ventricular support in the setting of high-risk PCI. The median duration of support for these patients is well within that labeled duration, ranging from 60 to 80 minutes. And the majority of these patients, as has been mentioned by this morning's presentation, have been turned down for surgery.

We do believe that sufficient evidence exists on Impella to identify the risks and benefits of the device when used in accordance with its

cleared duration of support. We have prepared for the Panel a complete bibliography on Impella. That's comprised in total of 193 peer-reviewed publications spanning the last 18 years; 124 of those do meet the regulatory definition of valid scientific evidence, and 57 of those pertain to the use of the device in under 6 hours.

Particularly for that duration of support, the largest studies describing the risks and benefits of the device are the European and U.S. registry studies in high-risk PCI, as well as the FDA IDE studies, PROTECT I and PROTECT II. In total, this series of published studies representing 564 patients, 245 of which were studied under an FDA-approved protocol, we believe, supports a reasonable assurance that Impella is safe and effective when used in accordance with its cleared indications for use and including high-risk PCI.

And I'd like to ask, now, Dr. Popma to come up and elaborate further on this and other valid scientific evidence.

Dr. Popma.

DR. POPMA: Thank you, Dr. Weber.

Dr. Page, distinguished Panel members, my name is Jeffrey Popma. I'm Director of Interventional Cardiology at the Beth Israel Deaconess Medical Center, and Professor of Medicine at Harvard Medical School.

My pertinent disclosures are that we did perform a research

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grant to my institution for the performance of an angiographic analysis as part of the PROTECT II trial. I served on a single advisory board, for which I received compensation, and my travel was paid for to this meeting.

I want to congratulate the FDA team, Dr. Avila-Tang and the epidemiology group, for a very thorough literature review. I think it was very, very useful, in the FDA summary, for me to prepare for this meeting.

Five studies were identified using the Impella device in patients undergoing high-risk PCI, consisting of 231 patients. We would request that the Panel also consider additional analyses that were published after the 2011 ACC/AHA/SCAI guidelines, and specifically in more detail about the PROTECT II trial published in *Circulation*.

And then two post hoc analyses, which will not be discussed here, first by George Dangas, evaluating the outcomes of the PROTECT II trial using only major adverse cardiac event rates, and a second analysis that we performed in our laboratory, looking at the extent of revascularization, those are available on abstract, but we won't discuss them here.

Most importantly is the USpella registry. This is an ongoing registry that looks at the postmarketing outcomes of patients with similar subsets. And we'll talk about those, as well.

I want to also congratulate Dr. Laschinger on a very concise and provocative interpretation of the PROTECT II study results, focusing on the primary endpoint. We believe that's important, and the details behind the

data safety monitoring committee's decision to terminate the trial were important.

But we would also request that the Advisory Panel also consider the predefined analysis population in the protocol, which was pre-specified, a pre-protocol analysis, which I'll show you, for predefined subgroup analyses that were specifically put in place before the analysis was done, in order to account for the complexity of the trial design in this population -- and we'll go into those details -- and finally, other registries and post hoc analyses that describe the totality of clinical evidence supporting the reasonable safety and efficacy of the Impella 2.5 device.

I'm going to summarize the literature down into a few studies that we'll focus. Dr. Weber has given you the comprehensive literature. Dr. Avila-Tang has given you another source of literature. We're going to focus on five particular studies for this trial.

Three of these studies have, in fact, been submitted to the FDA for review: PROTECT I and PROTECT II and the Euro registry. And two of these are larger-scale, randomized clinical trials, one, the PROTECT II, comparing Impella versus the intra-aortic balloon pump, and secondly, the cardio bypass, comparing some of the hemodynamic effects of the Impella device versus cardiopulmonary bypass, important safety information.

Now, I think Dr. Kandzari raised a very important point earlier. There is, I think, fairly substantial evidence that the Impella device improves

hemodynamics compared to intra-aortic balloon pumps. We saw from Dr. Laschinger earlier the ISAR-SHOCK trial, a study of 26 patients, not powered for mortality, but instead showed significant improvements in cardiac index associated with the Impella device versus the intra-aortic balloon pump; .49 L/min/M² cardiac index versus .31.

Secondly, in the USpella registry, patients who were in cardiogenic shock, 90% of which were already on a balloon pump, the use of crossover to the Impella device resulted in a significant increase in mean arterial pressure.

And, finally, and perhaps most importantly, the index of preserved cardiac power output. This is what the Impella device does, as Dr. Weber outlined, in the elective PCI population, a predefined secondary endpoint, significantly preserved cardiac power output with the Impella device compared to the intra-aortic balloon pump. Let me show you what this means in a patient.

This is an individual who was enrolled in the PROTECT I trial and had a left main stenosis, sole remaining vessel, left ventricular ejection of less than 35%. As this was a registry in PROTECT I, an Impella device was placed at about the red arrow, in the left ventricle. After balloon predilatation, there was a severe dissection of the left main coronary artery and complete cessation of flow to the sole remaining vessel. What resulted was an agonal ventricular rhythm.

Because the Impella device was in place, the mean arterial pressure was maintained at 71 mm/Hg for 10 minutes, allowing the operators to reverse the complication with the intra-coronary stent and reestablish flow to the vessel. This is the reason for the use of the Impella device, just as was outlined in the earlier discussions by the FDA.

We also agree with Ms. Wentz about the importance of safety endpoints. And these have been delineated and described in the FDA Executive Summary: alteration of blood composition, inadequate tissue perfusion, embolization, duration of use, fluid leakage -- I believe all of which have been addressed with the Impella device and the various types of data, which we're prepared to talk about during the question and answer period -- adverse tissue reactions, infections, and importantly the three components that were identified as new risks, that I believe have been identified in our studies thus far to address the safety concerns.

First of all, structural/tissue damage. No incidences of structural/tissue damage in the three FDA trials and registries. In the entire literature that comprises 1697 patients with Impella, one case of aortic regurgitation.

With respect to local heat generation and its propensity to thrombosis, the stroke rate, .5%; non-CNS thromboembolism rate, .8%. Very acceptable ranges for these types of patients.

And, finally, the flow dynamics I demonstrated earlier.

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Significant improvements compared to the balloon pump in flow dynamics, whether it be mean arterial pressure, cardiac index, or the preservation of cardiac power.

I would like to also clarify some of the perceptions that Dr. Laschinger did very eloquently describe earlier about the PROTECT II trial.

We believe that CABG is preferred in patients with complex anatomy and less than a high surgical risk. How do we do this as clinicians? We use two different types of indices. We use anatomic indices, which are described by the SYNTAX Score. How complex is that coronary anatomy? And we use the assessment of surgical comorbidities. How risky is the operation for the patients? And those sorts of metrics are with STS and EuroSCOREs.

And we do believe, in patients who have higher SYNTAX Scores, higher anatomic complexity, that CABG is preferred. The problem is how to manage those patients whose surgeons and interventionalists, as a heart team, decide are just too high risk for surgery. Well, that's the PROTECT II study, and in particular, providing left ventricular support in those patients who are both high anatomic risk and high surgical risk, where clinicians feel that some adjunct ventricular support is required. That is the construct of the PROTECT II trial.

How was it designed? Patients were selected by either having a last remaining vessel or an unprotected left main and an ejection fraction of

less than 35%, or having three-vessel disease and a left ventricular ejection fraction of less than 30%. Patients were randomized in a 1:1 fashion to the balloon pump or to the Impella device. The primary endpoint, as Dr. Laschinger indicated, intention-to-treat analysis, is a major adverse cardiac event rate at 30 days.

And to put this long list of event rates in perspective, it includes both the major adverse cardiac event rate and safety endpoints that were mutually decided and agreed upon by the FDA as part of this IDE submission for the study. So it's a longer list, but it has particular purposes. As Dr. Laschinger indicated, it includes both efficacy and safety.

Importantly, and a real struggle for clinicians is our question, was this effect sustained? Was this an effect that was only seen at 30 days and lost, or was it a sustained effect? And as a result of that, in the protocol and in the statistical analysis plan, there was a mandatory follow-up of all patients out to 90 days, with a reassessment of the major adverse event rate at 90 days to evaluate the sustainability of this effect that was achieved with the Impella device. So both of these sets of endpoints and both of these time points are extremely important in our opinion.

Now, was PROTECT II like SYNTAX? We've talked a lot about SYNTAX. My answer is no, it wasn't. It wasn't, because the frequency of diabetes was higher, prior myocardial infarction was higher, congestive heart failure was higher, prior PCI or bypass was higher. But most importantly,

PROTECT II is a unique dataset that has not been studied before.

Because 92% of patients had an ejection fraction of less than 30% compared to 1.3% in the SYNTAX study, 64% of patients were deemed to be nonsurgical candidates by the local site heart team versus none in the SYNTAX trial, because it was a randomized trial and a four times higher EuroSCORE metric for surgical risk.

So these are not the same populations, and we believe that this represents a patient population that is tremendously underserved in an interventional perspective.

Let's look at the timelines. Very important to understand the timelines.

The first patient was enrolled in the PROTECT II trial on November 27th, 2007; a 510(k) clearance, June 2008. Fifty percent of the enrollment was achieved on February 26th, 2010; 327 patients. That data was collected, collated, and prepared for interim analysis. When the DSMB looked at the preliminary analysis for the predefined subset analysis, the trial was halted for futility. During that period of time, an additional 125 patients were included, leaving the total sample size that we'll be looking at today. Not the sample size that the DSMB made its decision on, but the final analysis population that included the totality of patients, the DSMB-decision patients and an additional 125 patients. And of course that was only 69% of the recruitment goal in this study, where we find -- you've heard the results.

The primary endpoint of this study, a reduction in intention-to-treat major adverse event rates at 30 days, was numerically lower with the Impella device, but not statistically different. It missed its primary endpoint.

But extending that analysis out to 90 days, the durability of this, in fact, the numeric differences increase, the statistics become a trend towards positive, a p of .066. But look at these Kaplan-Meier curves. There are events that are occurring after 30 days that are an important over-event for patients that we need to consider when we look at the totality of the evidence base.

Now, safety. I agree with the FDA, we have to be comfortable with safety. We have a randomized trial that has been adjudicated by an independent CEC at Harvard Clinical Research Institute, specifically asked to determine device-related effects. And there were no device-related adverse effects associated with the Impella device, and there were three in patients who were treated with the balloon pump. I believe that looking at this listing of events, we understand at least a preliminary analysis of what safety is, compared to balloon pump, with this device.

Let's look at some more efficacy data, and let's look at the pre-specified analysis population per protocol. We'll also look at a predefined analysis looking at learning curve issues, looking at operator technique, which includes the rotational atherectomy, anatomic indices of three-vessel disease versus coronary artery disease, and extremely high-risk surgical mortality. In

the TAVR datasets, now we talk about Cohort C, those patients who do not benefit no matter what one does.

So let's dive into these. These were all pre-specified; they're all in the statistical analysis plan. All of this was written before we pooled the first statistical p-value.

First, let's look at the per-protocol analysis. In many ways, this is the important piece from my perspective, as a clinical perspective, because 21 patients were excluded from the intention-to-treat analysis. Why? Because they did not meet the inclusion/exclusion criteria for the protocol. This was all done prior to the analysis. And that meant that four patients had an ejection fraction of over 35%. Three patients had an active MI. Four patients had no left main or three-vessel disease. It's very important.

So when one went back and analyzed this, we wanted to analyze the patients who were intended for the clinical study. That's the per-protocol analysis. What do we find at 30 days? Numeric and trend towards a reduction in 30-day events. At 90 days, now 51% versus 40%, p of .023. Looking at these Kaplan-Meier curves, separation of these two curves began around 10 days. Very important for us to understand the durability of this result for our patients.

Let's look at some of these subsets. There was no learning curve, and there was no roll-in phase to the study. Now, that was a little bit of a challenge. This was oftentimes the first time patients -- the operators

had used this device in patients. But there was no allowed roll-in phase.

Excluding the first patient randomized to either the balloon pump or the Impella device at each institution, there's a significant reduction in both the intention-to-treat and the per-protocol analysis, just accounting for the first patient randomized, accounting for a learning curve, which we typically do now in complex device trials.

Moving on to the issue of rotational atherectomy, often misunderstood. We understand, from lots of data done so far, that rotational atherectomy, longer runs, more aggressive rotational atherectomy is associated with higher CKMB. That's a primary endpoint of the trial. We were concerned that there might be some operator-specific details that occurred, whether operators might be more aggressive. We said let's take that away.

In a predefined -- well, what happens if we don't use atherectomy at all as a potential confounding factor? Statistical reductions in both the intention-to-treat and the per-protocol analysis, removing the confounding factor of rotational atherectomy.

What about the three-vessel disease subgroup? Trending towards statistical significance in the intention-to-treat and significant in the per-protocol analysis.

And, finally, what about excessive surgical comorbidity? We never thought about this in a detailed fashion, until we came to the TAVR

data. The PARTNER B data, as we know, is not significantly different in higher STS risk scores. This is the same message, that if you have such significant excessive surgical comorbidities, probably no therapy is the right way to go. But when the STS is under 10 and the patients are still deemed to be non-operative candidates, statistical difference in intention-to-treat and the per-protocol analysis. Very profoundly important information in terms of patient selection.

Well, how do we monitor this? Well, Abiomed has instituted an ongoing USpella registry. It began in 2009. Nine hundred and forty-nine patients have been included at 41 centers, all consecutive patients unselected at each site. DSMB -- I'm sorry -- data monitoring done with source documentation, independent CEC for event adjudication, CEC-adjudicated events by the Impella criteria that were used from PROTECT II, so an ongoing registry after approval in clinical practice.

What does that show? Well, this has been published by Brij Maini. In the 175 patients who underwent high-risk PCI, we find very comparable results as what was seen in the PROTECT II trial. Very important for us, as we move from randomized clinical trials to clinical practices, to make sure that those results are consistent.

In addition, this is completely consistent with the European registry which was used for the 510(k) approval as part of -- along with PROTECT I. So very consistent results in high-risk patients in a registry

afterwards.

What is the summary? Well, I think the safety is mitigated by review of all of the clinical evidence base with the use of the Impella 2.5 device. We need to continue to monitor this. We need to establish controls to be able to do that. But I think the safety concerns have been defined in the data so far, and I think it's very useful for making our decisions.

Secondly, there's no question that this device improves the hemodynamics associated with randomized data versus the balloon pump, suggesting that both the cardiac index is increased, as well as preserved cardiac power. Very important for us as interventionalists during complex interventions.

And, finally, the examination of the totality of the clinical evidence associated with the use of the Impella 2.5 versus the balloon pump supports efficacy in very defined patient populations.

So we would conclude that the comprehensive review of the totality of the clinical evidence associated with the use of the Impella 2.5 device for its labeled less than 6 hours indication supports the safety and efficacy of this device, particularly in patients undergoing high-risk PCI.

And finally and most importantly, ongoing surveillance with a comprehensive national registry is recommended to understand patient outcomes for these and other indications when applied beyond a randomized study.

I'd like to turn this over to Dr. Weber again.

DR. WEBER: Thank you, Dr. Popma.

So having reviewed the scientific evidence which supports, we believe, a reasonable assurance of safety and effectiveness of the device, I'd like to now briefly move on to the controls.

Special controls that have been identified and already implemented for Impella range from extensive testing that is submitted with each of its 510(k) applications. On average, those applications include 41 different tests to performance standards. There is the Impella postmarket registry that Dr. Popma prescribed, that itself serves as a special control for the device. There is a detailed physician and staff certification program that trains and certifies on the use and management of the device. And there is, of course, ongoing management of the caution and warnings in the package insert, based on the postmarket data and experience.

For the record, we do believe that these controls, combined with the general controls that are in place, do mitigate the risks to health that have been identified, and particularly for the three specific risks identified by FDA for temporary ventricular support. We believe that these controls, and in particular the postmarket registry, are strong mitigation measures.

And to that end, and to further enhance these measures, our recommendation is to expand the USpella registry to establish an inclusive prospective national registry of percutaneous circulatory support that would

leverage the current infrastructure of the Impella registry. This ongoing registry, in cooperation with FDA and appropriate professional societies, would enhance the current risk mitigation controls for a Class II regulation of these devices and, combined with existing data, can potentially support future indications.

And the safety record of Impella, to date, supports the effectiveness of the current controls. Since its introduction, against the use of 15,000 implants worldwide, we have had no recalls in the United States and only one recall outside the U.S., which affected a total of four units. There have been a total of 49 MDRs since its introduction, for an MDR rate of about 1/3 of 1%, and only 16 of these MDRs were associated with adverse events, for an MDR with adverse event rate of about 1/10 of 1%.

So wrapping up, Impella was cleared in 2008 with the indication for use to provide partial circulatory support for periods up to 6 hours for procedures not requiring cardiopulmonary bypass. And the safety analysis within this clearance was based on clinical data comprised entirely of patients provided support during high-risk PCI procedures, which we believe inseparably ties the original clearance of the device to the use in the setting of high-risk PCI.

In conclusion, for temporary ventricular support up to 6 hours, including support during high-risk PCI, we believe Impella meets the requirements for a Class II designation. There is sufficient valid scientific

evidence to identify risks and benefits. The risks to health have been identified and quantified. Controls are currently implemented to mitigate these risks, and the safety record of the device supports the effectiveness of these controls.

Further, we recommend the establishment of a prospective national registry of percutaneous support as an added special control for Class II regulation of both this current device and future devices.

And with that, I thank you for your attention and look forward to your deliberation.

DR. PAGE: Thank you, Dr. Weber and Dr. Popma. You finished with 15 seconds to spare.

(Laughter.)

DR. PAGE: I can't thank you enough, as well as Mr. Middlebrook from Thoratec, for such well-prepared, concise presentations.

And with that, it's time to open both of these presentations up to the Panel for questions and discussion.

Okay, I saw Dr. Allen and Dr. Somberg.

Dr. Allen.

DR. ALLEN: This is a question for Mr. Middlebrook. In one of your slides you mention that there currently is a micro-axial pump that is routinely used in conjunction with an oxygenator in cardiopulmonary bypass

that's been approved since 2004.

What pump is that?

MR. MIDDLEBROOK: I don't remember saying in conjunction with cardiopulmonary bypass. If I did, I apologize. I should've said surgical procedures. And I was referring to the Impella device.

DR. ALLEN: So to your knowledge, there is no axial flow pump that's currently approved for cardiopulmonary bypass?

MR. MIDDLEBROOK: That is correct.

DR. ALLEN: Thank you.

DR. PAGE: Dr. Somberg.

DR. SOMBERG: Yes, my question really addresses -- and maybe Dr. Weber or Dr. Popma want to address this. It addresses the Abiomed presentation and specifically the axial pump as circulatory support in advanced PCI. I'm really satisfied with your safety discussion here.

But what do you base the efficacy on? Is it comparability to the intra-aortic balloon pump? And that certainly wasn't -- you had superiority endpoints. So have you, post hoc, changed your determination? Because you say there's a reasonable assurance of safety, which I think there is, but what about efficacy?

DR. WEBER: Thank you for the question, Dr. Somberg.

I'm going to suggest that perhaps Dr. O'Neill, who is --

COURT REPORTER: Sir, could you please state your name

before you speak?

DR. WEBER: David Weber with Abiomed.

I'm going to turn that question over to Dr. O'Neill.

DR. O'NEILL: This is Bill O'Neill. I'm Medical Director of the Center for Structural Heart Disease at Henry Ford Hospital, and previously Executive Dean of Clinical Affairs at the Miller School of Medicine at the University of Miami.

I have no conflicts. My travel was paid for by Abiomed for this meeting, but I have no other financial obligations to disclose.

You have to understand the PROTECT trial, in terms of the hemodynamics. We randomized the patients, and every 15 minutes during the procedure, the patients had blood pressure and cardiac output determination, and with that we were able to look at the cardiac power determination. And there was no question that, unequivocally, this device provided superior hemodynamic support.

The patients were much more stable through the procedure, and the cardiac power was more sufficiently maintained, to the point that, unfortunately, it changed and modified some of the ways that the physicians were actually treating patients. They were so comfortable with the device that they had a much more aggressive use of rotator, and that confounded the analysis.

So in terms of is it better in terms of a hemodynamic support

device compared to balloon pump, the answer is unequivocally yes.

Secondly, does that lead to better outcomes? The 30-day outcomes were chosen initially, again, more as sort of a surgical device, sort of historical. Why 30 days? You asked, why 6 hours? Well, why 30 days?

Okay. So we looked at 30 days, but we were also concerned because these patients had very poor ventricular function, and we knew from the SHOCK trial and from the BCIS trial that people with poor ventricular function had events curves that splayed over time. So we looked at the results at 30 days and at 90 days. And I think you can say that at 30 days there was actually very little difference in outcome. But at 90 days there was a difference, and it's very statistically significant and internally consistent in all of the subgroups.

So the answer is not much difference at 30 days, but a significant difference at 90 days.

DR. PAGE: Thank you.

Dr. Hirshfeld, then Dr. Katz.

DR. HIRSHFELD: Okay, I think this a question that's probably best addressed to Bill O'Neill. And Bill, I would like to ask you about the use of a very multi-component composite endpoint in your superiority determination that you've made for your 90-day assessment.

So I happen to be looking at Table 4 in your circulation manuscript, where you have the details of that out there. And I know that

the rest of the Panel can't see this, since I have it on my computer. But basically, the endpoints seem to be leveraged primarily by repeat revascularization and myocardial infarction that occurred between 30 days and 90 days. And if you look, for example, at death, there's actually a trend in favor of the balloon pump, although it's not statistically significant. And if you look at stroke, there are more strokes in the balloon pump group. But it seems that the principal thing is that they look good. Okay, thanks for bringing that up.

So I wonder whether we're really seeing effects that really, truly reflect the impact of the use of a support device at the time of the procedure in the 90-day analysis with the composite endpoint.

DR. O'NEILL: Yeah, I think that's a very key question, and we spent a lot of sleepless nights discussing that, because I've never been a big fan of multiple endpoints. I mean, basically you're saying is death the same as renal failure or other -- you know, just qualitatively it's hard. They could count the same statistically, but it's part of the problem with dealing with this space. It's a very underserved patient population, and it's very infrequent.

We can't do a 20,000-patient stent trial in this population of patients because it's probably 1% to 5% of all the patients that are eligible for this. So we had to come up with a group that was a reasonable size and event rates that were powered to allow us to do a study that was economically feasible for this small company. And that was really the reason

that drove -- all of the endpoints, I think, are biologically valid. I mean, death, stroke, MI, repeat revascular, all of those, I think, are clinically important. And also we did include safety, renal dysfunction, VT/VF, and damage to the aortic valve. So it was a combination of efficacy and safety.

And the only answer to it, John, I'd say is that this is first of the study, it's a landmark, because there hasn't really been a true, prospective, randomized trial in high-risk PCI. This will define it. And I think future studies and the FDA can use a lot of this data to really sort of say what is the kind of OPC endpoints that you're going to have, death, MI, repeat revascular, and other endpoints. So I would say that it's the first of what hopefully will be a future number of trials.

But it really emphasizes how difficult and how really, really hard it is to come up with an efficacy endpoint in a relatively small population of very complex, high-risk patients.

DR. PAGE: Thank you.

Dr. Katz. And then Dr. Cigarroa raised his hand.

Dr. Katz.

DR. KATZ: This is a question for Mr. Middlebrook. Can you tell me, is there a difference between the CentriMag RVAS and the CentriMag VAS, with respect to the pump meeting the cone, its driver, and the console?

MR. MIDDLEBROOK: No, I believe those pumps are completely identical. They're just approved for different uses. They're identical.

Thank you.

DR. PAGE: Thank you.

Dr. Cigarroa.

DR. CIGARROA: This is a question for Dr. O'Neill. Coming back to Table 4, any insights on the distinction as to the driver for repeat revascularization, both in the 30-day and the 90-day period?

DR. O'NEILL: Yeah, I think again, going back to sort of the psychology of the operators, the operators felt very comfortable working in this setting, and the case that Jeff showed typifies that. You can have a complete occlusion with cessation of forward blood flow and the patients still are stable and it allows you to sort of work. And as a result of that, there was more rotational atherectomy, higher balloon inflations, just more stuff that was done during the procedure. That's as close I could come to quantifying it, because we tried to sort of enumerate it and it's been a little bit of a struggle.

What we found -- and Jeff is preparing a paper that hopefully will be coming out early next year, on the extent of revascularization, and we found that the more extensive revascularization that occurred, the better the outcome. And our surgical colleagues assumed that complete revascularization is really one of the reasons why surgery works better than angioplasty in this population.

So the operators were more comfortable. They were able to do more during the procedures and this did result -- one thing that is quantified

is that there probably were more lesions that could've been treated in the balloon pump group and weren't, and then, subsequently, those caused problems after the 30 days and required readmission for repeat procedures.

DR. CIGARROA: So just as clarification, is it your perception that this was more, in a sense, a perceived comfort in ability, as opposed to a difference in clinical outcomes during the actual procedure, that precluded a more complete revascularization in the IABP versus Impella?

DR. O'NEILL: Well, there was actually -- it was more than perceived, because if we take a look at the balloon pump versus the Impella group, there was twice the use of rotational atherectomy in the Impella group compared to the balloon pump.

Furthermore, the rotational atherectomy was much more aggressive. The more runs, the more numbers of passes, the longer duration. And, perversely, this confounded it because of the very aggressive uses associated with an increase in CK release.

So definitely the operators felt more comfortable and could do more, and that's demonstrated by the improvement in cardiac power. The cardiac power was more significantly maintained with Impella compared to balloon pump, and therefore the operators were more aggressive in these complex, high-risk cases.

DR. PAGE: Thank you.

Dr. Doty.

DR. DOTY: I'd just like to touch on what Dr. Somberg talked a little bit about and your Slide 42, your conclusion. One of the tasks we have as a Panel is sufficient information and valid scientific evidence to identify risks and benefits.

You mentioned earlier in your talk -- this is for the Abiomed team -- that over 12,000 Impella devices have been implanted in the U.S. alone. We are discussing a single study that Dr. Laschinger brought to our attention. So their review identified only a single study, and by my count, that's 216 patients that had the Impella implanted.

So I'd like you to comment on our task as a Panel to review the benefit and utility of this device in barely over 200 patients, when 12,000 of these devices have been implanted. Could you comment on that, please?

DR. WEBER: So this is Dave Weber with Abiomed.

I think it's an important point to make. Within the 12,000 uses in the United States, first of all, all of those uses are subject to the MDR reporting, which I think other people have already outlined the underreporting that occurs in there and the imperfections in it. But certainly the MDR reports of the device are some reflection of the safety profile within that 12,000.

That said, in terms of clinical data, other than the PROTECT II, we also had the registries, the ongoing USpella registry. That gives us a very good look into the real-world use of the device. There have been European

registries. And the literature that's available on the device is another avenue.

In total, I think, of all of the literature on Impella, we have seen a total of about 1,500 - 1,600 patients who have presented in that literature bibliography. So it's not everybody, but it's a pretty good sample in my opinion.

DR. POPMA: And I'll use the slide right behind you. The tally that we have from the published literature, including some of the ones that weren't included in the FDA summary, actually has a tally up to 799 patients. So it's not 12,000, but it's not 250. So these are demonstrable places where we could actually look for outcomes.

DR. PAGE: Thank you.

Dr. Kandzari.

DR. KANDZARI: Thank you.

I have two questions for Dr. O'Neill. The first is that in high-risk PCI, to date, we do not have compelling evidence from randomized trials that support the planned prophylactic use of a balloon pump versus provisional use.

And I'm just curious. In the design of this trial, did it intentionally randomize patients to the Impella device versus planned intra-aortic balloon pump use, without the proven benefit of planned intra-aortic balloon pump use?

Had you considered, instead, either no balloon pump or

prophylactic balloon pump that perhaps might've demonstrated even greater disparity in outcome?

DR. O'NEILL: Well, you know, the groups that were in the trial were highly experienced operators that had a long-term history of use of devices in complex PCI. And one of the problems that we had is that many of the centers that we wanted to have participating in the trial actually withdrew once 510(k) clearance occurred, because they thought it was "unethical" to continue to enroll. It would've been nearly impossible to enroll these patients because the whole spirit of the trial was you have to need hemodynamic support. If it's ostial left main with a quick balloon inflation/deflation, I mean, you can do those from a radial 6 French sheath without any support. And there's definitely those patients.

But the centers, the sites had to say that these patients do need support. And that differentiates this trial from BCIS. In BCIS, there was equipoise because the patients could be randomized to no support. And so I think that really was what differentiates this trial.

So it was very difficult to recruit. It took over two and a half years to get all of these patients enrolled, and so, again, the difficulty enrolling kind of in a high-risk group of patients.

The spirit is, okay, you interventional cardiologists, you want to treat this really high-risk, largely inoperable, very symptomatic patient. How can you do it most safely? And if you feel you need hemodynamic support,

then which of the two is better? And that was kind of the spirit of the trial.

DR. KANDZARI: Thanks. My other question for you is, in clinical trials interpretation, I always struggle with divergence of curves and the timing of divergence, and particularly when an adjunctive device or drug is used. And I'll ask if you could comment.

If we believe that the adjunctive hemodynamic support made a true difference in the intervention per se, why do we see a divergence in event rates that do not occur until 10 to 20, 30 days, if not longer, depending on how we slice the data?

DR. O'NEILL: It's very important. It's a really, really crucial question because of the vast differences in the patient treatment, and that between 30 and 90 days. And if we look at those events, those are actually hard clinical events, congestive heart failure, death, stroke, repeat hospitalization, repeat revascularization, all hard endpoints. They're not sort of just numbers on a piece of paper. So I think those are very important. And it also demonstrates how cost effective this therapy is. And we've got a publication on that, as well.

The best data that I can come up with is that the doctors had better hemodynamic support and that patients had less hemodynamic perturbation during the trial and therefore less myocardial dysfunction and myocardial strain during the procedure. And this did end up in resulting with better long-term outcomes.

DR. PAGE: Thank you.

Dr. Zuckerman, did you have a comment?

DR. ZUCKERMAN: Yes, I do have a comment, but I would like to make it at the end of this very important discussion.

DR. PAGE: Fair enough. In that case I'll go on.

Dr. Naftel, I believe you had your hand raised, and then Dr. Hirshfeld.

DR. NAFTEL: As we start to talk about the special controls, and we talked about them yesterday too, is I look at what's proposed by FDA or industry, and I'm splitting them right down the middle, what are bench testing, good manufacturing practices versus what involves actual data from patients.

So to Don Middlebrook, I want to compliment you on your Slide 19, where you showed the rates of complaints and MDRs across time. That addressed something that we brought up about 10 times so far, that we don't have denominators, but you do. Industry does have denominators for most of these things.

So for sure, in all the discussions we have on special controls from here out, I will always push for at least a marrying of the MDRs and the actual implants. And, of course, it only works because we're essentially talking about short-term events. If we were talking about long term, we wouldn't know what to do. So I wanted to compliment you on that.

And then I had a question to Abiomed. On your U.S. registry, you said it was IRB approved, thank goodness. What about informed consent? Does a patient have to provide informed consent to get in the registry?

DR. WEBER: They do not.

DR. NAFTEL: Well, then I've just got to ask you, how on earth do you get away with that? Are you doing it under quality assurance or what? How do you get away with that?

DR. WEBER: It's a retrospective registry, and local IRBs will allow that in a retrospective registry. Not everywhere, but at the centers that we're at.

DR. NAFTEL: Well, my hat is off to you. I've never been able to pull that off.

DR. PAGE: Dr. Hirshfeld. He passes.

Dr. Allen.

DR. ALLEN: This isn't maybe so much of a question as maybe a comment, because I'm becoming confused as a panelist, as this question and answer goes on, because this meeting is sounding more and more like a PMA for the Impella 2.5 device, and it's my understanding that we're not here to look at Impella 2.5 as a PMA.

And I find it interesting that, as a class, non-roller pumps, not only do they include axial flow, but centrifugal pumps. And it's interesting

that the company that uses TandemHeart didn't make a presentation. There's been no data presented on TandemHeart. But yet, at the end of this, we're going to be asked to make decisions about a class of devices, not just Impella, not just TandemHeart or some future device from company innovation that comes up.

And so I guess I need help from the FDA on clarifying what exactly we're doing from a Panel standpoint.

DR. PAGE: Dr. Zuckerman, do you want to comment?

DR. ZUCKERMAN: Dr. Somberg, did you have a question first? Because I think Dr. Allen's point is critical as to what our charge is today, and I'll answer that in a moment. But if you have a quick question or comment.

DR. SOMBERG: Well, my question was to the industry panelists, and it relates to what you were just mentioning, because I think their discussion is that, for both of their devices, they're saying that there is enough information for 6 hours or less, is the impression I was getting. And I didn't hear anybody who was claiming that the 6 hours or more, that they wanted to have it down-classified.

But that's what I was going to ask. Is my summary true? Because that affects the whole gist of things here.

DR. WEBER: Yeah, Dave Weber with Abiomed.

You are exactly correct, Dr. Somberg. We proposed the PROTECT II data in these procedures, in these classification proceedings, as

valid scientific evidence to support a reasonable assurance of safety and effectiveness, and not in these proceedings as any sort of a PMA discussion.

MR. MIDDLEBROOK: Yes, Dr. Somberg. Don Middlebrook from Thoratec.

Yes, we are proposing exactly what you said, that devices intended for use for less than 6 hours, or 6 hours or less, can be reclassified to Class II with special controls, as we discussed. They have to be identified and really spelled out. We need to work with the FDA to do that. But yes, that's what we're proposing.

And as I showed you on the slides, for indications for uses over 6 hours, those are PMA uses, and we're seeking PMA approval for the use of the CentriMag, which is the non-roller centrifugal pump that we manufacture for those uses over 6 hours.

Thank you.

DR. PAGE: Thank you.

We'll have comments from Dr. Zuckerman before we close or adjourn for lunch.

Dr. Zuckerman.

DR. ZUCKERMAN: Yes. First of all, I'd like to thank the industry for two excellent presentations, because I think it helps bring exactly what this Advisory Panel is going to need to do after lunch. So please have a good lunch because you'll have some important work to do.

As Dr. Allen has reminded us, this is not a PMA Advisory Panel today. Today we have to take a 100-foot view and really decide whether the data out there for temporary ventricular support for a class of devices is adequate, such that we can go to a Class II, which from a clinically important perspective usually implies lack of clinical data in the evaluation.

Now, it's really important that this was a great discussion of one particular trial over the last half hour. And I certainly want to congratulate the investigators for completing this trial, and also the company for doing it, because as Dr. O'Neill indicated, these are difficult trials to do.

On the other hand, though, I've heard a great discussion from this Advisory Panel over the last 10 to 15 minutes of just the complexities and interpretations of this one trial. On top of that, I think, as experienced Panel members, you're aware that while there's an excellent publication in *Circulation* -- and we've heard a great publication presentation from Dr. Popma -- what you sometimes see in a PMA briefing book can be somewhat different from what is in the published literature.

So I'd like you to consider these things because frankly what you're being asked to do in the afternoon is to consider whether this dataset, as well as other datasets, really allows us to extrapolate to that 100-foot view and the implications of that 100-foot view, meaning moving this particular indication into Class II with all of the implications.

So while it will be important to focus on some of the

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granularity, as this Panel has done superbly over the last half hour, please don't forget the big picture, also. And Dr. Page will be able to guide you in making sure we also examine the big picture and the implications here.

Thank you.

DR. PAGE: Great, thank you.

I will now pronounce this portion of the Open Public Hearing to be officially closed.

(Whereupon, at 11:53 a.m., a lunch recess was taken.)

AFTERNOON SESSION

(12:52 p.m.)

DR. PAGE: Okay, we'll now proceed to the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Panel to present data, information, or views relevant to the meeting agenda.

Ms. Waterhouse will now read the Open Public Hearing disclosure process statement.

MS. WATERHOUSE: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your

statement, it will not preclude you from speaking.

DR. PAGE: Thank you very much.

There have been six requests, that I'm aware of, to speak, and I'll list the following names. And I'll allow you to introduce yourself and explain your interest on this topic.

The speakers will be: Dr. Vidovich, Dr. Mishkel, Mr. [sic] Dempsey, Dr. Vetrovec, Dr. Rose, and Mr. Landin, representing a patient.

Each speaker, I believe you've been informed already, has approximately 5 minutes -- it's 5 minutes -- to address the Panel. Once you've been asked to approach the podium, please be sure to state your name, company, and any affiliation you may have with the entities presenting today.

Again, we have a full agenda, a lot of discussion to take place, so I will ask people to keep their comments to 5 minutes.

Let's go ahead with the first speaker, Dr. Vidovich. And I apologize if I didn't say that correctly.

DR. VIDOVICH: Thank you for the opportunity to present to the Panel and the FDA.

I am Associate Professor of Medicine, University of Illinois at Chicago, and I'm Chief of Cardiology at the adjoining Jesse Brown VA at Chicago. Regarding conflict of interest, I received honoraria from Abiomed,

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and they have supported the travel today. I did, however, take a vacation day from both my federal and state employment for this presentation.

So to give you a background, I do practice at two different settings: one, at University of Illinois at Chicago. This is a standard university setting. We have a fellowship program. We do have a surgical backup on site. And our volume is about 200 PCIs annually. We do have two cardiac catheterization laboratories, and this is where we do have Impella support.

This is just a block away, the Jesse Brown VA Medical Center. It is a standard VA setting, again, with the same fellowship program. It does not have cardiac surgery backup. We have been the first VA in the nation to pioneer this program of not having cardiac surgery backup, and we adhere to very strict criteria as a model VA to make sure that this really, indeed, is done appropriately with patient safety. The volume is about equal to the university.

This is a typo, I apologize. There is one cardiac catheterization laboratory.

Given the type of procedures we perform, we are predominantly a radial access with excess of 90%. We do same-day PCI in both sites, just to show you, and then we are equipped with FFR and then OCT and near-infrared spectroscopy, IVUS imaging.

Quality-wise, we do ACC and CDR at the university and then, VA CardioSEAL program. Those of you who are not at the VA setting, it is a

centralized database which follows all complications, and all procedures are centralized and standardized in Denver.

So why we felt that this might be good for us:

One is revascularization. We were able to address patients that we could not tackle before at both sites. At the university, primarily, high surgical risk. And given that it is a downtown inner city university, we have a highly active liver transplant and kidney transplant program. And these patients are frequently felt to be too high surgical risk and turned down by surgeons.

So we instituted this system where we consistently calculate on all our patients who will undergo Impella placement the SYNTAX Score, probably 30 and plus. We do calculate their STS and EuroSCORE II mortality in about 10%. I can't give you a fixed number, but these are the rough numbers.

And then, per request of our surgeons, usually liver failure, Childs Class C and D, which doesn't feature -- they're not part of the STS calculator -- are frequently reason for turndowns.

And then patient preference. Not that many, I have to admit.

Complete revascularization is very important, as well. We may not be able to complete revascularization unless -- multi-vessel angioplasty in these very sick patients -- without availability of support.

And then a smaller group, probably in low double digits, is

cardiogenic shock, so patients who present ST elevation, myocardial infarction, and are in shock. This is particularly important for us at the VA center, where we don't have surgical backup support, so this allows us to stabilize these patients, perform PCI, and then transfer as needed.

Regarding safety, it was a new device, so we made sure that we have a comprehensive quality adherence to this and primarily with the access management. These are larger sheaths, we do not perform TAVR, we are not an ER site, so for us this was very important to make sure we do a good job with this. We follow valvular regurgitation, but it never really panned out to be a problem, but we do echo these people.

Hemolysis, particular to VA. We do check for hemolysis before and after quite consistently and have not noticed this to be a problem.

And then we track for admissions, particularly at the VA because it is quite important that we don't waste more money on these patients and I, especially, as chief over there -- does trigger an e-mail from my boss why our patients have been admitted.

This component, nurses and technology, training and competency, we found that this is 50% of the battle because the device being implanted, I think, for a physician, it's a reasonably straightforward process. It's a pigtail that's placed in the ventricle. However, 50% of the battle is nurses being competent and fast and knowing what they're doing, so we've instituted quite rigorous policies that the nurses know what process is in

place.

Surgical backup considerations, primarily, you can look at the STEMI with cardiogenic shock. We don't have a strict approach. Either it's balloon-pumped first or Impella first, depends on the situation.

I can give you this --

DR. PAGE: We've reached 5 minutes.

DR. VIDOVICH: Thank you.

DR. PAGE: I'll need you to wrap up --

DR. VIDOVICH: I will wrap up.

DR. PAGE: -- in the next minute.

DR. VIDOVICH: So surgical, we have a heart team approach of high-risk PCI, low threshold for vascular collaboration, and we do have peripheral skills to manage peripheral -- collaborate complications.

We did decrease admissions, we do have complete revascularization, and then we have reduced a number of fee bases from the VA for complex cases. We do have an Impella training program; it's a CME-approved program for physicians, nurses, and technologists. And, again, we developed and shared these policies and procedures, particularly at the VA site because they're federal property.

And this is it. Thank you very much for the opportunity.

DR. PAGE: Thank you very much. And if there are questions from the Panel at the end of all the presentations, we'll address them to you.

DR. VIDOVICH: I'd be glad to answer; thank you.

DR. PAGE: Our next speaker is Dr. Mishkel.

DR. MISHKEL: I'm going to do two things that I haven't done before. One of them is not use PowerPoint, and the second is read from an iPad.

Thank you very much, Mr. Chairman, and to the FDA, for the opportunity to speak. Beyond my travel expenses, which have been reimbursed by Abiomed, I have neither asked nor received any payment for today's statement.

While I appreciate the Panel's charge to survey these devices from the 100-foot horizon, I'm here to survey the situation as someone planted firmly on terra firma. I'm not a trialist, I'm not an epidemiologist, I'm not an academician, I don't work for industry, and I don't work for the FDA. I'm a doctor, and I work and advocate for patients.

I'm a practicing cardiac interventionalist, and I have been so for the last 23 years. I'm also the director of the cardiac cath lab at the Prairie Heart Institute in Springfield, Illinois for the last 20.

My group, Prairie Cardiovascular Consultants, is a large, single-specialty group that covers approximately 17,000 square miles of central and southern Illinois. Springfield, our home base and the state capital, is a small city surrounded by a wide expanse of rural farmland. Our group provides a sophisticated transfer network for rural patients to our tertiary receiving

centers to receive advanced cardiac care on both an emergent and elective basis. The cath lab that I'm directly responsible for is the largest in Illinois, proud to say dwarfing anything in the Chicago hospitals.

I hopefully can provide comfort regarding how these devices are used safely and effectively in the real world.

As an interventional cardiologist, I and my colleagues are responsible for the treatment of many cardiac patients with severe underlying coronary disease. Although the incidence of coronary disease and, gratifyingly, the mortality have fallen over the last two decades, paradoxically we are seeing a population with more advanced disease as patients live longer to develop more extensive disease. Many of these patients have failed medical therapy or are not amenable to CABG. For them, interventional therapy may be a last resort. As you can imagine, given their advanced disease, their ability to withstand even the slightest complication is often marginal.

Despite the appropriateness of the planned procedure, there's a population of patients for whom percutaneous intervention has a great chance of significant morbidity or mortality. To optimally treat these patients with advanced disease and marginal reserve, we must rely on mechanical cardiac support devices. For in the past, we have exclusively relied on pharmacological support or intra-aortic balloon pump, but this level of support is often insufficient or frankly even deleterious in the sickest of

patients.

In late 2008, to rectify what we viewed as deficiency of care in the cath lab for these patients, we undertook a review of commercially available mechanical support devices that would be most appropriate for percutaneous use in our busy cardiac cath lab. Keep in mind that our program does not have cardiology residents; the totality of care is provided by the cardiologists. Accordingly, it was important that the device or technology chosen not only be safe and effective but, importantly, be easy to implement and maintain. As such, devices that require surgical cannulation and/or extracorporeal circulation were not seen as suitable for the often urgent needs of our patients.

Our search ultimately led to the Abiomed Impella 2.5. From a physiological standpoint, we are impressed by its uniquely powerful effects of direct LBM loading in combination with increased coronary blood flow by augmenting mean arterial pressure and reducing LB and diastolic pressure.

A paramount advantage was an implantation technique that was familiar to any invasive cardiologist. Institution of support could be done expeditiously, if need be, and required only one femoral artery access site, a guide wire, and a sheath, and a pigtail-shaped pump. No surgical operation or a large vessel cannulation was required; no perfusionists were necessary. Our cath lab staff and ICU staff could maintain and manage perfusion.

Our first implant was February 20th, 2009, and to date we have

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implanted 53 of the 2.5 liters per minute devices. This represents approximately 1% of the total PCI volume of the same period.

It's interesting to note that until this year, the competing hospital in town transferred their sickest patients over to my hospital for their interventions. This practice was discontinued only after they purchased their own Impella device.

Ninety percent of the devices have been implanted prophylactically to support the case where a patient has markedly impaired cardiac function. In almost all of the cases, there has been an associated cardiac review of surgical options and the patient turned down by a cardiac surgeon. Once cardiac support has been instituted, these complex cases can proceed in a much more relaxed and controlled atmosphere as the patient remains stable throughout the course of the procedure and the device provides sufficient reserves should an untoward complication arise. Furthermore, a complete revascularization can often be achieved. Our clinical impressions, as you have heard, have been well supported in the literature.

In the remaining 10% of the cases, the device has been implanted in emergency circumstances. In the setting of unexpected complications or shock resulting from an MI, we need to achieve two simultaneous goals: prompt restoration of coronary perfusion and almost simultaneous cardiac support to rectify hemodynamics. It's impractical to

believe that anything other than this device can deliver this time-related performance.

Our cardiologists have been trained to obtain --

DR. PAGE: You'll need to wrap up.

DR. MISHKEL: -- an angiogram before every device insertion to assure appropriate vessel size, as well as the use of stiff guide wires to reduce vessel trauma. We frequently utilize newer percutaneous closure techniques to reduce post-procedural bleeding after device removal. Due to the familiarity of cardiologists with large sheath management in our trained staff, we've had no major vascular complications.

Common sense, to me, would dictate that if it's not broke, don't fix it. I would urge that this device panel not impose an increased regulatory burden on a device with an excellent track record of safety and efficacy and as a necessity in any quality cardiac cath lab.

Please allow me a final editorial comment: that a device that is percutaneous, automated, safe and effective, and is proposed to have a higher level of regulatory scrutiny simply because it is newer than the alternative intra-aortic balloon pump that is widely acknowledged to be less effective seems logically inconsistent to this doctor.

Thank you.

DR. PAGE: Thank you very much.

Our next speaker is Mr. Dempsey representing AdvaMed.

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MS. DEMPSEY: Happens all the time.

(Laughter.)

MS. DEMPSEY: Chairman Page, members of the Panel, I'm Ruey Dempsey, Associate Vice President, Technology and Regulatory Affairs at Advanced Medical Technology Association, AdvaMed.

AdvaMed is the world's largest association representing manufacturers of medical devices, diagnostic products, and health information systems that are transforming care through earlier disease detection, less invasive procedures, and more effective treatments. Our members range from the smallest to the largest medical technology innovators and companies.

Thank you for the opportunity to comment on the classification of non-roller type cardiopulmonary bypass blood pumps. AdvaMed commends the efforts of the FDA to reach classification determinations for the remaining preamendment Class III devices.

AdvaMed supports down-classification of the non-roller type blood pumps, including both centrifugal and micro-axial type pumps, to Class II, which would allow these products to continue to utilize the 510(k) pathway to take products to market. AdvaMed believes that these devices used per their labeling for up to 6 hours have an established safety record, and there is sufficient evidence to establish special controls to provide a reasonable assurance of the safety and effectiveness considered with the

definition of Class II devices.

Pumps in this category have a long history of safety and effectiveness, with some exceeding three decades. The category has broadened over the years to include smaller internal pumps that are minimally invasive and can be percutaneously placed. Labeling has evolved, as well, with micro-axial pumps having indications for use in surgical or non-surgical procedures.

Pumps in this category provide circular support in both the surgical suite and cath lab environments. Use of the 510(k) pathway for marketing clearance has encouraged this innovation, allowing patients in the United States timely access to improvements in circulatory support during all procedures of less than 6 hours duration.

Historically, the first type of blood pump to be widely used in cardiopulmonary bypass was the roller type, dating back to the 1950s. The roller type CPB pump is a life-sustaining device that has been classified by FDA as a Class II device. In 1979, when FDA first proposed classification of the two primary types of CPB pumps, the FDA recommended Class II for the roller type pumps and Class III for the non-roller type pumps. Because FDA cited the same arguments and reference list for both the roller and non-roller types of pumps, it appears that the difference in proposed classification was the result of the lack of sufficient information at the time for the non-roller type pumps.

In 1993, the Health Industry Manufacturers Association, now known as AdvaMed, submitted a petition for reclassification for the non-roller type pumps from Class -- CPB pumps from Class III to Class II, citing new evidence to show that application of special controls would provide reasonable assurance of the devices' safety and effectiveness. The petition showed low rates of medical device reports (MDRs) and customer complaints for these pumps. The petition cited clinical study data from 10 prospective studies that compared the use of roller versus non-roller type pumps.

All these studies showed either comparable or superior results for the patients supported with the non-roller type centrifugal pump compared to the patients supported with roller type. The centrifugal pump showed less blood trauma and no particulate microemboli or gross air embolism in comparison with the roller type pumps.

Almost 20 years ago, in 1995, the FDA convened an advisory panel and asked those expert panelists to consider the same issue you are addressing today: the request for reclassification for non-roller type pumps. That panel unanimously agreed to the reclassification to Class II with special controls for non-roller type cardiopulmonary blood pumps for use in the cardiopulmonary bypass circuits for periods of up to 6 hours. The FDA did not issue a regulation codifying the proposed reclassification and 11 years later withdrew the original proposed rule calling for a PMA for non-roller type pumps. In that time period, we believe the safety record of the

non-roller type bypass pumps had improved even more.

By now, the body of valid scientific evidence has grown substantially, and there is a significant amount of information to support the reclassification of the non-roller type pumps from Class III to Class II. Clinical and safety data show that the non-roller type pumps are as safe, if not safer, than the roller type pumps that are currently classified as Class II. As discussed today, both the centrifugal and micro-axial types of non-roller pumps exhibit low reported adverse events and recall rates when used in accordance with their labeling of less than 6 hours of use.

DR. PAGE: We're at 5 minutes.

MS. DEMPSEY: In summary, AdvaMed supports the reclassification of all non-roller type pumps, both centrifugal and axial type pumps, to Class II. The safety record of these devices demonstrates that the 510(k) pathway has provided adequate assurance of patient safety when supported by these devices.

We believe there is sufficient information and valid scientific evidence to identify the risks and benefits of these devices. And the general and special controls to be used provide reasonable assurance of safety and effectiveness. A Class II recommendation would bring consistency to the regulatory classification of cardiopulmonary bypass pumps by making both roller and non-roller types Class II.

Thank you again for this opportunity to comment.

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DR. PAGE: Ms. Dempsey, thank you very much.

Our next speaker is Dr. Vetrovec.

DR. VETROVEC: Good afternoon. My name is Dr. George Vetrovec. I am speaking today on behalf of The Society for Cardiac Angiography and Interventions, the SCAI.

I'm a Professor of Medicine, Director of the Adult Catheterization Laboratory in Virginia Commonwealth University. I'm also a past member of this Panel and a past president of the SCAI, and an active interventional cardiologist and investigator.

As a previous Panel member, I understand and respect the mission of the Panel and the FDA for today's meeting.

I acknowledge the following recent industry relations: I'm an investigator for Corindus, Medtronic, Cordis J&J, and I have been a speaker and consultant to Abiomed. I should note that my travel and lodging expenses for this meeting are being reimbursed by the SCAI.

The SCAI is the leader in science, education, and advocacy for interventional cardiologists and their patients. The society promotes excellence in cardiac catheterization angiography and interventional cardiology through physician education and through quality initiatives to enhance patient care. The society represents over 4,000 invasive cardiologists.

We appreciate the opportunity to have reviewed the FDA's

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Executive Summary on NRPs and the key questions. Our impression is that the FDA, in addition to directly evaluating the safety and efficacy of transient non-roller pump technology for left ventricular support, is also questioning why many of the patients in whom the devices have been utilized are being treated by percutaneous coronary intervention, or PCI.

The answer is relatively simple. Many of these patients have been turned down for surgery; and others, presenting with acute myocardial infarction, cannot endure the delay necessary for surgery. In both instances, the use of these support devices has provided transient hemodynamic safety and the option of additional ischemic time to safely optimize the PCI results. These devices assist in the treatment of some of the sickest patients undergoing clinically necessary and guideline-supported PCI, who most often are not acceptable for surgical revascularization.

In the PROTECT II trial, 64% of the patients were turned down for surgery, and another 10% refused surgery. Also, in the USpella registry, 56% of patients were non-surgical candidates, and another 10% of patients had turned down the surgical option. As one would suspect, the outcomes for such high-risk patients turned down for surgery are at times less optimal than expected for more routine procedures, but that is hopefully understandable for such sick patients with no other option.

We are here today to support continued patient access to NRPs. There is strong evidence supporting the safety and effectiveness of

these devices, and guidelines have recognized their utility. Likewise, recognizing and supporting optimal interventional practice, the SCAI would support the FDA in the following goals to be certain that, going forward, these devices are best utilized and evaluated.

Data collection on NRPs is one such area. The SCAI strongly supports the collection of data on NRPs. We would be happy to work with the FDA, industry, or others to explore data registry option.

Secondly, operator training. Since the devices are not used on most interventional cardiology patients, many operators, even those initially well trained on how to use these devices, may need additional training in order to improve the outcomes of procedures using these devices. While we support the collection of additional data on outcomes of patients for whom these devices are used, we hope that the FDA will also consider the impact of sudden new mandates to increase the regulation of these devices. Such actions may spur unfounded fears in patients, as well as physicians.

Additionally, in today's litigiousness environment, even unfounded assumptions that the FDA has found problems with these devices could lead to underutilization of left ventricular support in appropriate clinical circumstances for high-risk PCI with potentially unnecessary adverse outcomes for patients.

In conclusion, we thank you for accepting our testimony today. As always, we hope the FDA appropriately balances the needs of patients to

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have access to devices with concerns about the safety of those devices. We recommend that these NRP devices be down-classified to Class II with perhaps some general and special controls regarding postmarket data collection and the training of low-volume operators.

Thank you very much.

DR. PAGE: Thank you, Dr. Vetrovec.

Our next speaker is Dr. Eric Rose.

DR. ROSE: Good afternoon, I'm Eric Rose. I'm a Professor of Health Evidence and Policy and Cardiac Surgery at the Mt. Sinai School of Medicine. I'm also the co-director of the Data Coordinating Center for the NHLBI-supported Cardiothoracic Surgery Clinical Trials Network.

My conflicts include my chairmanship of the board of CircuLite. I've been a board member, in the past, of Abiomed. I've been an investigator for Thoratec. I was the PI for the REMATCH trial for use of devices as destination therapy in the first place.

So the reason I wanted to talk today to the Panel is that I strongly believe that regulatory science and innovation and circulatory support can be and should be complementary. More than 60 years since Gibbon, the temporary mechanical support tools that we now have, have served as an enabler for multiple interventions, the specific nature of which have been entirely unpredictable but the impact of which is undeniable. Gibbon's original intent in developing cardiopulmonary bypass was to address

patients with severe pulmonary embolis. It's pretty clear that that's not where this all went. But the enabling of unpredictable areas, I think, is still something that's clearly in the future for us.

I strongly believe the notion that tools which enable hemodynamic support are valuable. That proposition has face validity, and as such, the continued use of labels for devices for 6 hours of use or less, I think, is a very important concept for FDA to preserve.

The Class III designation for newer devices, especially balloon pumping and inotropic support, which haven't had much attention in these deliberations in the past two days, but I think that's the other control group that's obvious and potentially problematic. Those remain the obvious control groups. But I think that that Class III designation, as such, could have unintended adverse effects on innovation.

And I think the way to obviate that is the following: I think we should recognize that effective support for up to 6 hours of hemodynamics, itself, is a valid primary efficacy outcome. And Class III designation of these devices, I think if it's something the direction in which this all goes, that that designation for these devices should be coupled with the recognition that hemodynamic support, itself, is a valid primary outcome for such PMA-type requirements.

In my remaining minute and a half or less, I assume, I just want to make a couple of comments on trial design because I think there's a lot to

be learned with so few trials that are done in this space. Almost none of them are confirmatory trials; almost all of them are learning trials. And all these learning trials -- and we've certainly learned this in our own network -- they're typically powered to an endpoint. But the notion that you can only learn from that primary endpoint and you can't learn from anything else in the trial, I think is absurd.

I think the other thing that the data that we've looked at in the past several hours points out is that point estimates of complex composite endpoints as primary endpoints, I'd say, is not so good. I think looking at longer term Kaplan Maier-type plots of these complex outcomes is probably a better mirror of reality and efficacy. It's certainly possible to envision something that looks great at 30 days and all the patients can be dead at 90. And arguably, you'll argue for support based on the 30-day endpoint having been hit.

The other thing I think that is potentially dangerous is futility, pre-specified futility analyses, as parts of learning trial design, I think are potentially dangerous, especially if the primary endpoint is a complex composite. I think they are also potentially a disservice to the patients who agree to be randomized in the first place. The reason that they do that is for us to learn from their participation in these trials, and I think a premature declaration of futility when all that we can learn is still not learned is something that we should not be doing.

Thanks for the opportunity to present to you today. Thanks.

DR. PAGE: Thank you very much, Dr. Rose.

Our final scheduled speaker is Mr. Landin, representing a patient perspective. Welcome.

MR. LANDIN: Thank you, Chairman Dr. Page, Federal Officer Waterhouse, distinguished Panel members all.

I'd like you to meet four individuals that I'm also representing and by extension will speak of others, as well: Iman, Dan, Curtis, and Mike, who are with us also.

We come before you courtesy of Abiomed, who is responsible for our travel and accommodations. There were no other offers of remuneration, enticement, or coercion associated with our presence. Let's just get that off the table.

We ended this morning's session talking about the big picture. I'd like to address and frame the issue and my comments relative to that.

Collectively, we represent the demographic diversity and geographic expanse of our country. We're in 50% of our population; 150,000,000 people have risk factors for heart disease, this resulting in 700,000 or 29% of all deaths annually, disproportionately represented in African American, Hispanic women, and populations of poverty.

Every 34 seconds, someone dies of heart disease. In the time I have to speak, 10 people will die. So this is about making every second

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count.

I believe that each of us has been chosen to be here today. We are not here by chance, coincidence, or circumstance. This is a convergence of stakeholders with the opportunity to manage risk, provide choice, and establish value as relates to the most pervasive healthcare crisis in America. We have a choice and a chance to do something that is in the best interest and greater good of the most people.

As I understand it, you are here to assess and evaluate data to determine the viability of devices like the Impella to be reclassified as Class II or simply, "How can we save more lives safely?" In our legal system, evidence would be presented. You would be the jury charged with deciding whether sufficient evidence has been presented to prove beyond a reasonable doubt the case.

With a 1% risk factor in almost all categories, the Impella not only meets that criteria, it exceeds it. I didn't understand until last night, when I met other beneficiaries of this technology, that my case was different because I had a choice; they did not. Their doctors had a choice, but in a reactive response, or as a last resort, to an occurrence that had already transpired. Reclassification of this device to Class II would provide others the same opportunity I had to take a proactive, preemptive approach to coronary treatment, reducing cost, severity of incidents, and recapturing lost productivity while significantly enhancing quality of life, individual life, your

family's life, community life.

Within 48 hours of my procedure, I was able to return to an active life, sharing a board meeting of a community organization that serves 26,000 families in the city of Detroit, just for starters.

This really isn't about "instead of"; it's about "in addition to." The value proposition that devices like the Impella pose are an average cost of 25% compared to surgical treatment options. Recovery time, 2% as compared to surgical options. On scale, heart disease costs this country \$150 billion a year, the equivalent of our net national income, and multiplied over 10 years would equal the 1.5 trillion that down the street they're arguing about in terms of how they're going to recapture to support our national budget.

Over and above the exponential benefits, all said and done, this is about saving lives, and that's priceless. When I wake up in the morning, I need purpose. When I go to bed at night, I need a sense of achievement. This provides my life meaning. If I, if we, our collective experiences, have in any way contributed to what we hope will be an affirmative resolution to reclassify the Impella, then on this day you will truly have provided these essential elements for hundreds of thousands of people.

On behalf of all of us who have benefited from this Class III device and the millions more who could benefit from the device being reclassified, thank you for the privilege of sharing these thoughts with you.

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DR. PAGE: Thank you very much. So I do appreciate you and the others being here to represent patients.

Are there any other speakers who wish to address this Panel today? I see someone coming up to the microphone. If you would, please tell us your name, affiliation, and indicate any financial interest you might have.

MR. MORRIS: Thank you for the opportunity.

My name is John Morris. I am the Chief Executive of CardiacAssist; we are the manufacturers of the TandemHeart. And despite not having prepared remarks, I certainly am willing to offer whatever assistance to the Panel and the FDA that we can be.

I will say that in 10 years of commercial availability, we believe we have pretty significant experience in hemodynamic improvement of patients. We think that with an MDR rate well under 1%, that we have a pretty comfortable experience with safety, and we certainly do support the down-classification of CPB applications. We also support the "for longer than 6 hours" of cardiac support, the PMA process, and that's a process we're going through right this moment.

So I merely wanted to offer our support, and if we can be of any assistance, we're happy to.

Thank you.

DR. PAGE: Thank you, Mr. Morris.

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Is there anyone else who wishes to address the Panel?

(No response.)

DR. PAGE: Do any of the Panel members have questions for any of the speakers in this open comment section?

(No response.)

DR. PAGE: I see none. And as such, I pronounce this Open Public Hearing to be officially closed.

I want to thank all of the speakers, especially the patients who came forward. And I assure you, on behalf of the committee, patients are at the heart of everything we're doing here. Whether or not, no matter what direction this committee goes, it's with patients' interest in mind. So I really appreciate you being here and reminding us of your perspective.

With that, we'll proceed with panel deliberations.

This is open to public observers; public attendees, however, may not participate except at the specific request of the Panel Chair.

In addition, we request that all persons who are asked to speak identify themselves each time. This helps the transcriptionist identify the speakers.

The purpose now is to allow the committee to ask any questions that they might have regarding the presentations we received today.

Dr. Cigarroa.

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DR. CIGARROA: Thank you. This is a follow-up to a comment and perspective that Dr. Allen provided early this morning.

As the morning progressed and as a panel, as we listened to the different presentations, understanding the distinction between going through a PMA process for a particular device, there was a lot of focus on the Impella this morning.

And a paucity of data on other devices that would be reclassified from III to II and the potential impact that that will have -- and I want to make sure that, as a panel, we understand the implications of this, that this is not simply about a particular device made by a particular company, but as a reclassification scheme.

And I'd like to ask the appropriate person from the FDA insights in terms of the data presented both in the presentation and in the packet that was provided us with regards to what's not present with other devices that would be reclassified.

DR. ZUCKERMAN: Let me begin, Dr. Cigarroa, because I think you've made a critical point here, and I think the Panel should seriously think about this in contradistinction to yesterday's reclassification discussion with IABPs.

Yesterday there was a wealth of data presented, multiple randomized trials, and the Panel did not, to my knowledge and recollection, at any time discuss one particular device as opposed to a class of devices and

whether we were ready for down-classification from Class III to Class II.

The tenor of the discussion has been very different today in that, as Dr. Cigarroa mentions, you primarily heard about one device with an interesting technology and design. And really what you need to think about, as an advisory panel giving independent advice to FDA regarding a general reclassification question is, can knowledge of how one device performs in this complex field really be extrapolated to determine safety and effectiveness for the entire field?

From our perspective, Dr. Cigarroa, we gave you the best compilation of the data out there and, as you point out, it seems to be centered on one particular device for a certain indication.

DR. CIGARROA: Thank you.

DR. PAGE: Other questions to the FDA? Questions for clarification?

Yes, Dr. Doty.

DR. DOTY: Dr. Zuckerman, I'd kind of like to build on a little bit more, if you could comment. We heard this morning, from Ms. Shulman, again, about the examples of Class II and Class III devices, and looking at that list of Class III devices, we have things with broad, long-term data on many patients in the vascular grafts, coronary stents, pacemakers. So could you just kind of clarify, for the Panel, why those devices are still Class III and how that would sort of impact our decision-making today?

DR. ZUCKERMAN: Well, generally for life-supporting/life-sustaining devices, for two reasons they start out in Class III.

One, they're life-supporting/life-sustaining and, two, there's no prior predicate, and the PMA pathway is an appropriate pathway for evaluating these devices that can have significant benefit but also can have significant morbidity, as you know.

And I think a general paradigm that one needs to really recognize is that not all devices are created equal in terms of technology and clinical utility, such that the PMA Class III paradigm works very well, and respects that because for a Class III PMA, we need to see individual clinical data for that particular device to understand that there's a reasonable assurance of safety and effectiveness for that device.

When we move to Class II 510(k) paradigm, we're moving to a paradigm of substantial equivalence, and generally, we have concluded, for these high-risk devices, that as a class, we can better -- we understand both their preclinical and clinical aspects such that we can define the preclinical testing characteristics appropriately and we don't need individual clinical data for each particular device.

Now, this is an appropriate paradigm for device development in many circumstances because, as you know, devices, as opposed to drugs, undergo maturation and iteration such that, in many cases, a class of devices converges to certain standard design principles.

As Ms. Shulman indicated in her talk, PTCA catheters are a great example. In 1976, when they were first introduced, they were life-supporting/life-sustaining Class III PMAs; but over time, with an accumulation of a wealth of data and a better understanding of how designs were maturing, the Agency felt very comfortable with the industry, in 2005, in down-classifying these devices to Class II such that now, when we evaluate new PTCA catheters as opposed to in the past, it's essentially a preclinical bench evaluation with no clinical data, which is very different than the past.

So, you know, there's the potential for any class of devices always to consider a reclassification from Class III to Class II, as we're doing right now, but I think the key question is, is it the appropriate time. And what this advisory panel is charged with and really where we need your help is, is there enough safety and effectiveness data for this class of devices to consider the Class III-to-Class II paradigm where the evaluation of devices is substantially different because we're using the substantial equivalence determination methodology?

Does that help you, Dr. Doty?

DR. PAGE: And, Dr. Zuckerman, if I may further clarify for my own benefit and perhaps that of the committee, in terms of if it was decided that this was to be a Class III device and if, subsequent to that time, non-roller pump technology was brought forward for ventricular support as a PMA and was approved subsequent to that time, other devices essentially

equivalent could come through in a 510(k) for similar technology, similar indication for the same patient group. Is that correct? Once there were a predicate.

Right now we don't have a predicate, but once there is a predicate, for example, with PCI devices, those are now approved, is that from 510(k), since there are -- as was described, a predicate that gives comfort with that technology, safety, efficacy in that patient population?

DR. ZUCKERMAN: Not quite. So let's take a step back.

What the FDA is suggesting today is a split regulation where certainly use of non-roller pumps for the traditional cardiopulmonary bypass indication would be Class II/510(k) where we would use the 510(k) system that Dr. Page just mentioned.

But the Agency at this time is advocating that because we don't have enough safety and effectiveness evidence as a class to really conclude, as a class, that there is an adequate risk/benefit profile, that for the temporary ventricular support indication, that this should be a Class III PMA indication.

As such, what that implies is that each manufacturer of a device has to present their own data, including clinical data, to get PMA approval. So if Device A got a PMA and then Device B comes along and it has some attractive characteristics, it could not leverage the PMA for Device A. It would need to stand on its own at this point in time, Dr. Page.

DR. PAGE: Okay. Thank you for clarifying that.

So if I understand you, and I think for the Panel's benefit, as well, then each subsequent device that comes through would undergo a separate PMA and there is -- at what point is a predicate established such that a 510(k) can be an option for similar technology, similar patient population? And a predicate that has been demonstrated through a PMA process, that there is both efficacy and safety that's satisfactory?

DR. ZUCKERMAN: You know, we would ideally envision the situation similar to the balloon pump situation where, you know, ideally, there would be a number of manufacturers and trials that would be performed.

If we, meaning both the Panel, industry, and FDA, saw consistency in results that allowed us to conclude that there's a reasonable maturation of technology producing consistent results both pre-clinically and clinically, we can always consider this at a later date. But I think the problem that the Agency has right now is that we don't see these preclinical and clinical datasets before us.

DR. PAGE: I think we all understand that fully. Thank you very much for that clarification.

The next point to clarify -- and for the record, I sat on a similar panel that discussed whether to reclassify AEDs, and as I recall, because for the obvious reason that one would not want to suddenly not have this

technology available, there was a grace period. For this indication, and that being ventricular bypass or high-risk PCI for non-roller pumps, if that were given a Class III, as long as there is an effort within a certain number of days to develop a PMA, devices would be available for a grace period such that the physicians who we've heard loud and clear believe these are necessary at the time, that those devices would still be available during the process where PMA was being developed and pending review by a panel for efficacy and safety. Is that correct?

DR. ZUCKERMAN: Yes.

First of all, I want to thank the physicians and patients who just spoke in the previous presentation. I think it's very important to recognize the message that we heard from SCAI, individual physicians, and I suspect, from the physicians on this Panel, that the devices are an important class of devices and that, from a public health perspective, we need to respect the availability of these devices and while at the same time developing a constructive regulatory pathway.

So, for example, with respect to the company that we heard from today in significant detail, you know, again, this is just one thought that we need to explore with individual industry sponsors. It may not be necessary to collect additional data as opposed to having a thorough review of the data that is presently available. As I stated before the lunch break, I was impressed with the Panel in that it was trying to conduct a PMA-level

review.

So one option is for each manufacturer in this space to really get together, efficiently, the presently available data that's applicable and that may be pertinent for certain manufacturers in this space.

On the other hand, there may be other manufacturers that may need additional data, and certainly, from the FDA perspective, given the importance of this field, we would work diligently with those manufacturers and recommend that they utilize our pre-submission process so that we can get aligned with regards to necessary data requirements.

DR. PAGE: Thank you. But if I may summarize, there is the potential for a grace period? These devices would not be removed? They would be available pending companies undertaking a PMA process; is that correct?

DR. ZUCKERMAN: Yes. And if you want the specifics of how that works, can Margie Shulman come back to the podium if she's still here?

DR. PAGE: I don't know that we need the specifics.

DR. ZUCKERMAN: Okay.

DR. PAGE: I just believe that --

DR. ZUCKERMAN: Yeah.

DR. PAGE: -- people need to be aware that this would not be a sudden withdrawal of this technology being available to patients and their physicians all of a sudden.

I see a few hands up, but I had someone else raise their hand before, unless this is specifically related to this issue.

Dr. Somberg.

DR. SOMBERG: It was clarified in our last two-day -- yesterday's meeting, that there is a period when they finalize a ruling, and after that point there's 90 days for a PMA to be submitted. And that may take up to a year, so we talked about a year plus 90 days for the PMA process. But whenever that final demand for a PMA is put forth, you have 90 days; otherwise, you are essentially selling a misbranded product.

DR. PAGE: Just to be clear, maybe it will help, Margie, if you don't mind commenting, that the 90 days is just to have given notice that you're anticipating submission of a PMA; is that correct?

MS. SHULMAN: Kind of.

(Laughter.)

DR. PAGE: Make it clear for us, please.

MS. SHULMAN: Hi, Marjorie Shulman.

The 90 days would be to submit a file-able 510(k), so -- PMA. 510(k), you know. A file-able PMA.

So it would have to have all the required administrative elements for it, so it doesn't have to be a complete PMA.

DR. PAGE: Okay, thank you.

DR. SOMBERG: What is the distinction between a file-able and

a complete one? You have to have the data in the PMA to be file-able. You can always submit supplements subsequently.

MS. SHULMAN: You're absolutely right; I misspoke. I mean, it has to have most -- it has to have all the administrative elements and the data, but then we may need additional data so we could put the PMA not approvable or approvable pending deficiency to get the remaining data.

DR. PAGE: Dr. Naftel.

DR. NAFTEL: Well, I thought I understood. Now I realize I don't.

(Laughter.)

DR. NAFTEL: So I understand there could be a year before you come up with the final rule and then you've got this 90-day clock going, but what we discussed yesterday some and we all know this, a PMA tends to take 2, 3, 4, 5, 6 years to design the study, collect the data, and all that, so I'm a little -- well, I'm totally confused.

Are you talking about a real, live PMA that's submitted or are you talking about --

DR. ZUCKERMAN: Okay. So Dr. Naftel -- Margie.

MS. SHULMAN: Oh, go ahead. No. I mean --
Marjorie Shulman.

It would be a real, live PMA or it would be a complete -- as complete as they have, but it does not have to be approved for that company

to continue marketing.

DR. NAFTEL: Yeah, but I am -- well, I know I'm correct because I've worked with a lot of companies. A PMA takes 3, 4, 5 years, not 90 days.

MS. SHULMAN: Correct.

MR. AGUEL: Can I?

MS. SHULMAN: Yes.

MR. AGUEL: Can I add some clarifying words, hopefully?

Pending whatever recommendation we get and advice that we get from the advisory committee, FDA takes that back and considers putting out a proposed final rule. Once that goes out, there's a period for public comment, where we consider all the comments and come up with a final rule at which point, after that, there could be a call for PMAs. Once a call for PMA goes out, there's a 90-day period to submit a PMA to FDA.

DR. NAFTEL: But 90 days? I'm talking 4 years. I'm still not understanding. Nobody does it in 90 days. You don't get your IRB approval at the local institutions in 90 days.

(Laughter.)

MR. AGUEL: I think maybe you're referring to 4 years to collect data, and as Dr. Zuckerman said, there might be the potential for just submitting in the PMA data that may already be in existence that -- as part of the PMA. Maybe Dr. Foreman can clarify.

DR. FOREMAN: So hi, this is Christy Foreman. Let me take a

stab at this.

So as we explained yesterday, you know, we're talking about devices that, in many cases, have been on the market for many, many years, so there is data out there. And as we said, with the 515 process, this is an administrative process where it is not our intent to remove devices from availability or from the market; we just need to put them in the correct regulatory pathway.

So what we would do is we would take the considerations from the Panel today, we will formulate a position, we will put out a proposed rule. Proposed order. I'm sorry, the law changed; proposed order. We get comments. We would then do a final order.

When that final order is sent out, the manufacturers have 90 days from when that final order is in effect, if we call for PMAs, to submit a PMA to the Agency. They may continue to market their product while it's under review with the Agency. So in many cases -- we talked about a lot of data today that's already available. We would fully anticipate that that PMA application would contain that information so there may or may not be a need to generate new de novo-type clinical data, that we will leverage existing knowledge. The question is how does that knowledge translate to the device individually versus as a class. And I think when you have a large body of knowledge on a particular device, that goes into a PMA review for which we would review and consider the risk/benefit profile.

DR. NAFTEL: And so let me just push a little more. So I understand what I think you're telling me, that a lot of data may exist and they can pull it together, but you're telling us today that the data doesn't exist for a lot of these devices. So it's not connecting.

DR. FOREMAN: So in part, we have "Is there data for the device type as a whole?" And what we are saying today, for non-roller pumps, for the standard bypass indication, we believe that there is sufficient information and we believe that we can -- essentially, what we're asking you to do is for bypass, change the indication. Right now we are dealing with a device that has already been determined by previous advisory committees to be Class III.

We believe there is sufficient information out there for the non-roller pump for bypass indications to say, you know what, let's actually take this down a regulatory class. Looking at the literature, there is sufficient information out there. We can say that we think we can regulate, with that body of knowledge and special controls, we can regulate that as Class II.

For the temporary ventricular support, we don't believe there is sufficient knowledge for the device class, as a whole, to support safety and efficacy for the device class, in part, because we're dealing with very different technologies. In one case you have a micro-axial pump for this indication; in another case, you have a centrifugal pump for this indication. The special controls for those two are somewhat challenging because they are very different devices.

I think you saw, in the Thoratec presentation, they had, I thought, a very nice presentation where they showed the different devices and you saw devices that looked very similar, and then you'd have this nice long catheter-based micro-axial pump, which is just a very different device.

So we spent a lot of time today talking about data that is available between PROTECT I, PROTECT II, the SYNTAX study. That data exists; we acknowledge that data exists. Our concern, as an Agency, is that how translatable is that data from a micro-axial pump to a centrifugal pump for that indication. That's what we're saying doesn't exist.

DR. PAGE: Does that help?

As I see it, what we have here is -- the group we're talking about, really, is the ventricular assist group under 6 hours. And the issue that I think the committee all has concern about is, if this partial group -- and I think we understand the recommendation of Class II for the bypass, cardiopulmonary and circulatory bypass, but for this other group, we're hearing clearly that we wouldn't want those devices to suddenly no longer be available, and we're hearing clearly that that would not be the case; there would be a grace period.

And what I'm hearing is that the data that we have seen might be put forward as a PMA. I'm not saying how a panel -- it would be a different panel -- would review this, but that could be put forward. And pending that, there would be no change in availability of that device.

What we need to keep in mind, as a panel today -- and we've been kind of in the weeds in terms of looking at specific data on one trial, especially for safety and efficacy of one device; that's not what we're doing here today. This is not the PMA panel. This is the panel that's looking at this class of device, what's available, what might be available in the future, and should this be considered a Class III as a group or be split by indication, maintain Class III for the group and have each device come up with its own PMA, and the circulatory or cardiopulmonary bypass be downgraded to Class II.

Did I fairly summarize, Dr. Zuckerman?

DR. ZUCKERMAN: Yes, that's our general charge today.

DR. PAGE: Great.

Now, I had hands raised. The first one I saw was Dr. Cigarroa and then Dr. Brinker.

Dr. Naftel, I know you wanted to ask some questions about the statistical analysis. Is that still -- do you want to be on the list?

DR. NAFTEL: Just a small --

DR. PAGE: Okay. So we'll start with those two.

Dr. Cigarroa.

DR. CIGARROA: My question was answered, that is, continued availability through a PMA process should we decide to classify as -- remain at III for the temporary ventricular assist under 6 hours.

DR. PAGE: Great.

Dr. Brinker.

DR. BRINKER: So I'd just like to clarify a couple of things. How confident is the FDA that they need more information to establish special controls for these devices as a class? It seems to me, over all these years, you should know what the odds and ends are, and you should know what would encompass the control of the manufacture of these devices. And it's really independent of efficacy, if we assume that we're looking at indication directed efficacy.

So, really, how much more do you need for special controls as one part of this whole discussion? Is that something you don't have any confidence in establishing?

DR. ZUCKERMAN: I think you've raised a critical question to -- I think the review team will start and then I may add a few comments.

MS. WENTZ: So your question is how much confidence do we have in developing special controls in a technology, and this ventricular support that you say has been out there for a while and we have some data; is that correct?

DR. BRINKER: Yeah. Basically, the construct of the devices that you're looking at has been around for at least 6 years, 4 years. Six years. And you should know that's what the special controls are, really. The manufacturer doesn't involve, really, efficacy issues.

MS. WENTZ: Okay. So special controls aren't just manufacturing, okay. Special controls are developed to mitigate the risks that we identify for the device.

DR. BRINKER: But those are all something you can do with the product pretty much on a bench top, isn't it?

MS. WENTZ: Not always.

DR. BRINKER: You're not asking for any clinical data.

MS. WENTZ: Not always. And we don't know. At this point, what we're saying is that we don't understand the risks well enough to know whether or not the special controls are all going to be bench related or whether we're going to need animal or whether we may need clinical.

One other thing I wanted to point out is that the patient population that is being treated with these specialized devices is a relatively new patient population, so we really don't have the history that you're talking about. There may be data out there; we have not seen a lot of it. And that's basically what we're saying here, is that if we go to Class II, we're out. There may be data out there that we have not seen that may be individualized for these different devices, and they may be able to pull together this data that they have that we have not seen that may be able to support a PMA.

DR. ZUCKERMAN: So, Dr. Brinker, let's take a step back.

I think you're asking a fundamental question regarding reclassification, but I think reclassification has two components.

The first component is really to understand is there enough safety and effectiveness data out there, especially clinical data, for a device class to go from Class III to Class II.

And then the second question is, if we conclude that, you know, can we develop the appropriate special controls for Class II regulation.

And certainly, from the FDA perspective, I think the bigger issue that we have, at this point in time, is that we don't see enough safety and effectiveness data out there, especially from a clinical perspective, to say that this whole class of devices has a favorable risk/benefit profile to go from Class III to Class II.

Then the second part of it would be, as you and Catherine were discussing, developing the special controls. Certainly, I do think we would be challenged, but we could employ experts to help us out. But I do think we have to first get past point Number 1, which is what I just mentioned.

DR. BRINKER: So I'm glad you mentioned that. I want to go back a little bit to find -- just explore how we got into this situation.

When the 510(k) was approved as a Class III device, was there the implication that they would need to involve with that, that there would need to be this extra data generated before there was full approval?

MS. WENTZ: So when this 510(k) was originally cleared, it was cleared with a very broad indication. And I think somebody came up from Abiomed and presented that the 510(k) included clinical data in there all from

high-risk PCI patients.

I need to make it clear that that data was not used to make a safety and effectiveness determination on that patient population, but was used for other reasons. There was clinical data in there, but it was not used to support the high-risk patient, PCI patient, population. And that device was cleared with a broad indication that matched the predicate, and that's what the 510(k) process is about, is about equivalence to a predicate device.

DR. BRINKER: Okay. So I wasn't trying to talk about one product, and I'm glad you did. I was just saying the whole issue of predicate devices, 510(k) approval as a Class III device, are all of them -- was there an assumption for all of those, they would need to provide the kind of PMA-type data? So the answer is no?

MS. WENTZ: No.

DR. BRINKER: Okay.

MS. WENTZ: And we have to go back to the original definition of that classification of devices, which was for cardiopulmonary bypass and bypass procedures.

DR. BRINKER: Okay. So now I want to -- let's just look at the example you brought up by yourself. And that is you would be happy, would you not, if the indications that you approved the device or cleared the device as, as a 510(k), if they use the exact indication that you just suggested, that was your understanding, you would be happy to -- or maybe not -- approve

that device as a Class -- rate down, regulated to a Class II for that indication, and does that allow for other indications to be processed under a PMA, if necessary?

MS. WENTZ: Not quite sure I understand what you're saying. So they were cleared for a very broad indication.

DR. BRINKER: Yes.

MS. WENTZ: Okay. And they can market it under that indication.

DR. BRINKER: Yes.

MS. WENTZ: If we decide here that the temporary ventricular support indication does not fall within that broad indication, that it should be Class III, and if they want to promote it for that, then they need to go the Class III PMA regulatory pathway.

If they want to continue promoting it for the other indications that we have considered as Class II, then they wouldn't need to provide anything else, no other clinical data.

DR. BRINKER: So the point I'm confused about is the high-risk angioplasty as a subgroup as opposed to all the other things that might fall into that group, into that approval. And you're really asking us sort of a different question: Does high-risk angioplasty require a separate dataset to distinguish that indication, but not necessarily the device for the other indication it was originally approved for?

MS. WENTZ: Correct. And that is actually going to be part of our questions. We're going to throw that question right back to you.

DR. BRINKER: So, again, we're talking about everything as -- everything in this class of 510(k) approvals for assist devices or bypass devices, and there is the possibility that we could end up saying that for some of these devices, you can weed out the high-risk angioplasty support, those special areas, indications, specific indications that you think there's not enough information for and require more information for that, but still approve the device for marketing under its original charter, which is --

MS. WENTZ: Correct.

DR. BRINKER: -- Class II?

MS. WENTZ: Correct. So if there's a device on the market that is currently being used for both and we do split the regulation, that company can continue to market their device under the Class II indications for use and gather data for the Class III indication, correct.

DR. PAGE: Things clear, Dr. Brinker?

DR. BRINKER: No. Only in that we've called this a Class III indication and the only thing that makes it a Class III indication is that we don't have enough data, historically, to say that it should be a Class II -- we don't have enough data to set a ground rule. So I'm not sure that the Class III is only a function of data as opposed to being a different kind of device; it's a sub-categorization based on indication.

MS. WENTZ: Right. And I think we said at the beginning, this is very difficult -- I think Dr. Yuh brought it up -- in that we're actually considering both.

So there was a new technology that was introduced in 2008 along with the old technology that was starting to be used for this indication. And at the same time, these technologies started becoming very prevalent in use in high-risk PCI and other ventricular support, temporary ventricular support, indications. So we are splitting the regulation based on technology and based on indication.

DR. BRINKER: One final question. I just talked about this Abiomed device in the last few minutes. And I suppose that you're going to weed out the high-risk angioplasty indication for all -- we're going to be talking about all the devices lumped into that. So you have no problems -- am I correct? -- that you have no problems in a Class II down-regulation for everything except -- for all these devices except for the high-risk angioplasty?

MS. WENTZ: No, not exactly. So it's not -- the buckets aren't high-risk angioplasty and everything else. The buckets are cardiopulmonary bypass and circulatory bypass, as we discussed.

DR. BRINKER: Right.

MS. WENTZ: And then temporary ventricular support, which includes other --

DR. BRINKER: Okay.

MS. WENTZ: -- procedures besides high-risk PCI.

DR. ZUCKERMAN: Okay. And for clarification on that, the Panel members can look at FDA Slides 100 and 101 to understand that split regulation.

DR. PAGE: Could we put those up again? I've seen almost every panelist raise their hand during this discussion. I think, in part, because you believe you understand this and can clarify it for the rest of us. Let's just look up --

(Laughter.)

DR. PAGE: Look at the slide and then I'm going to -- I've seen Dr. Hirshfeld, Dr. Dehmer, Dr. Allen, Mr. Barrett, and Dr. Katz all raise their hands, and that's the list I have right now. And, Dr. Slotwiner, you were in there, as well.

But if we can pull that up and just look at that once and for all and then raise your hand again if you still have comments about this specific issue, and then I'm going to go on to other questions because this is our last opportunity to ask questions of the FDA and the speakers that we've heard this morning and this early afternoon.

So if we can put those slides up, please.

And I should also mention we will parse these out. I know all the panelists have read all the questions in advance. We will parse these out when we go through the questions. So right now, we want to be clear on

what we're being asked, and we want to ask any questions further of the FDA and the other speakers today.

Who from FDA would like to take us through these two slides?

MS. WENTZ: This is Catherine Wentz.

So do you just want me to read through it?

DR. PAGE: I think that would not be a bad idea.

MS. WENTZ: Okay, all right. So, again, we are recommending that the use of these two technologies be split into two categories based on new identifications for non-roller type cardiopulmonary bypass blood pumps.

So the first bucket is for cardiopulmonary and circulatory bypass. And the new identification for this part of the regulation is as follows: "A non-roller type cardiopulmonary and circulatory bypass blood pump is a device that uses a method other than revolving rollers to pump the blood through an extracorporeal circuit for periods lasting 6 hours or less for the purpose of providing either (a) full or partial cardiopulmonary bypass" -- that is a circuit that includes an oxygenator -- "during open surgical procedures on the heart or great vessels or (b) temporary circulatory bypass for diversion of flow around a planned disruption of the circulatory pathway necessary for open surgical procedures on the aorta or vena cava."

Next slide.

DR. PAGE: And just to clarify, the recommendation is for a Class II --

MS. WENTZ: Class II, correct.

DR. PAGE: -- with special controls.

MS. WENTZ: Yes.

DR. PAGE: All of these are centrifugal pump devices at this time.

MS. WENTZ: Currently. Currently, the technology that has been cleared through the 510(k) regulation or through this regulation and the 510(k) pathway has been the centrifugal pump --

DR. PAGE: Thank you. Let's go on to the next slide, please.

DR. BRINKER: Can I -- the point of order, question.

DR. PAGE: Tell you what, Dr. Brinker --

DR. BRINKER: This is vital to your question. Please. Because I still don't understand how the micro-axial device was approved with what you say --

DR. PAGE: Dr. Brinker, please. Let us --

DR. BRINKER: But --

DR. PAGE: Please hold your question --

DR. BRINKER: Okay.

DR. PAGE: -- and let us go through this, and then if that's not clear -- but micro-axial, you'll notice, was not mentioned at all in that. It's a non-roller pump.

Now, please, let's proceed with the next slide.

Thank you.

MS. WENTZ: Okay, thank you.

So the second bucket that we are considering for Class III, premarket approval application, is for temporary ventricular support. And the identification for these devices is as such: "A non-roller type cardiac support blood pump is a device that uses any method resulting in blood propulsion to provide the temporary ventricular assistance required for support of the systemic and/or pulmonary circulation during periods when there's ongoing or anticipated hemodynamic instability due to immediately reversible alterations in ventricular myocardial function resulting from mechanical or physiologic causes. Duration of use would be ≤ 6 hours."

If you notice, with this definition, we do not specify only high-risk PCI patients because it does include other procedures, as well.

DR. PAGE: So just to summarize, it's Class III, that is a subgroup of the left ventricular support, and this includes both centrifugal and micro-axial pumps in the current technology that has come through the 510(k) process; is that correct?

MS. WENTZ: Correct.

DR. PAGE: Okay, great.

Dr. Brinker, I'm sorry to cut you off, but I just wanted to make sure we're all on the same page with that, and now you wanted to visit the question of how this different technology got through this.

DR. BRINKER: Was approved under the 510(k).

DR. PAGE: That's a great question.

MS. WENTZ: That is a great question.

So the device, when it came in, was, as I said, approved with a very broad indication, and the indication matched the predicate indication, which was basically for -- it was one of the evolved indications that went from cardiopulmonary bypass to both cardiopulmonary and circulatory bypass.

It was approved for that use -- or it was cleared for that use, excuse me, and then we subsequently found out that the clinical use of the device was for this temporary ventricular support, specifically for high-risk PCI, which when you read the very broad indications, it could possibly be interpreted as including that patient population, as well.

We, as FDA, do not believe that it should be interpreted that way; we have never interpreted it that way. It has always been pretty clear that it was for cardiopulmonary bypass and circulatory bypass. So that's why we're here today, to try to categorize the use of these devices into the appropriate classification.

DR. PAGE: So to summarize, there's been both indication creep and technology creep in this general area. Again, we're looking at the general area today, not any specific device. But we may be parsing things out.

Now, the people who had their hands up I mentioned before, please raise them again just so I can know who is asking for -- and

Dr. Hirshfeld, I think you were the first I noticed.

DR. HIRSHFELD: Okay. I've been trying to bring some order out of all this as we've been messing through this. And I'm looking back to the parallel of what we did yesterday with the balloon pumps, because we basically cleared balloon pumps to Class II based on the fact that they had demonstrated hemodynamic support, and so it was basically the fact that they were demonstrated to be effective as hemodynamic support rather than that they had been shown to be effective in clinical outcomes.

And so now we're in a different situation because we're now holding this technology, which albeit is not as mature and is considerably more complex, we're considering holding it to a clinical outcome standard rather than to a hemodynamic improvement standard. And so I think that if the standard were to demonstrate that these devices improved hemodynamic profiles and hemodynamic performance, that would be one criterion by which you could determine that they were effective.

So what's happening now is that there's a feeling that there has to be a clinical outcome determination of effectiveness other than a measured outcome determination of effectiveness. And I think that it would be a value to examine the relative merits of those two standards and why the Agency feels that the outcome standard is important.

And if I just might make a comment about the efficacy data that we've seen. I'm not at all surprised that the failure to demonstrate

efficacy in PROTECT II occurred because the likelihood is that most of the data are noise. In any trial of supported angioplasty, probably 85% of the patients would have done just fine without the support. The problem is that the physicians performing the procedure don't know who the other 15% are, and so they frighten easily and they want to support the patient.

DR. ZUCKERMAN: Okay. So Dr. Hirshfeld, let me take a stab at that because I think this morning, as a hemodynamicist, you actually pointed out some of the problems with extrapolation of just devices providing hemodynamic support.

And so there are several issues here, but the paradigm that I'd like the Panel to continue to concentrate on is the following: Instead of talking about a class of devices, we're again honing in on one particular device, and as you noted this morning, the cardiac power output increases significantly, but yet in this particular trial, the periprocedural MI rates went in the wrong direction.

Now, the Sponsor has proposed an explanation perhaps why that occurred, and our goal here is not to debate whether or not we believe that, but just to point out that for this particular device, there are some safety and effectiveness questions; there's still a question mark regarding benefit to risk; and this is supposedly the best dataset in this particular field. And so that's where our conundrum is.

Certainly, there is some combination of hemodynamics and

clinical effectiveness; it doesn't need to be a mortality endpoint, as you were suggesting. But I do think we need to be realistic with what we're dealing with in this particular class of devices where we're still debating the merits of one particular trial that really is defining the whole device class.

DR. PAGE: And, again, you're asking us not to do that,

Dr. Zuckerman. You're asking us to look more broadly.

Dr. Naftel, do you have any other --

DR. HIRSHFELD: Could I just --

DR. PAGE: I'm sorry.

DR. HIRSHFELD: Bram, I thank you for stating it more articulately than I was able to because what you basically said -- I was raising the question as to whether a measurable efficacy endpoint in terms of functional performance as opposed to a clinical outcome endpoint should be the standard to which the device should be held. And I think you just answered that question, so thank you.

DR. PAGE: Thank you.

Dr. Naftel, did you have any other comments or questions?

DR. NAFTEL: Just a comment on the presentation on the Impella. I wanted to say to the company I thought the analyses were just absolutely excellent where you added that extra 125 patients, and I would have been proud to have been part of that.

However, I do just want to really remind everybody, and

especially me, of what Dr. Zuckerman said this morning, and that is, those analyses, as good as they were, if they had gone through a PMA process, they likely would have been a bit different and maybe - - well, they would have been different. They would have been a little more subdued, might be the right word.

And I think this is really important as we talk about these possible PMAs based on existing data that -- and forgive me, I don't even think presentation of existing data could happen in three months because there would be a lot of back and forth with the FDA over what they thought was appropriate, they'd want to look at the data, so I'm totally hung up on the three-month thing, in case you can't tell.

(Laughter.)

DR. PAGE: Thank you.

MS. WENTZ: Can I make one comment? I'm going to try -- I'll be the fourth person to try to clarify that.

So the 90-day period, I think as Margie and Christy said, is the period by which the sponsor would have to put together their PMA and submit it and have it be filed. The review process will go through everything you just said, the back-and-forth, the additional -- you know, if we need additional information, so the review process takes longer than 90 days. But to gather the information needed for the PMA, for a file-able PMA, would be 90 days.

DR. NAFTTEL: Okay, just one last shot, and I will not bring this up again. I have been in the middle of many, many PMAs, and there's over three months to define the primary outcome and the secondary outcome in the adverse event definitions and setting up meetings and deciding on the design. This is not a three-month process.

DR. PAGE: Let me take a shot at this.

It has to be submitted. All of that other time can happen beyond the 90-day period and it can go on months, if not more than a year or more. All the while, the device is in its grace period.

DR. NAFTTEL: But it has to be data that's presented; that's what I'm saying you can't do in three months.

DR. PAGE: Well, I think we're hearing that there is going to be a back-and-forth and if the data aren't -- everything that was needed, then it might -- they might be asking for more data. But once it's been filed --

DR. ZUCKERMAN: Okay. Dr. Page, I think you've got it, and I would just ask that given the importance of this discussion, we not dwell on that topic, Dr. Naftel. In addition to everything you've heard, we have regulatory discretion. We understand, as a class of devices, how important this field is, and let's go on to some other topics.

DR. PAGE: I think it's important to document, though, Dr. Zuckerman. You are reassuring us that the device would be available through a reasonable period of time as defined by both the FDA and industry

to get things together if it were a Class III, and the device would still be available during that time for patients and physicians in the use in a grace period?

DR. ZUCKERMAN: Yes, because we've heard the significance of this --

DR. PAGE: So I just want to make sure everybody heard that.

DR. ZUCKERMAN: -- device -- set of devices here.

DR. PAGE: Great, thank you.

Dr. Allen, I did have you on my list, too, for a comment or question.

DR. ALLEN: I'm going to take a swing at clarifying for Dr. Brinker and maybe John's comments.

Let's look at it this way: We've spent two days here talking about devices we're going to reclassify, and yesterday morning we looked at extracorporeal counter-pulsation. Not once did we talk about Company A, Company B, Company C that manufactures whole different kinds of devices. And it was very easy for us to come to the conclusion that yeah, we could reclassify that as Class II because all the devices are the same.

In the afternoon, we spent a long time talking about balloon pumps. Not once did somebody talk about a Datascope balloon being better than an Aero balloon being better than a Medtronic balloon. And it was very easy to come to the conclusion to reclassify those as Class II because all

balloons are the same.

The conundrum we're in today, which I hope we can all understand, is that not all roller pumps are created equal -- non-roller pumps are created equal. And the dilemma for the FDA is they can't develop special controls to regulate devices that function completely differently.

DR. PAGE: Thank you.

Dr. Slotwiner.

DR. SLOTWINER: Yes, I want to follow along the same lines and urge my fellow panel members to recognize that these centrifugal pumps are incredibly new. This is such a young, young field.

DR. PAGE: You mean axial?

DR. SLOTWINER: Axial, I'm sorry. Thank you.

Axial pumps -- I don't want to use a name -- are so new. The other devices we've been talking about are 40 years old. It's very difficult to know what safety and efficacy -- difficult to predict what they're going to be used for in the future. Already I have alluded to one indication that is changing the practice of electrophysiology. These are going to change so dramatically over the next 10 years that it's very difficult to predict what safety and efficacy goals we're going to want to look at in the future. So I would hate to restrict the Agency's hands to be only able to look at hemodynamic data and not clinical data.

DR. PAGE: Great, thank you.

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Dr. Dehmer.

DR. DEHMER: I was beginning to think the Chair did not recognize this side of the --

(Laughter.)

DR. DEHMER: So on this panel and other panels that I've had the privilege to serve on, I'm usually labeled as the quiet one because I firmly believe it's better to remain silent and have people think you're stupid than to open your mouth and remove all doubt.

That being said and with the indulgence of the Agency, I'm still trying to struggle a little bit with understanding how we got here. And what seems to have occurred is the Agency, working within the construct of the rules that it must follow -- and you cannot make up new rules as you go -- had these newer types of support pumps come along. And the request was made to have these approved under the 510(k) umbrella with there being a predicate device, not so much a device, perhaps, as a predicate classification that this new device was said to fall underneath.

And now what has happened is, after a period of time, everybody has come to realize that these newer devices, these axial pumps, are not really appropriate for falling underneath the non-roller pumps. They are substantially different. So now what the Agency is trying to do is to just get this classification straightened out without any looking back and saying, well, this never should have happened or, you know, it is what it is.

And I mean -- I'm looking at you, Bram, but I mean you're just trying to more or less say we need to get this revised so that things are in the right class where they belong. Fair?

DR. ZUCKERMAN: I'm going to let Ms. Wentz also comment, but I think that's a very good summary. We just want to get a logical construct developed for moving devices through the process with appropriate regulatory paradigms.

DR. PAGE: And, Ms. Wentz, if a yes works, you can just answer with a yes.

MS. WENTZ: You got it.

DR. PAGE: Perfect, thank you.

Dr. Cigarroa.

DR. CIGARROA: So as a person who spends a fair amount of his time doing high-risk coronary work as an interventional cardiologist in a university setting, I utilize this class of devices in select patients. And the interesting thing, it is a class of devices. The current ones that are available to us, each have unique characteristics, unique impacts on hemodynamics, fundamentally different way of device insertions, and a different set of complications.

And so, as a user, to me, now looking at it from your perspective, special controls as Class II, which seem quite challenging given how different the technology is -- and we went through this yesterday with

intra-aortic balloon pumps. And the statement was made, one of our concerns was, as the field continues to evolve, if there's a fundamental transformation of technology as it relates to the class of IBP, it would not be maintained in Class II despite the downgrade. It would be looked at as Class III. I think that's the situation that, whether we like it or not -- and myself, as a user who depends upon this, find ourselves in.

DR. PAGE: Thank you, Dr. Cigarroa.

Mr. Barrett.

MR. BARRETT: Well, it's a long way back to one of your first questions in the afternoon, but I wanted to make a comment.

You were seeking to clarify some of the regulatory implications of having the device remain in Class III and then have the PMAs called for. And I think it was clarified that you can't use a predicate anymore, that each sponsor has to have an independent set of data and that has to stand on its own to receive the PMA approval to stay in Class III. And it was correctly stated that there is a process at some point in the future where those Class III devices could be down-classified again.

Just to provide some industry perspective, that's certainly true; the regulations allow for that. But that's not, in my opinion, an easy or a routine route. It takes a tremendous amount of inertia when a class of devices are in Class III to get to the point where the discussion starts to happen and the process starts to happen to move back down to Class II, and

it essentially requires something like what we're doing now to happen again at some future date. I just wanted to clarify that.

DR. PAGE: Yeah, I appreciate that, and I like to think of it being less inertia but more due diligence for safety and effectiveness, but I certainly -- your point is very well made.

I've seen Dr. Katz, Dr. Kandzari, and Dr. Greenfield's hands up, so Dr. Katz.

DR. KATZ: It seems to me that a lot of the difficulty, as stated by Dr. Allen, is in the classification of this waste basket of non-roller type blood pump. And because I haven't heard many concerns about centrifugal pumps -- there have been lots of concerns raised about the micro-axial technology. And if they're left together, the message that I'll get, as a clinician, is that I can take my centrifugal pump-based cardiopulmonary bypass circuit and use it today to do a coronary bypass operation or replace a valve, but if, God forbid, I run a stick of catheter in a coronary artery and blow it up, I can't do that even though it's the exact same equipment.

MS. WENTZ: This is Catherine.

As we stated yesterday, we don't regulate the practice of medicine.

DR. KATZ: But you are. But de facto, you are, because you'll be saying, I can use this as a heart/lung machine to use it for bypass, is what it says, but it would be Class III if I wanted to use it to assist in a high-risk PCI.

Same exact equipment.

MS. WENTZ: You can use the device as you see fit for your patient. The device cannot be labeled or promoted for a Class III indication unless it's got an approved PMA.

(Pause.)

(Laughter.)

DR. PAGE: Thank you.

Dr. Kandzari.

DR. KANDZARI: At the risk of deafening applause, I'm going to ask an entirely independent question.

DR. PAGE: Thank you so much.

DR. KANDZARI: Catherine, you mentioned earlier today that we don't use postmarket surveillance for measures of safety, and that struck me as unusual given I thought that was a principal directive of postmarket studies.

DR. ZUCKERMAN: Okay. Dr. Kandzari, I'm glad that you brought up this key point, so I'll let Catherine begin, and then I'd like to add a few comments.

DR. KANDZARI: Okay. I would also just like to finish my comment, too, is that is it in that context, then, can we not use additional data to support measures of safety that might be outstanding concerns even if these products were downgraded to a Class II?

Thank you.

MR. AGUEL: I can certainly give it the first shot.

Fernando Aguel, FDA.

Postmarket surveillance can and does collect safety information. What postmarket surveillance cannot be used for is to collect data on safety outstanding for the premarket process, so to support the initial safety and effectiveness conclusion.

It can collect safety data to see long-term effects of safety of the device, but not for collecting the safety data that is necessary to show the safety and effectiveness of the device before approval or clearance.

DR. KANDZARI: But yet you agree that data, then, could be used on a revisited basis to be incorporated into the product labeling in the IFU?

MR. AGUEL: Yes.

DR. PAGE: Thank you.

Dr. Greenfield.

DR. GREENFIELD: Yes. I have some concerns about terminology here. And I may be the only one.

It bothers me that we're defining this new class by what it isn't rather than what it is. And I think we make a very large assumption with that, that the only alternative to non-roller type blood pumps would be a magnetic centrifugal pump. And there may be other technology that comes along. I

mean, we may find ourselves with capabilities in electrical, electromagnetic, other kinds of electromagnetic dark forces, whatever, but I would be questioning whether or not this is opening the door too wide to any other technology besides the centrifugal magnetic pump.

DR. ZUCKERMAN: Okay. So I would ask the Panel to again refer back to Slide 100, and Ms. Wentz can take us through the 510(k) process when there's a significant difference in indications or technology, how that type of pump would then become a PMA and would have to generate its own data to show us a reasonable assurance of safety and effectiveness.

MS. WENTZ: This is Catherine Wentz.

We've been talking about the centrifugal pump for cardiopulmonary and circulatory bypass because that's what's been cleared.

You're right; down the road there may be new technologies that could be used for cardiopulmonary or circulatory bypass that don't look anything like the centrifugal pump.

If they try the 510(k) process, they would come in, they would use the centrifugal pump for their predicate, and we would go through our decision tree, and the first question is about intended use. If the intended use matches, which it would, because they're looking for a cardiopulmonary or circulatory bypass indication, then they'd go down to technology.

We would then have to compare the technologies. If there are major differences, then we ask do these differences raise new types of safety

and effectiveness questions. That's a very broad term, it's a very difficult thing to understand and to interpret, but we have to do that.

And if we do find that there are new questions of safety or effectiveness as compared to the predicate device, then that would then automatically become a Class III PMA device based on technology. If we find that the technology does not raise new safety and effectiveness questions, then they can continue down the 510(k) pathway with their original predicate.

You don't believe me.

(Laughter.)

DR. GREENFIELD: Well, I just don't know why we're afraid to define what you want to put in Class II other than by what it's not.

MS. WENTZ: Afraid to define. I'm not understanding what you're saying. We're afraid to define --

DR. PAGE: We're going to be going through the specifics as we parse out these, when we go through the questions, Dr. Greenfield. Unless there are specific questions of either the other speakers or the FDA, I might move forward.

DR. GREENFIELD: Well, I just wondered why it wasn't defined.

MS. WENTZ: Okay, I understand what you're saying.

DR. GREENFIELD: I asked what it is rather than what it isn't.

MS. WENTZ: Okay, I understand what you're saying.

Because we try to define things broadly enough to permit advancements, tiny advancements, in technology that may not raise new safety and effectiveness questions, to promote, you know, advances in technology. If we were to very narrowly define this Class II indication for a specific design of centrifugal pump, then there would not be any -- there would be no incentive for people to try to improve on that technology incrementally.

Any better?

DR. PAGE: I'm going to call this portion of today's session to a close. Ms. McCall, do you have any questions or comments at this point?

(No audible response.)

DR. PAGE: Okay.

That being the case, I think we'll now take a 15-minute break, and then at 5 of 3:00, we're going to resume and start handling the FDA questions one at a time. Thank you.

(Off the record.)

(On the record.)

DR. PAGE: Okay, I'll ask the Panel to reconvene.

At this time, let us focus our discussion on the FDA questions. Copies of the questions are in the folders. I want to remind the Panel this is a deliberation period among the Panel members only. Our task at hand is to answer the FDA questions based on the data in the panel packs, the

presentations we heard this morning, and the expertise around the table.

With this said, I would ask each Panel member to identify him or herself each time he or she speaks unless specifically called on by me and then it will be obvious.

And let's show the first question, please.

MS. WENTZ: Okay. Thank you, Dr. Page.

So the first question: FDA has identified the following risks to health for non-roller type blood pumps intended for cardiopulmonary and circulatory bypass based on the input of the prior classification panels, review of industry responses to the 2009 515(i) order, the Manufacturer and User facility Device Experience (MAUDE) database, and FDA's literature review:

- Alteration in blood composition
- Inadequate tissue perfusion
- Embolism
- Duration of use
- Fluid leakage
- Adverse tissue reaction
- Infection

Part (a) of this question: Is this a complete and accurate list of the risks to health presented by non-roller type blood pumps intended for cardiopulmonary and circulatory bypass? Please comment on whether you disagree with inclusion of any of these risks or whether you believe any other

risk should be included in the overall risk assessment of non-roller type blood pumps intended for cardiopulmonary and circulatory bypass.

DR. PAGE: Thank you.

And during this period, I'm going to want to make sure I get the sense of the entire group and any dissenting opinions, if I end up summarizing. We're not having a formal vote today, although on a couple of the questions later, I think it would be useful perhaps to hear from each and every Panel member.

Let's put this first question out to the Panel and just ask you to answer Question 1a.

MS. WENTZ: This is Catherine.

Do you want me to go back to the slide with the risks?

DR. PAGE: I think we all have it written before us. I just need a panelist or two to say, yeah, I think this is reasonable, and we can move on or -- because we do have plenty to do with the other questions, but we need to get through each one.

Dr. Somberg and Dr. Allen.

DR. SOMBERG: Yes.

DR. PAGE: Well said.

Dr. Allen.

DR. ALLEN: Affirmative, yes.

DR. PAGE: Thank you.

I'm looking around and no one is pushing their -- yes,
Dr. Dehmer.

DR. DEHMER: This came up the yesterday. If embolism is on there, do we want to include stroke and death?

DR. PAGE: Good question. It might be seen as implied, but maybe we should cull that out as the most devastating complications thereof.

Any other comments or clarifications?

Dr. Somberg.

DR. SOMBERG: We had this discussion yesterday, and I forgot the outcome, but I'll just -- it's easier to forget after a few hours here in this low-circulation room, air circulation.

But I must say that I think they're looking for specific risks from the device, and that can be mitigated against and, you know, death is not a specific risk from the device like a leakage or a clot forming on it or something like that. May be a semantic point, but I don't think we serve -- you know, tell me what benefit we serve by identifying it and then -- because we're not going to be able to come up with something specifically to mitigate it. If you can, let me know. I want to include it in my practice, preventing death.

DR. PAGE: I understand your point. I'm sure this has been handled by the FDA before, and we might leave it to them to be as specific or not, as they see fit. Would people be comfortable with that?

(No audible response.)

DR. PAGE: So, Dr. Zuckerman, with regard to Question 1 --

DR. KANDZARI: Dr. Page.

DR. PAGE: Yeah.

DR. KANDZARI: Can I add, I would suggest adding limb ischemia to this.

DR. PAGE: As in limb ischemia to the embolism?

DR. KANDZARI: Yeah, we have inadequate tissue perfusion, but it's not clear if that's solid organ hypoperfusion or limb -- and the cannula associated with some of these devices can induce limb ischemia.

DR. PAGE: Great, thank you.

So for 1a, Dr. Zuckerman, the Panel generally agrees with these complications as listed with the particular additions as you've heard.

DR. ZUCKERMAN: Thank you.

DR. PAGE: So let's go on to 1b.

DR. CIGARROA: Chair.

DR. PAGE: Oh, Dr. Cigarroa.

DR. CIGARROA: Just one clarification. I believe that the limb ischemia would be most appropriately under the additional as the initial portion for cardiopulmonary is simply the pump, itself, whereas the second section for temporary ventricular assist, I think, is more along the lines, I believe, of temporary ventricular assist devices, i.e., Tandem and Impella.

DR. PAGE: I guess for clarification, isn't it used sometimes for femoral cannulation for bypass?

DR. CIGARROA: Correct.

DR. PAGE: So it would be included, I guess.

Okay, great. Let's go on to (b), please. Or to -- yes, to (b).

MS. WENTZ: Correct. In addition to the risks outlined above, FDA has identified the following additional risks to health for non-roller type blood pumps intended for temporary ventricular support:

- Structural/tissue damage to the heart
- Local heat generation
- Flow dynamics

Do you agree that the risks to health identified for non-roller type blood pumps intended for cardiopulmonary and circulatory bypass are also applicable to non-roller type blood pumps intended for temporary ventricular support?

DR. PAGE: I'm seeing a bunch of heads nodding.

DR. SOMBERG: Yes.

DR. PAGE: Dr. Allen.

DR. ALLEN: Yes.

DR. PAGE: So, Dr. Zuckerman, I'm seeing a concurrence with Question 1b.

Going on to 1c.

MS. WENTZ: 1c: Are the additional risks to health identified for non-roller type pumps for temporary ventricular support complete and accurate? Please comment on whether you disagree with inclusion of any of these risks, or whether you believe any other risks should be included in the overall risk assessment of non-roller type blood pumps for temporary ventricular support.

DR. PAGE: So, again, now it's for ventricular support. Same complications.

DR. CIGARROA: List is complete.

DR. PAGE: No additional complications are added. So you have concurrence with Question 1.

Dr. Zuckerman, is this adequate?

DR. ZUCKERMAN: Yes, it is. Thank you.

DR. PAGE: Thank you.

Let's move on to Question 2, please.

MS. WENTZ: Question 2: As defined in 21 C.F.R. 860.7(d)(1), there is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. As defined in 21 C.F.R. 860.7(e)(1), there is a reasonable assurance of effectiveness if there are clinically significant results

in a significant portion of the target population when the device is used for its indications for use and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use.

The FDA believes that available scientific evidence supports a reasonable assurance of safety and effectiveness for non-roller type blood pumps, for use within an extracorporeal bypass circuit for periods lasting no longer than 6 hours and provides either:

- i. full or partial cardiopulmonary bypass (i.e., includes an oxygenator) during surgical procedures on the heart or great vessels, or
- ii. temporary circulatory bypass for diversion of flow around a planned disruption of the circulatory pathway necessary for surgery on the aorta or vena cava;

Question 2a: Do you agree that the available scientific evidence is adequate to support a reasonable assurance of safety and effectiveness for non-roller type blood pumps for these indications?

DR. PAGE: And why don't we take (b) at the same time?

MS. WENTZ: Okay. 2b: Do the probable benefits to health from use of non-roller type blood pumps for these indications outweigh the probable risks to health?

DR. PAGE: So our question is safety, effectiveness, and adequate balance of safety and effectiveness. I'll ask panelists to give their

opinion, and we'll see if we have some consensus.

Dr. Doty.

DR. DOTY: Yes and yes.

DR. PAGE: Yes and yes.

Dr. Slotwiner.

DR. SLOTWINER: Yes and yes.

DR. PAGE: Dr. Greenfield.

DR. GREENFIELD: Yes.

DR. PAGE: I'm hearing yes for both from Dr. Greenfield.

I'm seeing -- may I now ask for anybody who dissents from this?

Dr. Katz.

DR. KATZ: This is where it falls apart for me because I don't see how the mini axial flow device fits into (a) partial cardiopulmonary bypass including an oxygenator, because it's not relevant. So if I block that part out of my mind, I could say yes.

DR. PAGE: And I think you're being asked to block that part out of your mind.

(Laughter.)

DR. KATZ: Okay.

DR. PAGE: And I'm not being facetious. What we're asked about is an indication for which we've seen data on safety and effectiveness. It happens to all (b) in this non-roller -- the centrifugal pump technology, but

just focusing on this, are you in agreement with Questions (a) and (b)?

(No audible response.)

DR. PAGE: Is anybody in disagreement?

(No response.)

DR. PAGE: Seeing nobody disagreeing.

Dr. Zuckerman, the Panel, with regard to Question 2a and b, the Panel agrees. I'm not seeing concerns other than needing to clarify the population we're discussing. And with that clarification, I think we're in concurrence.

Is this response and our deliberation adequate, Dr. Zuckerman?

DR. ZUCKERMAN: Yes, it is. Thank you.

DR. PAGE: Thank you.

Question 3, please.

MS. WENTZ: Question 3: FDA believes that the following special controls can adequately mitigate the risks to health for non-roller type pumps intended for cardiopulmonary and circulatory bypass, and provide a reasonable assurance of safety and effectiveness:

1. Non-clinical performance testing must provide a reasonable assurance of safety and effectiveness with respect to the operating parameters, dynamic blood damage, heat generation, air entrapment, mechanical integrity, and durability/reliability to perform as intended over the intended

- duration of use;
2. The device must be demonstrated to be biocompatible;
 3. Sterility and shelf life testing must demonstrate the sterility of patient-contacting components and a shelf-life for the device that results in a safe (and as intended/labeled) functioning device at the end of the intended shelf-life;
 4. Labeling must include information regarding the duration of use, a detailed summary of the device-related and procedure-related complications pertinent to use of the device, and appropriate warnings and contraindications.

Question 3a: Do you agree that these special controls are adequate to mitigate the risks to health for non-roller type pumps intended for cardiopulmonary and circulatory bypass, and provide a reasonable assurance of safety and effectiveness?

Question 3b: Please comment on whether you disagree with inclusion of any of these special controls, or whether you believe any other special controls are necessary.

DR. PAGE: Thank you. Questions or comments from the Panel, please.

Dr. Naftel.

DR. NAFTEL: Just to clarify on the last bullet on labeling, it says, "a detailed summary of device-related and procedure-related complications."

Do you mean a listing of what they are, or does this mean a summary of existing data? Rates of these. I just --

MS. WENTZ: Good question. I think, at this point, the rates are probably pretty well known in the clinical community, so maybe a listing would be all that is needed.

DR. NAFTEL: Okay. Then could I add a bullet to this or try to --

DR. PAGE: Yes. Please make your recommendation.

DR. NAFTEL: Okay, so I would recommend that we formally do what we saw from Thoratec this morning, that we formally ask the company to give FDA the denominator once a year to help you with your MDRs to look at the rates. So that's not a big imposition on the company and at least it gives us some data --

MS. WENTZ: Are you talking in the context of the labeling?

DR. NAFTEL: No, no. I'm going to a whole other bullet, you know, new bullet. Company provides annual uses, not sales, but actually how many times it's used.

DR. PAGE: Dr. Somberg, did you want to make a comment, and Dr. Zuckerman, I think --

DR. SOMBERG: Yeah, I don't think that's appropriate because why should we single out this particular area in this particular instance to require these things? I mean, you're sort of setting a new policy.

I agree, maybe all companies should -- and that should be

factored in and this whole thing should be overhauled. But let's not do it in a series of recommendations for a panel in one specific group of devices. I was going to say wastepaper basket, but that's not really -- they're important.

DR. PAGE: Thank you.

Dr. Zuckerman.

DR. ZUCKERMAN: Yeah. It's an interesting concept posed by Dr. Naftel, but I'd like the Panel to weigh in on the potential added value. And we had a similar discussion yesterday where Dr. Allen was quite helpful, and maybe he can comment again where he pointed out (1) the MDR system remains in place; it's been reasonable for tracking significant blips. And (2) we wouldn't be at this panel reclassification today if we didn't think there was reasonable safety and effectiveness for this indication. But I don't want to put words in your mouth.

Dr. Allen, can you help us here?

DR. ALLEN: Dr. Zuckerman, I think you recapitulated what I said yesterday quite nicely.

DR. PAGE: So you would not add that added bullet or --

DR. ALLEN: I would not.

DR. PAGE: Okay.

DR. ALLEN: I don't think -- Dr. Somberg, I think it's inappropriate to add that for a specific thing. I think it's appropriate for the FDA to take that under advisement and consider it as a future policy change,

but not today.

DR. PAGE: Okay.

Yes, Dr. Naftel.

DR. NAFTEL: Just a short, not rebuttal, necessarily, but when you listed the possible special controls, one of them was requiring a postmarket study, so I kind of felt like I was being incredibly nice and backing off from what we have the authority to recommend, so -- but I like the idea of just incorporate it in something that FDA might consider for all devices in the future. So I'm retracting my suggestion.

DR. PAGE: And I see Dr. Somberg's finger up.

DR. SOMBERG: I'll put my whole hand from now on.

DR. PAGE: There you go.

DR. SOMBERG: Dr. Naftel, I thought it was that they -- you know, that was a list of things that they may require, not that they were requiring postmarketing data -- okay.

DR. PAGE: I think we can move on from this. I think the point is well made, and it's an interesting issue to consider on other devices.

Any other comments as to whether you agree or disagree with inclusion of these special controls?

(No response.)

DR. PAGE: I'm seeing no other concerns.

Then, Dr. Zuckerman, regarding this Question 3, the Panel is in

agreement with the bullets that were put forward in terms of special controls and with only the suggestion, kind of in general, to perhaps track complications over long term in other devices as well as this. We're satisfied with what's been put forward. Is this adequate?

DR. ZUCKERMAN: Yes, thank you.

DR. PAGE: Thank you.

Let's move on to Question 4.

MS. WENTZ: Question 4: The FDA believes that the safety and effectiveness of non-roller type blood pumps used for temporary (≤ 6 hours) prophylactic or non-prophylactic ventricular support is not well established. FDA bases this determination on the lack of scientific evidence to support the safety and effectiveness for these uses, and therefore, FDA does not believe that special controls can be established to assure the safety and effectiveness of non-roller type blood pumps for these temporary ventricular support indications.

4a: Do you agree that the available scientific evidence is not adequate to support a reasonable assurance of safety and effectiveness for non-roller type blood pumps for these temporary ventricular support indications?

And b: If you do not agree --

DR. PAGE: Let's stop with (a).

MS. WENTZ: Okay.

(Laughter.)

DR. PAGE: And we'll go on to (b) as necessary.

I'd like to have the Panel speak up. This is an important one. And I'm actually going to ask that everyone at one time or another weigh in. But let's just have the discussion now.

And I've seen Dr. Katz, Dr. Kandzari, Dr. Somberg, Mr. Barrett all raise their hands. So let's take comments and questions in that order.

Dr. Katz.

DR. KATZ: So my answer would be no for the reasons I've previously stated, though I think there is adequate evidence for at least the centrifugal pumps, but you could raise other questions in other areas.

DR. PAGE: Okay.

Dr. Kandzari.

DR. KANDZARI: Tuesday afternoon, before I took my flight here, a patient came into my cath lab, and he was telling me about his family and his profession, and he was in course of ventricular fibrillation. And he was able to talk with me and was alert because of a non-roller pump device. And he would be dead otherwise.

And if we -- it's hard to avoid moving into Question 5, but trying to keep away from declassification, if we consider classification as a Level II for only the cardiopulmonary bypass support, we would be ignoring that potential benefit, and that's a benefit that has been demonstrated with both

axial and centrifugal devices for hemodynamic support. Consistently, these studies have demonstrated an improvement in mean arterial pressure, a reduction in the pulmonary capillary wedge pressure, and improvements in both cardiac index and power that have not only been superior to no therapy, but in most instances superior to a balloon pump.

I think we've been a bit overly focused on a single clinical application and a singular device in this discussion, but the hemodynamic benefit with these devices is shared amongst all these technologies that are under our purview of consideration.

And it would be a double standard for us, particularly in light of yesterday's panel meeting, to not consider the benefit of these technologies for hemodynamic support and say that we're going to hold it to a Class III because of the absence of a clinical efficacy endpoint when we don't really have that consistently demonstrated with the balloon pump that we considered and debated yesterday, as well.

The issue that I would suggest as we move forward would be that for particular indications, extended support beyond 6 hours for the application and electro-physiologic and percutaneous revascularization procedures, these can be Class III PMAs. But for hemodynamic support -- and perhaps we might change that from ventricular support to hemodynamic support in the wording, but I think here we have consistent evidence across the devices.

DR. PAGE: Okay, thank you.

Mr. Barrett and I think Dr. Somberg was the fourth one who raised his hand.

MR. BARRETT: Really, the previous two speakers already beat me to the punch. What I was going to say is that it would be very interesting and important to the industry to get feedback from the Panel as to how they might answer 4a if you were to further dissect the indication for use statement or take that indication and look at the devices in the sub-classes that fit within the non-roller pump category. So, really, that's what both the previous speakers were leading to.

DR. PAGE: Dr. Somberg and then Dr. Allen.

DR. SOMBERG: I think it's important to be consistent, and we saw yesterday, when we were dealing with a series of very old devices and down-classification, that the data was inadequate in many instances, but we took the totality of it and in, at least, the former one, I was in the minority. I've always been an advocate of having randomized control trials and I feel the FDA's concern here. But at the same time, we're talking about temporary ventricular support and for a whole host of reasons.

First it was with the centrifugal pumps, then it was the axial pumps. They have been available, and we have thousands of patients who have been exposed to it, and now we're saying that no, that's inadequate for non-bypass scenarios and we need more data. Contrary. We have -- and I

think that most people at the table who have hands-on experience, which I don't have with these devices, but hands-on experience would say that many of these pumps provide better ventricular temporary support than the intra-aortic balloon on a hemodynamic basis.

So how can we, in all honesty, say that we have insufficient -- I mean, if we have 4 years, 5 years of information there, maybe we have to go through it more carefully, et cetera, but just because we have 30 or 40 years with something that's inferior doesn't make us have to be inconsistent.

So, therefore, I'm not going to repeat this for a number of instances, but I think we have a good inclination that there is temporary ventricular support adequacy for these non-roller different pumps and that there could be special controls developed, including clinical data, to substantiate the effectiveness and safety in each individual category as needed by the regulatory body.

My conundrum is I'm not the regulatory body; I can't force you guys to come up with those special controls, so I'm really at a loss for what course we should take, but I think everyone should give thought to stories like Dr. Katz's [sic] statement right now, patient comes in -- talking to him, supported by this. I hate to advocate from anecdotal experience, but that's the way it is and we have that out there, so we have to sort of accommodate reality and not say, well, let's start again.

DR. PAGE: Dr. Zuckerman, I think I know what you're going to

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say, but go ahead.

DR. ZUCKERMAN: Would you like to say it?

DR. PAGE: Well, I think you were going to comment that nobody ever walked in with a less than 6-hour approved device, so the anecdotal report was from a device that was PMA approved, if I'm right, that your patient walked in who was being supported in VF, was a PMA approved device and not one that we're considering today.

DR. KANDZARI: That's correct, but --

DR. PAGE: Yeah.

DR. KANDZARI: Yeah.

DR. PAGE: Dr. Zuckerman.

DR. ZUCKERMAN: Okay. You know, this is --

DR. KANDZARI: My point is about -- but notwithstanding, forget the anecdotal stories, that everybody can share them. We've heard from public speakers. The issue is that these devices that are under discussion today, both axial and centrifugal, have demonstrated hemodynamic improvement and hemodynamic parameters.

DR. PAGE: Thank you.

MS. WENTZ: And can I make an important clarification on that point?

DR. PAGE: If Dr. Zuckerman yields, because he -- I called on him.

DR. ZUCKERMAN: Okay, Ms. Wentz can start first, but then I'd like to add some comments because this has been a really rich discussion up to now, and I want to continue the discussion.

MS. WENTZ: Okay. The clarification is about the term used for effectiveness and how yesterday we talked about hemodynamic support being an effectiveness endpoint for intra-aortic balloon pumps and that that was okay by you all.

Effectiveness is back on the slide that had Question 2. Effectiveness in our regulations is defined as clinically significant results in a significant portion of the target population when the device is used for its indications for use.

Now, if you remember, for intra-aortic balloon pumps, before PCI came along, before the drugs came along, intra-aortic balloon pumps showed clinical benefit, showed that level of effectiveness. It wasn't until it got lost in the noise of all the other treatments that we then focused on the hemodynamics. These class of devices have not been able to show that level of clinical benefit yet, or at least we have not seen the data.

DR. PAGE: Thank you.

Dr. Allen raised his hand. And, Dr. Katz, we'll give you a chance to comment, but I'm looking for the entire spectrum of opinions from the committee.

DR. ALLEN: I think it's a very challenging question, and once

again, I hearken back to and continue to repeat in my mind that this is not a PMA, this is not a PMA; I'm from Kansas, we're not in Kansas anymore. And it's not a PMA, and as a user of these devices, I can't fathom how they can be regulated with special controls when they're not the same devices. And to me, that seems an impossibility.

So when you have devices in a class, as a whole, that are very similar, are manufactured the same and do the same thing, then I think that's an appropriate way to manage them, with special controls. But in this case, going back to Dr. Barrett, or to Mr. Barrett's comment, you now have different devices, different types of devices, and they need to be managed differently, and they need to be separated and reclassified.

And I think if you did look at the data as a PMA and the PROTECT II trial came up to panel, at least the distinguished panel members that I've been involved with on other panels would look at the PROTECT II trial, and while we applaud it being done and it's randomized, a trial that was stopped prematurely and didn't meet its primary endpoint and had a composite endpoint that had 10 pieces to it with a lot of post hoc analysis, I can't imagine any panel approving that, as a primary PMA panel.

So I think we need to lend credence to what the FDA is asking for, what this panel is charged with, which is give clarity to the field of mechanical circulatory support.

I don't care how we got into this mess, but let's not kick the can

down the road like they're doing down the road --

(Laughter.)

DR. ALLEN: -- and let's clean this mess up and reclassify devices that are the same, put those in one bucket, and devices that are different, put them in a bucket, which is all I think the FDA is asking. So with that, I would say my answer to (a) is that, you know, I would agree with the FDA.

DR. PAGE: Thank you.

Dr. Zuckerman.

DR. ZUCKERMAN: Yeah. I just want to thank Dr. Allen, again, just for helping the Panel focus on what advice the FDA needs today. I fully respect the comments made by Dr. Kandzari, and I'm looking today at a panel of highly experienced interventionalists who understand that devices of this type are needed for care in the United States for the type patients that Dr. Kandzari just related.

And we're not talking about removal of a device or approval/disapproval of a particular device today. We're instead asking you, again, to act more as a regulator today to help us develop a reasonable, logical, and efficient regulatory paradigm that will help all parties involved, meaning patients, physicians, and regulators.

And I think that Dr. Allen has pointed out key points because in the end, we're all interested in safety and effectiveness and good patient care, and the logical extension right now, again, of using one device

company's data primarily to move to Class II can be a big leap given the varieties of designs that we've seen and the different particular technological characteristics that may be inherent with different designs. So I would like you to thoughtfully consider Dr. Allen's comments and continue this very important discussion.

DR. PAGE: Thank you.

DR. KANDZARI: May I respond to that, then?

DR. PAGE: Can I hear from others?

DR. KANDZARI: It was just directed, I think, towards my comment, so --

DR. PAGE: Well, I think it was -- if I may, I'd like to hear everybody's voice, and then we'll continue the conversation.

Dr. Slotwiner.

DR. SLOTWINER: Yeah, I wanted to indicate my support for Dr. Allen's perspective. I wish I could articulate it as well. And just say again that I appreciate the Agency's challenge on trying to evaluate effectiveness of these different technologies as -- in applications that we probably can't even imagine yet. And so I think we need to look at clinical outcomes as they are evaluated.

DR. PAGE: Thank you, Dr. Slotwiner.

Dr. Doty.

DR. DOTY: So my short answer is I agree with Dr. Allen, that I

agree with the FDA, there is not adequate scientific evidence to support a reasonable assurance of safety and effectiveness. And to support that, I want to make two points.

One is to refer back to Dr. Laschinger's Slide 90 from his presentation where he talks about different populations, different indications, uncertain benefit/risk profile with different technologies and evolving technologies.

And then he points to what I think is another very valuable and incredible document, the ACC/AHA/SCAI 2011 recommendation on PCI where it says elective insertion of an appropriate hemodynamic support device as an adjunct to PCI may be reasonable; and that's Class IIb with an evidence level of C, so I agree with Dr. Kandzari that these are important devices, they provide hemodynamic support. I do not dispute that. But I think we have some backup from the American Heart and associated organizations that the level of evidence is low and not sufficient, in my opinion.

DR. PAGE: This is a very valuable discussion we're having here. What I'd like to do -- I see your hand, Mr. Barrett, and I'm going to call on you after I've heard from the others, if I may.

I'd actually like to go across the table here, from those from whom I haven't heard already, to feel free to say a yes or a no, if you want to say why or who you might agree with, but good perspectives have already been shared. Just kind of get a feeling for where we are because it's clear, no

matter what, we're going to want to go on to (b) and have the people who feel that the answer is no here to help us work out what would be suggested for those questions.

But if I may, may I call on you, Dr. Greenfield?

DR. GREENFIELD: Agreed.

DR. PAGE: Would you turn on your microphone, please?

DR. GREENFIELD: Yes, agreed.

DR. PAGE: So that's a yes.

Dr. Brinker.

DR. BRINKER: I agree, as well. But I also feel that this discussion has brought out the benefits of these devices, the likely -- a very likely result of them being formally approved and since the FDA -- as a PMA. Since the FDA, as Bram has said, has a great deal of regulatory discretion, I don't think this would be an onerous process.

DR. PAGE: Thank you.

Dr. Cigarroa.

DR. CIGARROA: I agree with the FDA's position, separating our task today in terms of classifying how devices are regulated versus how they're currently used and our understanding of the importance of hemodynamics versus different clinical outcomes. I don't see how special precautions can protect against different technologies, and so I agree with the FDA's position.

DR. PAGE: Thank you, Dr. Cigarroa.

Dr. Yuh.

DR. YUH: Yeah, when I asked a question five hours ago about the difference in this device, I probably should have been more forceful about it because I still think it's a different device. And I think that if we down-classify the entire group, we're turning a blind eye to the fact that it's a different device and requiring, possibly requiring, different special controls. So I agree. I agree with Dr. Allen and the rest of the group thus far.

DR. PAGE: Thank you.

Dr. Dehmer.

DR. DEHMER: I agree that the available scientific evidence is not adequate.

DR. PAGE: Thank you.

Dr. Naftel.

DR. NAFTEL: I agree, as a class, there's not enough information, but I'm sure that FDA will weigh how much information there is per existing device as you go forward with your regulatory pathway.

DR. PAGE: Thank you.

Dr. Hirshfeld.

DR. HIRSHFELD: Yeah. First of all, I agree and I think that the attempt to combine all these disparate devices together under one class is one of the problems.

The other problem, I think, is the problem of definition of effectiveness, and at the risk of paraphrasing a famous Supreme Court justice, I think effectiveness is difficult to define but you know it when you see it. And so I think that, moving forward on this, what we need is to really try to come up with a really good definition of what true effectiveness is, and now it should be the standard to which the sponsor should be held.

DR. PAGE: Thank you very much.

During this conversation, I put off briefly Dr. Kandzari and Mr. Barrett. Did you have other comments at this point?

DR. KANDZARI: Yeah, I just want to clarify. I think it's a relevant issue that pivots around effectiveness. I do not agree that the evidence is inadequate to support that these devices improve hemodynamics.

With regard to clinical effectiveness, I do agree with the statement. My issue is that we are looking at this as if there is one glass that is half full and one that is half empty, and all I'm suggesting, Dr. Zuckerman, is that there may be more than one glass, that we could perhaps consider down-classification to extend the hemodynamic support aspect of these devices, but for these clinical effectiveness issues, these would remain Class III.

DR. PAGE: Thank you.

Mr. Barrett.

MR. BARRETT: I want to try to clarify my earlier comments

again to Dr. Allen and others.

I think what everybody just said reflects the dilemma, and it all goes back to how this bucket, if you will -- you've been calling it a bucket -- or this class has been defined. And we've put multiple different technologies and multiple clinical indications together and asked this question. And so the default answer is the answer we just heard, and what I'm wondering is, if we split this class -- and this class is not codified in the federal regulations; it's a proposal -- by device type or by more specific indication, would the Panel's answer to 4a for some of those split-out portions be different? It's the two glass --

DR. PAGE: Thank you. I think we're already having enough challenge with the way things are split now, so I'm not going to advocate right now we further split.

Ms. McCall, you've been patient. Do you have any other comments or concerns at this time, representing patients?

MS. McCALL: And I thought yesterday's discussion was intense. No, I agree with what's been said so far.

DR. PAGE: Thank you very much.

So, Dr. Zuckerman, with regard to Question 4, we actually took a straw vote, if you will, and I believe we don't -- much as we respect and appreciate Mr. Barrett, he is not a voting member. So of the voting members here present, we have a no from Dr. Katz, we have a no from

Dr. Somberg, and a no from Dr. Kandzari. And the others were affirmative. And I am now weighed in.

DR. ZUCKERMAN: Thank you.

DR. PAGE: Thank you.

Let's move on to (b) because we have very well-stated perspectives that disagree with this. So let's go on to (b) and let's explore the questions raised in 4b.

MS. WENTZ: Thank you. Question 4b: If you do not agree, please discuss the following:

- i. The scientific evidence available in support of the safety and effectiveness of non-roller type blood pumps for these temporary ventricular support indications.

That doesn't make any sense. Scientific evidence is -- I guess it does support it.

- ii. Special controls that you believe would be sufficient to provide adequate assurance of safety and effectiveness of non-roller type blood pumps for these temporary ventricular support indications.

DR. PAGE: Anybody want to put forward any evidence that we might not have heard or highlight any evidence that we have heard today to support the perspective that there's adequate safety and effectiveness for non-roller pumps for this indication of ventricular support for less than 6

hours?

Dr. Kandzari.

DR. KANDZARI: I would only add that my suggestion would be that we could continue -- clinical practice evolves, as it always will, and that we could continue through postmarket studies, perhaps, to use that safety data to update the labeling of these products as it may pertain to them individually.

DR. PAGE: Thank you.

Dr. Katz.

DR. KATZ: Well, first, I would say that I agree with Mr. Barrett's statement from before. Secondly, in response to this, I would say that you could use the data used to support the cardiopulmonary bypass indication. That would answer both questions.

DR. PAGE: Any other additional comments?

(No response.)

DR. PAGE: So, Dr. Zuckerman, with regard to Question 4b, there was satisfaction that safety and effectiveness were adequately demonstrated among at least a portion, a minority, of the Panel and that perhaps postmarket studies or the data from cardiopulmonary bypass could help inform in terms of temporary support indications and special controls. Is this adequate?

DR. ZUCKERMAN: Okay. That's very helpful for the folks who

voted no, but I'd like to hear a little bit more from the folks that voted yes, that we aren't quite where we need to be today in terms of safety and effectiveness. And I think I'd like to first start with Drs. Brinker and Hirshfeld, who have a long experience in the field of interventional cardiology.

For one particular sponsor today, you've seen preliminary data from a randomized trial and other data. You've pointed out to the FDA that due to clinical practice changes -- in other words, we have better stents, better pharmacology -- perhaps our initial expectations in the randomized trials were overly optimistic.

So can you better define, Drs. Brinker or Hirshfeld, exactly what pornography has -- just kidding -- what effectiveness is?

(Laughter.)

DR. ZUCKERMAN: Realistically.

DR. HIRSHFELD: I was trying to get Dr. Brinker to go first and he's -- well, I think that there are two components to it. The first is to what degree does the device facilitate and make safer and less stressful the conduct of the procedure itself. In other words, what does it do to the excitement quotation of conducting the procedure?

And then the second is what does it do to influence the long-term outcome after the procedure, and I think FDA has argued primarily that the long-term outcome -- in other words, how many people are standing free of adverse events 90 days later is the true outcome, and I just would say that,

as a proceduralist, I'm also interested in how stressful it is for me to undertake the procedure and how secure I feel undertaking certain aspects of the procedure.

So I think that if you are looking for a way to demonstrate the value of this device in using metrics other than just 90-day body counts, that you need, in some way, to measure how successful and effective the procedure, itself, was.

DR. BRINKER: So I think that I agree with the dual definition of effectiveness. One is, does a device do what it says it's going to do mechanically, does it increase cardiac output, does it hemodynamically rectify a deteriorating situation? And the second is whether there's ultimate clinical benefit of that action.

And we had this dichotomy going back into whether thrombolytic therapy helped. It's the original evidence used to support thrombolytic therapy, was whether it dissolved a clot in the coronary artery, and that was rejected only when it was determined that it salvaged myocardium in terms of ejection fraction, was it approved, so there's always been this issue of defining clinical benefit associated with the action.

I believe that it's absolutely established that the devices that we're -- the class of devices that we're discussing today for ventricular support do benefit hemodynamics. What remains difficult for the FDA is whether they deliver on the ultimate clinical outcome. It's not as clearly

defined as they want, and I think that's true.

DR. PAGE: Dr. Somberg.

DR. SOMBERG: My suggestion to industry to go forward would be to not -- you're not going to be able to compare to placebo in this situation for a host of reasons. The intra-aortic balloon is now, as of yesterday's standards, the standard device for this type of support, and to think even though that might be inferior in some ways for ventricular support, how much support do you need? And it seems what the PROTECT study told us was you don't need that much support early on, maybe at 90 days, but that may or may not be correct.

So to go forward, one should look for a non-inferiority endpoint between the two. The problem with the PROTECT study, and why we got into all this minutiae, was that it was a superiority study and it was futile to go forward. So do a non-inferiority study; you have wide margins here and you will be non-inferior.

DR. PAGE: Dr. Somberg, let me follow up on that, if I may. And what you're suggesting is a comparison, non-inferiority to IABP, presumably in the high-risk PCI group. And I guess your having sat at the Panel yesterday for the IABP, were you satisfied that the IABP independently demonstrated benefit in that patient population?

I know it was approved, and I know there was mortality data, there were mortality data early on, but in terms of any data that clearly

demonstrate benefit of IABP, I would personally see it as problematic showing that it's non-inferior if the comparison has never been rigorously evaluated.

DR. SOMBERG: First of all, yesterday the focus was on the early original studies in the age before PCI and then in terms of the PCI. We weren't necessarily looking at the very small subgroup of people who now are very high-risk who need hemodynamic support. That has changed. So the field has changed.

But what I'm saying is unless obviously the regulators don't agree with that comparison, the PROTECT study was developed, I heard, in conjunction with FDA, but the problem is it was a superiority study and to say we know how much hemodynamic support is needed. I would turn it around and turn into your field, in VT. You know, VT ablation, what are you going to say? You were able to do the procedure and not the procedure, you're going to do it versus a placebo, or are you going to do it versus some other alternative control? These are very difficult issues.

So I'm saying if you go forward, which the majority of people said, that it becomes a PMA requisite, then you have to figure out how to do a study. And it seems to me yes, we do not know for sure in this very high-risk population, but it is standard medical practice. And that's what usually a comparator is, standard medical practice, for instance, to do a left main high-risk PTCA with stent is usually done with intra-aortic balloon. So if you can do

that and show you're not -- you're saying that's not the correct -- high risk, if you're non-operable and you have a high-risk patient?

DR. PAGE: Dr. Allen.

You raised good points, thank you.

Dr. Allen.

DR. ALLEN: I guess I would caution that advice to industry because device trial design, with the increasing cost of devices, it's not just a matter of having the FDA or a panel approve a product. It becomes almost more important to figure out who's going to pay for that product. And so I think we have to be cautious in advising industry to design non-inferior trials if the product that they're going to promote comes at a very high cost to society and the medical healthcare system. So it comes back to the three-legged stool that we talked about yesterday. I think you have to be cautious.

DR. PAGE: Thank you.

Dr. Cigarroa.

Before we move on, Dr. Zuckerman, are you comfortable?

We've kind of morphed to a discussion of what effectiveness criteria might be employed in a PMA trial, but at the same time it seems like this might be valuable. So if it's okay with you, I'd like to continue this discussion for a couple more minutes.

DR. ZUCKERMAN: Thank you. This is quite valuable.

DR. PAGE: Good, thank you.

Dr. Cigarroa.

DR. CIGARROA: So the challenge of efficacy here is difficult.

Does one look at procedural success with intent for the completeness of revascularization that one thought might be able to accomplish if hemodynamics permitted? In the absence of ischemia, hemodynamic instability, ventricular irritability, and then the complications associated with the add-on is one possibility. And then how does one do that when this is not blinded, right?

And one of the things we heard earlier is, irrespective of which device it is, right, one would have to do this for these different classes of different types of devices within this classification, is how comfortable am I, as a proceduralist, knowing the degree of differences in support, to complete what I wanted to do and feeling that a particular device might be able to keep me out of harm's way. And so, you know, I see these confounding variables in assessing efficacy of these devices.

DR. PAGE: Thank you, Dr. Cigarroa.

Are there other comments about efficacy?

(No response.)

DR. PAGE: So, Dr. Zuckerman, I believe I answered for (b) to you and then you asked another question, but to summarize, this has been a very valuable discussion of what efficacy criteria might be used. And through this day we've heard hemodynamic improvement as being something to

consider; Dr. Cigarroa mentioned other endpoints; the issue of superiority or non-inferiority versus the balloon in the setting where it seems like it is standard of care to provide some sort of support; that's going to be difficult.

But, again, is this conversation valuable to you and suffice in terms of Question Number 4?

DR. ZUCKERMAN: Yes. But I think a few other people wanted --

DR. PAGE: Yes, Dr. Kandzari had a comment.

DR. KANDZARI: Again, I think we're overly focused on this adjunct for high-risk PCI issue because the statement up there and the terminology we're talking about is related to ventricular support. It doesn't say as an adjunct to EP procedures; it doesn't say high-risk PCI. And so I'll just remind this panel, we uniformly seem to agree that these devices provide hemodynamic support.

And I think, Dr. Somberg, you stated it well that keeping just things as Class III still doesn't resolve this high-risk PCI issue. It's not going to resolve the adjunct to an aortic valvuloplasty or an EP issue unless people specifically study that and that's what -- if you want that indication, as I suggested, that's what you'd have -- you'd have to do the study.

DR. PAGE: Thank you. Let's move on, then, to Question Number 5.

MS. WENTZ: Okay, I need to preempt this question with the

fact that there seems to be support for both down-classification to Class II, as well as maintaining the current Class III regulation for non-roller type pumps.

So we had many discussions about high-risk PCI. As such, we would like some guidance from the Panel regarding the high-risk PCI patient population in the context of both the Class II down-classification as well as maintaining the Class III classification.

So keeping that in mind, I'll read Question 5: The 510(k) cleared indications for non-roller type blood pumps have been general in nature, essentially describing what the pump does (i.e., a tool). Through practice of medicine, which FDA does not regulate, the use of a subset of non-roller type blood pumps has evolved into a more specific use, high-risk percutaneous coronary intervention (HRPCI), which has been documented in clinical practice guidelines, such as the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. Although FDA is most specifically considering what is classified (cleared) under the current regulation at today's panel meeting, we recognize that manufacturers may seek indications which are consistent with clinical practice guidances in the future. As such, FDA requests that the panel comment on the following with respect to use of non-roller type blood pumps for HRPCI:

5a: Are the risks to health identified for non-roller type blood pumps intended for ventricular support the same as the risks for non-roller type blood pumps intended for HRPCI? If no, what new risks do you believe

are associated with the use of non-roller type blood pumps for HRPCI?

DR. PAGE: And, again, let's stop right there. We're just talking about risks. Anybody have concerns with this?

(No response.)

DR. PAGE: So essentially the answer to 5a is yes, Dr. Zuckerman. May we proceed?

DR. ZUCKERMAN: Thank you.

MS. WENTZ: Question 5b: Does use of non-roller type blood pumps for HRPCI have a significantly greater impact on public health as compared to use for temporary ventricular support?

DR. PAGE: Let's open this up to the audience. We heard the numbers, and the numbers were that the majority were being used, I believe, in high-risk PCI in terms of ventricular support, but comments with regard to this, would you say they have a significantly greater impact on public health compared to ventricular support?

I'm not sure why that really matters here, frankly, but I'd love to have the Panel give some input so I can provide something for Dr. Zuckerman.

DR. ZUCKERMAN: Okay. And Dr. Page, that's a good question to start out with, first, back to the FDA.

I think, because of the numbers, we were impressed. If somehow we should call high-risk PCI out of temporary ventricular support or

leave it in that bucket -- and that's why we'd like to hear some Panel comment.

DR. PAGE: So does everybody understand? Does it make sense to cull it out or keep it together? And perhaps if you want to comment, how you would study it if you -- one way or the other, whether it be high-risk PCI study would apply to the other indications.

Dr. Slotwiner.

DR. SLOTWINER: I just don't think we have much information other than the high-risk PCI. I think the ventricular support for other reasons remains a big question, so I don't -- I think we don't --

DR. PAGE: I'm not sure I have the answer for you.

Dr. Somberg.

DR. SOMBERG: Here's the conundrum. Yes, each one may be a little bit different, but then, again, the devices are going to be available for the intra-operative support, so it's going to be left with more onus on the interventionist to use these devices on a sort of an off-label basis. But, unfortunately, is a company going to break down the VT group, the PCI group, maybe the heart failure group that's acute and in some sort of bridge and do individual large outcome studies for each one of these? I don't think so, but I'm not against it.

So I think you're going to have to leave it together or be willing to say we'll study one of these, like high-risk PCI, give ventricular support to

that group, and by virtue of fact of a positive efficacy and safety balance, are willing to extrapolate that to some other situations.

DR. PAGE: Thank you.

Dr. Brinker.

DR. BRINKER: So the common denominator of classifications, as to potential benefit, is ventricular support, and the only reason that you would put it in a high-risk angioplasty patient is because you're worried about the small but finite risk of not having enough ventricular function to get you through the procedure should a problem develop during the procedure.

And I think the same thing for VT ablation. You don't put it in except to guard against the need, the occurrence, of a situation where there's not enough intrinsic ventricular activity because of arrhythmia or multiple shocks that occurred and depressed the left ventricular function, so that you need some ventricular support. And just the function of how often you'll actually require the support as opposed to having it put in as a prophylactic device.

DR. ZUCKERMAN: Right. So, Dr. Brinker, can you extend your comments? As you point out, some of those other indications may be niche uses, so do you agree with Dr. Somberg, for example, that if you could do a definitive trial in high-risk PCI, one could extrapolate results to give an indication for temporary ventricular support to cover a wider gamut, as you're suggesting, that might be useful?

DR. BRINKER: Yes, but I'm not sure, from -- I think the company, whatever the company is, should be fixated on perhaps doing even a more select group that has developed ventricular dysfunction acutely as opposed to prophylactic use of the device, especially in the situation where applying direct therapy as in PCI, and we see what happened in the prior studies, that it may not be a fruitful -- may require large numbers of patients, where if you had a short ventricular dysfunctional situation and then put the device in, I think it would be more obvious and less demanding.

DR. PAGE: Yes. But, actually, Dr. Cigarroa had his hand raised.

DR. SOMBERG: But there's a direct question. I just want to know what he would compare it to in that -- I mean, would he use an intra-aortic balloon or something?

DR. BRINKER: You could, as a comparator.

DR. PAGE: Thank you.

Dr. Cigarroa.

DR. CIGARROA: So I do think that the non-roller type blood pumps for high-risk PCI have significantly greater impact on public health. And that statement primarily culls in on one of the types of devices that we utilize in that particular patient group. I think it is somewhat challenging to extrapolate the use of these devices in high-risk PCI for hemodynamic support in EPVT procedures.

You know, the issues of potential myonecrosis and

complications of the revascularization procedures are very different than what occurs in the EP laboratory and I would say, in the EP laboratory, it's really about hemodynamic support. In the catheterization laboratory, I think that hemodynamic support primarily is to mitigate when one has no reflow for whatever reason, being able to sustain that operative ischemia.

So I think the noise would potentially be quite different and not applicable. So I think in the scenario for EP, is it adequate in the presence of a rhythm that is inadequate to support perfusion to be the buffer zone to allow you to do a procedure that you would be unable to do otherwise?

DR. PAGE: Dr. Kandzari and Dr. Slotwiner, did you want to say something?

Go ahead, Dr. Kandzari.

DR. KANDZARI: With regard to Question 5, I do think that high-risk PCI needs to be culled out. I think the issue that's just not being formally addressed here in the room is that there's a concern with this comment with regard to public health impact, that the device would take off if declassified to Level II as sole use for high-risk PCI because that has been a dominant use. And I think, like I said in the beginning, it says ventricular support, not high-risk PCI, and those can be studied in a different trial.

But, remember, in your suggestions of how to do such a trial, a balloon pump has not been demonstrated to be superior to provisional use alone, so how you design that trial, I think, is going to be a challenge when

the control is not well established. And to suggest that you could use a high-risk PCI trial successfully to expand it to heart failure or other indications, I think all that has to be studied. Instead, perhaps, you can put the language of the trial and the trial results in the product labeling to remind clinicians about where this is beneficial and where it has not been definitively established.

DR. PAGE: Great, thank you.

Dr. Slotwiner.

DR. SLOTWINER: Yeah, thanks. I just wanted to follow up on Dr. Cigarroa's comments.

And the wording of (b) is confusing, but I think you touched upon what I was trying to say, is that the use of this support for high-risk PCI is very different than the use of it in, for example, VT ablation where somebody could be ischemic for long periods of time, and so yes, I think that the public impact could be great and not just the high-risk PCI.

DR. PAGE: Dr. Allen.

DR. ALLEN: You know, I think that's a moving target because it really depends upon answering the question how much ventricular support do you need, and that's a moving target within these very cleverly designed axial flow devices. There's a 2.5, there's a 4, and as these devices mature and new iterations come down the road, they become smaller and flow increases. While high-risk PCI may be the predominant use now, 2, 3, 4, 5 years from now, these devices may be used more for heart failure than they are in high-

risk PCI, so I'm not sure which has a greater impact.

DR. PAGE: Fair enough. I'm going to make an effort to keep us moving along.

Dr. Zuckerman, to answer 5b, which is a fairly simple question to which we gave a fairly complicated but, I think, valuable answer, "Does use of non-roller type blood pumps for high-risk PCI have a significantly greater impact on public health as compared to use for ventricular support," I'm hearing that at least numerically, currently, yes. But you've heard guidance or suggestions regarding the populations that may change over time. One is for EP study.

The issue that I think would need to be addressed in creating any trial would be whether or not to include other populations and whether, on the base of that trial, the results would allow labeling for other populations, for example, if it were only studied in high-risk PCI. While it might be used by the practice of medicine in EP procedures, would it stand to potentially have a label for that? And I think that's a conversation that would need to precede any trial. Is that helpful to you?

DR. ZUCKERMAN: This has been a very helpful conversation; thank you.

DR. PAGE: Great, thank you.

I'd like to move on to (c), which I think is going to be fairly simple.

MS. WENTZ: 5c: Is the target population different for non-roller type blood pumps intended for high-risk PCI compared to use for ventricular support?

DR. PAGE: Let me take a stab. We think it probably is.

DR. BRINKER: Actually, this is the question -- this is a comment that I wanted to make for the last one and that is, for -- a regulatory question.

If a sponsor could establish a benefit for longer than 6 hours of support, could that be pushed back to less than 6 hours?

So, for instance, a heart failure indication, patient with acute heart failure, usually would be a no-brainer, if it's severe heart failure, to randomize a balloon to one of these devices, but you'd usually want them in for longer than 6 hours. So if you did the study for -- if you allowed the study for 24-36 hours, could you use that data for the larger population, perhaps? That would be less than 6 hours in the high-risk angioplasty group.

DR. ZUCKERMAN: Again, just on the face of it, I think my personal bias would be it's a different type of population, and I'd have a hard time understanding how you could make that extrapolation, unless other Panel members want to comment and help Dr. Brinker.

DR. PAGE: Dr. Cigarroa, did you have a comment?

DR. CIGARROA: So I think it is a different patient population, and I think that the use of these devices for heart failure indications, on a clinical level, not on how they had been approved, typically goes as follows:

Either it is a bridge to decision and that is a reversal of hemodynamics associated with an improvement in in-organ perfusion, and an improvement of markers as synthetic function of the liver and the kidney. And those things typically do not happen magically in the first 6 hours. And so I think that it's a distinctly different population.

DR. ZUCKERMAN: Okay, but I do want to, again, thank

Dr. Cigarroa for making that excellent comment because certainly the FDA is interested in working with industry to develop these bridge-to-decision trials. This may be an extremely important use of this device technology, but the thinking from the FDA is as Dr. Cigarroa indicated. I think these trials can be done in a reasonable fashion, and we certainly would encourage sponsors to think about what Dr. Cigarroa just said.

DR. PAGE: Do you need a further synthesis of Question -- Part (c), Dr. Zuckerman?

DR. ZUCKERMAN: No, I think we're okay.

DR. PAGE: Okay, good. Let's move on to Question 5d.

MS. WENTZ: Question 5d: Is the general knowledge base with respect to use of non-roller type blood pumps for HRPCI reflective of the existing understanding of use of these devices for ventricular support?

DR. PAGE: Question for the Panel.

Dr. Allen, your light is on, but I don't think you meant -- thank you. We won't comment on that.

Dr. Cigarroa.

DR. CIGARROA: So I believe the answer, with regard to the knowledge base, is the purported mechanism of action that Dr. Kandzari has mentioned, and that is the improvement in hemodynamics associated with it. Whether that translates into clinical efficacy outside of that, I think is different, but at least, in terms of purported mechanism, I would say the answer is yes.

DR. PAGE: Dr. Allen.

DR. ALLEN: So I'll turn my light on, and I would actually say it's not. And one of the issues with these devices is that a patient in cardiogenic shock, 2.5 l of flow or 1.9/2.1 l of flow isn't adequate to sustain. So I'm not sure that the knowledge base is. What you need to do -- a prophylactic high-risk PCI is very different than what you may need to do full ventricular support.

DR. PAGE: Dr. Cigarroa.

DR. CIGARROA: So what you've stated is an affirmation of our understanding of the principles and the limitations with regard to support a flow of certain devices, and so as one takes that particular patient that you just discussed, the utilization or more importantly, not utilizing a 2.5 and either using a 5 or utilizing a different system in order to maintain output is well understood.

In terms of the magnitude of forward cardiac output that can

be supported by Device A versus Device B and within Device A, classification of Device A1, A2, A3, A4, et cetera.

DR. PAGE: Are you catching that, Dr. Zuckerman?

I think you're both not disagreeing. Basically, the knowledge base with respect to roller type blood pumps for high-risk PCI doesn't fully reflect the existing understanding of these devices for ventricular support. There is applicability to both indications, but also there are unique aspects to both, as was just mentioned. In one, it's a prophylactic device, and another, you've got to put in something to support output when you know that the cardiac output is low.

DR. ZUCKERMAN: I agree. This was a very helpful discussion. Thank you.

DR. PAGE: Great. Let's move on to Question 5e.

MS. WENTZ: Question 5e: To what extent can the performance or clinical endpoints used to evaluate non-roller type blood pumps intended for ventricular support be applied to the evaluation of non-roller type blood pumps for HRPCI?

DR. PAGE: So this is kind of turning the question the other direction. We had a good conversation about the fact that there are certainly differences. Some overlap, some not.

Other comments from the Panel?

Dr. Doty, thank you.

DR. DOTY: So I think we do have a good extent of performance of these devices. I mean, we have a long history of how they work, the function of them, but I think Dr. Kandzari's point is excellent. We don't have, perhaps, the adequate clinical endpoints specifically for high-risk PCI using these devices.

DR. PAGE: Thank you.

Dr. Zuckerman, you got that?

DR. ZUCKERMAN: Yes.

DR. PAGE: I think we can move on to Question 6.

MS. WENTZ: Okay, Question 6: 21 C.F.R. 860.93 describes the classification of implants, life-supporting or life-sustaining devices, and states that "the classification panel will recommend classification into Class III of any implant or life-supporting or life-sustaining device unless the panel determines that such classification is not necessary to provide reasonable assurance of the safety and effectiveness of the device. If the panel recommends classification or reclassification of such a device into a class other than Class III, it shall set forth in its recommendation the reasons for so doing..." FDA believes that non-roller type blood pumps are life-supporting, which was supported by the original classification panel.

Question 6a: Do you agree that non-roller type blood pumps are life-supporting?

DR. PAGE: This seems to me like a lob, so --

(Laughter.)

DR. PAGE: -- may I suggest that the Panel would say yes?

DR. ZUCKERMAN: Thank you.

DR. PAGE: Now comes really the crux of our discussion, and I'm happy to open this up to further discussion. A lot of this basically is informed by our previous discussion. I think it still would be worthwhile going through and giving each member of the Panel the opportunity to comment and really be answering -- I haven't let you read this, have I?

MS. WENTZ: No, you haven't.

DR. PAGE: Once you read this -- and I'm going to ask you to read (b)(i)-(iii) and (c) with the suggestion, if it works for the Panel, that we each give our comments and response to these questions. So why don't you go ahead and read and then we'll see if that works.

MS. WENTZ: Okay. Question 6b: Based on the available scientific evidence and proposed special controls, what classification do you recommend for

- i. Cardiopulmonary bypass;
- ii. Circulatory bypass; and
- iii. Temporary ventricular support?

And Question 6c: In accordance with 860.93, if you recommend a classification other than Class III for any of these indications, please discuss the reasons for your recommendation.

DR. PAGE: Great. Why don't we go from this side, if we may, and go ahead and we'll start with Dr. Slotwiner. And we can have any further discussion we like, but I think it would be useful to -- since my impression is we've discussed this adequately. I'm looking around and I'm seeing nods. Okay, great.

Dr. Slotwiner.

DR. SLOTWINER: Sure. So I think, you know, as you said, we've talked about, I think cardiopulmonary bypass and circulatory bypass could be adequately regulated under Class II with special controls. I guess I'm combining (b) and (c), but based upon the available scientific evidence.

And temporary ventricular support, however, I think we don't have sufficient evidence, and so Class III would be more appropriate.

DR. PAGE: Thank you.

Dr. Somberg.

DR. SOMBERG: Sorry. John Somberg.

I believe it's for all three that we have imperfect evidence, but we have evidence of hemodynamic support, the same evidence we had with the intra-aortic balloon. So I won't belabor the point, but I hope at some point we try to address how one would move forward with a study because I heard so many different opinions here that if it did come to panel, people might go forth, invest millions and years, and we still wouldn't have an answer. So you don't have to just satisfy one person, you have to satisfy a

large number plus the regulatory people, so that's where the problem arises. I think we've already addressed this.

DR. PAGE: So you would say II, II, II. Is that correct? For the three choices, you would have them all in Class II?

DR. SOMBERG: Oh, yeah. Yeah.

DR. PAGE: Yes, thank you. I just wanted to make sure that was clear. Thank you.

Dr. Katz.

DR. KATZ: So I would have to answer this question differently for the two different classes of devices that are in here and think it's very artificial to lump them together and answer the question, so I would have to abstain.

DR. PAGE: And just so we understand, how would you pose the question? What would you be satisfied with?

DR. KATZ: You know, again, it's getting back to the fact that I think just lumping all these non-roller pump devices into one wastebasket is very artificial, and we probably could have had this meeting in an hour if we were able to separate the devices out because we've been having parallel discussions about the two.

And I feel that the centrifugal pumps, I would put them all in Class II and the micro-axial pumps I would put in III. Micro-axial pumps don't really -- I mean, they only pertain to Number (iii), not Number (ii).

DR. PAGE: Thank you very much.

Dr. Allen.

DR. ALLEN: I've run out of euphemisms at this late hour to clarify anymore, so I think for Number (i), cardiopulmonary bypass would be II with special controls; circulatory bypass would be II with special controls; temporary ventricular support would remain as a Class III.

DR. PAGE: Thank you.

Dr. Kandzari.

DR. KANDZARI: I think if we were to consider the classification as we did yesterday, balloon pumps based on the past three years of clinical data with balloon pumps, we would not have made the same conclusion because the data have not been supportive for balloon pumps in either cardiogenic shock or high-risk PCI, but a uniform conclusion of this group was that it does provide hemodynamic support. And in this particular regard, both independent studies with both axial and centrifugal devices have demonstrated hemodynamic support; they've actually demonstrated it is superior to a balloon pump. So for me, for cardiopulmonary bypass, Class II; for circulatory bypass, Class II.

By the letter of the statement -- and, again, it does not include high-risk PCI, it does not include other clinical indications -- for ventricular support, I say Class II.

But I would suggest to FDA that they include the high-risk PCI

data within the product labeling to perhaps relieve the concerns of inappropriate use or at least unfounded use as of yet and, further, to use postmarket safety data that may be a requirement for Class II status to guide additional safety data that could be included in the product labeling.

DR. PAGE: Thank you very much. That was a II, II, and a II.

Just so I'm clear, as I interpret this, temporary ventricular support includes high-risk PCI, as well.

DR. KANDZARI: Temporary ventricular support, that's the art of medicine, right? I mean, whatever the clinicians elect to use it for is their discretion, but for temporary ventricular support, which to me implies improvement in hemodynamics, Class II.

DR. PAGE: Thank you.

Dr. Hirshfeld.

DR. HIRSHFELD: I would go II, II, and III, and I would qualify the III by saying that I think there should be a major effort to separate the various devices that are currently lumped in that class. And I think that the pump devices need to be held to the standard of superiority compared to intra-aortic balloon pump because of their inordinately greater complexity and cost.

DR. PAGE: Thank you.

Dr. Naftel.

DR. NAFTEL: I also would go II, II, and III. I would just add that

for cardiopulmonary bypass and circulatory bypass, under the special controls, I just want to make sure we include some kind of patient outcome in that, and I'm back to MDRs. I'm not asking for a post-approval study, but I just -- I don't want to say that once the device leaves the manufacturer, we say great, it's safe and effective. I still want to tie it to patients, so I want to make sure we have that control.

And then for the temporary ventricular support, I want III, but maybe a little bit of a PMA -- not lite, that's not nice, but --

(Laughter.)

DR. NAFTEL: -- I want to make sure that you do just what you say you do, that you take into consideration all of the available data, the outside U.S. data, the MDR data, all the published reports, and you do what you're so good at, synthesizing all of it, and not necessarily demanding a brand new randomized trial or tough study.

DR. PAGE: Thank you.

Dr. Dehmer.

DR. DEHMER: The first two are easy. It would be a II, a II.

For Number (iii), temporary ventricular support, I'm going to stick to what is exactly on the paper, and that is, does the device provide temporary ventricular support, and I think that has been shown, so I would put down a II.

DR. PAGE: Thank you.

Dr. Yuh.

DR. YUH: I don't think I have anything meaningful to add to the discussion in terms of the rationale, but I think I would go with II, II, and III.

DR. PAGE: Thank you.

Dr. Cigarroa had to leave.

Dr. Brinker.

DR. BRINKER: II, II, III.

DR. PAGE: Well stated.

Dr. Doty.

DR. DOTY: II, II, and III, to second Dr. Hirshfeld's excellent summary.

DR. PAGE: Dr. Greenfield.

DR. GREENFIELD: II, II, III with an effort to continue to collect data on the reclassified II's.

DR. PAGE: Thank you.

Mr. Barrett.

MR. BARRETT: Nothing on this. I'll have one closing comment at the end.

DR. PAGE: Great, thank you. And this is not an official vote, so I'm happy to have you weigh in, if you cared to.

Ms. McCall.

MS. McCALL: I agree with the II, II, III, and particularly with

Dr. Greenfield's reasoning.

DR. PAGE: Thank you very much.

So, Dr. Zuckerman, if I may, of the voting members here -- and you heard the comment from the non-voting Patient Representative -- you had unanimity for cardiopulmonary bypass and circulatory bypass being "downgraded" or I think "right-graded," if you will, to Class II with special controls.

For indication of temporary ventricular support, which includes high-risk PCI, of course, you had a majority voting for or favoring Class III being maintained.

There were three votes, straw votes, for re-grading to II.

If I may weigh in, I would also vote for II, II, and III.

Comments that I think are relevant were, if a PMA were to be applied: There was one comment that superiority should be considered. Dr. Naftel reiterated that with re-grading to Class II, some sort of follow-up should be maintained.

Is this adequate, Dr. Zuckerman?

DR. ZUCKERMAN: Yes, this was very helpful.

DR. PAGE: With that, we don't have the usual closing comments from industry or from the FDA.

I do want to allow Mr. Barrett to make a comment, and then I'll ask the committee if there are any further comments.

MR. BARRETT: Yeah. Thanks, Dr. Page.

DR. PAGE: Mr. Barrett.

MR. BARRETT: Two quick comments.

I hope that, when the FDA gets the transcript and I have a chance to go back and reread the discussion today, that they'll again carefully consider how the class was developed for temporary ventricular support. There was a diversity of opinion at the Panel today about the construct of that class.

The last thing I wanted to touch on, and Dr. Naftel went there twice -- and I do think it's important now, with the outcome of the meeting, and it has to do with what happens next. And, certainly, I think the industry was assured by Dr. Zuckerman's comments that there's a lot of regulatory discretion about how this transition occurs. But I heard Dr. Naftel say jeez, this takes 2, 3, 4, 5 years. Well, it does if you have to design a prospective, randomized study.

And for the PMA to be filed, if that's a requirement, you'd need a run-up period of time to design the study, get it approved, and collect the data. So I think the sooner that the industry can get some visibility as to what is the level of clinical evidence that might be required in these PMAs, even before they're called for, so that that interim period of time can be used, if studies need to be started, to begin the dialogue on the designs and get them started will have a big impact on what ends up happening with some of these

products out there in patient use every day today.

Thank you.

DR. PAGE: Thank you, Mr. Barrett.

Ms. McCall, did you have any other comments?

MS. McCALL: Yes, thank you.

I'd like to thank Mr. Landin and the other patients that came today. You put a face on why we're here today and why we went through this very long day and this in-depth discussion.

I think we made good decisions today and had really great discussions, and I look forward to coming back to another panel and re-discussing the ventricular assist portion.

DR. PAGE: Thank you very much.

And if I may comment on behalf of the committee, you couldn't have said it better. The reason we're here is patients and the public good. We're listening to the physicians who, in a tough situation, need this technology. All of our understanding is this technology doesn't go away based on our recommendation here today. There is a grace period.

We've also heard that the PMA could be filed, that it may take a while, but in the meantime, I personally don't know how the study would look and what the right endpoints are, but if nothing else, to put forward the data that we've seen today on PROTECT II, for example, in terms of supporting a PMA could potentially be justified and then considered.

And in closing, I really want to thank our industry sponsors who are industry representatives who, I think, presented their case very well, and I want to thank the FDA. I want to thank this Panel, and especially, I do want to thank the patient representatives who remind us why we are here.

With that, Dr. Zuckerman, do you have any final remarks?

DR. ZUCKERMAN: No, I think you summed it up well. I was really impressed with how all parties worked together today to help the FDA; the FDA received extremely valuable comments.

And I hope everyone a safe trip back and want to thank Dr. Page for chairing an excellent panel.

DR. PAGE: Well, thank you very much.

And I should point out that this Panel has worked hard. I'm tired and I was just here today, and you have been at this for two days. You stayed with us, you provided great input. I know this is going to be helpful to industry, to the FDA, and to the public good.

So with that, the December 6th meeting of the Circulatory System Devices Panel is now adjourned. Thank you very much.

(Whereupon, at 4:31 p.m., the meeting was adjourned.)

CERTIFICATE

This is to certify that the attached proceedings in the matter of:

CIRCULATORY SYSTEM DEVICES PANEL

December 6, 2012

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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